IMPROVING ATOPIC ECZEMA CARE THROUGH INTERNATIONAL COLLABORATION

IN A MAJOR MATTER, NO DETAILS ARE SMALL

ANNELIE H. MUSTERS

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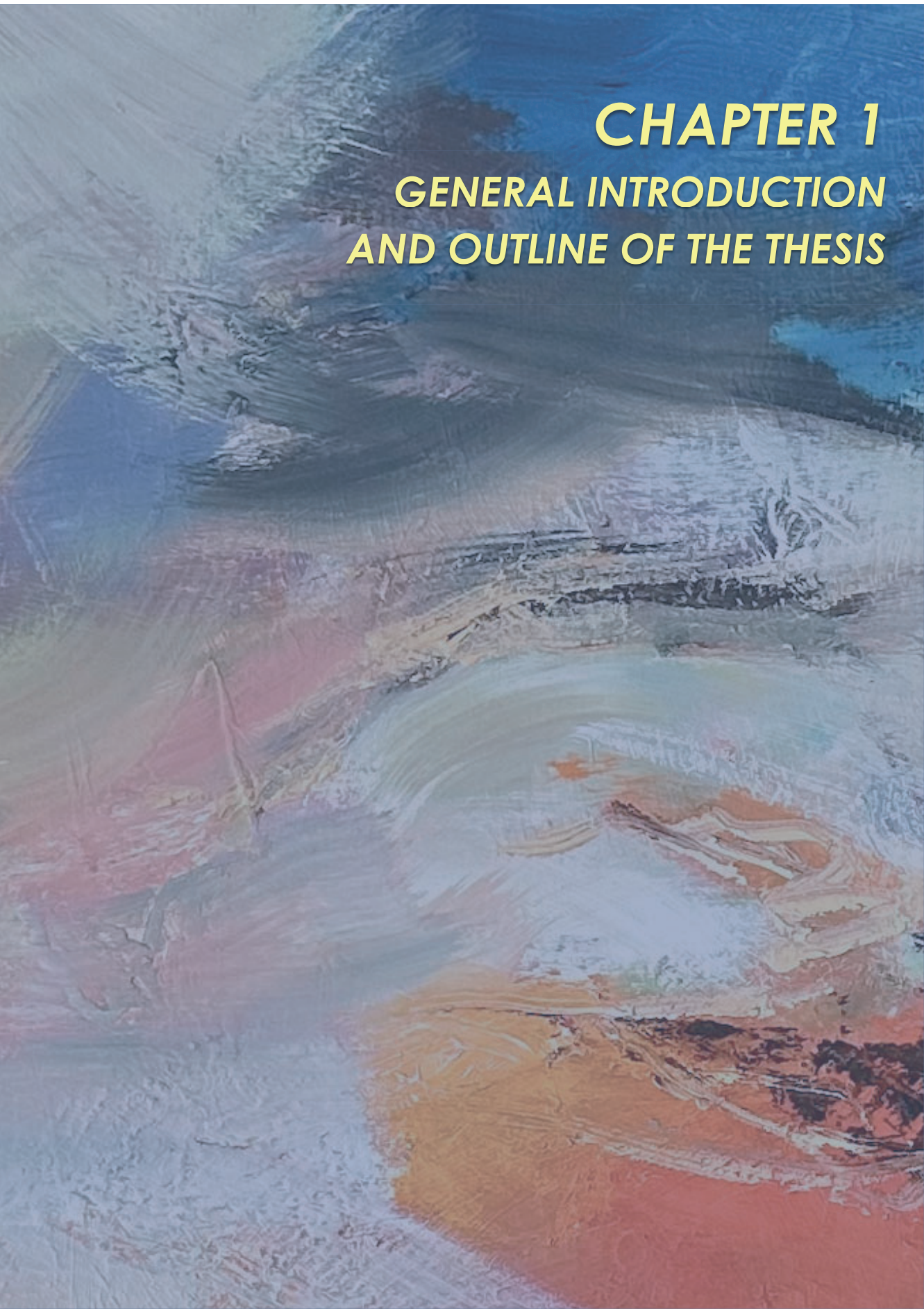


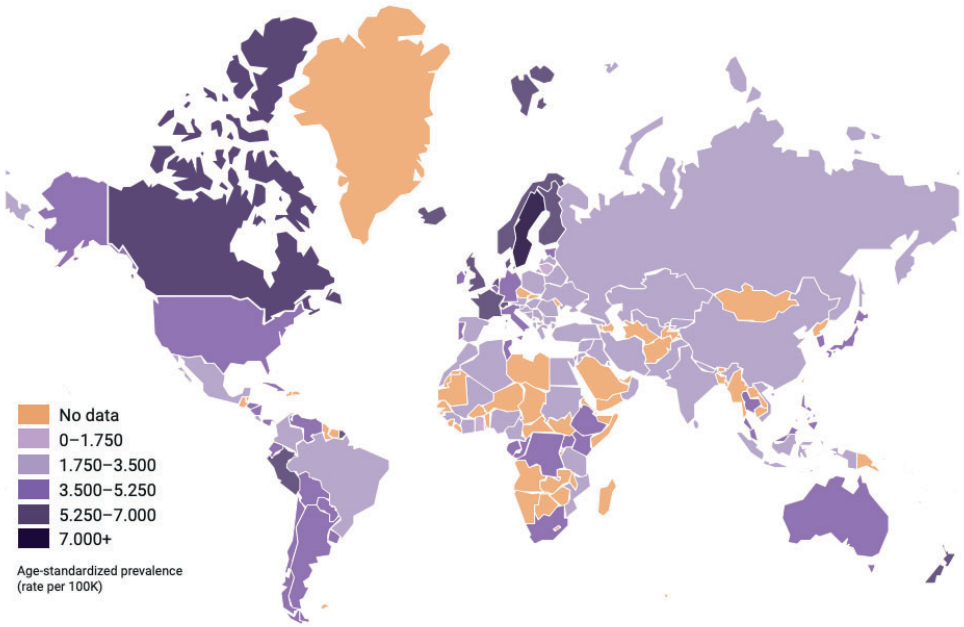
CHAPTER 1
GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

GENERAL INTRODUCTION

Atopic eczema

Atopic eczema, also known as atopic dermatitis, is a prevalent chronic inflammatory skin condition with an increasing global prevalence, affecting up to 20% of children and 10% of adults in developed countries.[1,2] Atopic eczema predominantly onsets in early childhood, although it can occur at any stage of life. Recent research highlights a significant prevalence in adults, including both persistent and adult-onset disease.[3,4]

Figure 1. Age-standardized prevalence (rate per 100.000) of atopic eczema per country, 2017.[5]



Atopic eczema is driven by a complex interaction of genetic, environmental, and immunological elements, resulting in the breakdown of the epithelial barrier and a dominant type 2 immune system imbalance.[6–8] The disease is often found alongside other atopic diseases, such as asthma and allergic rhinitis.[8] Symptoms include recurrent eczematous lesions and chronic pruritus (itch).[8] Disease severity of atopic eczema is variable, with symptoms ranging from mild, localized erythema to moderate or severe cases, characterized by widespread erythema, oozing, crusting, and secondary infections.[8] The intense pruritus and persistent xerosis (dry skin) cause significant discomfort, leading to disturbances in sleep, psychological distress, and social difficulties. The impact of atopic eczema extends well beyond the physical symptoms, contributing to a significant disease burden.[9,10]

The socioeconomic impact of atopic eczema is substantial, driven by the direct costs of treatment and the indirect costs stemming from missed work and school, alongside loss of productivity.[11–13] The disease imposes a heavy burden not only on the healthcare system but also on the economy at large, with varying costs reported due to differences in treatment

settings, disease severity, and healthcare systems across countries.[13,14] The advent of targeted therapeutics for moderate-to-severe atopic eczema raises questions about the economic burden and the impact on patients' quality of life, suggesting a need for a more nuanced understanding of these dynamics in the context of new treatment modalities.

Navigating the challenges in diagnosing atopic eczema

Atopic eczema remains largely a clinical diagnosis, as there is no accurate diagnostic laboratory marker. To facilitate diagnosis, clinicians assess the presence of pruritus and eczematous skin lesions. Important supportive features are early onset, atopy, and xerosis. Additional suggestive features encompass hyperlinear palms, ichthyosis, atypical vascular responses, perifollicular accentuation, lichenification, prurigo lesions, keratosis pilaris, pityriasis alba, or ocular and periorbital changes.[15,16] Due to the varied manifestations of the disease, the differential diagnosis of atopic eczema is extensive. According to American Academy of Dermatology's guidelines, diagnosing atopic eczema involves ruling out other conditions such as impetigo, scabies, seborrheic dermatitis, contact dermatitis, ichthyoses, cutaneous T-cell lymphoma, psoriasis, photosensitivity dermatoses, immune deficiency diseases, and erythroderma from various causes.[15,17] Signs and symptoms of atopic eczema may also vary across different ages and ethnic groups.[8,18–20] This variability in presentation poses challenges for accurate diagnosis. Over the years, a variety of diagnostic criteria have been developed for and used in observational and intervention studies, making it difficult to compare studies.[21,22] Despite the existence of several validated diagnostic criteria, there remains a lack of consensus on which diagnostic criteria are most accurate for atopic eczema and there is inconsistency in the application of these criteria. A systematic review of diagnostic criteria used in atopic eczema randomized controlled trials (RCTs) including 212 RCTs found that the Hanifin and Rajka (H&R) and the U.K. Working Party (UKWP) diagnostic criteria are the most frequently utilized in RCTs, accounting for 41% and 9% of studies, respectively.[21] However, in the 212 examined RCTs, a total of 10 different diagnostic criteria sets were utilized and in 37.3% of the RCTs no diagnostic criteria were specified.

A systematic review on the diagnostic accuracy of diagnostic criteria for atopic eczema conducted in 2008 recognized the UKWP criteria as being the most thoroughly validated.[22] Subsequent studies have assessed existing diagnostic criteria and proposed new ones, indicating ongoing potential for improvement. Additionally, the diagnostic accuracy of patient-assessed criteria (questionnaires) has not been previously evaluated. These criteria are crucial in large population-based cohort studies aiming to understand atopic eczema prevalence, disease associations, or genetic risk factors. This necessitates an updated and broadened synthesis of the evidence generated by diagnostic accuracy studies.

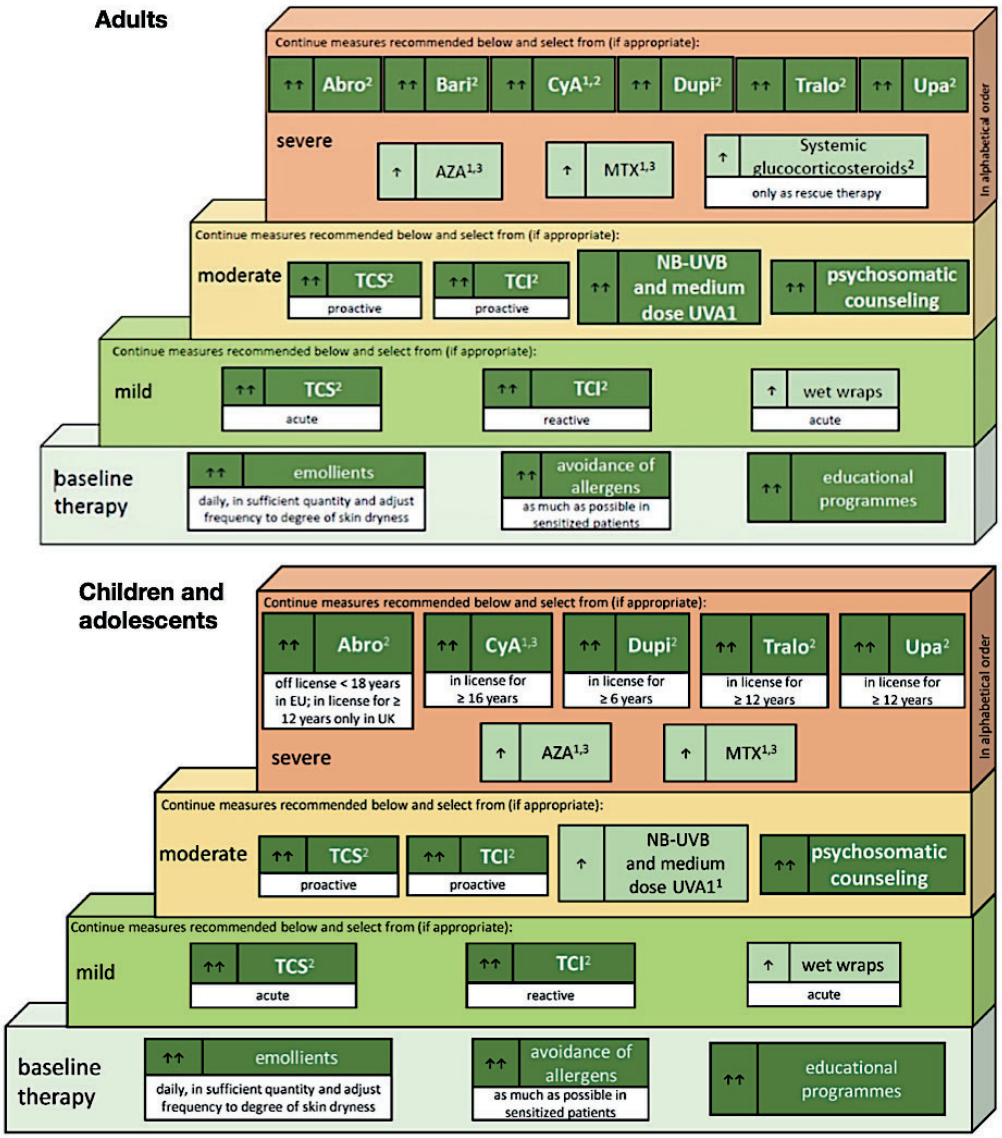
There is a necessity to standardise the use of diagnostic criteria for atopic eczema per study setting. Such standardisation would enhance the comparability and consistency of studies, improve the reliability of atopic eczema diagnosis, and ultimately enhance patient care.[23,24]

Therapeutic options for atopic dermatitis: old friends and new opportunities

The majority of atopic eczema patients present with mild disease severity, and can be effectively managed with avoiding triggers, emollients, and topical anti-inflammatory agents such as corticosteroids and calcineurin inhibitors. However, for patients unresponsive to these treatments, other options such as phototherapy or systemic immunomodulatory drugs may

be considered. The European Dermatology Forum has published a stepped-care plan for children, adolescents and adults with atopic eczema (Figure 2).[25]

Figure 2. The EuroGuiDerm Guideline for Atopic Eczema stepped-care plan for adults, children and adolescents with atopic eczema.[25]



[1]refer to EDF guideline text for restrictions, [2]licensed indication, [3]off-label treatment. ↑↑ (dark green) strong recommendation for the use of an intervention, ↑ (light green) weak recommendation for the use of an intervention. AZA=azathioprine, CyA=ciclosporin, Dupi=dupilumab, MTX=methotrexate, TCI=topical calcineurin inhibitors, TCS=topical corticosteroids, Upa=upadacitinib, UVA1=ultraviolet A1, NB-UVB=narrow-band ultraviolet B.

In 1992, phototherapy for atopic eczema was applied for the first time when ultraviolet A1 (UVA1) was introduced.[26] Today, various forms of phototherapy are used in Europe as a treatment method for atopic eczema, with narrow-band ultraviolet B (NB-UVB) being the most commonly prescribed, followed by less frequently utilized UVA1 and psoralen plus UVA (PUVA).[27] PUVA, a form of photochemotherapy, involves the use of ultraviolet light-activated photosensitizing drugs. Mechanistically, phototherapy works through several anti-inflammatory and immunosuppressive pathways.[28–30] UVB primarily affects the epidermis and superficial dermis, suppressing antigen-presenting Langerhans cells, inducing T-cell apoptosis, and thickening the stratum corneum to reduce susceptibility to pathogens. PUVA inhibits DNA replication, causes cell cycle arrest, and modifies cytokine expression, thereby effectively suppressing lymphocyte activity.[31] Although phototherapy is frequently prescribed, there is a lack of evidence for all phototherapy modalities in atopic eczema.[32] Especially as new expensive systemic treatment modalities emerge and systemic treatment is not an option for all patients (e.g. patients who are pregnant or attempting to conceive), more high-quality research into the efficacy, safety, and cost-effectiveness of phototherapy is needed.

Approximately 15% of patients exhibit moderate-to-severe atopic eczema.[33] In these cases, topical treatments are often insufficient for achieving adequate disease control, necessitating phototherapy or systemic immunomodulating therapies.[34,35] To date, various systemic therapies are available for atopic eczema. Before 2017, ciclosporin was the sole systemic treatment for atopic eczema approved by the European Medicines Agency (EMA). Ciclosporin has been proven effective for the treatment of atopic eczema, but may cause side effects. Other conventional systemic therapies, often prescribed off-label, include methotrexate, azathioprine, mycophenolic acid, mycophenolate mofetil, and systemic corticosteroids.[35,36] Oral corticosteroids, although used extensively, are limited to short-term use due to the risk of severe rebound flares upon discontinuation.[37,38]

Recent advancements have introduced biologics and Janus kinase (JAK) inhibitors to the treatment arsenal. Dupilumab, the first biologic approved for moderate-to-severe atopic eczema, targets the Th2-related cytokines IL-4 and IL-13 by binding to the IL-4 receptor α (IL-4Rα).[39] Approved since 2017, it has shown significant improvement in atopic eczema symptoms and an acceptable safety profile for both adults and children.[40] Other newly approved systemic treatments available since 2021 and 2022, include the biological tralokinumab, and the JAK inhibitors baricitinib, upadacitinib and abrocitinib.[41–44] These treatments offer additional options for patients and are reshaping the treatment landscape for moderate-to-severe atopic eczema. With even more therapeutic options arriving soon, including the biologics lebrikizumab and nemolizumab, the ongoing need for long-term real-world data is crucial to optimize treatment strategies and ensure safe and effective use of these advanced therapies.[45–51] However, the financial burden associated with the use of biologics and JAK inhibitors make it essential to keep investigating cost-effective alternatives. Additionally, these novel treatment options might not be available in all parts of the world, necessitating research into well-accessible options.

The value of registries collecting real-world data

While large multicenter randomized placebo-controlled trials are essential for the registration of new drugs, their results are not always fully applicable to everyday clinical practice. This is

where prospective observational cohort studies, such as registries collecting real-world data, become invaluable. These registries collect long-term safety and effectiveness data for various therapies in real-world settings, reflecting routine healthcare conditions without the selective exclusion of patients typically seen in RCTs.[52] For example, children are often not included in RCTs.[53] Observational research registries allow for the prospective collection of data from patients in daily practice, addressing research questions that RCTs cannot adequately explore. The EMA has recognized the importance of these registries, developing guidelines to ensure that registry populations are representative of the entire target population, covering all disease aspects and patient characteristics.[54] Unlike post-marketing studies funded by pharmaceutical companies, which often have limited sample sizes and confidentiality obligations, registries can provide large participant numbers and long-term follow-up data needed to detect rare adverse events.[55] This is particularly important for assessing the safety of new drugs over extended periods.
Patient registries also have limitations due to their observational nature, leading to possible biases like selection and information bias. Unlike RCTs, they lack randomization, controlled environments, and strict monitoring, which can affect data validity. Maintaining high-quality registries is resource-intensive and complicated by data security regulations. Additionally, inconsistent data collection across regions hinders data comparison. Efforts to improve registries include standardizing data collection and fostering international collaboration.

The TREatment of ATopic eczema (TREAT) Registry Taskforce is dedicated to producing reliable real-world data on the long-term effectiveness and safety of both conventional and novel systemic immunomodulatory treatments and phototherapy in patients with atopic eczema across multiple countries.[56] To accomplish this, an international network of independent prospective multi-centre registries was established in 2014. To ensure uniform data collection, the TREAT Registry Taskforce developed a core dataset consisting of specific domains and domain items with corresponding measurement instruments, following the HOME recommendations.[57]
The TREAT core dataset includes 19 core domains and 69 domain items, comprising 49 baseline items and 20 follow-up items, thus defining both "what to measure" and "how and when to measure". The dataset encompasses 118 measurement instruments and outlines the follow-up frequency and visit windows.[58,59] However, even with the implementation of a core dataset, variations in data collection are anticipated for various reasons, including the utilization of different data entry systems. Differences may also emerge from diverse interpretations of the core dataset and the selection of optional items based on feasibility. Additionally, patient inclusion and exclusion criteria may vary across countries, influenced by differences in treatment reimbursement policies and prescribing practices.
Over the years, several registries from various countries have joined the TREAT Registry Taskforce. At present, the TREAT Registry Taskforce comprises eight independent registries from fourteen different countries, including Belgium, Brazil, Denmark, France, Germany, Ireland, Italy, Norway, Portugal, Spain, Sweden, Switzerland, the Netherlands, and the United Kingdom. The TREAT NL/BE (TREatment of ATopic eczema, the Netherlands and Belgium) registry, established in 2017, collects long-term observational data from patients with atopic eczema who start treatment with immunomodulating systemic therapy or phototherapy in daily practice. This registry includes multiple participating centers.

Collecting large amounts of data from different countries and many centers offers great opportunities in research. It enables the investigation of rare outcomes and adverse events that require extensive datasets to reach statistically significant conclusions. The diversity and volume of data enhance the potential for comprehensive analysis, facilitating the identification of patterns and trends that may not be apparent in smaller, localized studies. Furthermore, this collaborative approach fosters cross-border research initiatives, promoting the sharing of knowledge and expertise across the international dermatology community.

Evaluating the safety of systemic immunomodulatory treatments using real-world data

The long-term safety data for systemic immunomodulatory therapies used in AD within real-world settings remains sparse.[60] Both patients and healthcare providers need detailed safety profiles to properly weigh the risks and benefits of these treatments. While the Summary of Product Characteristics (SmPC) offers some guidance, it often differs from real-world data due to its reliance on spontaneous reports, preclinical trials, and post-authorization marketing studies.[61]

The majority of drug-related adverse event data comes from a limited number of RCTs, which typically exclude a substantial portion of atopic eczema patients who require systemic treatment. Additionally, RCTs often do not include paediatric populations, which limits their applicability.[53] Regulatory agencies also depend on post-marketing studies to identify rare adverse events, but these studies usually have insufficient sample sizes to significantly enhance drug safety monitoring.[52] Therefore, recognizing the differences between real-world data and SmPCs is essential for better clinical decision-making.

At the onset of the coronavirus SARS-CoV-2 (COVID-19) pandemic, numerous clinical questions arose, particularly concerning the safety of continuing systemic immunomodulatory therapy. There was a pressing need to elucidate the factors influencing COVID-19 outcomes and to determine if immunomodulatory treatments for atopic eczema impacted the risk of morbidity and mortality. To address these concerns, the SECURE-AD (Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion - Atopic Dermatitis) Physician Registry was established in April 2020. This registry aims to evaluate the effects of systemic immunomodulatory treatment on COVID-19 outcomes in atopic eczema patients.[62–64]

AIMS & OUTLINE OF THE THESIS

This thesis aims to enhance the care of atopic eczema through a robust framework of international collaboration. To achieve this, it focuses on several key areas. First, it reviews the evidence regarding the diagnostic accuracy of criteria for atopic eczema, aiming to standardize diagnosis practices. Second, it evaluates the efficacy of phototherapy as a treatment option for atopic eczema. Third, it emphasizes the importance of international collaboration to standardize real-world data collection through global registries. Finally, it assesses the safety of systemic treatments using real-world data. By examining these components, this thesis aspires to create a more cohesive and effective international approach to managing atopic eczema, emphasizing the importance of international collaboration and real-world data in improving patient outcomes.

Part I: Diagnosing atopic eczema
This part evaluates the diagnostic accuracy of various diagnostic criteria for atopic eczema. **Chapter 2** features a systematic review that updates and summarizes existing evidence, aiming to identify valid diagnostic criteria that can be used per research setting.

Part II: Phototherapy for atopic eczema
Chapter 3 presents a Cochrane systematic review that synthesizes the current evidence on phototherapy for atopic eczema. The aim of this chapter is to determine the efficacy of different phototherapy regimens in managing atopic eczema.

Part III: International collaboration through the TREAT Registry Taskforce: generating real-world data across country borders
In part III, we focus on enhancing and evaluating the international standardization and cooperation through the TREAT Registry Taskforce. **Chapter 4** presents a mapping exercise that examines the overlap and pooling potential of data across eight established registries. This chapter aims to enhance international standardization and cooperation, enabling comprehensive research on the effectiveness and safety of therapies for atopic eczema. As a sequel to this work, **Chapter 5** presents the first cross-border analyses of patients treated with various therapies across seven European TREAT registries. This chapter provides insights into patient demographics, disease severity, and prescribing practices, highlighting differences and commonalities across Europe. By exploring the opportunity to conduct cross-border analyses, we aimed to pave the way for addressing many significant research questions in the future.

Part IV: Evaluating the safety of systemic treatments for atopic eczema using real-world data
Part IV examines the safety of various systemic treatments for atopic eczema using real-world data. **Chapter 6** describes adverse drug reactions associated with systemic immunomodulatory therapy, comparing real-world incidence rates with official product summaries. This chapter aims to provide a clearer picture of the safety profile of these treatments. In **Chapter 7**, we delve into the incidence and clinical outcomes of (hyper)eosinophilia in patients treated with dupilumab, using real-world data from the TREAT NL/BE registry. This chapter aims to offer management guidance for healthcare providers. Finally, **Chapter 8** investigates SARS-CoV-2 infection outcomes in atopic eczema patients treated with systemic immunomodulatory therapies, using real-world data from the global

SECURE-AD registry. This chapter aims to evaluate the impact of these treatments on COVID-19, providing critical information for patient management during the pandemic.

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PART I
DIAGNOSING
ATOPIC ECZEMA

CHAPTER 2

DIAGNOSTIC ACCURACY OF PHYSICIAN- AND PATIENT-ASSESSED DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background
Despite the availability of numerous validated diagnostic criteria for atopic dermatitis (AD), new criteria continue to be developed, and a lack of consensus on their use results in inconsistent application. This systematic review aims to synthesize the evidence on the diagnostic accuracy of diagnostic criteria for AD.

Methods
Searches were performed using OVID MEDLINE and OVID EmBASE, from inception to December 2023. Studies included children and adults and assessed the diagnostic accuracy of physician-assessed and patient-assessed diagnostic criteria against a reference standard (clinical diagnosis of AD by a dermatologist or other physician). Two authors independently screened abstracts, extracted data and assessed methodological quality using QUADAS-2. The certainty of the evidence was evaluated using the GRADE tool. Data synthesis involved constructing two-by-two tables and meta-analysing sensitivity and specificity using a bivariate method.

Results
The search identified 2071 articles, resulting in 39 included studies encompassing 99,822 patients from 25 countries. The UK Working Party (UKWP) criteria, evaluated in 23 studies, showed a pooled sensitivity of 56.8% (95% CI: 42.9-69.7) and specificity of 96.4% (95% CI: 93.6-98.0). The Hanifin and Raijka (H&R) criteria, assessed in 6 studies, had a pooled sensitivity of 83.9% (95% CI: 36.5-97.9) and specificity of 92.3% (95% CI: 78.5-97.5). The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire, analysed in 7 studies, demonstrated a sensitivity of 54.9% (95% CI: 40.9-68.2) and specificity of 85.0% (95% CI: 60.7-95.4). GRADE assessments indicated low quality of evidence for the UKWP and H&R criteria, and very low quality for the ISAAC questionnaire, primarily due to issues with inconsistency, imprecision, and risk of bias. Our review found that many new patient-reported diagnostic criteria have been proposed, but they need validation in multiple studies before their diagnostic utility can be confirmed.

Conclusions
The H&R criteria had the highest combined sensitivity and specificity, despite low evidence quality. The value of newly proposed diagnostic criteria remains uncertain. Our study highlights the need to standardize the use of AD diagnostic criteria for different research settings globally. Such standardization will improve the quality and comparability of AD research and ultimately enhance patient care.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease, with a prevalence of up to 20% in children and 10% in adults.[1,2] AD signs and symptoms are heterogenous and vary between different age groups, ethnicities and skin types.[3,4] This wide spectrum of manifestations can make the diagnosis challenging. Adding to this complexity, research has identified a significant variation in AD phenotypic classifications and their associated characteristics, underscoring the need for standardized definitions and methodologies to improve diagnostic accuracy and applicability. Various diagnostic criteria for AD have been developed and used across observational and intervention studies over the past decades.[5,6] Although different validated sets of diagnostic criteria are available, there is still disagreement about the definition of AD and a lack of uniformity in the use of diagnostic criteria. It has been shown that the most commonly used criteria in randomized controlled trials (RCTs) are the Hanifin and Raijka (H&R) and the U.K. Working Party (UKWP) diagnostic criteria, used in 41% and 9% of RCTs, respectively.[6] Moreover, a previous systematic review on diagnostic criteria for AD from 2008 identified the UKWP diagnostic criteria as the most extensively validated.[5] However, there have been further studies assessing the existing diagnostic criteria and proposing new criteria for AD published since, as there is still room for improvement. Therefore, we aim to update and widen the scope of this previous work, synthesising the evidence generated by diagnostic accuracy studies published since. In addition, this systematic review includes studies proposing new diagnostic criteria, as well as studies where the diagnosis of AD is made based on patient-assessed diagnostic criteria (questionnaires). Such criteria are important in large population-based cohort studies which are becoming more prevalent in order to understand AD prevalence, disease association or genetic risk factors. It is pertinent to better understand their diagnostic accuracy for their implementation in various population cohort studies. An updated analysis therefore provided a timely update and additional information on the performance of patient-assessed (questionnaire-based) diagnostic criteria.

Because the use of numerous different diagnostic criteria for AD by various studies may compromise the external validity and comparability of results across different populations, we aim to summarize the evidence concerning the diagnostic accuracy of diagnostic criteria for AD and to identify valid diagnostic criteria that can be used per research setting.

METHODS

The protocol for this systematic review has previously been published on PROSPERO.[7]

Inclusion and exclusion criteria

We included studies investigating both children and adults suspected of having AD, for whom a definite diagnosis should be made. We included any study investigating the diagnostic accuracy of one or more physician-assessed, or patient-assessed (questionnaire-based) diagnostic criteria for AD, using a reference standard (most frequently a clinical diagnosis by a dermatologist). We also included studies that validated new diagnostic criteria or validated existing diagnostic criteria in a new population.

Studies were required to report sensitivity, specificity, positive predictive value (PPV) or negative predictive value (NPV) or to provide data allowing for the calculation of these

outcome measures. These were usually cross-sectional studies, but longitudinal studies, such as randomized controlled trials, were included if they provided sufficient data to estimate the accuracy of the criteria used.
We did not include studies that recruited patients with the disease of interest separately from those without the disease of interest (case-control design or two-gate design), as this may lead to bias and as the included participants may not be representative for practice. Studies aiming to develop diagnostic criteria for AD were also eligible for inclusion, provided an assessment of the diagnostic accuracy in a clinically relevant population was reported.
Studies in which the complete set of diagnostic criteria was not considered (e.g. only the major or the minor criteria of the H&R criteria) were excluded, as were studies evaluating modified UKWP diagnostic criteria (pruritus plus two, plus four, or plus five additional criteria) as the recommended criteria for epidemiological studies are pruritus plus three or more other features (REF – Williams et al). Conference abstracts were excluded.

Searches
An information specialist performed a systematic search between May 2020 and December 2023 in OVID MEDLINE and OVID EmBASE from inception onwards, using controlled terms (including MeSH-terms) and text words for AD and 1) specific diagnostic criteria like the UKWP criteria or 2) diagnostic criteria combined with a filter for diagnostic accuracy. There were no date or language restrictions. The search included an iterative process to refine the search strategy through adding search terms as new relevant citations were identified via reference and citation checking of relevant papers. The bibliographic records retrieved were imported and deduplicated using EndNote.[8] We manually searched key reviews and background articles for any relevant citations that might have been missed by electronic searches. The search strategy can be found in the *Supplementary material*.

Study selection
Two authors independently screened all titles and abstracts of the identified studies using Rayyan as a tool.[9] The full texts of studies that potentially meet the criteria have been examined, as well the studies for which abstracts did not provide sufficient information. Any disagreement was resolved through discussion with a senior member of the team. Two authors independently extracted the received data. For studies that meet the inclusion criteria, we extracted relevant information into evidence tables, using an a priori defined proforma.

Assessment of methodological quality and grading the certainty of the evidence
The methodological quality of the included studies has been independently assessed by two authors using the Quality Assessment of Diagnostic Accuracy tool (QUADAS-2).[10] QUADAS-2 is a checklist for the assessment of methodological quality of diagnostic accuracy studies, assessing both risk of bias and concerns regarding applicability. We assessed the overall certainty of the evidence included in the review using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.[11]

Strategy for data synthesis
Two-by-two tables including true positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) were composed for each evaluated diagnostic criteria from each included

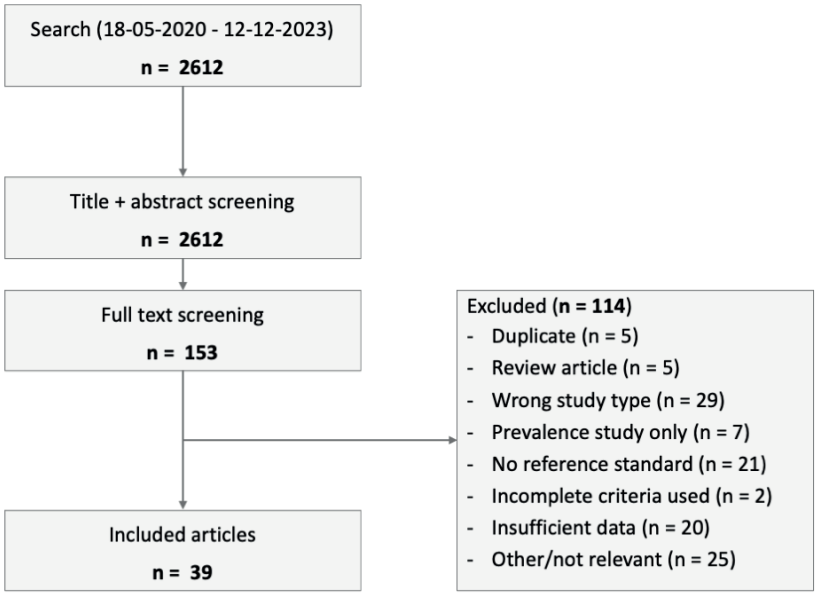
study. These were visibly inspected using forest plots and raw receiver operating characteristic (ROC) plots. The data were meta-analysed for each set of criteria separately. Heterogeneity was evaluated using the same model, by adding covariates to the model. We did not formally test for difference in accuracy between the different criteria. We conducted subgroup analyses based on age (adults [≥18 years] vs children [<18 years], assessor (physician vs patient-assessed), prevalence (1-year vs point prevalence), and setting (hospital vs population-based).

RESULTS

Results of the literature search

A total of 2612 articles were identified (*Figure 1).* No additional articles were found through manual searches. Following title and abstract screening, 153 articles underwent full-text review. Subsequently, the full-text review excluded 114 articles. Of these, 5 articles were duplicates, 5 studies were review articles, 29 studies had the wrong study type (e.g. case-control studies), 7 articles reported AD prevalence only, 21 articles did not report the use of a reference standard, 2 articles used the incomplete set of criteria.

Figure 1. Flowchart



Included studies

39 articles published between 1993 and 2023, involving 99,822 patients from 25 countries, were included in this review.[12,13,22–31,14,32–41,15–21] The diagnostic criteria and their requirements assessed by the included studies are shown in *Table 1*. Since only the UKWP criteria, H&R criteria, and ISAAC questionnaire were evaluated by multiple studies, they were included in the meta-analysis. The remaining studies were grouped under 'other diagnostic criteria or questionnaires'. A complete overview of the study characteristics is shown in *Table 2*. Most studies included children (n=26) or a mix of children and adults (n=8). Five studies only

included adult patients. Overall, there was an approximately even distribution of males and females included in the studies. Of the studies that reported ethnicity, most studies (n=19) included White patients, followed by Asian-Chinese (n=6) and Black-African (n=5) ethnicities. Sixteen studies were hospital based, 21 studies were population based, 1 study was both hospital and population based and 1 study was university based. 35 cross-sectional studies, 2 longitudinal studies, 1 prospective cohort study and 1 retrospective study were included. The reference standard was most often a clinical diagnosis of AD by a dermatologist (n=35), while 2 studies used a clinical diagnosis made by another physician, and one study compared the diagnostic accuracy with diagnosis made using the UKWP criteria as the reference standard. *Table 3* shows the results for hospital-based studies. *Table 4* shows the results for population-based studies. The overall sensitivity and specificity of each set of diagnostic criteria was summarized through meta-analysis of 53 2x2 tables.

Table 1. Diagnostic criteria and their requirements assessed by the included studies.

Study + year	Substudy	Diagnostic criteria group	Diagnostic criteria description and/or criteria requirements (if reported)
Benn 2003		Other	Telephone interview: each woman was asked if her child suffered from itchy rash (Main Question A). If she answered no, she was asked if her child had AD (Main Question B). If she answered yes to question A, she was asked if it was recurrent (A1) or lasted more than 2 weeks (A2). If she answered no to the subsequent questions A1 and A2, she was asked question B. If she answered yes to one or both of A1 and A2, she was later asked if the rash was AD (A3). If she answered no to A3, she was asked question B. Thus, all women were asked question A. Women who answered no to question A, and women who answered yes to question A but subsequently no to both A1 and A2, or no to A3 were all asked question B. This way, question B functioned as an extra possibility of detecting AD.
Buser 1993		Other	Questionnaire based on H&R criteria
Chalmers 2006		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Dharma 2018		Other	Parental questionnaire: parents were asked “Has your child had any rash in the last 3 or 6 months?” If “yes,” parents were asked “Where was the worst rash located?” with options: face, inside elbow(s), dia- per area, wrist/hand(s), back of knee(s), scalp, ankle(s) and other. The next question asked the parent to “Describe the rash,” with options: wet, red, dry and scaly. Parents could select more than one option for each question. A child was considered to have AD by this measure if the worst rash was in a classical or typical location for infants (on the face, inside of elbow, wrist/hands or back of knees) AND was described as either red or wet.
Dotterud 2000		Other	Questionnaire: ever had a rash lasting more than 4 weeks combined with itching and/or localised in typical areas such as face and flexural areas (e.g. elbows and knees)?
Endre 2021	(A)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Endre 2021	(B)	H&R criteria	3 major + 3 minor (out of 27)
Firooz 1999		UKWP criteria	Pruritus + 3 minor criteria (out of 6)

Foley 2001		Other	Questionnaire about general demographic information on the child, present or past skin conditions, and family history of skin problems or related diseases.
Girolomoni 2003		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Guo 2016		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Guo 2019	(A)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Guo 2019	(B)	H&R criteria	3 major + 3 minor (out of 27)
Guo 2019	(C)	Other	Novel Chinese diagnostic criteria: (i) onset after 2 weeks of birth; (ii) pruritus and/or irritability and sleeplessness comparable with lesions; (iii) all two items above with one of following items can reach a diagnosis of AD: (i) eczematous lesions distributed on cheeks and/or scalp and/or extensor limbs, (ii) eczematous lesions on any other parts of body accompanied by xerosis.
Hamada 2005		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Harris 2001		Other	Reporting of maternally diagnosed atopic dermatitis
Hogewoning 2011		ISAAC questionnaire	Score > 3 (out of 7)
Johnke 2004	(A)	Other	Danish Allergy Research Centre (DARC) criteria: 3 features (out of 3)
Johnke 2004	(B)	H&R criteria	3 major + 3 minor (out of 27)
Johnke 2004	(C)	Other	Schultz-Larsen criteria: ≥ 50 points (6 criteria)
Johnke 2004	(D)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Lan 2009	(A)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Lan 2009	(B)	ISAAC questionnaire	Score > 3 (out of 7)
Lee 2016	(A)	Other	Reliable Estimation of Atopic Dermatitis in Childhood (REACH): 11 questions including 2 major and 9 minor criteria. AD is diagnosed as the major group of 'eczema on the antecubital or popliteal fossa' to fulfill the 2 major criteria (2M), and the minor group of 'eczema on the non-antecubital or popliteal fossa' to fulfill the 1 major plus 4 or more minor criteria (1M+4m).
Lee 2016	(B)	ISAAC questionnaire	Score > 3 (out of 7)
Leitenberger 2017	(A)	Other	Modified Childhood Eczema Questionnaire: 1. Does your child have, or has your child had, a red rash or eczema that comes and goes?; 2. If yes, has this caused itching or scratching?; 3. Has this red rash or eczema affected any of the following areas during these episodes in the last week?; Around the eyes, ears, scalp, cheeks, forehead, neck, trunk, folds of the elbows/behind the knees, wrist or ankle, outer arms, or legs.; 4. Has this red rash or eczema affected any of the above areas in the last 6 months?
Leitenberger 2017	(B)	Other	Original Childhood Eczema Questionnaire: (1) Does your child have or has your child had a red rash/eczema which can come and go? (2) If yes, has this caused itching or scratching Diagnostic accuracy of physician- and patient-assessed diagnostic criteria for atopic dermatitis: a systematic review? (3) Has this red rash/eczema affected any of the following areas during the last week: around the eyes, ears, scalp,

			cheeks, forehead, neck, trunk, folds of the elbows/behind the knees, wrist or ankle, outer arms/legs?
Marks 1999	(A)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Marks 1999	(B)	Other	New questionnaire (no details of the question or diagnosis method)
Minasyan 2015		Other	Comprehensive Early Childhood Allergy Questionnaire (CECAQ) (20 items in total). Q1-Q12 are related to FA, asthma, and AD. The rest were additional questions assessing family history of allergy, parental socioeconomic status, parental smoking, and child's breastfeeding. AD related criteria (adapted from the UKC), a child with: 1) Itch or red rash coming and going in the past 12 months (If yes, how often) 2) Rash affecting any of the following areas: cheeks and/or around eyes, elbow folds, wrist folds, chest/tummy, nappy area, front of knees or ankles, around ears, neck, back, under the buttocks, behind the knees 3) A doctor's conformation that your child has eczema.
Ortiz 2003		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Ozkaya 2005		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Popescu 1997	(A)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Popescu 1997	(B)	ISAAC questionnaire	Score > 3 (out of 7)
Sabry 2011		Other	Sabry's Arabic Questionnaire for Allergy Diagnosis-143 (SAQAD-143): A detailed seven section questionnaire including 143 closed questions covering almost all of the usual and unusual symptoms of various allergic diseases, in Arabic language.
Saeki 2007	(A, B, C)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Saeki 2009		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Samachocki 2012		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Samochocki 2007		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Schram 2011	(A)	Other	Millennium diagnostic criteria: Allergen-specific IgE + 2 principal (4)
Schram 2011	(B)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Schram 2011	(C)	H&R criteria	3 major + 3 minor (out of 27)
Silverberg 2015	(A)	Other	Self-reported 1-year history of eczema (by patient)
Silverberg 2015	(B)	Other	Self-reported 1-year history of eczema (by caregiver)
Silverberg 2015	(C)	Other	Self-reported ever history of eczema (by patient)
Silverberg 2015	(D)	Other	Self-reported ever history of eczema (by caregiver)
Smidesang 2008	(A, B)	ISAAC questionnaire	Score > 3 (out of 7)
Strina 2010	(A)	ISAAC questionnaire	Score > 3 (out of 7)
Strina 2010	(B)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Sybilski 2015		Other	Comprehensive Early Childhood Allergy Questionnaire: 1) "Have you ever had an itchy rash that was coming and going for at least 6 months?" 2) "Have you had this itchy rash in the

			last 12 months?" 3) "Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks or around the neck, ears or eyes?"
Thyssen 2020		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Udkoff 2023	(A)	Other	American Academy of Dermatology (AAD) concensus criteria: 3 major + 2 or more out of 4 features OR 4 or more out of 9 features.
Udkoff 2023	(B)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Udkoff 2023	(C)	H&R criteria	3 major + 3 minor (out of 27)
Uter 2001		Other	Erlangen Atopy Score (self-administered questionnaire)
Wang 2016		UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Williams 1996	(A, B)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Yue 2023	(A, D, G)	Other	Chinese criteria of AD for children (CCAD): based on (i) pruritus; (ii) 'typical morphology and distribution' or 'atypical morphology and distribution with xerosis'; and (iii) a chronic or chronically relapsing course.
Yue 2023	(B, E, H)	UKWP criteria	Pruritus + 3 minor criteria (out of 6)
Yue 2023	(C, F, I)	H&R criteria	3 major + 3 minor (out of 27)

Table 2. Characteristics of the included studies

U.K. Working Party (UKWP) criteria															
Study	**Subgroup or substudy**	**Assessor**	**Reference standard**	**Study type**	**Setting**	**Age (range)**	**Age group**	**Gender (male / female)**	**Ethnicity**	**Country**	**Translation or original language**	**Prevalence measure**	**Total n participants**	**AD prevalence in diagnostic criteria group**	**AD prevalence in reference standard group**
Chalmers 2006	-	Trained bilingual observer	Clinical diagnosis	Cross-sectional	Pop	3-11 years	Children	1557 / 1607	Black-African	South Africa	Original language	Point	3067	76	32
Endre 2021 (A)	-	Dermatologist, trained observer	Clinical diagnosis	Longitudinal	Hos	3-12 months	Children	1261 / 1134	White	Sweden	Original language	1 year	1834	27	329
Firooz 1999	-	Researcher	Clinical diagnosis	Cross-sectional	Hos	<4, 4-10, >10 years	Mix	146 / 270	White	Iran	Original language	1 year	416	-	-
Girolomoni 2003	-	Dermatologist	Clinical diagnosis	Cross-sectional	Pop	9 years	Children	-	White	Italy	Original language	-	1369	77	88
Guo 2016	-	Dermatologist	Clinical diagnosis	Cross-sectional	Pop	1-7 years	Children	-	Asian-Chinese	China	Original language	Point	13998	667	1811
Guo 2019 (A)	-	Dermatologist	Clinical diagnosis	Cross-sectional	Pop	1-12 months	Children	3273 / 2694	Asian-Chinese	China	Original language	Point	5967	798	1819
Hamada 2005	-	Parent	Clinical diagnosis	Cross-sectional	Pop	<5 years	Children	302 / 263	Japanese	Japan	Original language	-	565	51	39
Johnke 2004 (D)	-	Dermatologist, other physician	Clinical diagnosis	Longitudinal	Pop	0-18 months	Children	-	White, Asian-Chinese, South-Asian, Asian - other	Denmark	Original language	1 year	441	33	54
Lan 2009 (A)	-	Patient	Clinical diagnosis	Cross-sectional	Hos	-	Adults	7 / 1124	-	Taiwan	-	1 year	1131	42	90
Marks 1999 (A)	-	Dermatologist	Clinical diagnosis	Cross-sectional	Pop	4-18 years	Children	1174 / 1317	-	Australia	Original language	-	2491	280	414
Ortiz 2003	-	Dermatologist, patient	Clinical diagnosis	Cross-sectional	Hos, Pop	3-17 years	Children	-	White	Spain	Translation	Point	237	17	-
Ozkaya 2005	-	Dermatologist	Clinical diagnosis	Retrospective	Hos	19-71 years	Adults	29 / 34	White	Turkey	Original language	-	63	49	63
Popescu 1997 (A)	-	Parent	Clinical diagnosis	Cross-sectional	Pop	6-12 years	Children	601 / 513	White, mixed, other	Romania	Original language	-	1114	27	27
Saeki 2007 (A)	2001/2002 substudy	Patient	Clinical diagnosis	Cross-sectional	Pop	6-7, 11-12 years	Children	-	-	Japan	Original language	1 year	16152	2794	1742

Saeki 2007 (B)	2004/2005 substudy (1 year preva-lence)	Patient	Clinical diagnosis	Cross-sectional	Pop	6-7, 11-12 years	Children	-	-	Japan	Original language	1 year	3849	592	401
Saeki 2007 (C)	2004/2005 substudy (point preva-lence)	Patient	Clinical diagnosis	Cross-sectional	Pop	6-7, 11-12 years	Children	-	-	Japan	Original language	Point	3849	394	401
Saeki 2009	-	Patient	Clinical diagnosis	Cross-sectional	Hos	20-69 years	Adults	1050 / 1086	Japanese	Japan	Original language	Point	2120	217	128
Samochocki 2007	-	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	4-15 years	Children	67 / 99	White	Poland	Translation	-	166	107	108
Samachocki 2012	-	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	4-15 years	Children	100 / 150	White	Poland	Original language	-	250	157	173
Schram 2011 (B)		Dermatologist	Clinical diagnosis	Cross-sectional	Hos	-	Mix	90 / 119	-	Nether-lands	Original language	1 year	210	-	44
Strina 2010 (B)	-	Trained observer, parent	Clinical diagnosis	Cross-sectional	Pop	4-12 years	Children	758 / 661	Hispanic or Latino	Brazil	Original language	1 year	1445	78	-
Thyssen 2020	-	Dermatologist	Clinical diagnosis	Cross-sectional	Pop	>18 years	Adults	1289 / 2545	White	Denmark	Original language	1 year	3834	2727	3834
Wang 2016	-	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	-	Mix	3183 / 3025	Asian-Chinese	China	Translation	-	6208	594	975
Williams 1996 (A)	Point preva-lence	Trained observer, parent	Clinical diagnosis	Cross-sectional	Pop	-	Children	339 / 356	White, South Asian, Black-African, mixed, other	United Kingdom	Original language	Point	695	41	41
Williams 1996 (B)	1 year preva-lence	Trained observer, parent	Clinical diagnosis	Cross-sectional	Pop	-	Children	339 / 356	White, South Asian, Black-African, mixed, other	United Kingdom	Original language	1 year	695	70	70
Udkoff 2023 (B)	-	Trained observer	Clinical diagnosis	Cross-sectional	Hos	3 months - 18 years	Children	57 / 43	White, Black-African, Asian-other, Hispanic or Latino	United States of America	Original language	Point	100	56	58

Yue 2023 (B)	-	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	19-95 years	Adults	462 / 572	Asian-Chinese	China	Original language	Point	1034	-	-
Yue 2023 (E)	Age: 19–60 years	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	19-60 years	Adults	293 / 423	Asian-Chinese	China	Original language	Point	716	-	-
Yue 2023 (H)	Age: 61–95 years	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	61-95 years	Adults	169 / 149	Asian-Chinese	China	Original language	Point	318	-	-

Hanifin & Raijka (H&R) criteria

Study	Subgroup or substudy	Assessor	Reference standard	Study type	Setting	Age (range)	Age group	Gender (n male / female)	Ethnicity	Country	Translation or original language	Prevalence measure	Total n participants	AD prevalence in diagnostic criteria group	AD prevalence in reference standard group
Endre 2021 (B)	-	Dermatologist, trained observer	Clinical diagnosis	Longitudinal	Hos	3-12 months	Children	1261 / 1134	White	Sweden	Original language	1 year	1834	65	329
Guo 2019 (B)	-	Dermatologist	Clinical diagnosis	Cross-sectional	Pop	1-12 months	Children	3273 / 2694	Asian-Chinese	China	Original language	Point	5967	1245	1819
Johnke 2004 (B)	-	Dermatologist, other physician	Clinical diagnosis	Longitudinal	Pop	0-18 months	Children	-	White, Asian-Chinese, South-Asian, Asian - other	Denmark	Original language	1 year	441	43	54
Schram 2011 (C)	-	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	-	Mix	90 / 119	-	Nether-lands	Original language	1 year	210	-	44
Udkoff 2023 (C)	-	Trained observer	Clinical diagnosis	Cross-sectional	Hos	3 months - 18 years	Children	57 / 43	White, Black-African, Asian-other, Hispanic or Latino	United States of America	Original language	Point	100	57	58
Yue 2023 (C)	-	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	19-95 years	Adults	462 / 572	Asian-Chinese	China	Original language	Point	1034	-	-
Yue 2023 (F)	Age: 19–60 years	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	19-60 years	Adults	293 / 423	Asian-Chinese	China	Original language	Point	716	-	-
Yue 2023 (I)	Age: 61–95 years	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	61-95 years	Adults	169 / 149	Asian-Chinese	China	Original language	Point	318	-	-

International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire

Study	Subgroup or substudy	Assessor	Reference standard	Study type	Setting	Age (range)	Age group	Gender (n male / female)	Ethnicity	Country	Translation or original language	Prevalence measure	Total n participants	AD prevalence in diagnostic criteria group	AD prevalence in reference standard group
Hogewoning 2011	-	Trained observer, parent	Clinical diagnosis	Cross-sectional	Pop	4-20 years	Mix	2373 / 2458 *(8 missing)*	Black-African	Ghana, Gabon, Rwanda	Original language	Point	4839	64 *(partially measured)*	67
Lan 2009 (B)	-	Patient	Clinical diagnosis	Cross-sectional	Hos	-	Adults	7 / 1124	-	Taiwan	-	1 year	1131	107	90
Lee 2016 (B)	-	Patient, Parent	Clinical diagnosis	Cross-sectional	Pop	4-12 years	Children		Asian - other	South Korea	Original language	-	1191	172	141
Popescu 1997 (B)	-	Parent	Clinical diagnosis	Cross-sectional	Pop	6-12 years	Children	601 / 513	White, mixed, other	Romania	Original language	-	1114	78	27
Smidesang 2008 (A)	Yes to 2 questions	Parent	Clinical diagnosis	Cross-sectional	Pop	23-26 months	Children	201 / 189	White	Norway	Original language	-	390	80	62
Smidesang 2008 (B)	Yes to at least 1 of the questions	Parent	Clinical diagnosis	Cross-sectional	Pop	23-26 months	Children	201/ 189	White	Norway	Original language	-	390	153	62
Strina 2010 (A)	-	Parent, trained observer	Clinical diagnosis	Cross-sectional	Pop	4-12 years	Children	758 / 661	Hispanic or Latino	Brazil	Original language	1 year	1445	150	

Other diagnostic criteria

Study	Subgroup or substudy	Assessor	Reference standard	Study type	Setting	Age (range)	Age group	Gender (n male / female)	Ethnicity	Country	Translation or original language	Prevalence measure	Total n participants	AD prevalence in diagnostic criteria group	AD prevalence in reference standard group
Benn 2003	-	Parent	Clinical diagnosis	Cross-sectional	Hos	18-22 months	Children	-	-	Denmark	Original language	-	60	32	37
Buser 1993	-	Parent	Clinical diagnosis	Cross-sectional	Pop	-	Children	-	-	Germany	Original language	-	320	97	93
Dharma 2018	-	Parent	Clinical diagnosis	Cross-sectional	Hos	1 year	Children	1594 / 1420	White, South Asian, Asian-Chinese, Asian - other, Hispanic	Canada	Original language	-	3014	926	248

									or Latino, Black-African, Afro-Caribbean, mixed, other						
Dotterud 2000	-	Patient	Clinical diagnosis	Cross-sectional	Pop	7-12 years	Children	-	White	Norway	Original language	-	424	551	424
Foley 2001	-	Parent	Clinical diagnosis	Cross-sectional	Pop	0-5 years	Children	567 / 549	White	Australia	Original language	-	1116	321	346
Guo 2019 (C)	-	Dermatologist	Clinical diagnosis	Cross-sectional	Pop	1-12 months	Children	3273 / 2694	Asian-Chinese	China	Original language	Point	5967	1472	1819
Harris 2001	-	Parent	UKWP criteria	Cross-sectional	Pop	1-2 years	Children	329/284	-	United Kingdom	Original language	Cumm u-lative prevale nce	624	193	85
Johnke 2004 (A)	-	Dermatologist, Other physician	Clinical diagnosis	Longitudinal	Pop	0-18 months	Children	-	White, Asian-Chinese, South-Asian, Asian - other	Denmark	Original language	1 year	441	33	54
Johnke 2004 (C)	-	Dermatologist, Other physician	Clinical diagnosis	Longitudinal	Pop	0-18 months	Children	-	White, Asian-Chinese, South-Asian, Asian - other	Denmark	Original language	1 year	441	36	54
Lee 2016 (A)	-	Patient, Parent	Clinical diagnosis	Cross-sectional	Pop	4-12 years	Children	-	Asian - other	South Korea	Original language	-	1191	-	-
Leitenberger 2017 (A)	Modified Childhood Eczema Questionnaire	Parent	Clinical diagnosis	Cross-sectional	Hos	<24 months	Children	01:01	-	United States of America	Original language	-	242	70	61
Leitenberger 2017 (B)	Original Childhood Eczema Questionnaire	Parent	Clinical diagnosis	Cross-sectional	Hos	<24 months	Children	01:01	-	United States of America	Original language	-	242	57	61
Marks 1999 (B)	-	Patient, Parent	Clinical diagnosis	Cross-sectional,	Pop	4-18 years	Children	1174 / 1317	-	Australia	Original language	-	2491	408	414

Minasyan 2015	-	Parent	Clinical diagnosis	Cross-sectional	Hos	1-5 years	Children	86 / 64	White	Australia	Original language	-	150	54	43
Sabry 2011	-	Patient	Clinical diagnosis	Cross-sectional	Uni	3-65 years	Mix	310 / 543	White	Saudi Arabia	Original language	-	854	-	388
Schram 2011 (A)	-	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	-	Mix	90 / 119	-	Nether-lands	Original language	1 year	210	-	44
Silverberg 2015 (A)	Self-reported 1-year history of eczema (by patient)	Patient, Parent	Clinical diagnosis	Cross-sectional	Hos	-	Mix	-	-	United States of America	Original language	1 year	722	104	155
Silverberg 2015 (B)	Self-reported 1-year history of eczema (by caregiver)	Patient, Parent	Clinical diagnosis	Cross-sectional	Hos	-	Mix	-	-	United States of America	Original language	1 year	722	104	155
Silverberg 2015 (C)	Self-reported ever history of eczema (by patient)	Patient, Parent	Clinical diagnosis	Cross-sectional	Hos	-	Mix	-	-	United States of America	Original language	Lifetime	722	117	155
Silverberg 2015 (D)	Self-reported ever history of eczema (by caregiver)	Patient, Parent	Clinical diagnosis	Cross-sectional	Hos	-	Mix	-	-	United States of America	Original language	Lifetime	722	117	155
Sybilski 2015	All ages	Patient, Parent	Clinical diagnosis	Cross-sectional	Pop	6-44 years	Mix	8601 / 10016 female	White	Poland	Original language	-	18617	727	311
Udkoff 2023 (A)	-	Trained observer	Clinical diagnosis	Cross-sectional	Hos	3 months - 18 years	Children	57 / 43	White, Black-African, Asian-other, Hispanic or Latino	United States of America	Original language	Point	100	53	58
Uter 2001	-	Dermatologist	Clinical diagnosis	Cross-sectional	Pop	-	Mix	119 / 2206	-	Germany	Original language	-	2352	-	176
Yue 2023 (A)	-	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	19-95 years	Adults	462 / 572	Asian-Chinese	China	Original language	Point	1034	-	-

Yue 2023 (D)	Age: 19–60 years	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	19-60 years	Adults	293 / 423	Asian-Chinese	China	Original language	Point	716	-	-
Yue 2023 (G)	Age: 61–95 years	Dermatologist	Clinical diagnosis	Cross-sectional	Hos	61-95 years	Adults	169 / 149	Asian-Chinese	China	Original language	Point	318	-	-

Table 3. Results for hospital-based studies

U.K. Working Party criteria								
Study	**Specificity**	**Sensitivity**	**PPV**	**NPV**	**TP**	**FP**	**TN**	**FN**
Endre 2021 (A)	95.7%	8.2%	29.7%	82.7%	27	64	1441	302
Firooz 1999	98.3%	10.0%	50.0%	86.6%	6	6	350	54
Lan 2009 (A)	99.6%	42.2%	90.5%	95.2%	38	4	1037	52
Ortiz 2003	94.4%	14.3%	35.3%	83.6%	6	11	184	36
Ozkaya 2005	100%	77.8%	100%	0.0%	49	0	0	14
Saeki 2009	93.5%	68.8%	40.6%	97.9%	88	129	1863	40
Samachocki 2007	94.8%	88.4%	97.5%	78.5%	153	4	73	20
Samochocki 2012	94.8%	88.4%	97.5%	78.5%	153	4	73	20
Schram 2011 (B)	72.9%	97.7%	48.9%	99.2%	43	45	121	1
Udkoff 2023 (B)	83.3%	96.6%	88.9%	94.6%	56	7	35	2
Wang 2016	95.4%	37.9%	62.3%	88.4%	370	224	4628	605
Yue 2023 (B)	97.4%	56.0%	89.6%	84.8%	164	19	722	129
Yue 2023 (E)	98.2%	54.5%	92.7%	84.0%	114	9	498	95
Yue 2023 (H)	95.7%	59.5%	83.3%	86.8%	50	10	224	34
Hanifin & Raijka criteria								
Study	**Specificity**	**Sensitivity**	**PPV**	**NPV**	**TP**	**FP**	**TN**	**FN**
Endre 2021 (B)	95.7%	19.8%	50.4%	84.5%	65	64	1441	264
Schram 2011 (C)	48.8%	100%	34.1%	100%	44	85	81	0
Udkoff 2023 (C)	71.4%	98.3%	82.6%	96.8%	57	12	30	1
Yue 2023 (C)	97.3%	58.0%	89.5%	85.4%	170	20	721	123
Yue 2023 (F)	100%	58.4%	93.1%	85.1%	122	9	498	87
Yue 2023 (I)	94.9%	57.1%	80.0%	86.0%	48	12	222	36
International Study of Asthma and Allergies in Childhood questionnaire								
Study	**Specificity**	**Sensitivity**	**PPV**	**NPV**	**TP**	**FP**	**TN**	**FN**
Lan 2009 (B)	92.9%	36.7%	30.8%	94.4%	33	74	967	57
Other diagnostic criteria								
Study	**Specificity**	**Sensitivity**	**PPV**	**NPV**	**TP**	**FP**	**TN**	**FN**
Benn 2003	91.3%	81.1%	93.8%	75.0%	30	2	21	7
Dharma 2018	82.7%	65.3%	27.0%	96.1%	162	439	2099	86
Leitenberger 2017 (B)	92.8%	72.1%	77.2%	90.8%	44	13	168	17
Leitenberger 2017 (B)	92.8%	72.1%	77.2%	90.8%	44	13	168	17
Minasyan 2015	84.8%	88.4%	70.4%	94.7%	38	16	89	5
Sabry 2011*	16.3%	86.1%	50.0%	54.6%	334	334	65	54

Schram 2011 (A)	98.8%	81.8%	94.7%	95.3%	36	2	164	8
Silverberg 2015 (A)	95.6%	70.5%	76.4%	94.1%	55	17	366	23
Silverberg 2015 (B)	95.8%	73.4%	89.2%	88.4%	58	7	160	21
Silverberg 2015 (C)	97.2%	43.5%	92.0%	69.9%	81	7	244	105
Silverberg 2015 (D)	89.3%	83.3%	81.4%	90.5%	35	8	67	7
Udkoff 2023 (A)	95.2%	91.4%	96.4%	88.9%	53	2	40	5
Yue 2023 (A)	92.7%	84.0%	82.0%	93.6%	246	54	687	47
Yue 2023 (D)	94.3%	83.3%	85.7%	93.2%	174	29	478	35
Yue 2023 (G)	89.3%	85.7%	74.2%	94.6%	72	25	209	12

*University based

PPV = positive predictive value, NPV = negative predictive value, TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

Table 4. Results for population-based studies

U.K. Working Party criteria								
Study	**Specificity**	**Sensitivity**	**PPV**	**NPV**	**TP**	**FP**	**TN**	**FN**
Chalmers 2006	98.0%	43.8%	18.7%	99.4%	14	61	2971	18
Girolomoni 2003	99.3%	77.3%	88.3%	98.4%	68	9	1269	20
Guo 2016	99.9%	36.3%	98.5%	91.3%	657	10	12164	1154
Guo 2019 (A)	98.7%	41.0%	93.5%	79.2%	746	52	4096	1073
Hamada 2005	94.7%	59.0%	45.1%	96.9%	23	28	498	16
Johnke 2004 (D)	98.4%	50.0%	81.8%	93.4%	27	6	381	27
Marks 1999 (A)	95.0%	42.8%	63.2%	89.3%	177	103	1973	237
Ortiz 2003	94.4%	14.3%	35.3%	83.6%	6	11	184	36
Popescu 1997 (A)	98.9%	74.1%	62.5%	99.4%	20	12	1075	7
Saeki 2007 (A)	89.3%	71.8%	44.7%	96.3%	1250	1544	12866	492
Saeki 2007 (B)	91.3%	72.8%	49.3%	96.7%	292	300	3148	109
Saeki 2007 (C)	95.4%	58.9%	59.9%	95.2%	236	158	3290	165
Strina 2010 (B)	62.7%	70.4%	24.4%	92.5%	19	59	99	8
Thyssen 2020	86.3%	50.5%	96.0%	21.2%	1936	81	512	1898
Williams 1996 (A)	92.8%	69.5%	47.1%	97.0%	41	46	590	18
Williams 1996 (B)	97.2%	79.5%	80.5%	97.0%	70	17	590	18
Hanifin & Raijka criteria								
Study	**Specificity**	**Sensitivity**	**PPV**	**NPV**	**TP**	**FP**	**TN**	**FN**
Guo 2019 (B)	97.7%	63.2%	92.4%	85.8%	1150	95	4053	669
Johnke 2004 (B)	97.2%	59.3%	74.4%	94.5%	32	11	376	22
International Study of Asthma and Allergies in Childhood questionnaire								
Study	**Specificity**	**Sensitivity**	**PPV**	**NPV**	**TP**	**FP**	**TN**	**FN**
Hogewoning 2011	97.2%	59.3%	74.4%	94.5%	2	7	332	4

Lee 2016 (B)	97.9%	33.3%	22.2%	98.8%	97	75	975	44
Popescu 1997 (B)	92.9%	68.8%	56.4%	95.7%	19	59	99	8
Smidesang 2008 (A)	62.7%	70.4%	24.4%	92.5%	43	37	291	19
Smidesang 2008 (B)	88.7%	69.4%	53.8%	93.9%	60	93	223	2
Strina 2010 (A)	70.6%	96.8%	39.2%	99.1%	24	126	40	41
Other diagnostic criteria								
Study	**Specificity**	**Sensitivity**	**PPV**	**NPV**	**TP**	**FP**	**TN**	**FN**
Buser 1993	96.9%	96.8%	92.8%	98.7%	90	7	220	3
Dotterud 2000	94.8%	61.5%	87.3%	80.9%	96	14	254	60
Foley 2001	67.4%	29.4%	8.8%	89.9%	25	258	534	60
Guo 2019 (C)	100%	80.8%	99.9%	92.2%	1470	2	4146	349
Harris 2001	35.0%	96.0%	78,2	76,8	68	19	414	125
Johnke 2004 (A)	98.3%	57.4%	86.1%	92.5%	31	5	282	23
Johnke 2004 (C)	98.7%	51.9%	84.8%	93.6%	28	5	382	26
Sybilski 2015	95.9%	21.2%	26.4%	94.6%	66	184	4288	245
Lee 2016 (A)	73.7%	55.7%	14.6%	95.4%	98	573	1603	78
Marks 1999 (B)	91.4%	55.6%	56.4%	91.2%	230	178	1899	184
Sybilski 2015	95.9%	21.2%	26.4%	94.6%	66	184	4288	245
Uter 2001	99.6%	42.2%	90.5%	95.2%	38	4	1037	52

PPV = positive predictive value, NPV = negative predictive value, TP = true positives, FP = false positives, TN = true negatives, FN = false negatives.

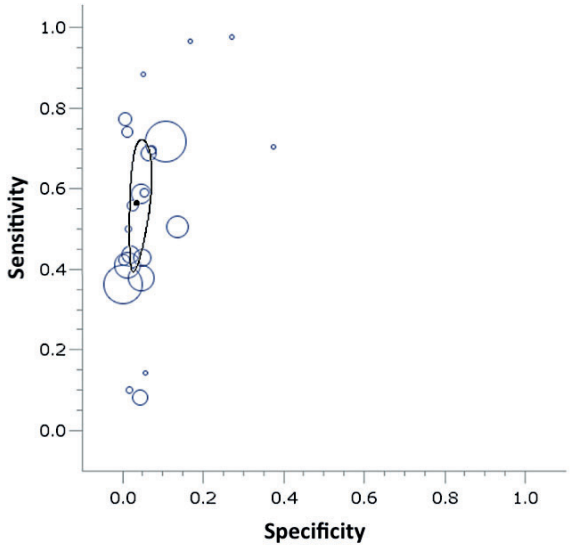
UK Working Party (UKWP) criteria

The pooled estimates (n=23) for sensitivity and specificity of the UKWP criteria were 0.568 (95% CI: 0.429-0.697) and 0.964 (95% CI: 0.936-0.980) respectively (*Figure 2* and *Supplementary table 1)*. In 15 studies, the diagnostic criteria were applied by a dermatologist or trained researcher, in six studies the patient or a parent or caregiver, and in two studies both the patient and a trained person applied the criteria. To assess the difference between patient-assessed and physician-assessed, we combined the studies in which a dermatologist or a researcher applied the criteria. The summary estimate in this group was compared to the estimates generated from patient-assessed studies, where the patient or parent/caregiver applied the criteria. One study used a trained interviewer: we interpreted this as a patient assessed. The pooled estimates for physician/researcher-assessed criteria were 56.5% (95% CI: 39.4-72.2) for sensitivity and 96.8% (95% CI: 93.7-98.5) for specificity, while the sensitivity and specificity for patient-assessed criteria were 57.4% (95% CI: 34.3-77.7) and 95.3% (95% CI: 88.2-98.2), respectively.

Eight studies used 1-year prevalence, while nine studies used point prevalence. Six studies did not report what prevalence was used. Dummy variables were created to summarize the estimates for three separate groups: point prevalence, 1-year prevalence and studies where the prevalence was not reported. Pooled estimates for sensitivity ranged from 55.7% to 68.4% while that for specificity ranged from 91.4% to 97.3%.

Nine studies were hospital-based, thirteen were population-based and one study used a mix of patients. The study with mixed recruitment was included with the population-based studies. Pooled estimates according to the setting the studies did not significantly differ. They ranged from 54.4% to 60.5% in terms of sensitivity and 95.6% to 96.8% in terms of specificity. Four studies included adult patients only, sixteen studies included paediatric patients only and three studies included a mix of ages, so age subgroup analyses were not conducted.

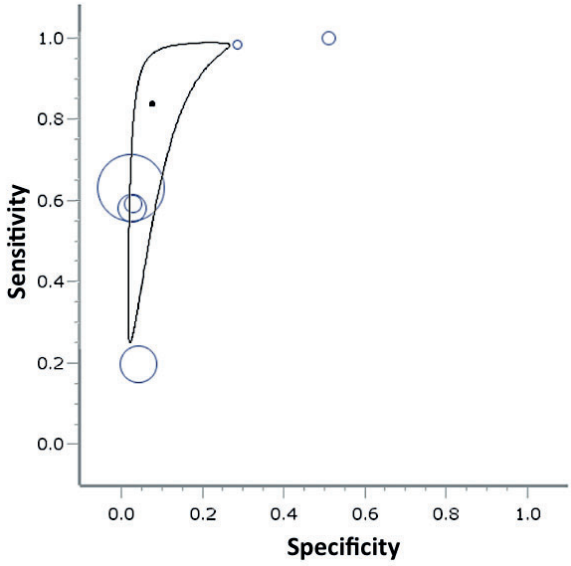
Figure 2. Receiver Operating Characteristic plot for the diagnostic accuracy of the U.K. Working Party (UKWP) criteria (n=23).



Hanifin and Raijka (H&R) criteria

Six studies estimated the diagnostic accuracy of the H&R criteria and provided data for the two-by-two tables. Results are shown in *Figure 3* and *Supplementary table 2*. In one study (Udkoff 2023), the H&R criteria were applied by researchers, in the other studies the criteria were applied by a dermatologist. Two studies were in a population setting and four studies were in a hospital setting. Four studies included only paediatric patients, one study included only adult patients and one study included both paediatric and adult patients. The pooled estimate for sensitivity for the H&R criteria was 83.9% (95% CI 36.5-97.9) and the specificity was 92.3% (95% CI 78.5-97.5). There was notable heterogeneity, as illustrated in *Figure 3*. The number of studies was insufficient to conduct subgroup analyses.

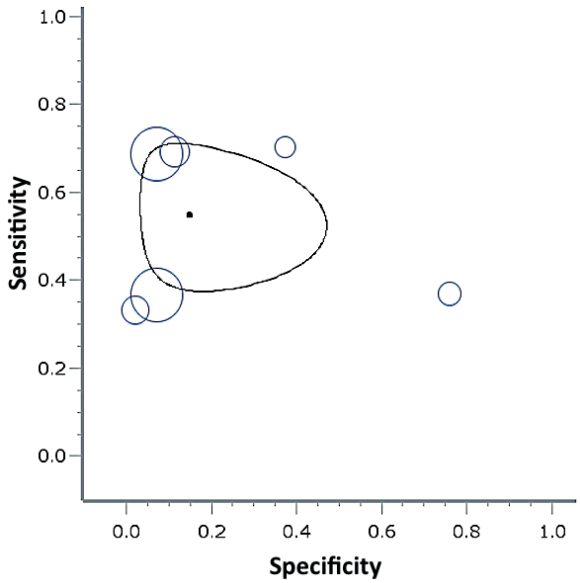
Figure 3. Receiver Operating Characteristic plot for the diagnostic accuracy of the Hanifin & Raijka (H&R) criteria (n=6).



International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire

Seven studies estimated the diagnostic accuracy of the ISAAC questionnaire, of which six provided data for further analysis (*Figure 4* and *Supplementary table 3).* In four studies, the ISAAC questionnaire was completed by the patient or caregiver. In two studies, the ISAAC questionnaire was completed both by a parent and trained personnel. Six studies were in a population-based setting. Four studies included paediatric patients only. The overall pooled estimates for sensitivity and specificity were 54.9% (95% CI: 40.9-68.2) and 85.0% (95% CI: 60.7-95.4) respectively. Although the summary estimates for both sensitivity and specificity were higher in studies where the ISAAC questionnaire was applied by the patients themselves, the confidence intervals are broad and the difference was not statistically significant.

Figure 4. Receiver Operating Characteristic plot for the diagnostic accuracy of the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire (n=6).



Other diagnostic criteria or questionnaires

Twenty-three studies provided 18 unique two-by-two tables on the diagnostic accuracy of the other diagnostic criteria (*Figure 5* and *Supplementary table 4)*. The diagnostic criteria and their requirements assessed by the included studies are shown in *Table 1.* In thirteen studies, the criteria were applied by the patient (or a parent/caregiver); and in five studies by a dermatologist. The prevalence was not reported for twelve two-by-two tables; three studies used 1-year prevalence, two studies used point prevalence and one study used the cumulative prevalence. Ten studies were population-based, while seven were conducted in a hospital-based setting and one at a university (which we combined with the hospital-based studies). Twelve studies included paediatric patients only, five studies included a mix of adults and children, and one study included adult patients.

While studies included in this analysis were assessing various different diagnostic criteria, the sensitivity and specificity appeared largely similar and clustered together. The overall pooled sensitivity was 70.9% (95% CI: 60.3-79.7), while specificity was 93.3% (95% CI: 85.8-97.0). The summary estimates for sensitivity were similar between patient-assessed and dermatologist-assessed criteria, however specificity was significantly higher in studies where a dermatologist assesses the criteria. The summary estimates for sensitivity were higher for hospital-based studies, while the specificity was higher for population-based studies.

Methodological quality and certainty of evidence

The QUADAS-2 tool was used to assess both risk of bias and concerns regarding applicability when evaluating the methodological quality of included studies. Majority of the studies had low risk of bias and low concerns regarding applicability (Figure 6).

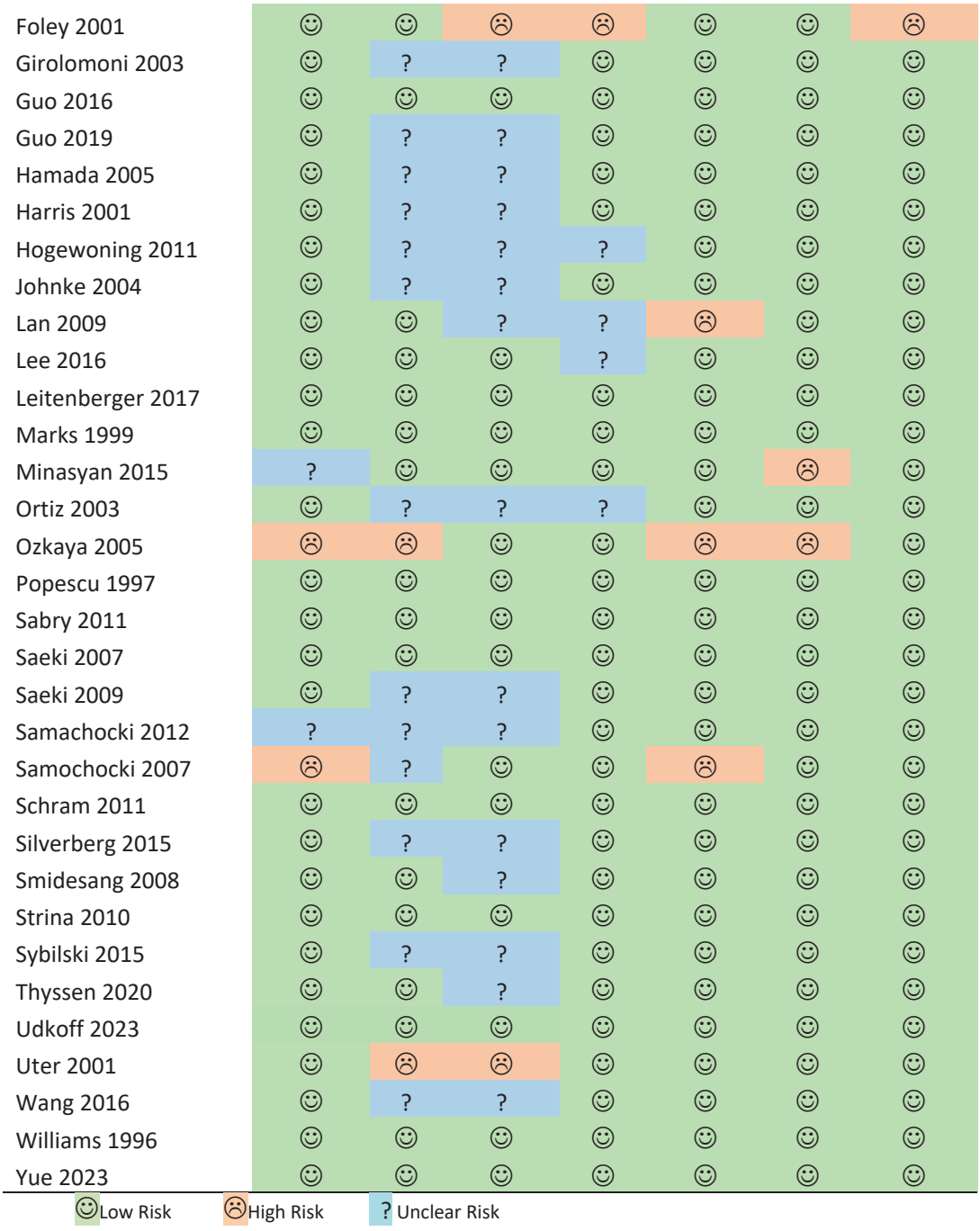
The quality of evidence regarding the diagnostic accuracy of the UKWP and H&R criteria, and ISAAC questionnaire was assessed using the GRADE tool. For the UKWP criteria, the risk of bias did not warrant any downgrading, as 12 studies had an unclear risk (<50%), and only 3 studies were identified as having a high risk (<25%). No downgrading was required for indirectness, as only 3 studies categorized as high risk. Inconsistency was downgraded by one level due to heterogeneity in sensitivity across the studies. Imprecision was also downgraded by one level because the sensitivity showed a confidence interval (CI) greater than 0.2, indicating imprecision. Publication bias was not assessed in these criteria, so no downgrading was applied. Overall, the UKWP criteria were rated as having low quality of evidence due to issues with inconsistency and imprecision.

For the H&R criteria, the risk of bias was not downgraded. Only one study (<25%) presented an unclear risk, and another study (<50%) was at high risk. Indirectness required no downgrading, as no studies were considered high risk. Inconsistency was downgraded by one level due to heterogeneity in sensitivity among the studies. Imprecision was similarly downgraded by one level, as the sensitivity exhibited a CI greater than 0.2. As publication bias was not assessed, no downgrading occurred. Consequently, the H&R criteria were rated as having low quality of evidence, primarily due to issues with inconsistency and imprecision.

Regarding the ISAAC questionnaire, the risk of bias was downgraded by one level. Four studies (>50%) were at an unclear risk of bias, although none were categorized as high risk. Indirectness did not necessitate downgrading, as only one study (<50%) was considered high risk. Inconsistency was downgraded by two levels, reflecting significant heterogeneity in both sensitivity and specificity across studies. Imprecision was similarly downgraded by two levels, with both sensitivity and specificity showing CIs greater than 0.2, indicating substantial imprecision. Publication bias was not assessed, so no downgrading was applied. Overall, the ISAAC questionnaire was rated as having very low quality of evidence due to serious concerns in risk of bias, inconsistency, and imprecision.

Figure 6. QUADAS-2 assessment

STUDY	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Benn 2003	?	☺	☺	☹	☺	☺	☺
Buser 1993	☺	☺	?	☺	☺	☺	☺
Chalmers 2006	☺	☺	☺	☺	☺	☺	☺
De 2006	☺	?	☺	?	☺	☺	☺
Dotterud 2000	☺	?	☺	☺	☺	☺	☺
Endre 2021	☺	☹	☺	☺	☺	☺	☺
Firooz 1999	☺	☺	☺	☺	☺	☺	☺


Foley 2001
Girolomoni 2003
Guo 2016
Guo 2019
Hamada 2005
Harris 2001
Hogewoning 2011
Johnke 2004
Lan 2009
Lee 2016
Leitenberger 2017
Marks 1999
Minasyan 2015
Ortiz 2003
Ozkaya 2005
Popescu 1997
Sabry 2011
Saeki 2007
Saeki 2009
Samachocki 2012
Samochocki 2007
Schram 2011
Silverberg 2015
Smidesang 2008
Strina 2010
Sybilski 2015
Thyssen 2020
Udkoff 2023
Uter 2001
Wang 2016
Williams 1996
Yue 2023
Low Risk
High Risk
Unclear Risk

DISCUSSION

This systematic review identified 39 studies evaluating the diagnostic accuracy of various physician- and patient-assessed criteria for AD. We updated an existing systematic review and widened the scope by examining several newly proposed AD diagnostic criteria, as well as including patient-assessed (questionnaire-based) diagnostic criteria. Unlike the previous systematic review, we excluded case-control studies. The UKWP criteria (n=23) remained the most extensively investigated diagnostic criteria. The number of studies evaluating the accuracy of the H&R criteria (n=6) has now surpassed that of the Schultz-Larsen criteria (n=1). Also, the frequently used American Academy of Dermatology (AAD) criteria were assessed by 1 of the included studies only. This review is the first to evaluate the diagnostic accuracy of patient-assessed criteria, with the ISAAC questionnaire being the most frequently evaluated (n=7).

Meta-analysis of these diagnostic accuracy studies demonstrated that the H&R criteria has the highest summary estimate for sensitivity, as well as the highest combined sensitivity and specificity estimates, whereas the highest summary estimate for specificity was for the UKWP criteria. The performance of the H&R criteria may be explained by the large number of minor criteria items, which facilitates the identification of diverse AD phenotypes and thus maximizes the criteria's sensitivity.

Overall, our findings indicate that diagnostic criteria for AD tend to be more specific than sensitive. Additionally, while the summary estimates for sensitivity were higher in hospital-based studies, specificity was higher population-based settings. These differences were not statistically significant. The quality of evidence, assessed using the GRADE approach, was determined to be low (for UKWP and H&R criteria) to very low (ISAAC criteria).

Our review also highlights that numerous new patient-reported diagnostic criteria have been proposed. These criteria require validation in multiple studies before definitive conclusions can be drawn about their diagnostic utility, as they were largely similar in terms of sensitivity and specificity. This observation reflects the prevailing situation where novel diagnostic criteria have been proposed, aiming to improve the sensitivity and specificity in various population settings, but with insufficient evidence validating their performance in different settings.

Strengths and limitations

We updated an existing systematic review and widened the scope by examining several newly proposed AD diagnostic criteria, as well as including patient-assessed (questionnaire-based) diagnostic criteria. Our review provides an up-to-date comprehensive assessment of different published AD diagnostic criteria, yet significant questions remain unanswered.

A limitation of our review is the heterogeneity of the studies included in the meta-analyses of the 'other diagnostic criteria or questionnaires', which combined questionnaire-based criteria with physician-assessed criteria.

Moreover, studies evaluating the diagnostic accuracy of various diagnostic criteria across different population groups are lacking, notably with regards to different phenotypes, skin types and ethnicity. This limitation prevented subgroup analyses, highlighting the need for more inclusive and diverse studies, especially as differences exist between AD in light and dark skin types.[4,42] Current studies often focus on typical flexural disease, overlooking non-flexural, discoid, and follicular patterns common in darker skin types. One of the main limitations of

the UKWP criteria is their focus on flexural disease, contributing to their lower sensitivity in identifying diverse AD presentations.
In terms of age groups, most studies included children (n=26) or a mix of children and adults (n=8), and a few (n=5) studies included only adult patients. There are significant differences in the clinical features of AD between children and adults.[43] The lack of diagnostic criteria for adults makes it difficult to accurately diagnose AD in adult cohort studies. Some commonly used minor criteria items of diagnostic criteria, such as onset before age 2, or history of atopy, may be affected by recall bias when administered in an adult population.
Addressing these disparities is essential to ensure that AD research is generalizable, and to identify any potential differences in treatment efficacy among different demographic groups.

Future perspectives and recommendations
Moving forward, the dermatology research community must consider whether the development of additional diagnostic criteria is necessary. While numerous new diagnostic criteria have been proposed over the last decades, their added value remains uncertain. This highlights the pressing need for a systematic critique of the existing evidence of the various diagnostic criteria and a consensus among the research community for a more widely validated and universally accepted diagnostic criteria used in various research studies. The fact that the AD community has not produced a universal set of diagnostic criteria highlights the underlying challenge of AD as a heterogenous skin disease, necessitating alternate criteria for different population groups. Consistent documentation of participant demographics would be a step towards more equitable access to AD research studies.
Evaluating diagnostic criteria for AD extends beyond the traditional measures of validity, such as sensitivity and specificity. In large-scale epidemiological studies, especially in low-resource settings, the availability of dermatologists and feasibility of physical examinations are limited. Questionnaire-based diagnostic criteria, while potentially less accurate than physical examinations, provide a practical alternative in settings where clinical resources are scarce. However, it is important to acknowledge and report their limitations, particularly their tendency to underestimate disease prevalence. Efforts should be made to standardize the approach for identifying AD cases in electronic health records to improve the reliability of large-scale epidemiological studies.
The disparities in diagnostic criteria underscore the need for initiatives like Harmonizing Outcome Measures for Eczema (HOME), which aim to develop core outcome sets for AD clinical trials.[44] We advocate for further standardization of diagnostic criteria and inclusion criteria for AD clinical trials. It is noteworthy that AD RCTs most commonly utilise the H&R diagnostic criteria. Our work supports this practice, as the H&R criteria had the highest combined sensitivity and specificity estimates. However, RCTs using the UKWP criteria, which is more specific, would benefit from less misdiagnoses and erroneous recruitment of those without AD.
In conclusion, this systemic review demonstrated that the H&R criteria exhibited the highest combined summary estimates for both sensitivity and specificity, although the quality of evidence was low due to inconsistency and imprecision. Our study underscores the need for ongoing efforts to standardize the use of diagnostic criteria for AD globally, and to and to identify various diagnostic criteria that can be used per research setting. Such standardization will improve the quality and comparability of AD research and ultimately enhance patient care.[45,46]

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SUPPLEMENTARY MATERIAL

Supplementary material 1. Search strategy.

Supplementary table 1. Meta-analyses including subgroup analyses for the U.K. Working Party (UKWP) criteria.

Supplementary table 2. Meta-analyses including subgroup analyses for the Hanifin & Raijka (H&R) criteria.

Supplementary table 3. Meta-analyses including subgroup analyses for the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.

Supplementary table 4. Meta-analyses including subgroup analyses for the other diagnostic criteria.

A digital version of the Supplementary material can be found at:

PART II

PHOTOTHERAPY FOR ATOPIC ECZEMA

CHAPTER 3
PHOTOTHERAPY FOR ATOPIC ECZEMA

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ABSTRACT

Background
Atopic eczema (AE), also known as atopic dermatitis, is a chronic inflammatory skin condition that causes significant burden. Phototherapy is sometimes used to treat AE when topical treatments, such as corticosteroids, are insufficient or poorly tolerated.

Objectives
To assess the effects of phototherapy for treating AE.

Search methods
We searched the Cochrane Skin Specialised Register, CENTRAL, MEDLINE, Embase, and ClinicalTrials.gov to January 2021.

Selection criteria
We included randomised controlled trials in adults or children with any subtype or severity of clinically diagnosed AE. Eligible comparisons were any type of phototherapy versus other forms of phototherapy or any other treatment, including placebo or no treatment.

Data collection and analysis
We used standard Cochrane methodology. For key findings, we used RoB 2.0 to assess bias, and GRADE to assess certainty of the evidence. Primary outcomes were physician-assessed signs and patient-reported symptoms. Secondary outcomes were Investigator Global Assessment (IGA), health-related quality of life (HRQoL), safety (measured as withdrawals due to adverse events), and long-term control.

Main results
We included 32 trials with 1219 randomised participants, aged 5 to 83 years (mean: 28 years), with an equal number of males and females. Participants were recruited mainly from secondary care dermatology clinics, and study duration was, on average, 13 weeks (range: 10 days to one year). We assessed risk of bias for all key outcomes as having some concerns or high risk, due to missing data, inappropriate analysis, or insufficient information to assess selective reporting.
Assessed interventions included: narrowband ultraviolet B (NB-UVB; 13 trials), ultraviolet A1 (UVA1; 6 trials), broadband ultraviolet B (BB- UVB; 5 trials), ultraviolet AB (UVAB; 2 trials), psoralen plus ultraviolet A (PUVA; 2 trials), ultraviolet A (UVA; 1 trial), unspecified ultraviolet B (UVB; 1 trial), full spectrum light (1 trial), Saalmann selective ultraviolet phototherapy (SUP) cabin (1 trial), saltwater bath plus UVB (balneophototherapy; 1 trial), and excimer laser (1 trial). Comparators included placebo, no treatment, another phototherapy, topical treatment, or alternative doses of the same treatment.
Results for key comparisons are summarised (for scales, lower scores are better):

NB-UVB versus placebo/no treatment
There may be a larger reduction in physician-assessed signs with NB-UVB compared to placebo after 12 weeks of treatment (mean difference (MD) -9.4, 95% confidence interval (CI) -3.62 to

-15.18; 1 trial, 41 participants; scale: 0 to 90). Two trials reported little difference between NB-UVB and no treatment (37 participants, four to six weeks of treatment); another reported improved signs with NB-UVB versus no treatment (11 participants, nine weeks of treatment).
NB-UVB may increase the number of people reporting reduced itch after 12 weeks of treatment compared to placebo (risk ratio (RR) 1.72, 95% CI 1.10 to 2.69; 1 trial, 40 participants). Another trial reported very little difference in itch severity with NB-UVB (25 participants, four weeks of treatment).
The number of participants with moderate to greater global improvement may be higher with NB-UVB than placebo after 12 weeks of treatment (RR 2.81, 95% CI 1.10 to 7.17; 1 trial, 41 participants).
NB-UVB may not affect rates of withdrawal due to adverse events. No withdrawals were reported in one trial of NB-UVB versus placebo (18 participants, nine weeks of treatment). In two trials of NB-UVB versus no treatment, each reported one withdrawal per group (71 participants, 8 to 12 weeks of treatment).
We judged that all reported outcomes were supported with low-certainty evidence, due to risk of bias and imprecision. No trials reported HRQoL.

NB-UVB versus UVA1
We judged the evidence for NB-UVB compared to UVA1 to be very low certainty for all outcomes, due to risk of bias and imprecision. There was no evidence of a difference in physician-assessed signs after six weeks (MD -2.00, 95% CI -8.41 to 4.41; 1 trial, 46 participants; scale: 0 to 108), or patient-reported itch after six weeks (MD 0.3, 95% CI -1.07 to 1.67; 1 trial, 46 participants; scale: 0 to 10). Two split-body trials (20 participants, 40 sides) also measured these outcomes, using different scales at seven to eight weeks; they reported lower scores with NB-UVB. One trial reported HRQoL at six weeks (MD 2.9, 95% CI -9.57 to 15.37; 1 trial, 46 participants; scale: 30 to 150). One split-body trial reported no withdrawals due to adverse events over 12 weeks (13 participants). No trials reported IGA.

NB-UVB versus PUVA
We judged the evidence for NB-UVB compared to PUVA (8-methoxypsoralen in bath plus UVA) to be very low certainty for all reported outcomes, due to risk of bias and imprecision. There was no evidence of a difference in physician-assessed signs after six weeks (64.1% reduction with NB-UVB versus 65.7% reduction with PUVA; 1 trial, 10 participants, 20 sides). There was no evidence of a difference in marked improvement or complete remission after six weeks (odds ratio (OR) 1.00, 95% CI 0.13 to 7.89; 1 trial, 9/10 participants with both treatments). One split-body trial reported no withdrawals due to adverse events in 10 participants over six weeks. The trials did not report patient-reported symptoms or HRQoL.

UVA1 versus PUVA
There was very low-certainty evidence, due to serious risk of bias and imprecision, that PUVA (oral 5-methoxypsoralen plus UVA) reduced physician-assessed signs more than UVA1 after three weeks (MD 11.3, 95% CI -0.21 to 22.81; 1 trial, 40 participants; scale: 0 to 103). The trial did not report patient-reported symptoms, IGA, HRQoL, or withdrawals due to adverse events.
There were no eligible trials for the key comparisons of UVA1 or PUVA compared with no treatment.

Adverse events
Reported adverse events included low rates of phototoxic reaction, severe irritation, UV burn, bacterial superinfection, disease exacerbation, and eczema herpeticum.

Authors' conclusions
Compared to placebo or no treatment, NB-UVB may improve physician-rated signs, patient-reported symptoms, and IGA after 12 weeks, without a difference in withdrawal due to adverse events. Evidence for UVA1 compared to NB-UVB or PUVA, and NB-UVB compared to PUVA was very low certainty. More information is needed on the safety and effectiveness of all aspects of phototherapy for treating AE.

BACKGROUND

Description of the condition

Atopic eczema, also known as atopic dermatitis, is a chronic inflammatory skin condition that causes a significant burden to people with the condition and society. Atopic eczema can have a relapsing-remitting or a continuous disease course. The clinical presentation is characterised by xerosis (dry skin), pruritus, and flaky, excoriated "eczematous" lesions (Weidinger 2016). Atopic eczema is diagnosed clinically by its signs and symptoms, and its distribution, which varies in different age groups (Spergel 2003). Diagnosis is based on the presence of other atopic diseases, like asthma. In research settings, the most commonly used diagnostic criteria are the Hanifin and Rajka criteria (Hanifin 1980), and the UK Working Party Diagnostic Criteria for Atopic Dermatitis (Williams 1994).

The prevalence of atopic eczema is reported to be up to 20% in children, and between 7% and 10% in adults, and may be increasing (De Lusignan 2020; Flohr 2014). Often, atopic eczema manifests at infancy, but it can start at any age. A cross-sectional survey of 1760 children with atopic eczema found that 84% suffered from mild disease; 14% from moderate, and 2% from severe atopic eczema (Emerson 1998). Typically, the condition improves during childhood, with more than 50% of childhood atopic eczema resolving by adolescence (Williams 2005). However, some aspects of skin barrier and immune dysfunction may persist into adulthood (Abuabara 2018).

The International Study of Asthma and Allergies in Childhood (ISAAC) uses consistent measurement tools to study the prevalence of atopic eczema in children 6 to 7 years old, and 13 to 14 years old. One study within this research programme, examining time trends in the prevalence of atopic eczema, found a decreased prevalence of atopic eczema in developed countries, especially in Northwest Europe, between 2001 and 2003, compared to results from an earlier study that was conducted between 1994 and 1995. On the other hand, they found an increased prevalence, particularly for the younger age group, in many formerly low-prevalence, low-income countries in Latin America and Southeast Asia (Odhiambo 2009; Williams 2008). This variation in reported prevalence over time, and between different regions, suggests that disease prevalence is influenced by environmental factors. A large epidemiological study, using a UK primary care research database of 3.85 million children and adults, showed that the incidence of atopic eczema was higher in people with Black and Asian ethnicity than in white ethnic groups (De Lusignan 2020). A greater incidence of atopic eczema was seen in children younger than two years old with higher socioeconomic status, but for all

other age groups, higher socioeconomic status was associated with a lower incidence of the condition. Both incidence and prevalence of atopic eczema are higher in urban areas (De Lusignan 2020; Schram 2010). It seems that environmental factors play a role during early life, as a relatively higher atopic eczema prevalence is seen in children from immigrants who moved from a low-prevalence country to a country with higher prevalence (Martin 2013). The strongest determinant of atopic eczema is a positive family history (i.e. genetics (Apfelbacher 2011)).

The pathophysiology of atopic eczema is complex, and includes multiple interactions between genetic, immune, and external factors (Stefanovic 2020). It involves defects in epidermal structure and barrier dysfunction, alterations in cell-mediated immune responses and immunoglobulin E-mediated hypersensitivity (Weidinger 2016). An underlying genetic predisposition is identified with the discovery of mutations in the gene coding for the skin barrier protein, filaggrin (Palmer 2006). However, filaggrin mutations do not occur in all people with atopic eczema, so other genes and environmental factors seem to play an important role in its pathophysiology. The exposome is the total amount of external factors that an individual is exposed to throughout their lifetime (Stefanovic 2020). Exposomal influences play an important role in atopic eczema pathogenesis, and can be categorised into nonspecific exposures (e.g. human and natural factors), specific exposures (environmental factors, e.g. diet, allergens, humidity, ultraviolet radiation, pollution, and water hardness), and internal exposures (e.g. microbiota of the skin and gut, and host cell interaction (Stefanovic 2020)).

Atopic eczema causes a significant burden to both the person with the condition and their families, and it has been found that an increase in the condition's severity can result in lower quality of life, anxiety, and depression (Maksimović 2012). In addition, atopic eczema has important effects on society due to high medical costs, psychosocial effects, and co-morbidities (Mancini 2008). The Global Burden of Disease Study, providing annually updated numbers on disease-related morbidity and mortality worldwide, showed that atopic eczema disease burden, as measured by disability-adjusted life years (DALYs), ranks fifteenth among all nonfatal diseases, and has the highest disease burden of all skin diseases (Laughter 2020). The worldwide DALY rate was 123.31 per 100,000 (95% uncertainty interval 66.79 to 205.17) in 2017 (Laughter 2020). The outcomes of the Cochrane Skin Prioritisation Exercise 2020 showed that the total number of DALYs for atopic eczema in 2017 was 9,003,374 (Cochrane Skin 2020a).

The main physician-assessed outcome measures are the EASI (Eczema Area and Severity Index) score (Ricci 2009); the SCORAD (severity SCORing of Atopic Dermatitis) Index, which also includes a self-assessment component, the Subjective SCORAD (Kunz 1997); the SASSAD (Six Area Six Sign Atopic Dermatitis Severity) score (Charman 2002); and Costa's Simple Scoring System (Costa (Costa 1989)). Subjective tools used for self-assessment are the POEM (Patient-Oriented Eczema Measure) Scale (Charman 2004); the PO- SCORAD (Patient-Oriented SCORAD (Stalder 2011)); and the SA-EASI (Self-Administered Eczema Area and Severity Index) Rating Scale (Housman 2002). The Harmonising Outcome Measures for Eczema (HOME) initiative reached consensus that the EASI score should be the core instrument used for clinician-reported signs; POEM and NRS-11 (Numeric Rating Scale, 11-point scale for peak itch over past 24 hours) should be used for self-reported symptoms; RECAP (Recap of Atopic Eczema (Howells 2020)) or ADCT (Atopic Dermatitis Control Test (Simpson 2019)) should be used for

long-term control; and the DLQI (Dermatology Life Quality Index (Finlay 1994)), should be used for quality of life assessment (Schmitt 2014; Spuls 2017).
The severity of atopic eczema is variable, with symptoms ranging from mild disease with localised redness and localised involvement, to moderate to severe disease characterised by more generalised involvement of the whole body, with widespread redness, oozing, crusting, and secondarily infected lesions. Assessment of clinical severity is based on both objective clinical signs and subjective symptoms, such as itch and loss of sleep (Schmitt 2014). The EASI score corresponds to disease severity as follows: 0 = clear; 0.1 to 1.0 = almost clear; 1.1 to 7.0 = mild; 7.1 to 21.0 = moderate; 21.1 to 50.0 = severe; 50.1 to 72.0 = very severe (Barbarot 2016).

Description of the intervention
For people with moderate to severe atopic eczema, for whom topical treatments, including corticosteroids and emollients, are insufficient, systemic immunomodulating medication, phototherapy, or photochemotherapy are therapeutic options. Photochemotherapy is a subtype of phototherapy, which is defined as the use of phototherapy combined with adjuvant ultraviolet light-activated drug photosensitisers. Several types of phototherapy are beneficial for disease control in people with atopic eczema. These include: broadband ultraviolet B (BB-UVB; wavelength 280 nm to 315 nm); narrowband ultraviolet B (NB- UVB; wavelength 311 nm to 313 nm); ultraviolet A (UVA; wavelength 315 nm to 400 nm); ultraviolet A1 (UVA1; wavelength 340 nm to 400 nm); cold-light UVA1 (containing a cooling system eliminating wavelengths greater than 530 nm, decreasing the heat load); ultraviolet AB (UVAB; wavelength 280 nm to 400 nm); full-spectrum light (wavelength 320 nm to 500 nm, including UVA, visible, and infrared light); saltwater bath plus UVB (balneophototherapy); coal tar plus UVB (Goeckerman therapy); and excimer laser and excimer lamp (generating radiation in the ultraviolet B range (Garritsen 2014)). Photochemotherapy includes treatment with psoralen plus UVA (PUVA) and khellin plus UV. Phototherapy is usually administered in institutional settings, but for certain types of phototherapy, home phototherapy is also available.

Ultraviolet B (UVB)
UVB phototherapy can be administered using different wavelengths of emission. BB-UVB lamps deliver ultraviolet radiation in the range of 280 nm to 315 nm, while NB-UVB lamps deliver radiation of a much narrower spectrum, between 311 nm and 313 nm. UVB absorption occurs mainly through chromophores in the epidermis and superficial dermis (Weichenthal 2005). In order to increase the effectiveness of UVB therapy, and thereby, reduce UV exposure and risks, UVB treatment is often combined with topical agents (Mahrle 1987).
For psoriasis, it was shown that wavelengths around 311 nm were more effective than broad-spectrum UVB, which led to the development of NB-UVB lamps, which emit selective UVB spectra in the range of 311 nm to 313 nm (Fischer 1976; Parrish 1981). While the equivalent action spectra studies are not available for atopic eczema, NB-UVB is now the most established and widely used form of phototherapy for the treatment of a wide range of other skin diseases, including atopic eczema (Herzinger 2016; Honig 1994; Van Weelden 1988; Vermeulen 2020). NB-UVB devices contain fluorescent lamps emitting UVB in the 311 nm to 313 nm range (Van Weelden 1988). Although much less widely available in current times, devices used for BB-UVB emit wavelengths in both the UVB range (280 nm to 315 nm,

approximately two-thirds of the output) and the UVA range (320 nm to 400 nm, approximately one-third of the output (Jaleel 2019)).
The starting dose of UVB phototherapy is established by determining the person's minimal erythema dose (MED), and basing treatment on that (e.g. 70% MED as first dose), or it is based on the person's Fitzpatrick skin phototype (a system that classifies skin type by its reaction to exposure to sunlight). After treatment initiation, doses are gradually increased to 2000 mJ/cm^2 to 5000 mJ/cm^2, or to the maximum tolerated dose (Ibbotson 2004). Dose increments usually vary between 5% and 40% of the last dose used, most often in 10% to 20% increments. Treatment frequency varies from two to five times per week. Each treatment lasts from seconds at the onset of treatment, to minutes, depending on the type of device used. Guidelines on the dosimetry of NB- UVB have mainly been published for psoriasis, but the same dosing protocols are often used for atopic eczema (Beani 2010; Ibbotson 2004; Menter 2010; Sidbury 2014; Spuls 2004). UVB phototherapy can also be administered in the person's home, described as home phototherapy.
BB-UVB is sometimes combined with topical crude coal tar, in a regimen called Goeckerman therapy. This therapy was first reported by Goeckerman in 1925 for the treatment of psoriasis, but can also be used for the treatment of severe atopic eczema (Dennis 2013).
Balneotherapy (saltwater immersion) can also be combined with UVB (balneophototherapy). The addition of UVB phototherapy to balneotherapy may enhance the anti-inflammatory effect of thermal spring water. UVB can be administered simultaneously, or after saltwater immersion (Huang 2018).

Ultraviolet A (UVA)
The different types of UVA phototherapies can be sub-categorised into conventional UVA (315 nm to 400 nm) and UVA1 (340 nm to 400 nm). Conventional UVA requires longer exposure times for effective doses. However, as UVA1 equipment is relatively expensive to buy and maintain, conventional UVA lamps can still be used as a less costly alternative to UVA1, as 90% of their emission is in the UVA1 range (Darsow 2010; Legat 2003; Zandi 2012).
UVA1 lamps that eliminate ultraviolet A2 (UVA2; 320 nm to 340 nm) wavelengths from their emission spectrum have enabled higher doses to be delivered, while minimising risk of adverse effects, notably erythema. In practice, metal halide sources are required to achieve such high doses, as fluorescent sources at much lower irradiance are unable to achieve this. UVA1 can be administrated at a high dose (HD; 80 J/cm^2 to 130 J/cm^2), medium dose (MD; 40 J/cm^2 to 80 J/cm^2), or low dose (LD; less than 40 J/cm^2), with sessions lasting from 10 minutes to one hour (Darsow 2010; Legat 2003). Dosimetry has not yet been standardised internationally, but based on reports of the approximate dose needed to produce minimum erythema and treatment durations, it can be assumed that low, medium, and high doses are approximately equivalent between centres; although quoted dosages are unlikely to be precisely equivalent (Dawe 2003). Efficacy of high dose UVA1 has been reported in acute flares of severe atopic eczema, although the specific phenotype of atopic eczema that responds most effectively has not been evaluated, and is a matter for further study (Krutmann 1998).
For people receiving high dose UVA1, UVA1 cold light lamps that filter infrared radiation with a cooling ventilation machine, enable treatment to be delivered more comfortably, without the high levels of heat produced during high dose UVA1 exposure (Von Kobyletzki 1999b).

UVAB radiation includes wavelengths of both UVA and ultraviolet B (UVB), given either simultaneously by a single device (such as Metec Helarium©), or in subsequent emissions. Its use for atopic eczema was initiated by Jekler and Larkö, but it is rarely used today, as it has largely been replaced with other UV-based phototherapies (Grundmann 2012; Jekler 1990).
Full spectrum light (FSL) is an alternative modality of phototherapy, generating the full spectrum of light with a continuous wavelength ranging from 320 nm to 5000 nm, usually in combination with emollients (Byun 2011).

Photochemotherapy
Photochemotherapy uses ultraviolet light-activated drug photosensitisers combined with phototherapy. It typically uses a systemic drug photosensitiser combined with phototherapy. In photochemotherapy, the anti-inflammatory, anti-proliferative, and immunosuppressive effects only occur in the skin on irradiation, when the drug absorbs ultraviolet light. The most common form of photochemotherapy is psoralen-UVA (PUVA); during which the administration of UVA is combined with psoralen as the photosensitiser. Psoralen can be administered orally or topically, either by immersing in a bath, or applying it as soaks, creams, or gels. The main psoralens used for oral PUVA are 8- methoxypsoralen (8-MOP) and 5-methoxypsoralen (5-MOP). 8-MOP is most commonly used for bath PUVA, although this is not useful in atopic eczema if the face requires treatment. Usually, the dose and treatment schedule of PUVA is based on the minimum phototoxic dose (MPD) to ensure adequate drug bioavailability, or on people's sensitivity to sunlight, corresponding to the Fitzpatrick sun-reactive skin phototype (Sachdeva 2009; Sidbury 2014). The treatment schedule of PUVA is usually twice weekly for atopic eczema; the UVA radiation dose is gradually increased during the course of treatment by increments, often in the order of 20% to 40%. The total number of PUVA treatments per course will depend on disease response and tolerance. Cumulative treatment numbers will depend on individual factors.
Another form of photochemotherapy is khellin, combined with UV (natural sunlight or UVA). Khellin is a photosensitiser that can be administered topically or orally.

Excimer lamp and excimer laser
Excimer is a complex of excited gases, which upon decomposition, give off excess energy in the form of UV radiation. The excimer exists both as a lamp and a laser. The lamp is a polychromatic (wavelengths 306 nm to 310 nm), non-targeted (incoherent) light used to treat a range of body surface areas. On the other hand, the laser is a monochromatic (308 nm), targeted (coherent), intermittent (pulsing) light (Brenninkmeijer 2010; Park 2012).

Safety and adverse events
The various forms of phototherapy available for people with atopic eczema have different risk profiles that must be taken into account by the physician (Goldsmith 2012; Menter 2010; Morison 1998; Stern 1997). Common adverse events for any type of UV-based phototherapy are erythema, pruritus, and a sense of burning or stinging, although it is important to be aware that erythema from PUVA may not be apparent until 48 hours to 96 hours after exposure. Other less common consequences of phototherapy are induction of polymorphous light eruption, folliculitis, herpes simplex virus reactivation, and photo-onycholysis (with PUVA). The most common side effect of oral psoralen is nausea. Uncommonly, pain may occur, and

seems specific to PUVA rather than other UV- based phototherapies. It is likely that this is neuropathic in nature, and is important to recognise, as PUVA should be discontinued in that instance. The risk of squamous cell carcinoma is increased if people are exposed to high cumulative numbers of PUVA treatments (more than 150 to 200 (Stern 1998)). While a delayed risk of melanoma was reported, it has not been replicated, nor has a causal role been proven (Stern 1997). A larger Swedish study, including people with atopic eczema, did not show this association (Lindelöf 1991; Lindelöf 1999).

The incidence of adverse events of phototherapy is considered to be low, although the true incidence is unknown. Most publications on the safety and adverse events of phototherapy concern the treatment of people with psoriasis, and it is unclear how the outcomes of these studies relate to outcomes for people with atopic eczema. However, noncompliance rates secondary to side effects are very low in the available studies for atopic eczema (Clayton 2007; Grundmann-Kollmann 1999; Jekler 1988; Meduri 2007; Tay 1996).

Prescribing practices

A recent survey was conducted by the European TREatment of ATopic eczema (TREAT) Registry Taskforce. Invited via a mailing list of the European Academy of Dermatology and Venereology and national societies, 238 dermatologists from 30 European countries participated (Vermeulen 2020). The most common first- line non-topical therapy for people with moderate to severe atopic eczema was phototherapy, prescribed by 41.5% of survey participants, followed by day-care therapy (39.3%), and systemic therapy (26.6%). NB-UVB and PUVA were the most frequently prescribed first- and second-line choices of phototherapy for atopic eczema. Only a small minority of participants prescribed UVA1. The most important reason participants stated for using phototherapy was personal experience with the treatment (58.8%).

There is an absence of published data on phototherapy practice patterns for the treatment of atopic eczema for regions outside Europe. The guidelines of care for the management of atopic eczema by the American Academy of Dermatology (AAD) state that phototherapy is a second-line treatment, and that choice of phototherapy modality should be guided by factors, such as availability, cost, skin phototype, skin cancer history, and the use of photosensitising medications (Sidbury 2014). Anecdotally, different types of UVB (NB and BB) may be the most commonly used form of phototherapy for atopic eczema in North America. In general, NB-UVB is often recommended, taking into account its relative efficacy, low adverse effects profile, and availability (Sidbury 2014). A study on phototherapy utilisation and costs in the USA found that the total invoice of phototherapy services for all diseases increased 5% annually from 2000 to 2015. UVB comprised 77% of phototherapy volume, and 92% of phototherapy was prescribed by dermatologists (Tan 2018).

Previous evidence

A previous systematic review, using GRADE methodology, showed that phototherapy can be a valid therapeutic option for people with atopic eczema (Garritsen 2014). Garritsen and colleagues highlighted that the best evidence on efficacy is available for the use of NB-UVB and UVA1 (Garritsen 2014). These findings are in line with the recommendations in the *Atopic Eczema* treatment guideline from the European Dermatology Forum (Wollenberg 2018). The review further showed that there was little information available on the duration of remission,

long- term safety, efficacy in children, and in acute versus chronic atopic eczema. The review authors also identified some shortcomings in the quality of the included studies. They argued that studies should adequately measure the use of concomitant topical corticosteroids, and use validated diagnostic atopic eczema criteria and outcome measurements.

Another systematic review supported the findings of Garritsen 2014 regarding the evidence for the use of NB-UVB and UVA1 phototherapy in moderate to severe atopic eczema (Pérez-Ferriols 2015). These review authors found that there was scarce evidence supporting the use of PUVA, and little information on phototherapy for atopic eczema in children. The authors recommended standardisation of radiation methods, and the use of comparable criteria, scales, and minimum length of follow-up in future studies (Pérez-Ferriols 2015).

A randomised controlled trial (RCT) on high versus medium UVA1 phototherapy reported that UVA1 phototherapy should be considered among the first approaches in people with severe atopic eczema, and stated that high dose was more effective than medium dose UVA1 for dark skin types (Pacifico 2019).

In an observational multicentre study, researchers observed 207 people with psoriasis, and 144 people with atopic eczema, in eight centres (Väkevä 2019). For the people with atopic eczema, scores from the Patient-Oriented SCORing Atopic Dermatitis (PO-SCORAD) index and Dermatology Life Quality Index (DLQI) improved significantly during and after treatment (measured at three months or more). Alleviation of pruritus correlated with better quality of life. The study authors indicated that further studies in atopic eczema were necessary to determine the best treatment dose.

How the intervention might work

Several factors are believed to contribute to the effectiveness of phototherapy (Gambichler 2009). First, suppression of the antigen-presenting function of Langerhans cells is believed to be the mechanism of the immune-suppressing effect, together with induction of apoptosis of infiltrating T-cells (Majoie 2009). Second, phototherapy is found to thicken the stratum corneum. This causes the skin to be less susceptible to pathogens and antigens, resulting in smaller eczematous reactions (Jekler 1990). And last, there seems to be suppression of the colonisation of the skin with *Staphylococcus aureus* and *Pityrosporum orbiculare* (the yeast form of *Malassezia furfur*), which is helpful for people with atopic eczema, as their skin often shows superabundance of these organisms. *S. aureus* secretes toxins that drive atopic eczema (Alexander 2020; Faergemann 1987; Weidinger 2016), while *P. orbiculare* can trigger the development and persistence of atopic eczema through the generation of autoantigens (Nowicka 2019).

The mechanisms of action of different phototherapeutic options differ, but include anti-inflammatory, antiproliferative, and immunosuppressive effects, which will be of differing importance in contributing to the effects seen in different diseases. Anti- inflammatory and immunosuppressive effects are of importance in atopic eczema.

UVB exerts its effects mainly at the level of the epidermis and superficial dermis, while UVA-based phototherapies affect mid- and deep-dermal components, including blood vessels. UVB radiation is absorbed by endogenous chromophores, such as nuclear DNA, initiating a cascade of events. Absorption of UV light by nucleotides leads to the formation of DNA photoproducts and suppresses DNA synthesis. UV light stimulates the synthesis of prostaglandins and cytokines that play important roles in immune suppression. It can reduce the number of

Langerhans cells, cutaneous T- lymphocytes, and mast cells in the dermis. UV radiation can also affect extranuclear molecular targets located in the cytoplasm and cell membrane. The combination of immune suppression, alteration in cytokine expression, and cell cycle arrest contributes to the suppression of disease activity (Bulat 2011).

With PUVA, the conjunction of psoralens with epidermal DNA inhibits DNA replication, and causes cell cycle arrest. Psoralen photosensitisation also causes an alteration in the expression of cytokines and cytokine receptors. Psoralens interact with RNA, proteins, and other cellular components, and indirectly modify proteins and lipids via single oxygen-mediated reactions, or by generating free radicals. Infiltrating lymphocytes are strongly suppressed by PUVA, with variable effects on different T-cell subsets (Bulat 2011).

Studies in Asian populations have suggested that both NB-UVB, and a combination of UVA plus NB-UVB, are effective in the treatment of moderate to severe atopic eczema (Mok 2014). NB-UVB, which is usually the preferred modality for treating atopic eczema, requires higher doses in more pigmented skin types (Meduri 2007; Syed 2011a; Syed 2011b).

UVA1 is thought to be faster and more efficacious for treating acute atopic eczema, and is equally effective in skin types I to V, without requiring dose adjustments (Jacobe 2008; Mok 2014). However, it is not clear how atopic eczema disease phenotype (e.g. predominantly flexural versus discoid, or follicular) impacts on the responsiveness to the different types of phototherapy; this area requires further study.

Why it is important to do this review

A good summary of the evidence of the different types of phototherapy will be useful to detect the gaps of evidence and to determine the future research agenda. The knowledge gap and varying prescribing practices have led to limited reimbursement of phototherapy for atopic eczema by healthcare insurance companies in some countries, making a promising treatment modality unattainable for some people for whom topical corticosteroids are insufficient. The costs of atopic eczema per person are expected to rise in the coming years, when dupilumab, a fully human monoclonal antibody that inhibits IL-4 and IL-13, and baricitinib, a janus kinase (JAK) inhibitor are approved for the treatment of atopic dermatitis, and most importantly, because of the arrival of other new systemic treatments, such as new JAK inhibitors. Thus, high-quality research into therapeutic alternatives, which have longstanding track records for efficacy, safety, and cost-effectiveness, is very important.

Limitations on the reimbursement of phototherapy and other off- label treatments in the future, may lead to a shift to new on- label, and much more expensive systemic treatments that have been proven effective in RCTs. The question is whether this is desirable, as not all new treatments are widely available globally. Therefore, our aim is to investigate the effectiveness and safety of phototherapy in the treatment of atopic eczema. With the results, we aim to strengthen existing and evolving guidelines for atopic eczema, and provide meaningful evidence to support treatment decisions. We will also highlight the gaps in evidence in relation to this topic.

Cochrane Skin undertook an extensive prioritisation exercise in 2020 to identify a core portfolio of the most clinically important questions. The topic of phototherapy for eczema was identified as one of the top three titles (Cochrane Skin 2020b). This review is also directly applicable to, and is being conducted to inform the update of the European and American guidelines on the use of phototherapy for atopic eczema.

OBJECTIVES

To assess the effects of phototherapy regimens (e.g. narrowband ultraviolet B (NB-UVB), broadband ultraviolet B (BB-UVB), psoralen plus ultraviolet A (PUVA), ultraviolet A1 (UVA1)) for people with atopic eczema.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), including cross-over trials, and randomised within-participant trials.

Types of participants

We included studies conducted in participants with atopic eczema of any phenotype and severity. We included participants of all ages with a clinical diagnosis of atopic eczema. The diagnostic criteria could include the Hanifin and Rajka definition (Hanifin 1980), or the UK modification (Williams 1994), or they could have been diagnosed clinically by a healthcare professional, using the terms 'atopic eczema' or 'atopic dermatitis', for example. Studies in children who were described as having ‘eczema’, as opposed to ‘atopic eczema’, were also eligible.

We assessed the distribution of relevant participant characteristics, including severity of atopic eczema, age, and concomitant medications.

We imposed no restrictions on age, sex, or ethnicity of participants.

We excluded studies that included participants with other types of eczema, such as contact dermatitis, seborrhoeic eczema (seborrhoeic dermatitis), varicose eczema, discoid eczema, irritant dermatitis, and hand eczema.

We only included participants with diagnoses, such as 'Besnier's prurigo' or 'neurodermatitis' if there was additional descriptive evidence of atopic eczema in the flexures. We only included studies in which not all participants had atopic eczema if separate results were reported for the participants with atopic eczema.

Types of interventions

Any kind of phototherapy, including the following.

- Broadband ultraviolet B (BB-UVB; 280 nm to 315 nm)
- Narrowband UVB (NB-UVB; 311 nm to 313 nm; i.e. TL-01)
- UVA (315 nm to 400 nm)
- UVA1 (340 nm to 400 nm)
- Cold-light UVA1 (containing a cooling system eliminating wavelengths greater than 530 nm)
- UVAB (280 nm to 400 nm)
- Full-spectrum light (320 nm to 5000 nm, including UVA, visible, and infrared light)
- Saltwater bath plus UVB (balneophototherapy)
- Coal tar plus UVB radiation (Goeckerman therapy)

- Psoralen plus UVA (PUVA) with oral 8-methoxypsoralen (8-MOP)
- Psoralen plus UVA (PUVA) with 5-methoxypsoralen (5-MOP)
- Oral trimethylpsoralen with UVA (PUVA)
- Oral khellin plus UV
- Topical khellin plus UV
- Heliotherapy
- Excimer laser
- Excimer lamp

For the comparators, we accepted any other type of treatment regimen, namely: any type of phototherapy; systemic treatment (e.g. prednisolone, cyclosporin, methotrexate, azathioprine, biologics); topical treatment (e.g. topical corticosteroids, topical tacrolimus, coal tar); placebo; or no treatment. We included studies in which concomitant medications or co-interventions were given, as long as the medication regimen was the same in each treatment arm. We included treatment given in any setting, for example clinic- based or home phototherapy.
In studies where two treatment intervention groups from different categories were compared against a single comparator group, the relevant treatment group and the same comparator group were included in two separate pair-wise meta-analyses.

Types of outcome measures
We defined treatment outcomes as short-term (up to and including 16 weeks after initiating treatment, taking the measurement closest to 12 weeks if outcomes were measured at multiple time points), and long-term (more than 16 weeks after initiating treatment, taking the longest time point if outcomes were measured at multiple time points). Long-term control was defined as the closest time point to six months after the end of the course of phototherapy, assessed in the same way as the primary outcome for physician-assessed and participant-reported changes in signs and symptoms of atopic eczema. Outcomes of interest in this review were in accordance with the core outcomes (including core outcome instruments) of the Harmonising Outcome Measures for Eczema (HOME) initiative (Schmitt 2014).
We included studies in this review regardless of whether our primary and secondary outcomes were measured.
SASSAD (Charman 2002)

Primary outcomes
- Physician-assessed changes in clinical signs of atopic eczema
  - Using the following measurement instruments (in hierarchy, starting with the most preferred instrument): EASI (Ricci 2009), Objective SCORAD (or compound SCORAD if objective SCORAD was not reported (Kunz 1997), Costa (Costa 1989),
- Patient-reported changes in symptoms of atopic eczema, including itch
  - Using the following multi-item measurement instruments for atopic eczema symptoms (in hierarchy, starting with the most preferred instrument): POEM (Charman 2004), subjective SCORAD; and the following single-item

measurement instruments for itch (in hierarchy, starting with the most preferred instrument): peak numerical rating scale (NRS (Yosipovitch 2019)), average NRS, visual analogue scale (VAS (Reich 2012)), verbal rating scale (VRS (Phan 2012))

- Investigator Global Assessment (IGA)
- Health-related quality of life, measured with the (Skindex-29
- (Chren 1996), Dermatology Life Quality Index (DLQI (Finlay 1994)), Children's DLQI (CDLQI (Lewis-Jones 1995))
- Safety (adverse events and tolerability (i.e. withdrawals due to adverse events))
- Long-term control, at the closest time point to six months after the end of the course of phototherapy, assessed in the same way as the primary outcome (e.g. EASI or POEM)

Search methods for identification of studies

We aimed to identify all relevant RCTs, regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

The Cochrane Skin Information Specialist (Liz Doney) searched the following databases, using strategies based on the draft strategy for MEDLINE in our published protocol (Musters 2021).

• The Cochrane Skin Specialised Register (searched 13 January 2021, using the search strategy in Appendix 1);

• The Cochrane Central Register of Controlled Trials (CENTRAL; 2021, Issue 1) in the Cochrane Library (searched 13 January 2021, using the strategy in Appendix 2);

• MEDLINE Ovid (from 1946 to 13 January 2021), using the strategy in Appendix 3;

• Embase Ovid (from 1974 to 13 January 2021), using the strategy in Appendix 4.

Trials registers

The Cochrane Skin Information Specialist searched the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov; searched 19 January 2021, using the search strategy in Appendix 5). The World Health Organization International Clinical Trials Registry Platform (ICTRP; apps.who.int/ trialsearch/) was not available at this time, due to technical issues.

Searching other resources

Searching reference lists

We checked the bibliographies of included studies and any relevant systematic reviews for further references to relevant trials.

Searching by contacting relevant individuals or organisations

We contacted experts and organisations in the field to request additional information on relevant trials (Table 1).

Unpublished literature

We sought information about unpublished or incomplete trials by corresponding with investigators or organisations, or both, known to be involved in previous relevant studies (Table 1).

Correspondence with trialists, experts, and organisations
We contacted original authors for clarification and further data if trial reports were unclear (Table 1).

Adverse effects
We did not perform a separate search for adverse effects of phototherapy interventions used for the treatment of eczema. We only considered adverse effects described in included studies.

Errata and retractions
The Cochrane Skin Information Specialist ran a specific search to identify errata or retractions related to our included studies on 13 July 2021. No relevant retraction statements or errata were retrieved.

Data collection and analysis
We used the software, Covidence, to manage the study selection and Microsoft Excel for the data extraction process (Covidence).

Selection of studies
Two pairs of review authors (SM and AM, and SL and JH) independently screened all identified titles and abstracts using Covidence. We examined the full texts of studies that potentially met the criteria, as well as studies for which abstracts did not provide sufficient information. We resolved disagreements through discussion with a senior review author (PS).

Data extraction and management
Two pairs of review authors (SM and AM, and SL and JH) independently extracted outcome data from the included studies. One review author (JH) entered the characteristics of each study into Review Manager Web, and another reviewer (JH) checked these data for accuracy (RevMan Web 2020). For studies that met the inclusion criteria, we extracted relevant information into evidence tables, using an a priori defined proforma, piloting data extraction on a subset of studies before final extraction. We resolved disagreements through discussion with a senior review author (PS).

We extracted data on methodological quality, participants, interventions, and outcomes of interest, according to the Harmonising Outcome Measures for Eczema (HOME) consensus, from the included studies, using the following data extraction fields:

- Author and year of publication
- Year and country
- Sample size
- Study design
- Age

- Setting (hospital or population-based)
- Type of phototherapy
- Length and frequency of treatment
- Cumulative doses of UV radiation
- Duration of follow-up
- Primary outcomes:
    - Physician-assessed changes in the clinical signs of atopic eczema
    - Patient-reported changes in symptoms of atopic eczema, including itch
- Secondary outcomes:
    - Investigator Global Assessment (IGA)
    - Health-related quality of life
    - Safety (adverse events and tolerability (i.e. withdrawals due to adverse events))
    - Long-term control, at the closest time point to six months after the end of the course of phototherapy, assessed in the same way as the primary outcome
    - Translation (yes/no)

Assessment of risk of bias in included studies

Two review authors (EA and RB) independently assessed the risk of bias for the effect of assignment to the intervention, using the Cochrane RoB 2 tool (Higgins 2020b; Sterne 2019). We only assessed the outcomes in the summary of findings tables (see Summary of findings and assessment of the certainty of the evidence section).

We resolved disagreements through discussion. The RoB 2 tool addresses the following domains:

- Bias arising from the randomisation process
- Bias due to deviations from intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

We answered a number of signalling questions, which led to the tool algorithm assessing each domain as high risk, low risk, or some concerns. The tool algorithm also calculates an overall risk of bias, as high risk, low risk, or some concerns. To undertake these assessments, we used the RoB 2 Excel Tool. The answers to these signalling questions are available on an online repository.

We did not use the cross-over variant of the RoB 2 tool, because we only included data from the first phase of cross-over trials.

Measures of treatment effect

We presented continuous outcomes, where possible, on the original scale reported in each individual study, with a mean change from baseline and its associated standard deviation (SD). We used the standardised mean difference (SMD) as a measure of effect for continuous outcomes that used different scales (e.g. EASI and SCORAD). We calculated risk ratios (RR) for dichotomous outcomes, and presented either the number needed to treat for one additional beneficial outcome (NNTB), or the number needed to treat for one additional harmful

outcome (NNTH), when the results, including their measure of variance, fell on the same side of the line of no effect. We calculated odds ratios (OR) for within-participant studies, and in meta-analyses in which we combined parallel and within- participant studies.
If outcome data were reported as 'physician-assessments of the time needed until skin improvement', we presented these narratively, highlighting the general trend within the groups at the first time point at which an improvement was seen.
We reported all outcome data with their associated 95% confidence intervals (CIs), where possible.

Unit of analysis issues

Cross-over studies
Unit of analysis issues can arise in studies where participants have been randomised to multiple treatments in multiple periods, or when there has been an inadequate wash-out period. For cross- over trials, we used data from the first treatment period, due to concerns with carry-over effects, unless otherwise stated.

Within-participant studies
For paired data from studies with no suspicion of contamination across intervention sites, we planned to analyse using the generic inverse-variance method in Review Manager Web, after accounting for the within-participant variability (Higgins 2020a). In studies that reported paired data, but did not adjust for the within- participant variability, we planned to use a McNemar's test with the corresponding P value. However, no such data were available. When paired data were not reported, we performed variance corrections for the within-participant studies using the Becker- Balagtas method (Elbourne 2002). We assumed an intra-class correlation coefficient (ICC) of 0.5 in our calculations.
For dichotomous outcomes, we calculated OR for both study designs (number of participants with the event receiving the intervention, multiplied by the number of participants without the event in the control group, divided by the number of participants with the event receiving the control, multiplied by the number of participants without the event in the intervention group (Higgins 2020a)). A continuity correction of 0.5 was used in the case of zero events (Sweeting 2004). We pooled data from within-participant studies with data from parallel-group studies in meta-analyses using the generic inverse-variance method, inputting the natural log of the OR.

More than two treatment comparisons
We included multi-arm trials in the review if at least one arm examined a type of phototherapy for atopic eczema, and completed a separate data extraction for each pair-wise comparison. We included these studies as pair-wise comparisons. For future updates, to prevent double-counts of participants if treatment arms from multi-arm studies are pooled in more than one meta-analysis, we will partition them according to the number of comparisons carried out, and analyse them following the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2020a).

Dealing with missing data

If data were missing from trials that were carried out less than 10 years ago, we attempted to contact the investigators or sponsors of these studies. We re-analysed data according to the intention- to-treat (ITT) principle whenever possible. For dichotomous outcomes, if study authors had conducted a per-protocol analysis, and we had concerns about the level of missing data, we attempted to carry out an ITT analysis with imputation, using baseline values for the missing data, after checking the degree of imbalance in the dropouts between the arms, to determine the potential impact of bias (Higgins 2020a). We planned to carry out a per-protocol analysis instead of an ITT analysis for continuous outcomes.

Assessment of heterogeneity

We assessed clinical heterogeneity by examining the study characteristics, the similarity between the types of participants, interventions, comparisons, and outcomes, as specified in the criteria for included studies. Although a degree of heterogeneity between the studies included in a review is inevitable, we entered them into a meta-analysis if we could explain the heterogeneity by clinical reasoning, and make a coherent argument for combining the studies. We assessed statistical heterogeneity using the Chi^2 test and the I^2 statistic. We interpreted the I^2 as follows:

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 70% to 100%: considerable heterogeneity

We acknowledge that I^2 depends on magnitude and direction of effects, and the strength of the evidence for heterogeneity (e.g. the P values from the Chi^2 test). We explored heterogeneity through subgroup and sensitivity analysis. If we could not explain it through these methods, we downgraded the evidence for inconsistency in the GRADE assessments.

Assessment of reporting biases

Had we included a sufficient number of trials (10 or more) that assessed similar effects, we planned to assess publication bias according to the recommendations on testing for funnel plot asymmetry, described in the *Cochrane Handbook* (Higgins 2020a). If we did identify asymmetry, we planned to assess possible causes and explore these in the discussion section, if appropriate.

Data synthesis

One review author (EA) analysed the data in Review Manager Web, and reported them as specified in the *Cochrane Handbook* (Higgins 2020a). We carried out data synthesis only if we were able to identify two or more studies that investigated similar treatments, and reported data that could be pooled. We used a random-effects model to combine the results of individual studies. For comparisons where data synthesis was not feasible, we reported data separately in tables as 'Incomplete data on which further analysis is not possible', and presented them in a narrative summary, where appropriate. If applicable, for synthesis of data and reporting of analyses from multiple studies evaluating similar interventions, we took into consideration individual studies we had categorised at high risk of bias. When results were

estimated for individual parallel RCTs with low numbers of events (less than 10 in total), or when the total sample size was less than 30 participants, and we calculated a risk ratio, we reported the proportion of events in each group, together with a P value from a Fisher's Exact test.

Subgroup analysis and investigation of heterogeneity

- Adults versus children
- Different Fitzpatrick skin types
- participants with HIV/AIDS and atopic eczema

We planned to use the formal Chi^2 test for subgroup differences to test for subgroup interactions. We planned to compare subgroups using the analysis option of the 'Test for subgroup differences' in Review Manager Web (RevMan Web 2020).

Sensitivity analysis

We planned to explore reasons for heterogeneity in studies, and if necessary, we planned to perform sensitivity analyses, examining the effects of excluding study subgroups, e.g. those studies for which we had judged the results at high risk of bias, or we had some concerns.

Summary of findings and assessment of the certainty of the evidence

We generated summary of findings (SoF) tables for the most clinically important comparisons of this review:

- NB-UVB versus placebo/no treatment;
- NB-UVB versus UVA1;
- NB-UVB versus PUVA;
- UVA1 versus PUVA;
- UVA1 versus no treatment; and
- PUVA versus no treatment

The outcomes selected for inclusion in the SoF tables were:

- Physician-assessed changes in the clinical signs of atopic eczema (AE)
- Patient-reported changes in symptoms of AE including itch
- Investigator Global Assessment (IGA);
- Health-related quality of life and
- Safety (adverse events an

For each outcome result in the summary of findings tables, we assessed the certainty of the body of evidence using the GRADE approach (Schünemann 2013), and GRADEpro GDT software, which identify four levels of certainty (high, moderate, low, and very low). As all studies included in the review were RCTs, the starting level for all assessments was high certainty. We downgraded the level of certainty according to the presence of the following factors: study limitations (risk of bias); indirectness of evidence; unexplained heterogeneity; imprecision of results; and likelihood of publication bias. Two review authors (AM and PS) independently assessed the certainty of the evidence, with any disagreement resolved by discussion, or input from a senior review author (RB).

RESULTS

Description of studies

Results of the search

The database searches (see Electronic searches) retrieved a total of 616 records. We identified an additional three records through other sources (see Searching other resources), giving a total of 619 records. After removing duplicates, we had 613 records to screen. We excluded 514 records based on titles and abstracts. We obtained the full text of the remaining 99 records. We excluded 32 studies, reported in 33 references. We classified four studies (in seven references) as ongoing, and four studies as awaiting classification. We included 32 studies, reported in 55 references. For a further description of our screening process, see the study flow diagram (Figure 1).

Included studies

Please see the Characteristics of included studies tables for or a full description of the studies.

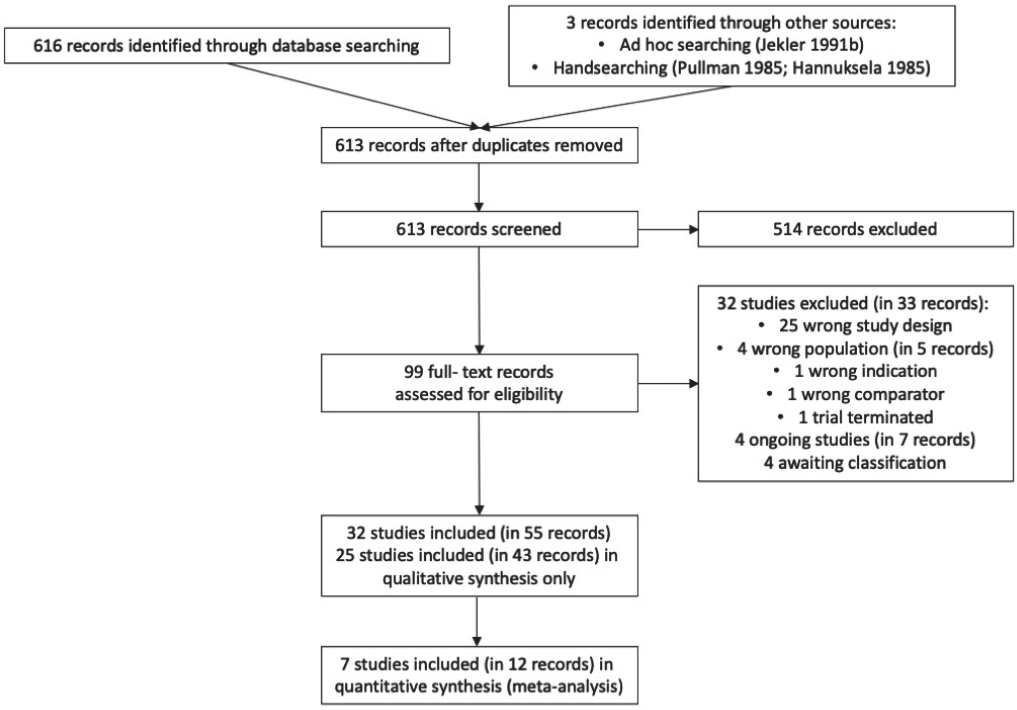
Design

All studies were prospective, randomised controlled trials. Seventeen of the studies were parallel group trials (Agrawal 2018; Byun 2011; Dittmar 2001; Granlund 2001; Heinlin 2011; Hoey 2006; Krutmann 1998; Krutmann 1992; Kwon 2019; Leone 1998; Maul 2017; Pacifico 2019; Qayyum 2016; Reynolds 2001; Von Kobyletzki 1999a; Youssef 2020; Zimmerman 1994). Thirteen of the studies were within-participant studies (Brenninkmeijer 2010; Der- Petrossian 2000; Jekler 1988a; Jekler 1988b; Jekler 1990; Jekler 1991; Jekler 1991b Study 1; Jekler 1991b Study 2; Legat 2003; Majoie 2009; Selvaag 2005; Tzaneva 2001; Tzung 2006). There were also two cross-over trials (Gambichler 2009; Tzaneva 2010).

The trial duration, including active treatment and follow-up, ranged from 10 days to 1 year; two trials did not mention the total length of follow-up (Hoey 2006; Maul 2017). The average trial duration was 13 weeks.

Five trials were multicentre (Granlund 2001; Heinlin 2011; Qayyum 2016; Tzaneva 2010; Zimmerman 1994). The rest of the studies were either single centre, or did not mention whether they were single- or multicentre.

Figure 1. Flowchart



Setting

All included studies recruited participants from secondary care clinics, the vast majority of which were dermatology outpatient clinics. The studies were conducted in many parts of the world. Nineteen studies were conducted in Europe (UK, Germany, the Netherlands, Finland, Norway, Sweden, Denmark, Switzerland, Austria, and Italy), five in Asia (Pakistan, Taiwan, and Korea), and one in Egypt. Seven studies did not report in which country they were conducted (Der-Petrossian 2000; Dittmar 2001; Krutmann 1992; Krutmann 1998; Legat 2003; Leone 1998; Von Kobyletzki 1999a).

Participants

Studies recruited participants ranging in age from 5 to 83 years, with a mean age of 28. Nine studies included paediatric < 18-year-old participants (Agrawal 2018; Jekler 1988b; Kwon 2019; Leone 1998; Qayyum 2016; Selvaag 2005; Tzung 2006; Youssef 2020; Zimmerman 1994). Five studies did not report the mean age; three of them focused on children, and two had a mix of adults and children of at least 16 years.

Five studies did not provide data on the gender of participants. Based on the studies that did provide data on gender, the number of male and female participants was almost equal (ratio 0.99 males:1 female).

Fitzpatrick skin type was reported by 21 studies. The majority of studies included participants with Fitzpatrick skin type II to IV. Only four studies included participants with skin type I, and only two studies included participants with skin type V or VI. One study evaluated physician-

assessed changes in clinical signs separately for participants with skin type II versus skin type III or IV, and compared a medium dose of UVA1 with a high dose UVA1 (Pacifico 2019).
The duration of atopic eczema was reported by 15/32 included studies; mean or median total disease duration ranged from 1 to 30.3 years.
Baseline atopic eczema severity was reported by all but two of the included studies. Studies used a variety of measurement outcomes to report the disease severity of their included participants. Thirteen studies used the SCORAD; however, only one study reported the use of the compound SCORAD. We assumed that most studies used either the compound or objective SCORAD. The range of (compound) SCORAD scores lies between 0 and 83. Mean or median baseline compound SCORAD of the participants included in these 13 trials ranged from 35 (moderate) to 67 (severe). Other outcome measures that were used to report baseline atopic eczema severity were the SASSAD (one study), Costa (three studies), Leicester sign score (one study), EASI (one study), Investigator Global Assessment (IGA; two studies), visual analogue scale (VAS) for itch (one study), or other (self-developed) measurement instruments to assess disease severity (nine studies).
None of the included studies reported HIV or AIDs comorbidity.

Sample sizes
A total of 1219 participants were randomised across the 32 RCTs included in this review, sample sizes ranged from 8 to 180 participants, with a mean of 38 participants.

Funding
Overall, 11 studies were funded by research grants, one study was sponsored by the pharmaceutical industry, one was sponsored by primary health insurance companies, two had no funding, and the rest of the studies did not report their source of funding.

Correspondence
We contacted 27 corresponding authors to obtain further information about their studies. For further details, see Table 1.

Interventions
The included studies fell into the following 10 broad phototherapeutic categories: narrowband ultraviolet B (NB-UVB; 14 RCTS), broadband ultraviolet B (BB-UVB; 5 RCTS), psoralen plus UVA (PUVA; 2 RCTS), UVA1 (11 RCTS), UVA (3 RCTS), UVB (unspecified; 1 RCT), UVAB (9 RCTS), full spectrum light (1 RCT), excimer laser (1 RCT), and other (Saalmann selective ultraviolet phototherapy lamp (SUP) cabin; 1 RCT). This list includes all types of phototherapy, included in both the intervention and comparator groups.

Comparisons
Sixteen studies included comparisons of phototherapy with other types of phototherapy, seven studies compared different dosages of the same phototherapy, six studies compared phototherapy with no treatment or placebo, three studies compared phototherapy with topical corticosteroid (betamethasone valerate 0.1%, clobetasol proprionate 0.05% fluocortolone 0.5%), one study compared phototherapy with systemic treatments (ciclosporin), two studies compared the same phototherapy in both arms with the addition of

a co-intervention in one arm (balneotherapy one study and pimecrolimus one study). Finally, one study used the same phototherapy in both arms with the addition of different concentrations of salt bath in the two comparator groups.
* We included multi-arm trials if at least one arm examined a type of phototherapy for atopic eczema, and separate data extraction was carried out for each pair-wise comparison. We included these multi- arm studies as pair-wise comparisons.

1. NB-UVB
Thirteen RCTs.

NB-UVB versus no treatment or placebo (Kwon 2019; Reynolds 2001*; Tzung 2006*; Youssef 2020)
Youssef 2020 compared NB-UVB with 85% glycerol. NB-UVB was administered three times a week for four weeks in a UV cabin (Waldmann GmbH, Germany), with 16 TL-01/100W fluorescent lamps producing NB-UVB with a peak emission at 311 nm. The starting dose was 70% minimal erythema dose (MED), with increments according to erythema response. The 85% glycerol was applied daily to the affected sites for four weeks.
Kwon 2019 compared NB-UVB against no treatment. Participants were treated with NB-UVB, administered two to three times a week for six weeks (12 to 18 treatments). The initial dose was 350 mJ/cm^2 to 400 mJ/cm^2, which was gradually increased to 1,100 mJ/cm^2. There was a follow-up period of three weeks.
Tzung 2006 compared NB-UVB combined with 1% pimecrolimus cream with 1% pimecrolimus cream alone. One half of the body was randomly selected to also be treated with NB-UVB twice a day for six weeks. NB-UVB was delivered using 24 Waldmann TL-01/100 fluorescent tubes, mounted in a UV 5001 BL cabinet (Waldmann, Villingen-Schwenningen, Germany). The starting dose was 70% MED with percentage-based increments every week (to a maximum of 1.5J/cm^2). After the six-week treatment phase, there was a post- treatment follow-up of four weeks.
Reynolds 2001 compared NB-UVB with visible fluorescent light. The NB-UVB unit contained 40 TL-100 W/01 lamps (Philips) and participants received a starting dose of 0.4 J/cm^2. Percentage- based increments were made weekly (maximum 1.5 J/cm^2, if tolerated). The cumulative dose was 24.8 J/cm^2 (range 2.8 to 32.2). The other group received visible fluorescent light through Philips' 75 to 85 W/96 Northlight fluorescent lamps (fitted into a Sovereign 8-tube vertical sunbed canopy). The exposure time was increased from 5 to 15 minutes, and participants were turned by 180o halfway through the treatment period. The median cumulative exposure time was 320 min (5 to 345). Participants in both groups were treated twice weekly for 12 weeks.

NB-UVB versus topical corticosteroid (betamethasone valerate 0.1%) *(Agrawal 2018)*
Agrawal 2018 compared NB-UVB, administered three times a week for eight weeks (closed chamber Philips TL-01), with betamethasone valerate 0.1%, applied twice a day for four weeks. The dose used for the NB-UVB started at 75% MED, and increased incrementally by 20% each visit, if well tolerated.

NB-UVB versus UVA1 *(Gambichler 2009; Legat 2003; Majoie 2009)*

Gambichler 2009 compared NB-UVB (delivered via a stand-up cubicle Cosmedico GP-42 (Cosmedico Medizintechnik GmbH, VS- Schwenningen, Germany) cabin fitted with ARIMED 311 fluorescent lamps; wavelength 310 nm to 315 nm (peak 311 nm)) with UVA1 (delivered via an air-conditioned UVA1 bed Sellamed 24000 (Sellamed, Gevelsberg, Germany), wavelength 340 nm to 400 nm). Both were delivered three times a week for six weeks. The initial dose of the NB-UVB therapy was 70% of MED, determined by a TL-01⁄12W lamp (Philips, Eindhoven, the Netherlands), with 10% to 20% increments, for a maximum dose of 1.2 J/cm^2 for skin phototype II, and 1.5 J/cm^2 for skin phototypes III and IV. The dose delivered for the UVA treatment was 50 J/cm^2.

Majoie 2009 compared NB-UVB, delivered using a light cabin (Waldmann, Schwenningen, Germany) with 20 311-nm lamps (TL-01, Philips, Eindhoven, the Netherlands), with UVA1, delivered using a light cabin (Waldmann, Schwenningen, Germany) with 40 lamps (TL-10R, Philips), emitting wavelengths of 350 nm to 400 nm only, with a maximum of ± 370 nm. The treatments were given three times a week for up to eight weeks. UVB treatment was started with an initial dose of 70% of the minimal erythemal dose. Subsequent dose increments were given on the basis of erythemic reactions of the skin. The intention was for each exposure to induce slight erythema. If the previous exposure failed to induce any reaction, the dose was increased by 20%. If the resulting erythema was slight, the dose was increased by 10%. Participants received median cumulative doses of 10.5 J/cm^2 of NB-UVB (range 9.9 to 11.5, average increment 10%/exposure) to one body side. The initial dose for the UVA1 treatment was 30 J/cm^2. In two steps, the dose was increased to 45 J/cm^2. The average dose of UVA1 was more than 40 J/cm^2. Participants received median cumulative doses of 930.6 J/cm^2 of MD UVA1 (range 717.1 to 1067.4) to the body side treated with UVA1.

Legat 2003 compared NB-UVB (delivered using a UV 7001 light box (Waldmann Medizinische Technik, Villingen-Schwenningen, Germany)) with UVA1 (delivered using a Sellas UV-A1 bench system (Sellamed 24000A; Sellas Medizinische Gerate GmbH, Gevelsberg, Germany)). Both were administered three times a week for up to eight weeks. The starting dose for the NB-UVB was 70% of the participant's minimal erythema dose, and dose increases were usually 10% to 20%, depending on the erythema response induced by the previous exposure. The NB-UVB median MED was 0.77 J/cm^2 , (range 0.55-1.56 J/cm^2). The starting dose for UVA1 irradiation was 10 J/cm^2, with 20 J/cm^2 applied at the second,30 J/cm^2 at the third, and 40 J/cm^2 applied at the fourth treatment. At the fifth, and each subsequent treatment, 50 J/cm^2 was administered. Participants received a median of 23 treatments (range 12 to 24 treatments), with a mean cumulative dose of 26.7 J/cm^2 NB-UVB (range 15.7 to 59.2 J/cm^2), and 1000 J/cm^2 UVA1 irradiation (range 500 J/cm^2 to 1150 J/cm^2).

NB-UVB versus UVA *(Reynolds 2001*)*

Reynolds 2001 compared NB-UVB (using 40 TL-100 W/01 lamps (Philips)) against UVA (40 fluorescent lamps (Performance 100 W, Philips)). Both treatments were given twice a week. The dosing schedule of NB-UVB was 0.4 J/cm^2, with percentage-based increments weekly (maximum 1.5 J/cm^2, if tolerated). Cumulative dose was 24.8 J/cm^2 (range 2.8 to 32.2). The dosing schedule of UVA was a starting dose of 5 J/cm^2, increasing to 10 J/cm^2, if tolerated,

then to a maximum of 15 J/cm^2. Cumulative dose of 315 J/cm^2 (range 15 to 345). Participants were treated for 12 weeks.

NB-UVB versus UVAB *(Leone 1998; Maul 2017)*

Maul 2017 compared NB-UVB with UVAB. The treatment regimen for NB-UVB alone, performed with a NB-UVB light cabin (model UV7001, Waldmann (Waldmann Lichttechnik GmbH, Kuttingen, Switzerland), 310 nm to 315 nm), was NB-UVB, started at a dose of 0.1 J/cm^2, with increments of 20% per session, if there were no side effects, to a maximum of 2.0 J/cm^2; three treatment sessions per week for 16 weeks. In the UVAB group, in addition to standard NB-UVB treatment, UVA was given at a starting dose of 0.5 J/ cm^2, and increased incrementally by 20%, to a maximum of 5.0 J/ cm^2. The treatment was performed with a UVA/NB-UVB light cabin (model UV7002, Waldmann, UVA 320 nm to 410 nm, to a peak of 351 nm; UVB output 310 nm to 315 nm, to a peak of 311 nm).

In two arms of a three-arm trial, Leone 1998 compared NB-UVB (using an irradiation bed equipped with 14 TL01/100w tubes) versus UVAB (phototherapy booth with F85/100W UV21 tubes emitting in the UVB, and F85/100W PUVA tubes emitting in the UVA). Participants were treated three times a week. The UVB irradiation protocol (for both narrowband and broadband UVB) was based on the MED: starting at 70% MED, with 40% dose increments after every third treatment, if tolerated, for a total of 10 to 15 treatments in both groups. In the UVAB group, the participants also received the UVA irradiation protocol; the initial dose was 3 J to 4 J (based on skin type) with a 1 J increment after every third treatment, up to a maximum of 10 J.

NB-UVB versus NB-UVB with a different dosing regimen *(Hoey 2006; Selvaag 2005)*

Hoey 2006 compared a standard increasing dose of UVB-TL01 treatment, with a fixed dose of UVB-TL01; the length of the study was unclear. In the standard increasing dose group, the first treatment was 70% of MED; subsequent treatments were increased by 20% increments. In the fixed-dose group, the first treatment was 70% of MED, followed by two subsequent increments; the maximum dose was then used for the remaining treatments. The number of treatments and the maximum dose was not reported in either case.

Selvaag 2005 compared a fixed dose of NB-UVB with an optimised regimen of UVB, with the dose based on skin reflectance measures. UVB was delivered using a bank of Philips TL-01 UVB tubes. One standard erythema dose (SED) is 10 mJ/cm^2 at 298 nm, using the International Commission on Illumination (CIE) erythema action spectrum, and is equivalent to 1.6 kJ/m^2 of the UVB lamp. Skin reflectance measurement was performed on non-lesional skin on the chest or between shoulder blades, with UV-Optimize 555 (MaticH, Copenhagen, Denmark). Participants were treated for up to six weeks, three to five times a week.

In the fixed regimen, a starting dose of 1.6 SED was used, with 25% incremental increases with each treatment session. The mean cumulative dose was 124 SED (range 29 to 186). In the optimised regimen group, UVB was administered according to skin reflectance measurements of skin pigmentation and erythema. The mean cumulative dose was 39 SED (16 to 88).

NB-UVB versus NB-UVB + pimecrolimus *(Tzung 2006*)*

Tzung 2006 compared NB-UVB (delivered using 24 Waldmann TL-01/100 fluorescent tubes mounted in a UV 5001BL cabinet (Waldmann, Villingen-Schwenningen, Germany)) with NB-UVB (delivered in the same way) plus topical pimecrolimus. The whole body was irradiated with NB-UVB twice a week for six weeks. Only lesions on one side of the body (randomly selected) received a thin film of pimecrolimus 1% cream (Elidel®, Novartis Pharma GmbH, Nuremberg, Germany), twice a day (1 hour after irradiation on days when phototherapy was received). The starting dose of NB-UVB was 70% MED, with percentage-based increments every week (to maximum of 1.5J/cm^2).

NB-UVB versus NB-UVB + synchronous balneotherapy *(Heinlin 2011)*

Heinlin 2011 compared NB-UVB (using a Phillips and Okkaido- Vario-System Tomesa® Alteglofsheim, Germany; wavelength 311 nm) with NB-UVB (delivered in the same way) plus synchronous balneotherapy. Both groups received treatments three to five times a week, for up to 35 sessions (approximately 7 to 12 weeks). The starting dose of NB-UVB was determined according to the individual skin type. All trial physicians were provided with a dose-escalation schedule for each skin type. The dose per treatment unit was increased by simultaneously prolonging the bathing time. Incremental steps to reach the final dose depended on the participant's skin type and individual acceptance (erythema threshold). Sessions lasted from 15 minutes to 30 minutes, including a bathing time of at least four minutes, before the UV light was started. In the group treated with synchronous balneotherapy, a 10% Dead Sea salt solution (Tomesa®) was delivered in an anatomically shaped bath tub with a computer-controlled purification system. Turning over every four minutes guaranteed a constant and total covering of the irradiated skin with the solution. In addition, participants moistened their face regularly with salt solution. Mean total light dose received was 34.9 J/cm^2. For the group that did not receive balneotherapy, participants lay on a couch placed in the tub instead of bathing. In this group, the mean total light dose received was 34.6 J/cm^2.

2. BB-UVB

Five RCTs.

BB-UVB versus placebo *(Jekler 1988a)*

In a split-body study, Jekler 1988a compared BB-UVB (delivered using 14 Philips TL 12 40 W and 14 Philips TL 12 20 W tubes arranged in a cubicle; wavelength 280 nm to 315 nm) with visible light (placebo tubes; ordinary daylight tubes — Osram L 36 W/30 — with no measurable UV content). Treatments were given three times a week, for up to eight weeks. For the side that received BB-UVB, each participant's MED of UVB was determined before the commencement of the phototherapy. The participants were randomised into two treatment groups — one starting with 0.5 MED, and one with 1 MED UVB, randomised to the right or left side of the body. In the 0.5 MED group, the dose was increased by 20% each time, until erythema appeared, at which point, the dose was decreased to half of the last dose given. Thereafter, the 20% increase schedule was resumed. In the 1 MED group, the doses were increased similarly. However, in this group, no dose reduction was made at the appearance of erythema. Instead, the dose was kept unchanged until erythema was no longer seen; after which, the 20% dose increase schedule was resumed. The initial doses were in the range of 20

mJ/cm^2 to 153 mJ/cm^2; the final doses in the range of 63 mJ/cm^2 to 816 mJ/cm^2; and the mean total dose was 3.18 J/cm^2.

BB-UVB versus UVA *(Jekler 1991)*
Jekler 1991 compared BB-UVB (14 Philips TL 12 40 W and 14 Philips TL 12 20 W tubes arranged in a cubicle) with UVA (delivered using a cubicle containing 24 Philips TL 85/100 W/09 (TL09) fluorescent tubes (Philips, Roosendaal, the Netherlands)). Both arms were treated three times a week for up to eight weeks, or until healing occurred. For the UVB, each participant was phototested before the start of treatment, and the initial dose was set at approximately 80% of the MED. Subsequently, dose increments of 10% to 25% were made at each treatment session. With the appearance of erythema, there was a reduction in the dose of about 10% to 30%. The mean initial dose was 20.8 mJ/cm^2 (SD 3.4; the mean final dose was 131 mJ/cm^2 (SD 49); and the mean total dose was 1589 mJ/cm^2 (SD 534). For the UVA, the initial dose was set at 7, 9, or 11 J/cm^2, depending on the participant's skin type and previous experience with solaria. At each subsequent treatment session, the dose was increased in steps of 2 J/cm^2, up to a maximum of 15 J/ cm^2. The mean initial dose was 7.9 J/cm^2 (SD 1.4); the mean final dose was 14.3 J/cm^2 (SD 1.5); and the mean total dose was 255 J/ cm^2 (SD 51).

BB-UVB versus UVAB *(Jekler 1990, Jekler 1991b Study 1)*
Jekler 1990 compared BB-UVB (14 Philips TL 12 40W and 14 Philips TL 12 20 W tubes arranged in a cubicle (Philips, Roosendaal, the Netherlands)) with UVAB (24 Wolff Helarium System tubes B1-12 100W (Cosmedico, Stuttgart, Germany) in an arrangement similar to that used for UVB therapy). Participants in both arms were treated three times a week for up to eight weeks, or until one body half was deemed to be healed. For the BB-UVB treatment, the initial dose of UVB was set at 80% of the MED. It was then increased each treatment session by 20%. With the appearance of erythema, the dose was reduced by 50%, and thereafter, the 20% increase schedule was resumed. For the UVAB treatment, a dose increment schedule was set at 5, 7, 10, 12, 15, 17.5, 20, 22.5, and 25 minutes. The dose that preceded the MED was set as the initial dose. The dose was incremented at every other treatment until a maximum of 25 minutes was reached (corresponding to 30 mJ/cm^2 UVB, and 8.3 J/cm^2 UVA). When erythema appeared, the dose was reduced to the preceding dose. In the treatment of participants with insensitive skin (MED ≥ 15 minutes; 18 mJ/cm^2 UVB, 5 J/cm^2 UVA), the steps at 17.5 and 22.5 minutes were omitted. With UVB, the mean initial dose was 37 mJ/cm^2. The mean final dose was 204 mJ/cm^2. The mean total dose was 2.47 J/cm^2. With UVAB, the mean initial dose was 13 mJ/cm^2 (range 6 mJ/cm^2 to 18 mJ/cm^2) UVB, and 3.7 J/ cm^2 (1.7 mJ/cm^2 to 5 J/cm^2) UVA. The mean final doses were 29 mJ/ cm^2 (range 18 mJ/cm^2 to 30 mJ/cm^2) UVB, and 8 J/cm^2 (range 5 mJ/ cm^2 to 8.3 J/cm^2) UVA. The mean total dose was 0.47 J/cm^2 UVB, and 130 J/cm^2 UVA.
Jekler 1991b Study 1 compared low dose BB-UVB with UVAB. The BB-UVB was administered using 14 Philips TL 12 40W and 14 Philips TL 12 20 W tubes arranged in a cubicle (Philips, Roosendaal, the Netherlands). The UVAB was administered using a cubicle containing 24 Wolff Helarium System tubes B1-12 100W (Cosmedico, Stuttgart, Germany), or a sunbed containing 20 tubes of the same kind. The wavelengths of the UVA irradiation were 315 nm to 400 nm

and the UVB 280 nm to 315 nm. Both treatments were given three times a week for up to eight weeks, or the healing of one body side. A mean of 18.5 (SD 4.4) treatments were given in 7.5 (SD 1.0) weeks. For the low dose UVB, each participant's minimal erythema dose of UVB was determined before the study, and thereafter, every other week. The aim was to give treatment with 20% of the MED. Dose increments were made stepwise, every other week, each time maintaining a dose of 0.2 MED. For the UVAB treatment, a dose increment schedule, depending on the participant's skin type was set up. The initial exposure time of 7 to 10 minutes was subject to an increment every, or every other treatment session of 2 to 5 minutes, to a maximum of 25 minutes (corresponding to 45 mJ/cm^2 UVB, and 10.5 J/cm^2 UVA). The mean initial BB-UVB dose was 10mJ/cm^2 (SD 3.6), the final dose was 18 mJ/cm^2 (SD 7.8), and total (cumulative) dose was 282 mJ/ cm^2 (SD 152). For the UVAB arm, the mean initial dose was 14 mJ/ cm^2 (SD 2.2) BB-UVB, and 3.2 J/cm^2 (SD 0.5) UVA: the mean final dose was 41 mJ/cm^2 (SD 6.8) BB-UVB, and 9.5 J/cm^2 (SD 1.6) UVA; and the mean total dose was 558 mJ/cm^2 (SD 193) BB-UVB, and 130 J/cm^2 (SD 45) UVA.

BB-UVB versus BB-UVB with a different dosing regimen *(Jekler 1988b)*

Jekler 1988b compared two different doses of BB-UVB, administered using 14 Philips TL 12 40W and 14 Philips TL 12 20 W tubes arranged in a cubicle (wavelength 280 nm to 315 nm) in a split-body study. Participants were treated three times a week for up to eight weeks, or until one half of the body was healed. The MED was determined every other week on the right and left body halves separately. One side of the body was treated with 0.4 MED, while the other was treated with 0.8 MED. Dose increments were made stepwise, every other week, on the basis of the MED. The initial doses on the 0.4 MED sides were in the range of 7 mJ/cm^2 to 36 mJ/ cm^2; on the 0.8 MED sides, they were 14 mJ/cm^2 to 72 mJ/cm^2. The final doses were in the range of 20 mJ/cm^2 to 77 mJ/cm^2 on the 0.4 MED sides, and 51 mJ/cm^2 to 173 mJ/cm^2, on the 0.8 MED side. The mean total dose for the UVB 0.4 MED group was 0.44 J/cm^2, and 1.08 J/cm^2 for the 0.8 group

3. PUVA

Two RCTs.

PUVA (8-methoxypsoralen plus UVA) versus NB-UVB *(Der- Petrossian 2000)*

Der-Petrossian 2000 compared PUVA (8-methoxypsoralen plus UVA) with NB-UVB. This was a within-participant study; first the participant received narrowband UVB treatment on one side of the body (according to a prior randomisation), then the participant bathed in the 8-methoxypsoralen (8-MOP) bath, then the participant received the UVA treatment on the previously unirradiated body half. The treatment was delivered three times a week for up to a maximum of six weeks. The NB-UVB treatment was delivered using a Waldmann UV 3003 lay-down irradiation unit (H. Waldmann, Werk fűr Lichttechnik, Schwenningen, Germany) equipped with 15 Philips TL 100W/01 fluorescent tubes. The initial dosage was one MED of NB-UVB. Subsequent dose increments in both regimens were set to elicit or maintain a slight erythematous reaction. In the absence of erythema, the UV dose was increased by 30% in participants with skin type III, and 15% in participant with skin types I or II. In the presence of erythema, the last dose was maintained. After irradiation with NB-UVB, the participant bathed

in the 8-MOP (1 mg/L) solution. The participant bathed for 15 minutes in 100 L of tap water at 38 °C. After the bath, the skin was gently dried, and the previously unirradiated body half exposed to UVA (Waldmann PUVA 4000 lay-down unit equipped with 40 Sylvania FR 90 T 12/PUVA fluorescent tubes). The initial dosage was 0.5 minimum phototoxic dose (MPD) for bath-PUVA. Subsequent dose increments in both regimens were set to elicit, or maintain a slight erythematous reaction. Owing to delayed erythema formation, the UVA dose was never increased before 96 hours after the last bath-PUVA exposure. The initial mean doses were: NB-UVB 235 mJ/cm^2, SD ± 55 mJ/cm^2; bath-PUVA 1.0 J/cm^2, SD ± 0.7 J/cm^2. The final mean single doses were: NB-UVB 922 mJ/ cm^2, SD ± 138 mJ/cm^2; bath-PUVA 3.3 J/cm^2, SD ± 1.7 J/cm^2. The mean cumulative UV doses were: NB-UVB 14.0 J/cm^2, SD ± 3.5 J/ cm^2; bath-PUVA 48.3 J/cm^2, SD ± 8.7 J/cm^2. The mean number of total treatments was 17, SD ± 1.4.

PUVA (5-methoxypsoralen plus UVA) versus UVA1 *(Tzaneva 2010)*
Tzaneva 2010 compared PUVA (5-methoxypsoralen (5-MOP) plus UVA) administered three times a week over five weeks, with UVA1 treatment administered five times a week over three weeks. The PUVA arm used 5-MOP treatment in the form of liquid capsules (Geralen®), at a dose of 1.2 mg/kg two hours prior to each irradiation with UVA. The MPD was determined before treatment for all participants in this group. The first dose was 70% of MPD, with no increments in week one. The UVA was increased by 20% in the second week, if there was no erythematous response (by 10% if there was a light reaction), but no fewer than 96 hours after the last increment. UVA treatment was delivered using Waldmann PUVA 7001 units equipped with Waldmann F15 T8 ⁄PUVA tubes (Waldmann, Schwenningen, Germany). The cumulative PUVA dose was 48.1 J/cm^2, SD ± 21.8 J/cm^2.
UVA1 phototherapy was delivered with a 24 kW Dermalight ultrA1 lay-down unit (Systems Dr Sellmeier, Gevelsberg Vogelsang, Germany). Prior to UVA1 treatment, the MED was determined. The participants in the UVA1 arm alone were treated with single exposure doses of 70 J/cm^2. If this was higher than the erythema threshold dose, treatment was initiated at one MED. The dose in this group was increased (if no erythema) by 10 J/cm^2, to a maximum of 70 J/cm^2. The cumulative UVA1 dose was 1138.8 J/ cm^2, SD± 350 J/cm^2.

4. UVA1
Seven RCTs.

UVA1 versus topical corticosteroid (fluocortolone 0.5%) *(Krutmann 1998*)*
Krutmann 1998 compared UVA1 (delivered with the UVASUN 30,000 Biomed (Mutzhas, Munich, Germany), filtered to give wavelengths of > 340 nm) with topical corticosteroid. Both treatments were given daily for ten days. The dose of the UVA1 treatment was 130 J/cm^2 per body half, with a maximum dose of 1300 J/cm^2. To rule out hypersensitivity to UVA1R, all participants in the high- dose UVA1 group were phototested before receiving phototherapy with increasing doses (0 to 130 J/cm^2 UVA1), with a UVASUN 5000 (Mutzhas) irradiation device, which emitted 100% wavelengths greater than 340 nm. Participants in the topical steroid arm applied fluocortolone 0.5% cream or ointment; the participant's entire body was treated with cream or ointment once a day.

UVA1 versus UVAB *(Jekler 1991b Study 2; Krutmann 1992; Krutmann 1998*; Von Kobyletzki 1999a*)*

Jekler 1991b Study 2 compared UVA1 (delivered using UVASUN 3000 lamp (Mutzhas, Munic, Germany) with a UVA filter eliminating wavelengths shorter than 340 nm) with UVAB (delivered via a cubicle containing 24 Wolff Helarium System tubes B1-12 100W (Cosmedico, Stuttgart, Germany) or a sunbed containing 20 tubes of the same kind, with wavelengths 315 nm to 400 nm, UVB 280 nm to 315 nm). Both treatments were given five times a week for three weeks, or until clearing of at least one body side (the study was a split-body study). A mean of 13.0 (SD 2.5) treatments were given in 2.9 (SD 0.42) weeks. For the UVA1 treatment, an initial dose of 10 J/cm^2 or 20 J/cm^2 UVA was increased by 10 J/cm^2 each treatment session, to a final dose of 30 J/cm^2. The mean initial dose of UVA was 11 J/cm^2 (SD 2.8), mean final dose was 30 J/cm^2 (SD 0), and total dose was 361 J/cm^2 (SD 75). For the UVAB treatment, depending on the participant's skin type, an initial exposure time of 8 to 14 minutes was determined for UVAB therapy. Dose increments of 2 to 4 minutes were made at each treatment session, to a maximum of 25 minutes. The mean initial dose was 16 mJ/cm^2 (SD 3.1) UVB, 3.8 J/cm^2 (SD 0.7) UVA; final doses were 43 mJ/cm^2 (SD 5.0) UVB, 10.1 J/ cm^2 (SD 1.2) UVA; and the mean total dosages were 466 mJ/cm^2 (SD 119) UVB, and 109 J/cm^2 (SD 27.7) UVA.

Krutmann 1992 compared UVA1 with UVAB. The treatment in both groups was administered daily; total number of treatments was 15. The device used to deliver the UVA1 treatment was the UVASUN 30,000 BIOMED (Mutzhas, Munich, F.R.G.) irradiation device. The emission was filtered with UVACRYL (Mutzhas) and UG 1 (Schott Glasswerke, Munich) and consisted exclusively of wavelengths greater than 340 nm. The device used to deliver the UVAB treatment was the Metec Helarium, model 1480 (Metec Helarium, Munich) radiation device, equipped with 20 Wolff Helarium System tubes B1-12 100W (Cosmedico, Stuttgart, F.R.G.). This delivered wavelengths of 300 nm to 400 nm. The dose for the UVA1 treatment was 130 J/cm^2 UVA1 per body half. The total dose for each participant was 1950 J/cm^2. To rule out hypersensitivity to UVA light, all participants in the high-dose UVA1 group were phototested before phototherapy with increasing doses (0 to 130 J/cm^2) of UVA1 with a UVASUN 5000 (Mutzhas) irradiation device, which emitted 100% UVA1 light. For the UVAB therapy, the dose preceding the MED for UVB was used as the initial dose. Subsequently, the doses were successively increased, up to a maximum of 30 mJ/cm^2 UVB, and 7.5 J/cm^2 UVA. If erythema was induced, the preceding dose was used for the next treatment. The mean final dose in the UVAB group was 28 mJ/cm^2 UVB, and 7 J/cm^2 UVA.

Krutmann 1998 compared UVA1 (delivered with a UVASUN 30,000 Biomed (Mutzhas, Munich, Germany), filtered to give wavelengths of > 340 nm) with UVAB (machine not specified). The total number of treatments in both cases was 10. The UVA1 treatment was administered daily; it was not clear how frequently the UVAB treatment was used. The dose of UVA1 treatments was 130 J/ cm^2 per body half, with a maximum dosage of 1300 J/cm^2. To rule out hypersensitivity to UVA1R, all participants in the high-dose UVA1 group were phototested before phototherapy with increasing doses (0 to 130 J/cm^2 UVA1) with a UVASUN 5000 (Mutzhas) irradiation device, which emitted 100% wavelengths greater than 340 nm. For the UVAB arm, the dose preceding the MED for UVB was used as the initial dose. Doses increased

by a maximum of 40 mJ/ cm^2 UVB, and 7.5 J/cm^2 UVA. If erythema occurred, the preceding dose was used for the next treatment. The mean final doses in the UVAB treatment group were 33 mJ/cm^2 UVB, and 6.8 J/cm^2 UVA.

Von Kobyletzki 1999a compared two forms of UVA1 (one being cold-light therapy) versus UVAB. The UVA1 was delivered using the Sellas WL 20,000 bed (Systems Dr Sellmeier, Ennepetal, Germany), which produced wavelengths of 340 nm to 400 nm (also scattered radiation higher than 530 nm, including infrared radiation, 780 nm to 3000 nm). The UVA1 cold-light therapy was delivered with the Photomed CL 300,000 liquid (Photomed, Hamburg, Germany) device. This produced wavelengths of 340 nm to 530 nm. The UVA1 treatments were both administered five times a week for three weeks. The dosing regimen for the UVA1 treatment was 2.3 J/ cm^2 per minute; the average time to apply 50 J/cm^2 was 44 minutes (22 minutes on each side). The dosing regimen for the UVA1 cold light therapy was 1.9 J/cm^2 per minute; the average time to apply 50 J/cm^2 was 52 minutes (26 minutes each side). With 50 J/cm^2 applied 15 times, the participant should receive a cumulative dose of 750 J/cm^2.

For the UVAB treatment, 40 fluorescent tubes (UVA – Waldmann F85/100-PUVA, UVB – Waldmann F85/UV6) arranged in a cubicle (Waldmann, Villingen-Schwenningen, Germany) were used. UVB treatment was started at 80% of the MED. After each session, the UVB dosage was increased by 20% of the MED, to a maximum of 0.3 J/cm^2. UVA was introduced at 2.0 J/cm^2, and then increased daily by 1.0 J/cm^2, to a maximum single dose of 8.0 J/cm^2. When erythema appeared, the UVA and UVB doses were reduced to the preceding dose. Successive dose increments were performed daily for 15 days, under close participant control. The mean final doses were 0.29 J/cm^2, SD ± 0.03 for UVB; and 7.9 J/cm^2, SD ± 0.4 for UVA.

UVA1 versus UVA1 with a different dosing regimen *(Dittmar 2001*; Pacifico 2019; Tzaneva 2001; Von Kobyletzki 1999a*)*

Dittmar 2001 compared UVA1 (delivered using the UVA1 24 kW, Sellas/Dr. Honle, Medizintechnik GmbH, Munchen, Germany device) across three different doses (wavelength 340 nm to 430 nm). Participants were treated five times a week for three weeks, and were scheduled to receive 15 treatments. The low-dose group received a maximum single dose of 20 J/cm^2, with a maximum cumulative dose of 300 J/cm^2. The medium-dose group received a maximum single dose of 65 J/cm^2, with a maximum cumulative dose of 975 J/cm^2.The high-dose group received one dose of a maximum of 60 J/cm^2, one dose of a maximum of 90 J/cm^2, and then received a maximum single dose of 130J/cm^2 at the remaining 13 sessions. The maximum cumulative dose for the high-dose group was 1840 J/cm^2. The mean cumulative doses were 276 J/cm^2 (SD ± 43) in the low-, 866 J/cm^2 (SD ± 152) in the medium-, and 1759 J/cm^2 (SD ± 104) in the high-dose group.

Pacifico 2019 compared a medium and low dose of UVA1 (administered using a Sellamed 24,000 lay-down unit (Systems Dr Sellmeier; Gevelsberg-Vogelsang, Germany)). The high-dose group received 130 J/cm^2 UVA1, while the medium-dose received 60 J/ cm^2. The cumulative dose was 1950 J/cm^2 in the high-dose group, and 750 J/cm^2 in the medium-dose group. Both groups were treated five times a week for three weeks.

Tzaneva 2001 also compared high and medium dose UVA1 using the 24 kW Dermalight UltrA1 lay-down unit (Systems Dr Sellmeier, Gevelsberg-Vogelsang, Germany) device, which emitted

UVA1 light (96.9% 340 nm to 400 nm). The high-dose group starting dose was the MED, with increments of 10 J/cm^2, providing there was no erythemal response (maximum of 130 J/cm^2). The medium-dose group received 50% of the high-dose regimen. Both treatments were delivered five times a week for three weeks. For the high- dose UVA1 group, the median final single exposure dose was 120 J/cm^2 (range 80 J/cm^2 to130 J/cm^2), and the median cumulative dose was 1710 J/cm^2 (range 1020 J/cm^2 to 1950 J/cm^2). For the medium-dose group, the median final single exposure dose was 60 J/cm^2 (range 40 J/cm^2 to 65 J/cm^2), and median cumulative dose was 855 J/cm2 (range 510 J/cm^2 to 975 J/cm^2; two participants received only 10 exposures).

Von Kobyletzki 1999b compared two forms of UVA1 (one of which was cold-light therapy). The UVA1 was delivered using the Sellas WL 20,000 bed (Systems Dr Sellmeier, Ennepetal, Germany), which produced wavelengths of 340 nm to 400 nm (also scattered radiation higher than 530 nm, including infrared radiation, 780 nm to 3000 nm). The UVA1 cold-light therapy was delivered using the Photomed CL 300,000 liquid device (Photomed, Hamburg, Germany). This produced wavelengths of 340 nm to 530 nm. The UVA1 treatments were both administered five times a week for three weeks. The dosing regimen for the UVA1 treatment was 2.3 J/ cm^2 per minute; the average time to apply 50 J/cm^2 was 44 minutes (22 minutes on each side). The dosing regimen for the UVA1 cold light therapy was 1.9 J/cm^2 per minute; the average time to apply 50 J/cm^2 was 52 minutes (26 minutes each side). With 50 J/cm^2 applied 15 times, the participant received a cumulative dose of 750 J/cm^2.

5. UVA

One RCT.

***UVA versus visible fluorescent light (placebo** (Reynolds 2001*))*

Reynolds 2001 compared UVA (40 fluorescent lamps (Performance 100 W, Philips)) against visible fluorescent light (Philips 75 W to 85 W/96 Northlight fluorescent lamps, fitted into a Sovereign 8-tube vertical sunbed canopy (Sun Health Services, Crowborough, UK)). Both treatments were given twice a week. The dosing schedule of UVA started at 5 J/cm^2, increasing to 10 J/cm^2 if tolerated, then to a maximum of 15 J/cm^2. The cumulative dose was 315 J/cm^2 (range 15 J/cm^2 to 345 J/cm^2). For the fluorescent light group (placebo), the exposure time was increased from 5 to 15 minutes, and participants turned 180o halfway through the treatment period. The median cumulative exposure time was 320 minutes (5 minutes to 345 minutes). Participants were treated for 12 weeks.

6. UVB (unspecified)

One RCT.

***UVB versus UVA** (Qayyum 2016)*

Qayyum 2016 compared whole body UVB (1.25 mW/cm^2, Waldmann 1000) with whole body UVA (4 mW/cm^2, Waldmann 1000). The treatments were delivered three times a week until skin cleared, or a maximum of 12 weeks. For the UVB, the starting dose was 75% of MED for the skin type, with 20% increments each visit according to the participant's tolerance. For the

UVB, the starting dose 1 J/cm^2, with 0.5 J/cm^2 increments until response. Mean cumulative dose for UVA was 121 J/cm^2; for UVB, it was 8151 mJ/ cm^2.

7. UVAB
Two RCTs.

UVAB versus topical corticosteroid (fluocortolone 0.5%) *(Krutmann 1998*)*
Krutmann 1998 compared UVAB therapy with topical corticosteroid. Participants received topical corticosteroid treatment for ten days, or a total of ten UVA-UVB exposures. The dose preceding the MED for UVB was used as the initial dose. Doses increased by a maximum of 40 mJ/cm^2 UVB, and 7.5 J/ cm^2 UVA. If erythema occurred, the preceding dose was used for the next treatment. The mean final doses were 33 mJ/cm^2 UVB, and 6.8 J/cm^2 UVA. Participants in the topical steroid group applied fluocortolone 0.5% cream or ointment; participants' entire bodies were treated with cream or ointment once daily.

UVAB versus ciclosporin *(Granlund 2001)*
Granlund 2001 compared UVAB (delivered with a Waldmann UV 8001 K phototherapy cabin) with oral ciclosporin. In both groups, treatment was administered intermittently, with a treatment period of eight weeks (treatment phase), followed by a period of only topical treatment (remission phase). Participants received at least 16 treatments per cycle, and could receive multiple cycles over the year during which the study took place. The phototherapy was received two to three times a week. The initial dose depended on the participant's skin type and previous experience with UVAB therapy. Successive dose increments were delivered at every other treatment visit, according to a standard treatment schedule, up to maximum doses of 15 J/cm^2 of UVA, and 0.26 J/cm^2 of UVB. If remission occurred before the maximum dose was achieved, there were no further dose increments. If erythema appeared, the dose was reduced to the preceding dose. Participants in the ciclosporin group received initial doses of 4 mg/kg/day. During the first two treatment cycles, the dose was either increased or decreased at each scheduled visit, in increments of 1 mg/kg/day, according to response. The lowest dose was 1 mg/kg/day; the maximum dose was 4 mg/kg/day. The second treatment phase was initiated using the lowest effective dose from the first treatment phase. The lowest effective dose in the second cycle was chosen as a constant maintenance dose in subsequent cycles.

8. Full spectrum light
One RCT.

Full spectrum light versus no treatment *(Byun 2011)*
Byun 2011 compared full-spectrum light (delivered using FSL®, BMC Co. LTD, Anyang-si, South Korea), which included wavelengths of 320 nm to 5000 nm, with no treatment. Phototherapy was administered twice a week for four weeks (total of eight treatments). The anterior side of the body was irradiated for 20 minutes, then the posterior side of the body for 20 minutes. The fluence of each irradiation was 530 J/cm^2, including 121 J/cm^2 of UVA, and 409 J/cm^2 of

visible and infrared light. Participants in the control group applied emollient twice a day, without any other treatment (emollient was also used in the FSL arm).

9. Excimer laser
One RCT.

Excimer laser versus topical corticosteroid (clobetasol proprionate 0.05%) *(Brenninkmeijer 2010)*
Brenninkmeijer 2010 compared excimer laser (308 nm xenon chloride excimer laser) with topical corticosteroid (clobetasol proprionate 0.05% ointment (Dermovate, GlaxoSmithKline)). Both treatments were used for 10 weeks. The laser treatment was administered twice a week (20 treatments), while the tropical corticosteroid was used once a day.

10. Other
One RCT.

Saalmann SUP cabin (295 nm to 335 nm) + 15% salt solution versus Saalmann SUP cabin (295 nm to 335 nm) + 3% saline solution *(Zimmerman 1994)*
Zimmerman 1994 compared two strengths of salt solution before irradiation. The intervention group bathed in a 15% salt solution of 35 kg synthetic Dead Sea salt in 220 L water. The control group bathed in a 3% saline solution for 20 minutes prior to irradiation. For both groups, irradiation was carried out in a Saalmann SUP cabin, 295 nm to 335 nm, in increasing time intervals and doses, according to the photosensitivity of the skin and manufacturer's recommendations, over four weeks.

Outcomes
Thirty out of 32 included trials (94%) measured our primary outcome of physician-assessed changes in clinical signs of atopic eczema, and 15 trials (47%) measured our primary outcome of patient-reported changes in symptoms of atopic eczema, including itch. Of the secondary outcomes, eight trials (25%) measured Investigator Global Assessment (IGA), and three trials (9%) measured health-related quality of life. Eighteen trials (56%) reported data on safety (adverse events and tolerability (i.e. withdrawals due to adverse events)). Long-term control, measured at the closest time point to six months after the end of the course of phototherapy was reported (assessed in the same way as the primary outcome) in four trials (13%).

Excluded studies
We excluded 32 studies due to: wrong study design (25), wrong population (4), trial terminated with no data available (1), wrong indication (1), and wrong comparator (1). More details about the excluded studies are listed in the Characteristics of excluded studies tables.

Studies awaiting classification
Four trials are still waiting for classification. For these studies, only the study title or abstract was available, and we were unable to get access to the full papers. Hannuksela 1985 involved ultraviolet light therapy; however, there was insufficient information to confirm whether the

study followed a randomised controlled trial design. Kim 2012 compared the StoneTouch® far-infrared device to a sham device in a randomised controlled trial; however, there was insufficient information in the abstract alone to judge if the study was appropriate for inclusion. Potapenko 2000 looked at photo- oxidised psoralen; however, no other information was available, and it was unclear if it followed a randomised controlled trial design. Pullman 1985 compared two UVA regimens; however, it was unclear if it followed a randomised controlled design. Limited further details can be found in the Characteristics of studies awaiting classification tables.

Ongoing studies

We identified four ongoing studies. These studies had no available data to include in this review. ACTRN12620000546954 is comparing NB-UVB therapy to natural sunlight with an amino acid lecithin cream, and appears to be a randomised controlled trial; however, this must be confirmed. Droitcourt 2019 is a randomised, controlled cross-over trial of phototherapy combined with vitamin D supplementation. Kromer 2019 is a randomised controlled three-arm trial of 415 nm versus 450 nm blue light compared to a non- therapeutically active dose of 450 nm blue light. NCT02915146 is a randomised controlled trial of NB-UVB combined with UVA1 versus NB-UVB monotherapy. Please see the Characteristics of ongoing studies tables for more details.

Risk of bias in included studies

EA and RB independently assessed the risk of bias, using the Cochrane RoB 2 tool (Higgins 2020b; Sterne 2019;). The results- level RoB 2 tables are located in the risk of bias section of the characteristics of studies section and in Table 2; Table 3; and Table 4, which also include domain judgements and support for judgement. Figure 2; Figure 3; Figure 4; Figure 5; and Figure 6 show graphical summaries for each outcome.

For the outcome Physician-assessed changes in clinical signs, we assessed results from nine studies for risk of bias (Der-Petrossian 2000; Gambichler 2009; Kwon 2019; Legat 2003; Majoie 2009; Reynolds 2001; Tzaneva 2010; Tzung 2006; Youssef 2020). We considered three of them at high risk (Gambichler 2009; Kwon 2019; Legat 2003); we had some concerns about the rest. The high risk of bias assessments were in the following domains: deviations from intended interventions (Gambichler 2009; Kwon 2019); missing outcome data (Gambichler 2009; Kwon 2019); and bias in the measurement of the outcome (Legat 2003).

For the outcome Patient-reported changes in symptoms, we assessed results from five studies for risk of bias (Gambichler 2009; Legat 2003; Majoie 2009; Reynolds 2001; Youssef 2020).

We considered two to be at high risk (Gambichler 2009; Legat 2003); we had some concerns about the rest. The high risk of bias assessments were in the following domains: deviations from intended interventions (Gambichler 2009); missing outcome data (Gambichler 2009); and bias in the measurement of the outcome (Legat 2003).

For the outcome Investigator Global Assessment (IGA), we assessed results from two studies for risk of bias (Der-Petrossian 2000; Reynolds 2001). We had some concerns for both: Reynolds 2001 in missing outcome data, and selection of reported results; and Der- Petrossian 2000 in all domains apart from measurement of the outcome.

For the outcome Health-related quality of life, there was the result from one study available to assess for risk of bias (Gambichler 2009). We considered the overall risk to be high, because

we assessed two domains at high risk of bias: deviations from intended interventions, and missing outcome data.

For the outcome Safety: withdrawals due to adverse events, we assessed results from five studies for risk of bias (Der-Petrossian 2000; Kwon 2019; Majoie 2009; Reynolds 2001; Youssef 2020). We considered one at high risk due to high levels of missing data (Kwon 2019). We had some concerns for the results from the other four studies, mainly with the measurement of outcome data (the studies did not specify how they monitored adverse events), and selection of reported result (no protocol available).

Across domains, we assessed risk of bias from randomisation as either low risk, or we had some concerns (none were at high risk). For Deviations from intended intervention, we assessed four studies at high risk of bias, we had some concerns for seven, and we assessed 11 at low risk of bias. For Missing outcome data, we assessed five studies at high risk of bias, we had some concerns for nine, and we assessed eight at low risk of bias. For Measurement of outcome, we assessed two studies at high risk of bias, had some concerns for seven, and assessed 13 at low risk of bias. For Selection of reported result, we assessed none at low risk of bias, one study at high risk, and had some concerns for the remaining studies (mainly due to no pre-registered protocols).

Figure 2. RoB 2 summary - Physician-assessed changes in clinical signs

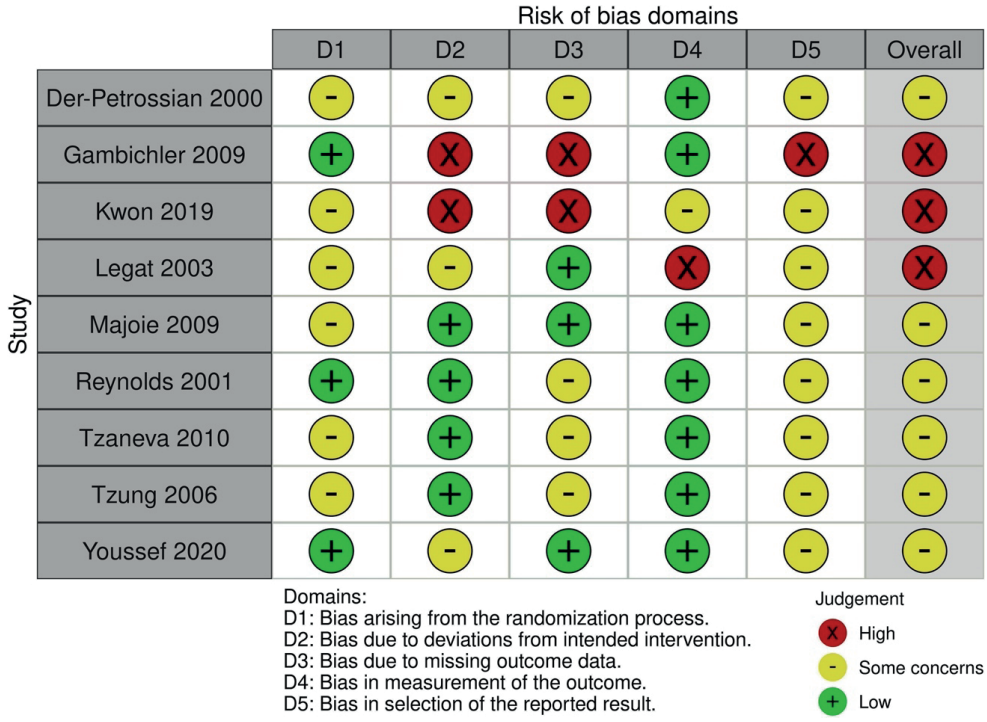


Figure 3. RoB 2 summary - patient-reported symptoms

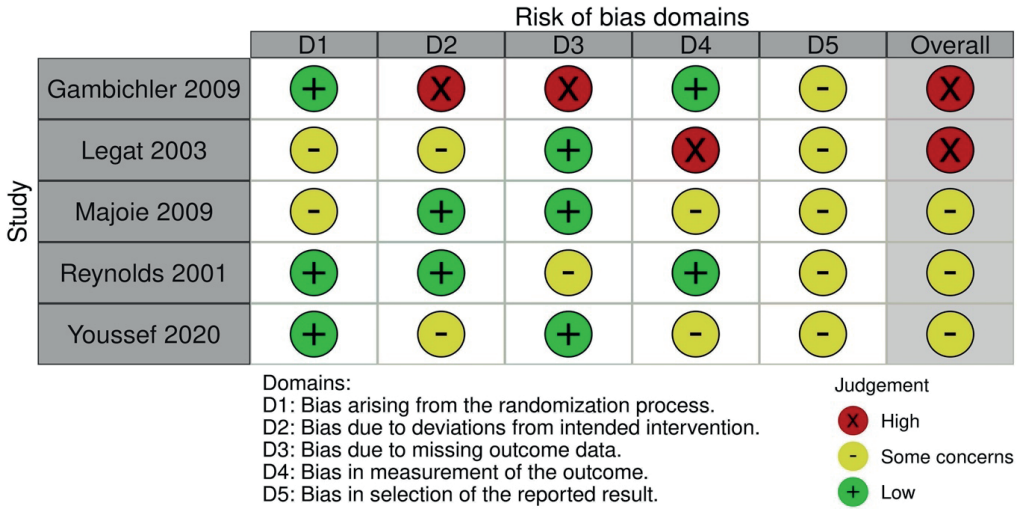


Figure 4. RoB 2 summary - Investigator Global Assessment (IGA)

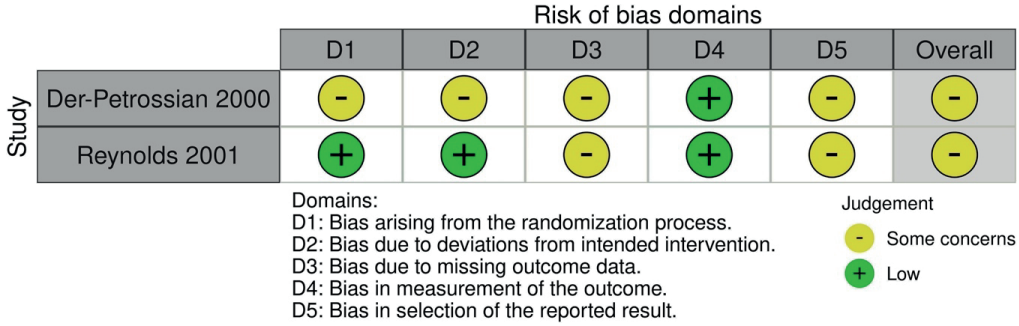


Figure 5. RoB 2 summary - HR QoL

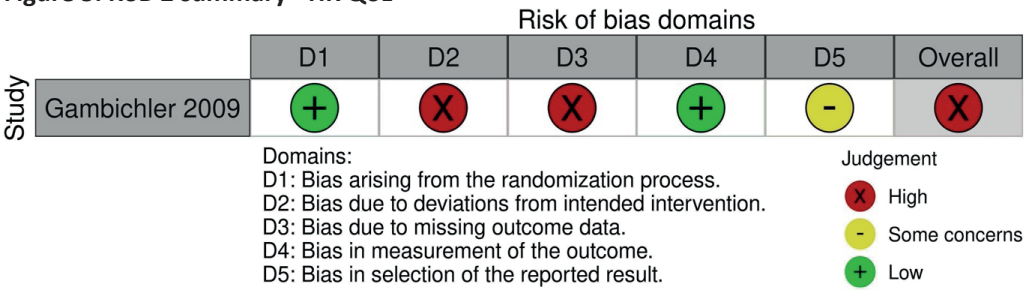
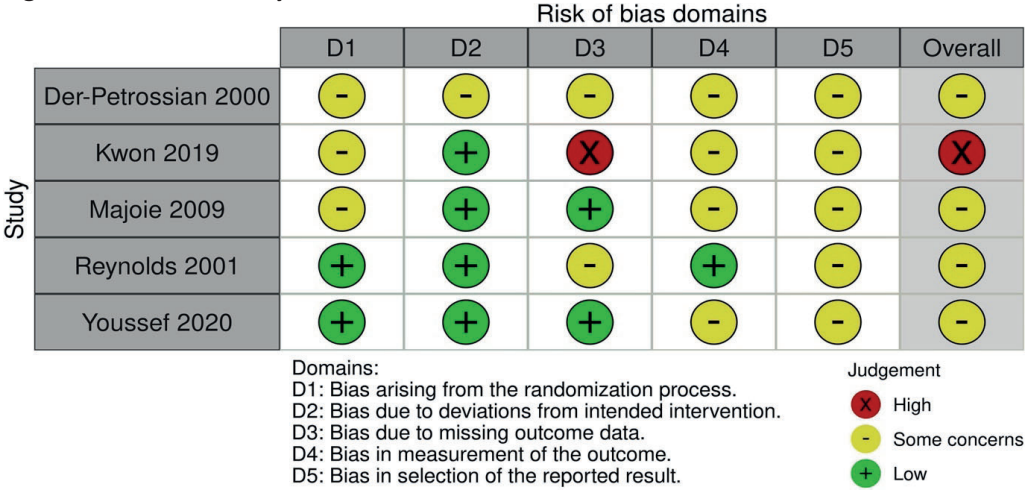


Figure 6. RoB 2 summary - withdrawals due to adverse events



Effects of interventions

See: **Summary of findings 1** Summary of findings table - NB-UVB compared to placebo for atopic eczema; **Summary of findings 2** Summary of findings table - NB-UVB compared to UVA1 for atopic eczema; **Summary of findings 3** Summary of findings table - NB- UVB compared to PUVA for atopic eczema; **Summary of findings 4** Summary of findings table - UVA1 compared to PUVA for atopic eczema

Throughout this section lower scores for continuous outcome scales are better.

Summary of findings 1. Summary of findings table - NB-UVB compared to placebo for atopic eczema

NB-UVB compared to placebo for atopic eczema

Patient or population: atopic eczema
Setting: outpatient or not stated (Egypt; Korea; Taiwan; UK)
Intervention:NB-UVB
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with NB-UVB				
Physician-assessed changes in clinical signs assessed with: mean reduction in total disease activity score: lower score is better Scale from: 0 to 90 follow-up: mean 12 weeks	The mean physician-assessed changes in clinical signs was **-0.4**	MD **9.4 lower** (15.18 lower to 3.62 lower)	-	41 (1 RCT)	⨁⨁◯◯ Low[a, b]	This result is from Reynolds 2001. Three other studies reported this outcome but did not report any dispersion data. In Kwon 2019, EASI score was 2.1 (n=6) with NB-UVB versus 3.6 (n=5) with no treatment (after 9 weeks). In Tzung 2005 (split-body study, 6 weeks, n=12), the side treated with NB-UVB had a mean reduction of 56% in EASI versus 54% with no treatment. In Youssef 2020 (n=25), SCORAD reduced by 50.8% with NB-UVB versus 48.6% with no treatment (4 weeks of treatment).
Patient-reported changes in symptoms assessed with: number of participants reporting a reduction in itch on VAS follow-up: mean 12 weeks	526 per 1000	**905 per 1000** (579 to 1000)	**RR 1.72** (1.10 to 2.69)	40 (1 RCT)	⨁⨁◯◯ Low[b, c]	This result is from Reynolds 2001 (19 of 21 participants with NB-UVB versus 10 of 19 with placebo). One other study reported this outcome but did not report any dispersion data. Youssef 2020 reported a -55.7% change in VAS itch after 4 weeks of treatment with NB-UVB (n=13), compared to a -53.6% change in VAS itch in patients with no treatment (n=12).
Investigator Global Assessment (short-term) assessed with: number of participants with moderate or greater improvement	211 per 1000	**592 per 1000** (232 to 1000)	**RR 2.81** (1.10 to 7.17)	41 (1 RCT)	⨁⨁◯◯ Low[b, d]	This result is from Reynolds 2001 (13 of 22 participants with NB-UVB versus 4 of 19 with placebo). Long-term data (measured at 6 months, 3 months post-treatment) showed a similar result (RR 1.89, 95% CI 0.92 to 3.89, n=35).

follow-up: mean 12 weeks				
Health-related quality of life - not measured	-	-	-	None of the studies measured this outcome
Safety: withdrawals due to adverse events (short-term) assessed with: number of participants follow-up: range 8 weeks to 12 weeks	See comments box for narrative description.	89 (3 RCTs)	⨁⨁⨀⨀ Low[b, e]	In Reynolds 2001, one patient in each group withdrew because of burning (measured up to week 12, n=41). In Youssef 2020, two patients withdrew because of adverse events: one patient in the NB-UVB group (phototoxic reaction) and one patient in the glycerol 85% group (severe irritation) (measured up to week 8, n=30). Kwon 2019 reported no withdrawals in both groups (measured up to week 9, n=18).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_425206404975446768.

[a] Downgraded one level due to risk of bias. Overall risk of bias was 'some concerns' in Reynolds 2001 due to concerns with missing outcome data (13% of participants withdrew but numbers were similar in both groups) and selection of the reported results (no protocol available). Kwon 2019 was considered high risk overall (deviations from intended interventions, missing outcome data). In Tzung 2005, overall risk of bias was 'some concerns' (concerns in all domains apart from measurement of outcome). In Youssef 2020, overall risk of bias was 'some concerns' (deviations from intended interventions and selection of reported result).

[b] Downgraded one level due to imprecision - small sample sizes.

[c] Downgraded one level due to risk of bias. Overall risk of bias was 'some concerns' in Reynolds 2001 due to concerns with missing outcome data (13% of participants withdrew but numbers were similar in both groups) and selection of the reported results (no protocol available). There were 'some concerns' with Youssef 2020 due to deviations from intended interventions, measurement of the outcome and selection of reported result.

[d] Downgraded one level due to risk of bias. Overall risk of bias was 'some concerns' in Reynolds 2001 due to concerns with missing outcome data (13% of participants withdrew but numbers were similar in both groups) and selection of the reported results (no protocol available).

[e] Downgraded one level due to risk of bias. Overall risk of bias was 'some concerns' in Reynolds 2001 due to concerns with missing outcome data (13% of participants withdrew but numbers were similar in both groups) and selection of the reported results (no protocol available). Kwon 2019 was considered 'some concerns' overall (deviations from intended interventions, missing outcome data). In Tzung 2005, overall risk of bias was 'some concerns' (concerns in all domains). In Youssef 2020, overall risk of bias was 'some concerns' (Measurement of outcome and selection of reported result).

Summary of findings 2. Summary of findings table - NB-UVB compared to UVA1 for atopic eczema

NB-UVB compared to UVA1 for atopic eczema

Patient or population: atopic eczema
Setting: not stated (Germany; the Netherlands)
Intervention:NB-UVB
Comparison: UVA1

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with UVA1	Risk with NB-UVB				
Physician-assessed changes in clinical signs (short-term) assessed with: SASSAD: lower score is better Scale from: 0 to 108 follow-up: mean 12 weeks	The mean physician-assessed changes in clinical signs (short-term) was **22**	MD **2 lower** (8.41 lower to 4.41 higher)	-	46 (1 RCT)	⨁◯◯◯ Very low[a, b]	This result is from Gambichler 2009. Two split-body studies could not be included due to insufficient data. Legat 2003 (n=7) reported median Costa (scale 0-123) score of 40 (range 26 to 89) and 58 (27 to 89) and median Leicester score (maximum 162) of 23 (12 to 56) and 52 (14 to 69) after 7 weeks with NB-UVB and UVA1, respectively. Majoie 2009 reported mean Leicester sign score (scale 0-108) of 9.2 and 11.6 in 26 body-halves (13 participants) treated with NB-UVB and UVA1, respectively (8 weeks).
Patient-reported changes in symptoms assessed with: VAS for itch Scale from: 0 to 10 follow-up: mean 6 weeks	The mean patient-reported changes in symptoms was **4.2**	MD **0.3 higher** (1.07 lower to 1.67 higher)	-	46 (1 RCT)	⨁◯◯◯ Very low[b, c]	This result is from Gambichler 2009. Two split-body studies could not be included due to insufficient data. After 7 weeks of treatment, seven participants in Legat 2003 reported a median VAS itch (scale 0-10) of 2 (0.1 to 8.5) for their body-half that was treated with NB-UVB, compared to 3.9 (0.2 to 8.4) for the UVA1 treated body-half. At week 8, Majoie 2009 showed a mean itch VAS of 2.9 and 3.6 for NB-UVB and UVA1 in 13 participants, respectively.
Investigator Global Assessment - not measured	-			-	-	
Health-related quality of life	The mean health-related	MD **2.9 higher** (9.57 lower to 15.37 higher)	-	46 (1 RCT)	⨁◯◯◯ Very low[b, d]	This result is from Gambichler 2009.

assessed with: German Skindex-29: lower score is better Scale from: 30 to 150 follow-up: mean 6 weeks	quality of life was **69.8**			
Safety: withdrawal due to adverse events assessed with: number of participants follow-up: mean 12 weeks	See comments box for narrative description (right).	13 (1 RCT)	⨁⊖⊖⊖ Very low[e, f]	Majoie 2009 was the only study that reported the number of withdrawals due to adverse events. There were no withdrawals due to adverse events in this split-body trial (13 participants, 26 sides).

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_425498097763422661.

[a] Downgraded by two levels due to very serious risk of bias. High risk of bias overall as there was high risk of bias due to deviations from intended interventions (did not follow intention to treat analysis, excluded participants due to ineliciency), missing outcome data (45% missing) and selection of reported results (retrospective clinical trial register entry which specified SCORAD been used instead). Legat 2003 was also rated high risk of bias overall (measurement of the outcome). Majoie 2009 had some concerns (randomisation process, selection of the reported result).

[b] Downgraded by one level due to serious imprecision - small sample sizes.

[c] Downgraded by two levels due to very serious risk of bias. High risk of bias overall as there was high risk of bias due to deviations from intended interventions (did not follow intention to treat analysis, excluded participants due to ineliciency) and missing outcome data (45% missing). Legat 2003 was also rated high risk of bias overall (measurement of the outcome). Majoie 2009 had some concerns (randomisation process, measurement of the outcome, selection of the reported result).

[d] Downgraded by two levels due to very serious risk of bias. High risk of bias overall as there was high risk of bias due to deviations from intended interventions (did not follow intention to treat analysis, excluded participants due to ineliciency) and missing outcome data (40% missing).

[e] Downgraded one level due to serious risk of bias. Majoie 2009 had some concerns (randomisation process, selection of the reported result).

[f] Downgraded by two levels due to very serious imprecision - single study with very small sample size.

Summary of findings 3. Summary of findings table - NB-UVB compared to PUVA for atopic eczema

NB-UVB compared to PUVA for atopic eczema

Patient or population: atopic eczema
Setting: not stated
Intervention:NB-UVB
Comparison: PUVA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PUVA	Risk with NB-UVB				
Physician-assessed changes in clinical signs assessed with: percentage reduction in modified SCORAD follow-up: mean 6 weeks	See comments box for narrative description.			20 (1 RCT)	⨁◯◯◯ Very low[a, b]	Data was only presented on a graph and it wasn't clear if standard deviations were shown. At week 6, a 64.10% percentage reduction in SCORAD was seen in the NB-UVB treated body-half, compared to a similar percentage reduction of 65.7% in the body-half treated with PUVA. This is a split-body study where the number of participants in the study was 10 - but there were 20 'sides' analysed.
Patient-reported changes in symptoms - not measured	-			-	-	
Investigator Global Assessment assessed with: number of participants with marked improvement or complete remission follow-up: mean 6 weeks	900 per 1000	**900 per 1000** (539 to 986)	**OR 1.00** (0.13 to 7.89)	20 (1 RCT)	⨁◯◯◯ Very low[a, c]	This is a split-body study where the number of participants in the study was 10 - but there were 20 'sides' analysed (which has been adjusted for in the analysis).
Health-related quality of life - not measured	-			-	-	
Safety: withdrawal due to adverse events assessed with: number of participants follow-up: mean 6 weeks	See comments box for narrative description (right).			20 (1 RCT)	⨁◯◯◯ Very low[b, d]	There were no severe adverse events and no withdrawals due to adverse events in this split-body study (10 participants, 20 sides).

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
CI: confidence interval; **OR:** odds ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_425498309567386282.

[a] Downgraded one level due to serious risk of bias. Some concerns in all domains apart from measurement of the outcome which was considered low risk of bias.
[b] Downgraded two levels due to very serious imprecision (small sample size; n=10 participants, 20 sides).
[c] Downgraded two levels due to very serious imprecision. Small sample size (n=10 participants, 20 sides) and a wide 95% CI.
[d] Downgraded one level due to serious risk of bias. Some concerns in all domains.

Summary of findings 4. Summary of findings table - UVA1 compared to PUVA for atopic eczema

UVA1 compared to PUVA for atopic eczema

Patient or population: atopic eczema
Setting: outpatient (Austria)
Intervention:UVA1
Comparison:PUVA

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	N of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PUVA	Risk with UVA1				
Physician-assessed changes in clinical signs assessed with: SCORAD: lower score is better Scale from: 0 to 103 follow-up: mean 3 weeks	The mean physician-assessed changes in clinical signs was **28.8**	MD **11.3 higher** (0.21 lower to 22.81 higher)	-	40 (1 RCT)	⨁◯◯◯ Very low[a, b]	
Patient-reported changes in symptoms - not measured	-			-	-	
Investigator Global Assessment - not measured	-			-	-	
Health-related quality of life - not measured	-			-	-	
Safety: withdrawals due to adverse events - not measured						

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_425498095256539586.

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[a] Downgraded one level due to serious risk of bias. Some concerns overall in randomisation, missing outcome data, and selection of the reported result.
[b] Downgraded by two levels due to very serious imprecision - small sample size and wide 95% CI.

1. NB-UVB versus no treatment or placebo

Four studies compared NB-UVB with no treatment (Kwon 2019; Tzung 2006; Youssef 2020), or placebo (Reynolds 2001). See Summary of findings 1.

Kwon 2019 compared NB-UVB against no treatment in 18 participants with moderate disease. Thirteen participants were treated with NB-UVB, administered two to three times a week for six weeks (12 to 18 treatments). Five participants were enrolled in the no treatment group. Participants in both groups received topical corticosteroids (methylprednisolone cream), applied to lesional skin only, plus an oral antihistamine. The participants received six weeks of active treatment, and were followed up for three weeks. Reynolds 2001, comparing NB-UVB with placebo, was a parallel-group study with three arms. The arm comparing NB- UVB with visible fluorescent light included 46 participants, 24 of whom were treated with NB-UVB, and 22 who were treated with visible fluorescent light; both groups received treatment twice a week for 12 weeks. Tzung 2006 was a multi-arm, split-body study. One arm of this trial, which compared NB-UVB combined with 1% pimecrolimus cream with 1% pimecrolimus cream alone, included 12 children with moderate to severe atopic eczema. One half of the body was treated with NB-UVB twice a day for six weeks. On the contralateral side, pimecrolimus cream was applied twice a day on all skin lesions; this side of the body was shielded from UV transmission, using tailored UV-filtering clothing. The study consisted of a six-week treatment phase, and four-week post- treatment follow-up. Youssef 2020 compared NB-UVB with 85% glycerol in 30 participants with mild to moderate disease, aged six years and older. Fifteen participants received NB-UVB three times a week for four weeks. The other 15 participants were treated with 85% glycerol, applied daily to affected sites, for four weeks.

Primary outcomes

Physician-assessed changes in clinical signs

Reynolds 2001 used their own disease activity score to measure physician-assessed changes in clinical signs. The disease activity score instrument assessed erythema, papulovesicles, excoriation, scaling or dryness, and lichenification, and graded these signs from 0 to 3 (a higher score indicates more severe disease) at six sites. NB-UVB reduced the total disease activity score more than placebo, measured at 12 weeks (mean difference (MD) -9.40, 95% confidence interval (CI) -15.18 to -3.62; 1 study, 41 participants; low- certainty evidence; Analysis 1.1).

After 9 weeks of treatment, participants who received NB-UVB (N = 6) had an EASI score of 2.1; and those who received no treatment (N = 5) had a score of 3.6 (low-certainty evidence; Analysis 1.2). At baseline, those in the NB-UVB group (N = 13) had a mean EASI score of 13; and those who received no treatment (N = 5) had a mean EASI score of 11.6. A higher EASI score is associated with more severe disease, so it appears that the participants in the NB-UVB-treated group had better outcomes; however, without any measures of dispersion available, we could not determine whether the results were conclusive (Kwon 2019).

After six weeks of treatment, Tzung 2006 (N = 24)reported a mean reduction in EASI of 56% for the body half that was treated with NB- UVB combined with pimecrolimus cream, versus a mean reduction in EASI of 54% in the body half treated with pimecroliumus cream alone (low-certainty evidence; Analysis 1.2).

After four weeks of treatment, Youssef 2020 (N = 25) reported a -50.8% change in SCORAD in participants treated with NB-UVB, compared to a -48.6% change in SCORAD in participants treated with 85% glycerol (low-certainty evidence; Analysis 1.2). Higher SCORAD and EASI

scores are associated with poorer outcomes; however, in the case of the later two studies there was very little difference between the treatment arms.

Patient-reported changes in symptoms
In Reynolds 2001, participants who received NB-UVB were more likely to report less severe itch than those who received placebo after 12 weeks (risk ratio (RR) 1.72, 95% CI 1.10 to 2.69; 1 study, 40 participants; low-certainty evidence; Analysis 1.3; number needed to treat for an additional beneficial outcome (NNTB) = 3).
Youssef 2020 (N = 25) reported a 55.7% reduction in itch, measured on VAS, after four weeks of treatment with NB-UVB, compared to a 53.6% reduction in itch in participants treated with 85% glycerol; therefore, very little difference was seen between the two treatment arms; (low-quality evidence; Analysis 1.4).

Secondary outcomes

Investigator Global Assessment (IGA)
Measured at 12 weeks, 13 out of 22 participants treated with NB-UVB compared to 4 out of 19 participants treated with placebo in the study by Reynolds 2001 showed a moderate or greater improvement in IGA (RR 2.81, 95% CI 1.10 to 7.17, NNT = 3). This result is in favour of NB-UVB. The IGA scale was a 6-point investigator global assessment (exacerbation of disease, no change, slight improvement, moderate improvement, marked improvement, or complete resolution). Three months post- treatment a moderate or greater improvement in IGA was seen in 12 out of 18 participants treated with NB-UVB and 6 out of 17 participants treated with placebo (RR 1.89, 95% CI 0.92 to 3.89). See Analysis 1.5. We rated the certainty of evidence (GRADE) for these outcomes as low.

Health-related quality of life
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
In general, the trials reported few adverse events. In one study of 41 participants (Reynolds 2001), one participant withdrew from each group because of burning. In another study (Youssef 2020) of 15 participants, one participant withdrew from the NB-UVB group because of a phototoxic reaction, and one withdrew from the glycerol 85% group because of severe irritation (low-certainty evidence; Analysis 1.6).

Long-term control
Analysis 1.7 shows long-term control in Reynolds 2001, measured 3 months post-treatment (6 months from baseline). The number of participants with a total disease activity score improved relative from baseline was 15 out of 18 participants compared to 8 out of 17 participants treated with NB-UVB and placebo, respectively (RR 1.77, 95% CI 1.03 to 3.05, NNT=3). This result is in favour of NB-UVB. For itch VAS, 14 out of 18 and 11 out of 17 participants treated with NB-UVB and placebo, respectively, reported improvement relative from baseline (RR 1.20, 95% CI 0.78 to 1.85).

2. NB-UVB versus UVA1

Three small studies compared NB-UVB with UVA1 (Gambichler 2009; Legat 2003; Majoie 2009). See Summary of findings 2.

The two-treatment, two-period cross-over trial by Gambichler 2009 included 47 participants, 22 of whom were randomised to NB-UVB, and 25 to UVA1 in the first period. There were two six- week treatment periods, separated by at least eight weeks. Legat 2003 compared NB-UVB with UVA1 in a split-body study of nine adults with atopic eczema. Another split-body study compared NB-UVB with UVA1 (Majoie 2009). Clinical effectiveness of both treatment modalities was assessed in 13 adult participants with moderate to severe atopic eczema. There was an eight-week, eight treatment period, followed by a four-week follow-up period.

Primary outcomes

Physician-assessed changes in clinical signs

The SASSAD severity score was used by Gambichler 2009 for physician-assesed changes in the clinical signs of AE. After 6 weeks of treatment, participants treated with NB-UVB had a mean SASSAD score (from 0 to 108) of 20 (SD 9.6) compared to a mean SASSAD score of 22 (SD 12.14) in the UVA1 group (mean difference (MD) -2.00, 95% CI -8.4 to 4.41). See Analysis 2.1. Legat 2003 reported a median Costa (scale 0-123) score of 40 (26 to 89) and 58 (27 to 89) over 7 weeks of treatment with NB-UVB and UVA1, respectively. The participants had a median Leicester sign score (maximum score 162) over 7 weeks of treatment of 23 (12 to 56) in the NB-UVB treated body-half and a much higher median Leicester sign score of 52 (14 to 69) in the UVA1 treated body-half. A higher score indicates more severe disease when AE is assessed using both of these instruments. Therefore, it appears from these results that NB-UVB provided better outcomes; however, as the studies did not report any measures of dispersion, we cannot determine whether this result is statistically significant. Majoie 2009 did not show such a difference between the two treatment modalities at week 8: a mean Leicester sign score (scale 0-108) of 9.2 was seen in the NB-UVB group compared to a score of 11.6 in UVA1. Four weeks after end of treatment (week 12), a mean Leicester sign score of 9 and 10.1 was seen for NB-UVB and UVA1, respectively. This study found lower scores with NB-UVB; however, again no measures of dispersion were reported therefore we were unable to determine whether this result was statistically significant. See Analysis 2.2.

We rated the certainty of evidence (GRADE) for these outcomes as very low.

Patient-reported changes in symptoms

Participants in the trial by Gambichler 2009 reported a mean itch VAS of 4.5 (SD 2.3) after 6 weeks of treatment with NB-UVB, compared to a mean itch VAS of 4.2 (SD 2.42); Analysis 2.3. Legat 2003 measured the VAS for skin lesions, overall effect, and itch. Over seven weeks of treatment, participants reported a median VAS for itch of 2 (range 0.1 to 8.5) for their body half that was treated with NB-UVB, compared to 3.9 (range 0.2 to 8.4) for the UVA1 treated body half. At week eight, Majoie 2009 reported a mean VAS for itch of 2.9 for the NB-UVB group and 3.6 for the UVA1 group. After four weeks of follow-up, participants reported a mean VAS for itch of 2.2 for the NB-UVB group, compared to 2.6 for the UVA group.

As higher itch scores are associated with more severe disease, these results appears to favour NB-UVB; however, as the studies did not report any measures of dispersion, we could not determine whether these results were conclusive (very low- certainty evidence; Analysis 2.4).

We rated the certainty of evifor itchdence (GRADE) for these outcomes as very low.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Health-related quality of life
To measure health-related quality of life, participants filled in a German version of the Skindex-29 questionnaire (range 30-150) in the study of Gambichler 2009. A mean score of 72.7 (SD 23.2) was reported by participants after 6 weeks of treatment with NB-UVB, compared to a slightly lower score of 68.8 (SD 19.94) when treated with UVA1 (MD 2.90, 95% CI -9.57 to 15.37). A lower score is more favourable. See Analysis 2.5.
There were baseline differences identified for this outcome (80.47 versus 69.8), meaning the end values may be unreliable. The percentage reduction given in the paper was 23.8% (SD 16.1) for NB- UVB group versus 13.56% (SD 12) for UVA1 group, favouring stated that those receiving NB-UVB therapy reported better health-related quality of life than those receiving UVA1 (MD -10.24%, 95% CI -18.37 to -2.11; Gambichler 2009).

Safety: withdrawals due to adverse events
Only one study measured the number of withdrawals due to adverse events: there were none (1 study, 26 participants; very low- certainty evidence).

Long-term control
None of the trials measured this outcome.

3. NB-UVB versus PUVA
One split-body study investigated the clinical effectiveness of NB- UVB compared to bath-PUVA. Der-Petrossian 2000 included 10 adults with chronic, severe atopic eczema. Each participant was treated with NB-UVB on one side of the body, then they bathed in an 8-MOP bath solution, then received UVA on the previously unirradiated body half (PUVA). Treatment was provided until there was complete remission on at least one-half of the body. Treatment was provided for a maximum of six weeks. See Summary of findings 3.

Primary outcomes
Physician-assessed changes in clinical signs
At week six, a 64.1% percentage reduction in SCORAD was seen in the NB-UVB treated body-half, compared to a similar percentage reduction of 65.7% in the body-half treated with PUVA. See Analysis 3.1. We rated the certainty of evidence (GRADE) for this outcomes as very low.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)

Marked improvement or complete remission (IGA 0, 1 or 2: moderate improvement, marked improvement or complete remission) measured at a maximum of 6 weeks was seen in 9 of 10 sides treated with NB-UVB and 9 of 10 sides treated with PUVA (OR 1.00, 95% CI 0.13 to 7.89). See Analysis 3.2. We rated the certainty of evidence (GRADE) for this outcome as very low.

Safety: withdrawals due to adverse events
There were no severe adverse events and no withdrawals due to adverse events reported in the Der-Petrossian 2000 study (20 participants). See Analysis 3.3. We rated the certainty of evidence (GRADE) for this outcome as very low.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

4. UVA1 versus PUVA
One cross-over study compared UVA1 with 5-MOP in 40 participants aged 18 years or older. Twenty-three participants were allocated to medium dose UVA1, and 17 participants were allocated to 5-MOP PUVA. UVA1 was administered five times a week over three weeks, and PUVA was given three times a week over five weeks (Tzaneva 2010). See Summary of findings 4.

Primary outcomes

Physician-assessed changes in clinical signs
Tzaneva 2010 shows a better response in participants treated with 5-MOP PUVA compared to UVA1. After 3 weeks of treatment, a mean SCORAD of 40.1 (SD 19.1) was seen in the UVA1 group, compared to a much lower mean SCORAD of 28.8 (SD 17.8) in the PUVA group (MD 11.30, 95% CI -0.21 to 22.81, 40 participants, Analysis 4.1). As higher SCORAD scores are associated with more severe disease, this result is in favour of PUVA. We rated the certainty of evidence (GRADE) for these outcomes as very low (see Summary of findings 4).

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
None of the trials measured this outcome.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

5. NB-UVB versus UVA
Two arms of the three-arm parallel-group study by Reynolds 2001 compared NB-UVB with UVA in participants aged 16 to 65 years old. Twenty-six participants were randomised to be treated with NB-UVB and 24 participants were randomised to be administered UVA. Approximately half of the participants had a Fitzpatrick skin type of I/II. Participants were excluded if they had mild disease. Treatment was given twice weekly for 12 weeks and participants were followed up at 3 months post-treatment end.

Primary outcomes

Physician-assessed changes in clinical signs
Reynolds 2001 used their own disease activity score as an instrument for measuring physician-assessed changes in clinical signs. The mean difference between groups was -5.00 (95% CI -10.60 to 0.60] in favour of NB-UVB measured at 12 weeks (n=41). However, the confidence interval included zero, so there is uncertainty around this result. See Analysis 5.1.

Patient-reported changes in symptoms
Patient-reported changes in symptoms were reported by Reynolds 2001. The number of participants reporting a reduction in itch measured using VAS (10cm; none at the left, severe at the right, a higher score is associated with more severe itch) after 12 weeks of treatment is shown in Analysis 5.2. Nineteen out of 21 participants in the NB-UVB group reported a reduction in itch VAS, versus 12 out of 19 participants in the UVA group (RR 1.43, 95% CI 0.99 to 2.07). This was measured at 12 weeks.

Secondary outcomes

Investigator Global Assessment (IGA)
At 12 weeks (Reynolds 2001), 13 out of 22 participants treated with NB-UVB compared to 7 out of 19 participants treated with UVA showed a moderate or greater improvement in IGA (RR 1.60, 95% CI 0.81 to 3.18). At 6 months (3 months post-treatment) 12 of 18 participants treated with NB-UVB showed a moderate or greater improvement in IGA compared to 6 of 19 treated with UVA (RR 2.11, 95% CI 1.01 to 4.42). This result is in favour of NB-UVB. See Analysis 5.3.

Safety: withdrawals due to adverse events
In Reynolds 2001, one participant in the NB-UVB arm (n=22) withdrew because of burning, no participants withdrew due to adverse events in the UVA arm (n=19). See Analysis 5.4.

Health-related quality of life
None of the trials measured this outcome.

Long-term control

Analysis 5.5 shows long-term control in Reynolds 2001, measured 3 months post-treatment (6 months from baseline). The number of participants with a total disease activity score improved relative to baseline was 15 out of 18 participants in the NB-UVB group compared to 9 out of 19 in the UVA group (RR 1.76, 95% CI 1.05 to 2.95, NNT = 3). This result is in favour of NB-UVB. For itch VAS 14 out of 18 participants in the NB-UVB group showed an improvement relative to baseline in comparison to 14 out of 19 in the UVA group (RR 1.06, 95% CI 0.73 to 1.52).

6. NB-UVB versus UVAB

Two parallel studies (Leone 1998; Maul 2017), both including adults, compared NB-UVB with UVAB. One study was in participants with severe AE (n=12) (Leone 1998), one study in participants with eczema severity unspecified (n=24) (Maul 2017). In the study by Leone 1998 participants received treatments thrice weekly for approximately 5 weeks (10-15 treatments). In the study by Maul 2017, participants also received treatment three times a week for up to 16 weeks. The skin type of participants was not reported in either study.

Primary outcomes

Physician-assessed changes in clinical signs

Leone 1998 reported that they measured physician-assessed clinical signs using the SCORAD score. They reported NB-UVB was significantly better than UVAB with a P value less than 0.05 (around week 5); however, no further data were provided per group to support this statement (6 participants were in each group). See Analysis 6.1.

Patient-reported changes in symptoms

None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)

None of the trials measured this outcome.

Safety: withdrawals due to adverse events

There were no withdrawals due to adverse events in the trial by Maul 2017 (Analysis 6.2).

Health-related quality of life

None of the trials measured this outcome.

Long-term control

None of the trials measured this outcome.

7. NB-UVB versus topical corticosteroids

Agrawal 2018 compared NB-UVB (n=30) with topical corticosteroids (n=30), specifically betamethasone valerate 0.1%, in a parallel study in adults and children (aged 5-60 years). Participants were included in the study if they had a SCORAD between 15 and 60 and a skin type of III or IV. Participants in the phototherapy group received treatment thrice weekly for

8 weeks, whilst those in the topical corticosteroid group received treatment twice daily for 4 weeks.

Primary outcomes

Physician-assessed changes in clinical signs
Mean SCORAD in the NB-UVB group (n=30) was higher than in the topical corticosteroid group (n=30) at week 4 (Agrawal 2018). The mean SCORAD was 25.93 (range 16.5 to 49) in the NB-UVB group and 15.07 (range 10.0 to 34.0) in the TCS group. A higher SCORAD score indicates a greater severity of AE. However, the absence of the standard deviation or similar measures of dispersion limited the interpretation of this result. See Analysis 7.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
None of the trials measured this outcome.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

8. Standard increasing NB-UVB versus fixed-dose NB-UVB
Hoey 2006 conducted a parallel group study (n=10) which compared a standard increasing dose of NB-UVB (UVB-TL01) against a fixed-dose dose NB-UVB (UVB-TL01). The age, severity and skin type of the participants was not reported. The length of the study was also unclear.

Primary outcomes

Physician-assessed changes in clinical signs
Hoey 2006 measured SCORAD; however, results were only reported narratively. It was also unclear how many participants were randomised to each group, as was the length of treatment. The authors noted that a significant difference was only noted between the two groups for the 18th session SCORAD though there is no information as to what this difference was. Three participants were reported to have a mild flare but it is unclear what proportion of the original groups this related to. See Analysis 9.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
None of the trials measured this outcome.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

9. NB-UVB with optimised dose by skin reflectance measurements versus NB-UVB with fixed-dose increments
Selvaag 2005 compared different dosing regimens of NB-UVB in a split-body study of 20 participants. The participants were adults with mild to moderate AE, skin type was not reported. Participants were treated for up to 6 weeks, 3-5 times per week. In the fixed- dose regimen, half of the body was treated with a starting dose of 1.6 SED with 25% increments with each treatment session. One SED is 10 mJ/cm^2 at 298 nm using the International Commission on Illumination (CIE) erythema action spectrum and is equivalent to 1.6 kJ/m^2 of the UVB lamp. In the optimised regimen group UVB was administered according to skin reflectance measurements of skin pigmentation and erythema.

Primary outcomes

Physician-assessed changes in clinical signs
Selvaag 2005 measured the number of weeks to a SCORAD measurement of <10 in both groups. The median time to SCORAD <10 was 3.0 weeks (5-95 percentile 2.0 to 5.5) in the optimised dose NB-UVB group (n=20) compared with 3.5 weeks (5-95 percentile 1.5 to 6.0) in the fixed-dose group (n=20). See Analysis 8.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
None of the trials measured this outcome.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

10. UVB 0.8 MED versus UVB 0.4 MED
Only one study, Jekler 1988b compared different dosages of UVB (0.8 MED vs 0.4 MED) in a split-body study that included 31 participants aged 16 years and over. In this split-body study, 31 participant were treated on both sides of the body for up to 8 weeks or until healing of at least one body part. The eczema was of unknown severity and the participant had the following skin types: 8 were type II, 15 type III and 2 type IV. Participants received treatment three times a week for up to 8 weeks or until the body half was healed.

Primary outcomes

Physician-assessed changes in clinical signs
Jekler 1988b used their own scale to assess clinical signs which assessed 8 variables; pruritus, lichenification, scaling, xerosis, vesiculation, excoriations and erythema and an overall evaluation, rated on a 4 point scale of 0=none to 3=severe, with a maximum score of 24. The mean severity score was 7 in the group treated with UVB 0.8 MED group (n=25 sides) and 6.6 in the group treated with UVB 0.4 MED (n=25 sides) at the final time point which was either 8 weeks or the time taken for healing of at least one body half. No dispersion data were reported, so this study could not be included in a forest plot. See Analysis 10.1.

Patient-reported changes in symptoms
The mean pruritus score (rated on a 4 point scale as above, Jekler 1988b) was 1.2 in the group treated with UVB 0.8 MED group (n=25 sides) and 1.2 in the group treated with UVB 0.4 MED (n=25 sides) at the final time point which was either 8 weeks or the time taken for healing of at least one body half. No dispersion data were reported, so this study could not be included in a forest plot. See Analysis 10.2.

Secondary outcomes

Investigator Global Assessment (IGA)
Jekler 1988b reported that 15 out of 25 sides of the body were healed or considerably improved by treatment in the 0.8 UVB MED group in comparison with 16 out of 25 sides in the group treated with 0.4 MED (OR 0.84, 95% CI 0.38 to 1.89) measured at 8 weeks or the time taken for healing of at least one body half. This result is uncertain as the confidence intervals are wide and cross the line of no effect. See Analysis 10.3.

Safety: withdrawals due to adverse events
In Jekler 1988b, one participant in the group that received UVB 0.8 MED withdrew due to experiencing UVB burn. See Analysis 10.4.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

11. UVB (unspecified) versus UVA
One parallel-design study (Qayyum 2016) compared UVB with UVA. The type of UVB that was used in this trial was not specified. The study included 60 participants, adults and children, with moderate to severe AE. Participants were treated three times weekly, up to 12 weeks.

Primary outcomes

Physician-assessed changes in clinical signs
The mean difference in SCORAD values in the study by Qayyum 2016 between UVA and UVB groups was 3 (95% CI -1.09 to 7.08), with the point estimate slightly in favour of UVA at week 12. However, the confidence interval crosses the line of no effect, so this result is uncertain. See Analysis 11.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
The number of participants achieving excellent improvement was 12 out of 30 in the UVB group compared to 17 out of 30 in the UVA group. The risk ratio calculated from this study was 0.71 (in favour of UVA treatment); however, this result crossed the line of no effect, so the result was uncertain (95% CI 0.41 to 1.21), see Analysis 11.2. This was measured at 12 weeks.

Safety: withdrawals due to adverse events
No participants withdrew from the UVA group (n=30) and two participants withdrew due to adverse events from the UVB group (n=30) in the study by Qayyum 2016, this study had up to 12 weeks of active treatment. See Analysis 11.3.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

12. BB-UVB versus placebo
Jekler 1988a was a within-participant trial comparing BB-UVB with placebo (ordinary daylight tubes) in 17 participants. The participants were randomized into two treatment groups—one starting with 0.5 MED and one with 1 MED BB-UVB, randomized to the right or left side of the

body. Treatment was given three times a week for a maximum of 8 weeks or until the healing of at least one body half. Participants were assessed for 8 variables scored 0 to 3 (0=none, 1=light, 2= moderate and 3= severe) on the following variables; pruritus, lichenification, scaling, xerosis, vesiculation, excoriations, erythema and an overall evaluation.

Primary outcomes

Physician-assessed changes in clinical signs
After 8 weeks of treatment, Jekler 1988a reported a modified severity score of 5 (n=17) in the body half that was treated with BB- UVB compared to a severity score of 8 (n=17) in the body half that received placebo. No dispersion data were reported, so this study could not be included in a forest plot. See Analysis 12.1.

Patient-reported changes in symptoms
Jekler 1988a showed a mean pruritis score of 0.8 (n=17) and 1.8 (n=17) on the sides treated with BB-UVB and placebo, respectively. No dispersion data were reported, so this study could not be included in a forest plot. See Analysis 12.2.

Secondary outcomes

Investigator Global Assessment (IGA)
Jekler 1988a reported that 13 of 17 participants were healed or considerably improved on the side treated with BB-UVB compared to 1 of 17 on the side treated with placebo at 8 weeks. This result favours BB-UVB with OR=52.00 (95% CI 9.01 to 300.17). See Analysis 12.3.

Safety: withdrawals due to adverse events
Jekler 1988a reported that one participant withdrew from the study because of a UVB burn experienced on the side treated with BB- UVB (n=28). No withdrawals were due to adverse events on the side treated with placebo. See Analysis 12.4.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

13. BB-UVB versus UVA
One study compared BB-UVB with UVA, Jekler 1991 (n=33 (though results and characteristics only reported for 21 participants)) was a split-body study and included those aged 15 years and over. Disease severity was not specified. Participants were treated three times weekly for up to 8 weeks. All but 2 participants had a skin type of III (the remaining had a skin type of II).

Primary outcomes

Physician-assessed changes in clinical signs
In the study by Jekler 1991 (which used a scale that measured the severity of clinical signs defined by the authors) no dispersion data were provided; therefore, it was not possible to include the data in a forest plot. However, the mean severity score was 6.4 on the sides treated with UVB (n=21 sides, split-body study) and 5.5 on the sides treated with UVA (n=21 sides, split-body study) at week 8. See Analysis 13.1.

Patient-reported changes in symptoms
Jekler 1991 reported a mean pruritus score (measured on a 4-point scale 0=none to 3=severe) for both treatments; however, again there were no dispersion data provided. The mean values for the sides treated with UVB was 1.3 (n=21) compared to 1 on the sides treated with UVA (n=21). See Analysis 13.2.

Secondary outcomes

Investigator Global Assessment (IGA)
The number considerably improved or healed was 13 of 21 sides treated with UVB compared to 15 of 21 sides treated with UVA. The odds ratio calculated was 0.65 in favour of UVA treatment; however, this result crossed the line of no effect, so the result was uncertain (95% CI 0.26 to 1.62), see Analysis 13.3. This was measured at 8 weeks.

Safety: withdrawals due to adverse events
No participants withdrew due to adverse events from Jekler 1991. See Analysis 13.4.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

14. BB-UVB versus UVAB
Two studies compared BB-UVB versus UVAB (Jekler 1990; Jekler 1991b Study 1), both split body studies, in participants aged 15 years and over with unspecified eczema severity. In both studies, the majority of participants had skin type of III. Participants were treated three times a week for up to 8 weeks or healing of one body side. In Jekler 1991b Study 1 a lower dose of UVB was used.

Primary outcomes

Physician-assessed changes in clinical signs
Both studies assessed physician-assessed clinical signs using an instrument defined by the authors, which assessed 8 variables; pruritus, lichenification, scaling, xerosis, vesiculation, excoriations and erythema and an overall evaluation, rated on a 4 point scale of 0 = none to 3 = severe. As the numerical data were incomplete (no usable measures of dispersion) it was not possible to include these studies in a meta-analysis. In Jekler 1990 (n=30 participants, 60 sides treated overall in both groups) the BB-UVB group scored a mean 6.1 with range of 0-17

whilst in the UVAB group the mean was 5.2 with a range of 0-15. In Jekler 1991b Study 1 (n=18 participants, 36 sides treated overall in both groups) the mean in the BB-UVB group was 8.8 with a range of 4.5 to 14, whilst in the UVAB group the mean was 5.3 with a range of 1.5 to 11. See Analysis 14.1.

Patient-reported changes in symptoms
Both studies (Jekler 1990; Jekler 1991b Study 1) reported itch measured on a 4 point scale (0=none, 1=light, 2=moderate and 3=severe). As the numerical data were incomplete (no usable measures of dispersion) it was not possible to include these studies in a meta-analysis. In Jekler 1990 (n=30 participants, 60 sides treated overall in both groups) the BB-UVB score was 1.2, whilst in the UVAB group the mean score was 1. The range was 0 to 3 in both arms. In Jekler 1991b Study 1, which used the same itch measurement scale (n=18 participants, 36 sides treated overall in both groups), the mean in the BB-UVB group was 1.5 whilst in the UVAB group the mean was 0.8. The range in both groups was 0 to 2. In both cases, the timepoint at which the outcome was measured was 8 weeks or upon healing of one body side. See Analysis 14.2.

Secondary outcomes

Investigator Global Assessment (IGA)
Both studies (Jekler 1990; Jekler 1991b Study 1) measured IGA. Both studies were split-body studies in which 48 participants were treated on both half of the body. On treatment with BB-UVB 30 out of 48 body sides were healed or showed considerable improvement whilst on treatment with UVAB, 45 out of 48 body sides were healed or showed considerable improvement (odds ratio 0.14, 95% CI 0.00 to 4.49). In both cases, the timepoint at which the outcome was measured was 8 weeks or upon healing of one body side. See Analysis 14.3.

Safety: withdrawals due to adverse events
No participants in either study (Jekler 1990; Jekler 1991b Study 1) withdrew due to adverse events. See Analysis 14.4.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

15. UVA1 versus UVAB
Four studies compared UVA1 to UVAB (Jekler 1991b Study 2, Krutmann 1992; Krutmann 1998; Von Kobyletzki 1999a).
Jekler 1991b Study 2 compared UVA1 and UVAB. Jekler 1991b Study 2 was a within-participant, randomised controlled trial and had 28 participants. Phototherapy in both arms was delivered five times a week for up to three weeks.
Krutmann 1992 was a parallel randomised controlled trial with 25 participants, with up to 15 treatments given daily over approximately two to three weeks.

Krutmann 1998 was a randomised, multi-centre, three- armed, parallel study with 53 participants, daily treatments conducted over a 10-day period.
Von Kobyletzki 1999a 1999 was a parallel, three-armed, randomised, active-control trial with 120 participants. Participants received treatment 5 times per week for 3 weeks with 4 weeks of follow-up post treatment.

Primary outcomes

Physician-assessed changes in clinical signs
Data on physician-assessed changes in clinical signs from these 3 studies were added to the meta-analyses. The pooled standardised mean difference was -2.10 (95% CI -2.84 to -1.35) in favour of UVA1. See Analysis 15.1.
In Analysis 15.1, values are given at end of treatment for Krutmann 1992 and Krutmann 1998. However, for Von Kobyletzki 1999a the values are given at 7 weeks (4 weeks after completing active treatment) as this is the closest timepoint to 12 weeks, as per our protocol. The end of treatment (at 3 weeks) mean SCORAD values (plus SD) for Von Kobyletzki 1999a were: UVA medium dose: 28.8 (6.9), UVA medium dose cold light: 23.3 (10.6) and UVAB: 41.4 (9.9), also showing lower values in the UVA groups compared to UVAB.
Jekler 1991b Study 2 could not be added to this meta-analysis as only the range was given (rather than another measure of dispersion such as SD). Disease severity was graded using a scale defined by Jekler 1991b Study 2 that comprised of 8 variables (pruritus, lichenification, scaling, xerosis, vesiculation, excoriations, erythema and an overall evaluation), scored 0 to 3 (0=none, 1=slight, 2= moderate and 3= severe). The mean disease severity total score at week 3 in the UVA1 arm was 7.2 (range 3 to 14) compared to 6 (range 1 to 12) in the UVAB arm. Results were reported for 25 participants treated on both sides of the body, therefore "50 sides". See Analysis 15.2.

Patient-reported changes in symptoms
Only Jekler 1991b Study 2 reported patient-reported changes in symptoms. The mean itch score (0=none, 1=slight, 2= moderate and 3= severe) at week 3 in the UVA arm was 1.3 (range 0 to 2) compared to 1.1 (range 0 to 2) in the UVAB arm. No dispersion data were reported, so this study could not be included in a forest plot. See Analysis 15.3. This was measured at week 3 or upon healing. Results were reported for 25 participants treated on both sides of the body, therefore "50 sides".

Secondary outcomes

Investigator Global Assessment
In Jekler 1991b Study 2, 17 of 25 sides treated with UVA achieved healing or considerable improvement compared to 23 of 25 receiving UVAB at 3 weeks. The odds ratio was 0.18 (CI 0.05 to 0.65). See Analysis 15.4. Results were reported for 25 participants treated on both sides of the body, therefore "50 sides".

Safety: withdrawals due to adverse events
Jekler 1991b Study 2 reported one withdrawal due to bilateral polymorphic light eruption. Results were reported for 25 participants treated on both sides of the body, therefore "50

sides". Krutmann 1998 reported no withdrawals due to adverse events. Von Kobyletzki 1999b reported a total of 6 withdrawals in the UVA1 arm (1 for bacterial superinfection treated with antibiotics; 5 due to exacerbation of disease) compared to 1 withdrawal in the UVAB arm (due to bacterial superinfection). See Analysis 15.5.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

16. High dose UVA1 versus medium dose UVA1
Three studies compared high dose UVA1 and medium dose UVA1 in adults; Dittmar 2001, Pacifico 2019 and Tzaneva 2001.
Dittmar 2001 was a randomised, controlled, parallel, prospective study conducted with 15 treatments (5 a week) over 3 weeks for a total of 34 participants.
Pacifico 2019 was a randomised, controlled, open, parallel-group study with 27 participants with a total of 15 treatments over 3 weeks.
Tzaneva 2001 was an investigator-blinded, within-participant study with 10 participants receiving treatment 5 times per week for 3 weeks.

Primary outcomes

Physician-assessed changes in clinical signs
Both Dittmar 2001 and Pacifico 2019 assessed the SCORAD score, and the mean difference between groups was -8.24 (95% CI -14.14 to -2.34), favouring high dose. See Analysis 16.1.
Tzaneva 2001 reported a mean modified SCORAD reduction of 34.7% (range 0 to 46.9%) at week 3 in the high dose UVA1 arm compared to 28.2% (range 0 to 46.9%) in the medium dose UVA1 group. No dispersion data were reported, so this study could not be included in a forest plot. See Analysis 16.2.

Subgroup analysis (Skin type): Physician-assessed changes in the clinical signs
Pacifico 2019 reported subgroup analysis for the SCORAD at week 3 of two different skin type groups: skin type II and skin type II/IV. In skin type II group they reported a mean difference of 2.30 (CI -1.85 to 6.45) at week 3. In skin type II/IV they reported a mean difference of -20.92 (CI -28.68 to -13.15) at week 3. See Analysis 16.3.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
Dittmar 2001 had no withdrawals due to adverse events (n=23) during 3 weeks of treatment. See Analysis 16.4.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

17. High dose UVA1 versus low dose UVA1
Only Dittmar 2001 compared high dose UVA1 to low dose UVA1. Dittmar 2001 was a randomised, controlled, parallel, prospective study conducted with 15 treatments (5 a week) over 3 weeks for a total of 34 adult participants.

Primary outcomes

Physician-assessed changes in clinical signs
The mean difference of SCORAD at week 3 in high dose UVA1 versus low dose UVA1 was -12.97 (CI -35.16 to 9.22). See Analysis 17.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
Dittmar 2001 had no withdrawals due to adverse events (n=22) after 3 weeks of treatment. See analysis Analysis 17.2.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

18. Medium dose UVA1 versus low dose UVA1
Only Dittmar 2001 compared medium dose UVA1 to low dose UVA1. Dittmar 2001 was a randomised, controlled, parallel, prospective study conducted with 15 treatments (5 a week) over 3 weeks. Eleven participants were treated with low dose UVA1 and 12 participants received medium dose UVA1.

Primary outcomes

Physician-assessed changes in clinical signs
Dittmar 2001 showed a mean difference in SCORAD at week 3 of -6.75 (CI -31.80 to 18.30) for medium dose UVA1 versus low dose UVA1. See Analysis 18.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
Dittmar 2001 had no withdrawals due to adverse events (n=23). See Analysis 18.2.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

19. UVA1 medium dose versus UVA1 medium dose cold-light
Von Kobyletzki 1999b compared medium dose UVA1 with cold light medium dose UVA1. This was a parallel, three-armed, randomised, active-control trial with 120 adult participants. Participants received treatment 5 times per week for 3 weeks with 4 weeks of follow-up post treatment.

Primary outcomes

Physician-assessed changes in clinical signs
Von Kobyletzki 1999b showed a mean difference in SCORAD of medium dose UVA1 versus cold light medium dose UVA1 at 3 weeks of 5.90 (CI 1.94 to 9.86) in favour of cold light treatment. See Analysis 19.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events

There were 6 withdrawals due to adverse events in Von Kobyletzki 1999b in the medium dose UVA1 arm (1 for bacterial superinfection, 5 due to exacerbation of disease); this is compared to 2 withdrawals in the cold light medium dose UVA1 (1 due to eczema herpeticum; 1 due to bacterial superinfection). See Analysis 19.2.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

20. UVA1 versus topical corticosteroids
Only Krutmann 1998 compared UVA1 to topical steroids. Krutmann 1998 was a randomised, multi-centre, three-armed, parallel study with 53 adult participants, daily treatments conducted over a 10- day period. They compared UVA1 (daily for 10 days) with topical steroids (fluocortolone 0.5% cream or ointment), applied to the entire body once daily for 10 consecutive days.

Primary outcomes

Physician-assessed changes in the clinical signs
Krutmann 1998 showed a -8.00 (CI -16.01 to 0.01) mean difference in Costa score between UVA1 versus topical steroids at 10 days. See Analysis 20.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
No participants in Krutmann 1998 withdrew due to adverse events. **Health-related quality of life**
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

21. UVA versus placebo
Reynolds 2001 compared UVA to placebo. This was a 3-arm randomised, controlled, double-blind, parallel-group study with 73 adult participants. 24 participant were randomised to receive UVA1 and 23 to visible fluorescent light (placebo). Phototherapy was administered to the whole body twice weekly for 12 weeks. After this, participants were followed up for a further 3 months. Disease severity was scored based on Sowden and colleagues (Sowden

1991) with the following parameters: erythema, papulovesicles, excoriation, scaling or dryness, and lichenification graded from 0 to 3 at six sites (maximum=90). Assessed at baseline, after 6, 12, 18, and 24 treatments, and 3 months after the final treatment.

Primary outcomes

Physician-assessed changes in the clinical signs (short-term)
Reynolds 2001 also reported a mean reduction in total disease activity score of -4.40 (CI -9.80 to 1.00) for UVA vs placebo at 12 weeks. See Analysis 21.1.

Patient-reported changes in symptoms (short-term)
Reynolds 2001 reported that 12 of 19 participants achieved a reduction in itch VAS on treatment with UVA compared to 10 of 19 treated with placebo at 12 weeks. This gave a risk ratio of 1.20 (CI 0.69 to 2.07). See Analysis 21.2.

Secondary outcomes

Investigator Global Assessment (IGA) (short-term)
Reynolds 2001 reported that 7 of 19 participants achieved moderate or greater improvement in IGA on treatment with UVA compared to 4 of 19 treated with placebo at 12 weeks. This gave a risk ratio of 1.75 (CI 0.61 to 5.01). See Analysis 21.3.

Investigator Global Assessment (IGA) (long-term)
Reynolds 2001 reported that 6 of 19 participants achieved moderate or greater improvement in IGA following treatment with UVA compared to 6 of 17 treated with placebo at 3 months after the 12-week treatment course. This gave a risk ratio of 0.89 (CI 0.36 to 2.25). See Analysis 21.3.

Safety: withdrawals due to adverse events
In Reynolds 2001 there were no withdrawals due to adverse events in the UVA arm compared to one withdrawal in the placebo arm (secondary to burning). See Analysis 21.4.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
Reynolds 2001 reported that 9 of 19 participants improved in total disease activity score following treatment with UVA compared to 8 of 17 treated with placebo at 3 months after the 12-week treatment course. This gave a risk ratio of 1.01 (CI 0.50 to 2.01). See Analysis 21.5.
Reynolds 2001 reported that 14 of 19 participants achieved a reduction in itch VAS following treatment with UVA compared to 11 of 17 treated with placebo at 3 months after the 12-week treatment course. This gave a risk ratio of 1.14 (CI 0.73 to 1.77). See Analysis 21.5.

22. UVAB versus topical corticosteroids

Krutmann 1998 was the only study that compared UVAB with topical steroids. It was a randomised, multi-centre, three- armed, parallel study with 53 adult participants with daily treatments (UVAB or Fluocortolone) conducted over a 10-day period.

Primary outcomes

Physician-assessed changes in the clinical signs
Krutmann 1998 showed a mean difference in Costa score of 7.00 (CI -1.59 to 15.59) at day 10. See Analysis 22.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
No participants in Krutmann 1998 withdrew due to adverse events. See Analysis 22.2.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

23. UVAB versus ciclosporin
Granlund 2001 was the only study that compared UVAB to ciclosporin. This was a randomised, controlled, parallel group, multi-centre study with 72 adult participants with 1 year follow- up, during which the participants received different cycles of treatment. UVAB was given 2-3 times a week with the intention that participants received at least 16 visits per cycle. Ciclosporin was given with initial doses of 4 mg/kg/day.

Primary outcomes

Physician-assessed changes in the clinical signs
The mean change in SCORAD from baseline in Granlund 2001 was -7.00 (CI -14.09 to 0.09] at week 10 (2 weeks after completion of round 1).

Patient-reported changes in symptoms
Granlund 2001 reported that 18 of 30 participants achieved very good or good effectiveness when treated with UVAB compared to 30 of 35 treated with ciclosporin at 8 weeks. The risk ratio was 0.70 (CI 0.51 to 0.97) in favour of ciclosporin. See Analysis 23.2.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
None of the trials measured this outcome.

Health-related quality of life
The mean difference in the eczema disability index score (range 0-6) (Salek 1993) for Granlund 2001 was 5.00 (CI -1.21 to 11.21) at 8 weeks and 1.00 (CI -4.56 to 6.56) at 1 year after up to 5 cycles of treatment. See Analysis 23.3.

Long-term control
For physician-assessed changes in clinical signs, the mean change in SCORAD from baseline in Granlund 2001 was - 2.00 (CI confidence interval-5.73 to 9.73] at 1 year (after up to 5 cycles of treatment). See Analysis 23.4.

24. Excimer laser versus topical steroid
Brenninkmeijer 2010 was the only study that compared excimer laser to topical steroids. This was a prospective, randomised, within-participant, controlled study with 13 adult participants conducted over 34 weeks. Participants were either allocated to receive excimer laser twice weekly laser for 10 weeks or clobetasol proprionate 0.05% ointment topically once daily for 10 weeks.

Primary outcomes

Physician-assessed changes in the clinical signs
The clinical signs in Brenninkmeijer 2010 were assessed using an unnamed scale incorporating number of nodules, excoriation, erythema, induration and pruritus (VAS). The mean difference for excimer laser versus topical steroid was -0.50 (CI -2.40 to 1.40) at 10 weeks. See Analysis 24.1.

Patient-assessed clinical symptoms
The mean itch VAS reported by participants in Brenninkmeijer 2010 was 3.5 when treated with excimer laser compared to 4.5 when treated with topical steroids at week 10. No dispersion data were reported, so this study could not be included in a forest plot. See Analysis 24.2.

Secondary outcomes

Investigator Global Assessment (IGA)
Brenninkmeijer 2010 reported that 1 of 10 participants achieved cleared or almost clear on IGA on the side treated with excimer laser compared to 0 of 10 on the side treated with topical steroid at 10 weeks: odds ratio of 3.32 (CI 0.28 to 39.42). At 34 weeks, 2 of 10 achieved cleared

or almost clear on the side treated with excimer laser compared to 0 of 10 on the side treated with topical steroid. This gave an odds ratio of 6.18 (CI 0.53 to 72.07). See Analysis 24.3.

Safety: withdrawals due to adverse events
There were no withdrawals due to adverse events in either arm of Brenninkmeijer 2010. See Analysis 24.4.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
For physician-assessed clinical signs, the mean difference between excimer laser versus topical steroid was -2.00 (CI confidence interval-3.92 to -0.08), favouring laser treatment at 34 weeks. See Analysis 24.5.
For patient-assessed symptoms, the mean itch VAS in Brenninkmeijer 2010 was 3 in the excimer laser group compared to 4 in the topical steroid group at week 34. No dispersion data were reported, so this study could not be included in a forest plot. See Analysis 24.6.

25. Full spectrum light versus no treatment
Byun 2011 was the only study comparing full spectrum light to no treatment. This was an open, randomised, controlled, parallel, prospective study with 38 adult participants receiving treatment for 8 weeks. Phototherapy was administered twice per week for 4 consecutive weeks. The control arm received only emollients twice a day.

Primary outcomes

Physician-assessed changes in clinical signs
The mean SCORAD in Byun 2011 was 36.81 (11.6 SD) in the full spectrum light arm compared to 35.39 (8.9 SD) in the no treatment arm at week 4.
The mean SCORAD was 30.76 (12.25 SD) in the full spectrum light arm compared to 33.85 (12.15 SD) in the no treatment arm at week 8 (4 weeks after completion of treatment). See Analysis 25.1.

Patient-reported changes in symptoms
The number of participants self-reporting an excellent improvement (76% to 100%) at week 8 in Byun 2011was 6/20 in the full spectrum light group compared to 2/18 in the no treatment group at week 8. See Analysis 25.2.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
No participants withdrew due to adverse events in either arm of the Byun 2011 study. See Analysis 25.3.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

26. NB-UVB versus NB-UVB + pimecrolimus
Only Tzung 2006 compared NB-UVB to NB-UVB + pimecrolimus. This was a single centre, prospective, randomised, investigator-blind, within-participant study. There were 26 participants receiving NB- UVB twice weekly for 6 weeks with or without pimecrolimus cream twice daily.

Primary outcomes

Physician assessed changes in the clinical signs
The mean reduction in EASI from baseline at 6 weeks in Tzung 2006 was 59% in NB-UVB + pimecrolimus compared to 55% in NB- UVB alone. See Analysis 26.1.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
None of the trials measured this outcome.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

27. NB-UVB versus NB-UVB + synchronous balneotherapy
Only Heinlin 2011 compared NB-UVB to NB-UVB + synchronous balneotherapy. This was a parallel, randomised, controlled trial with 180 participants over 24 weeks. Participants received 3 to 5 sessions a week of either NB-UVB alone or combined with balneotherapy for up to 35 sessions.

Primary outcomes

Physician-assessed changes in the clinical signs

The mean SCORAD of Heinlin 2011 at 7 to 12 weeks was 34.6 (22.3 SD) in NB-UVB alone compared to 25.6 (22 SD) combined with balneotherapy. See Analysis 27.1.

Patient-reported changes in symptoms
Using the Patient Global Assessment 6-point Likert scale (improvement from very good to very bad), 55.4% of participants judged their treatment to be very good or good at 7 to 12 weeks in the NB-UVB alone group compared to 76.3% in the combined group. See Analysis 27.2.

Secondary outcomes

Investigator Global Assessment (IGA)
None of the trials measured this outcome.

Safety: withdrawals due to adverse events
There were six withdrawals due to adverse events in the NB-UVB group compared to 2 in the combined with balneotherapy group. See Analysis 27.4,

Health-related quality of life
The mean Sickness Impact Profile summary score (Finlay 1990) at 6 months after end of treatment was 3.3 (5.7 SD) in the NB-UVB arm compared to 4.3 (7.4 SD) in the combined arm. The mean Sickness Impact Profile summary score at 7 to 12 weeks was 4 (5.5 SD) in the NB-UVB arm compared to 4.6 (6.8 SD) in the combined arm. See Analysis 27.3.

Long-term control
For physician-assessed changes in clinical signs, the mean SCORAD of Heinlin 2011 at 6 months after completing treatment was 25.3 (21.9 SD) in NB-UVB alone compared to 18 (16.4 SD) combined with balneotherapy.
For patient-reported symptoms, 49% of participants judged their treatment to be very good or good, 6 months after end of treatment in the NB-UVB alone group compared to 77.5% in the combined group. See Analysis 27.5.

28. Saalmann SUP cabin (295 nm to 335 nm) + 15% salt solution versus Saalmann SUP cabin (295 nm to 335 nm) + 3% saline solution
Zimmerman 1994 was the only study to compare Saalmann SUP cabin with 15% salt versus 3% salt. This was a prospective, randomised, parallel-group study with 8 participants. For both groups, irradiation was carried out in a Saalmann SUP cabin, 295 to 335 nm, in increasing time intervals and doses according to photosensitivity of the skin and manufacturer's recommendations over 4 weeks.

Primary outcomes

Physician-assessed changes in the clinical signs
None of the trials measured this outcome.

Patient-reported changes in symptoms
None of the trials measured this outcome.

Secondary outcomes

Investigator Global Assessment (IGA)
Both arms (Saalmann SUP cabin (295 to 335 nm) + 15% salt solution and Saalmann SUP cabin (295 to 335 nm) + 3% saline solution) of Zimmerman 1994 showed 3 participants with very good (complete healing) or good response at week 4. See Analysis 28.1.

Subgroup analyses
We were unable to perform subgroup analyses for 'adults versus children' or 'HIV/AIDS participants with atopic eczema' due to the small number of studies included in each comparison. In addition, these data were not presented separately in any of the studies. One study (Pacifico 2019) reported a subgroup analysis for different Fitzpatrick skin types (see Analysis 16.3).

Safety: withdrawals due to adverse events
None of the trials measured this outcome.

Health-related quality of life
None of the trials measured this outcome.

Long-term control
None of the trials measured this outcome.

DISCUSSION

Summary of main results
Atopic eczema is a common chronic inflammatory skin condition with several treatment options available. Therapeutic options for moderate to severe atopic eczema include phototherapy and photochemotherapy. We aimed to give a complete summary of the evidence on clinical effectiveness and safety of the different types of phototherapy, to detect the gaps in evidence, and to determine the future research agenda. We included 32 randomised controlled trials in this review that randomised a total of 1219 participants. Thirteen studies assessed narrowband ultraviolet B (NB-UVB), so most of the evidence was for this type of phototherapy. Data from the included studies were synthesised into 28 comparisons. We considered NB-UVB versus no treatment or placebo, NB-UVB versus UVA1, NB-UVB versus psoralen plus UVA (PUVA), UVA1 versus PUVA, UVA1 versus no treatment or placebo, and PUVA versus no treatment or placebo as the main comparisons in this review. We found studies assessing four of our six proposed key comparisons, which we reported in summary of findings tables.

NB-UVB versus placebo or no treatment
We included four studies (89 participants) that compared NB-UVB with no treatment or placebo. We rated the certainty of evidence for outcomes from these studies as low.
Physician-assessed changes in clinical signs (assessed using a total disease activity score) may improve more with NB-UVB than with placebo after 12 weeks of treatment.

For patient-reported changes in symptoms (number of participants reporting a reduction in itch), itch may be reduced more with NB- UVB than with placebo after 12 weeks of treatment. After four weeks of treatment, there seems to be very little difference reported between NB-UVB and no treatment.
NB-UVB may provide moderate or greater improvement (measured by Investigator Global Assessment (IGA)) than placebo after 12 weeks of treatment.
NB-UVB may not affect the rate of withdrawal due to adverse events compared to placebo or no treatment. In total, only 4 out of 89 participants withdrew due to adverse events, none of which were serious in nature (reasons for withdrawal included burning, severe irritation, or phototoxic reaction).
None of the studies measured health-related quality of life (HRQoL). For further details, see Summary of findings 1.

NB-UVB versus UVA1
We included three studies (66 participants) that compared NB- UVB with UVA1. These three studies provided very low-certainty evidence for each of the outcomes.
We are uncertain if there is a difference between groups in clinical signs measured by clinicians (using SASSAD), self-reported itch, or HRQoL, after six weeks of treatment.
One split-body trial (13 participants) reported no withdrawals over 12 weeks.
None of the studies measured IGA.
For further details, see Summary of findings 2.

NB-UVB versus PUVA
One study (10 participants, 20 sides) compared NB-UVB and PUVA (8-methoxypsoralen (8-MOP) bath plus UVA).
There was no evidence of a difference between treatment groups in physician-assessed (modified SCORAD) after six weeks (very low- certainty evidence). Patient-reported symptoms were not reported.
We are uncertain whether there is a difference between groups in marked improvement or complete remission (IGA; very low- certainty evidence). There were no withdrawals due to adverse events over six weeks (very low-certainty evidence).
The study did not report HRQoL.
For further details, see Summary of findings 3.

UVA1 versus PUVA
One study compared UVA1 with PUVA (oral 5-MOP) in 40 participants.
We are uncertain if there was a difference between groups in physician-assessed signs (SCORAD) after three weeks of treatment (very low-certainty evidence). The study did not measure any other outcomes.
For further details, see Summary of findings 4.
We did not identify any eligible trials for our other key comparisons
of UVA1 or PUVA compared with no treatment or placebo.

Adverse events
Reported adverse events from phototherapy included low rates of phototoxic reaction, severe irritation, UV burn, bacterial superinfection, disease exacerbation, and eczema herpeticum.

Overall completeness and applicability of evidence

This review gives a complete overview of the evidence that is available on phototherapy for atopic eczema. The 32 included studies assessed 12 different phototherapeutic interventions for atopic eczema. Our primary and secondary outcomes were addressed to varying degrees by the evidence we identified.

Although atopic eczema is common in children, the mean age of the study participants was 28 years (range: 5 to 83 years old; five studies did not report the mean age). Most studies recruited either adults or a mixture of adults and young people under the age of 18 years. In nine studies, paediatric participants younger than 18 years of age were eligible for inclusion. Most studies reported the gender of the participants; the number of males and females were similar.

Participants had different Fitzpatrick skin types and severity of disease. Thirteen studies did not report the skin type of their participants, which is limiting, as skin type is a factor that should be taken into account when determining dosage. However, in the studies that did report, almost 90% of participants had skin type II or III, and around twice as many participants had skin type III than II.

All studies, except two, reported baseline severity of atopic eczema. Most studies assessed moderate to severe disease, and mean or median total disease duration of the participants ranged from 1 to 30.3 years; many participants had eczema for over 10 years (only around half of the studies reported duration of the eczema).

Only one small study analysed data according to Fitzpatrick skin type. We were unable to conduct our planned subgroup analyses on either people with HIV or AIDS and atopic eczema, or adults versus children: HIV/AIDS status was not reported, and no studies exclusively investigated the age-related subgroups. In addition, there was a very small number of studies included in each comparison, and data were not presented separately in any of the studies. No studies made specific distinctions between atopic eczema phenotypes, so we are unable to draw conclusions on which of the phototherapies may be best used, for example for acute versus chronic atopic eczema disease. The effect of seasonal differences on the symptoms and severity of atopic eczema was not mentioned by the majority of the included studies; most trials did not report if they were conducted in summer or winter.

UVB was the most prevalent intervention type assessed by our included studies: approximately 40% of the studies assessed NB-UVB, which reflects its status as the most recognised and widespread form of phototherapy treatment for atopic eczema. A further five studies assessed BB-UVB, and one study assessed UVB, but did not specify the type. A quarter of the studies assessed ultraviolet A (UVA), with six studies investigating UVA1 (not including the studies where UVA1 was used as a comparator) given in various doses (low to high dose, including cold-light therapy).

According to a recent survey among 238 dermatologists in Europe, psoralen-UVA (PUVA) is the second most frequently prescribed second-line phototherapeutic treatment for atopic eczema (Vermeulen 2020); however, it was assessed by only two studies. Only single studies assessed full-spectrum light, balneotherapy, and excimer laser, which are infrequently used phototherapy types.

The following categories of phototherapy were not assessed by any of our included studies:

- coal tar plus UVB radiation (Goeckerman therapy);

- oral trimethylpsoralen with UVA;
- oral khellin in combination with UV;
- topical khellin in combination with UV;
- heliotherapy; and
- excimer lamp.

The trial duration, including active treatment and follow-up, ranged from 10 days to 1 year; two trials did not mention the total length of follow-up. The average trial duration was 13 weeks, which we defined as short-term. Whether longer-term UV treatment or intermittent courses would be helpful for atopic eczema needs further exploration. Only four studies measured outcomes at six months or more; it would have been more helpful to know how long the treatment lasted, rather than the follow-up period from start of treatment.

We were able to include 28 comparisons, 21 of which were active comparisons. We selected six comparisons as main comparisons for this review: NB-UVB, UVA1, or PUVA compared to placebo, no treatment, or to each other. However, only four of these comparisons were assessed by nine of the included studies, which provided low to very low-certainty evidence. We were only able to pool data for a very small number of outcomes, and only from a maximum of three studies each. NB-UVB versus PUVA was assessed by one study; PUVA versus UVA1 by one study; and NB-UVB versus UVA1 by three studies. Meta-analysis was often not feasible because many comparisons were assessed by only one study, or there were insufficient data (e.g. no dispersion data reported).

Half of the included studies compared one type of phototherapy or photochemotherapy to another type of phototherapy (10 comparisons assessed by 16 studies). Six studies compared phototherapy versus placebo or no treatment. Different dosing regimens of a certain phototherapy type, for example high-dose UVA1 versus medium-dose UVA1, were assessed by seven studies. NB-UVB was compared to NB-UVB combination therapy in two studies (pimecrolimus and synchronous balneotherapy). Three studies compared phototherapy with topical corticosteroids, one study compared UVAB with ciclosporin, and one study compared Saalmann selective ultraviolet phototherapy (SUP) cabin (295 nm to 335 nm) + 15% salt solution versus Saalmann SUP cabin (295 nm to 335 nm) + 3% saline solution. No studies reported that they provided phototherapy at home.

Most of the included studies (94%) reported our primary outcome, physician-assessed changes in clinical signs, and 47% assessed patient-reported changes in symptoms of atopic eczema. SCORAD (objective or compound) was the most commonly used tool for measuring physician-assessed changes (used by approximately half of the studies). EASI, which is the HOME (Harmonising Outcome Measures for Eczema) initiative approved core instrument for physician-reported clinical signs, was only used by 2 of the 30 studies assessing physician-assessed changes. Eight studies assessed the outcome using an unnamed total severity score. Other measurement tools used were Costa, SASSAD, and a modified version of the SCORAD. For patient-reported symptoms of AE, the POEM, which HOME recommends as the core instrument for measuring this outcome, was not assessed by any included study. Eighty per cent of the studies that assessed this outcome used a single-item measurement instrument for itch e.g. VAS itch. Other measurement tools used were PGA and Patients' overall assessment of efficacy. A reason why the HOME core outcomes for trials were not used by most of the included studies is that the majority was published before the core outcome set was developed.

Regarding our secondary outcomes, 18 studies (56%) reported data on safety (i.e. withdrawals due to adverse events), and 10 studies assessed Investigator Global Assessment (IGA). Long-term control (physician-assessed or patient-reported outcomes measured at the closest time point to six months after the end of the course of phototherapy) was evaluated by only four studies (13%). HRQoL was only evaluated by three studies, but again, no study used the HOME initiative's recommended tools (Dermatology Life Quality Index (DLQI), the Children's Dermatology Life Quality Index (CDLQI), the Infants' Dermatitis Quality of Life Index (IDQOL)). The measurement tools used were Skindex-29, Eczema disability index score, and the Sickness Impact Profile.
Almost half of the studies reported their source of funding, with two linked to potential commercial sponsors (Granlund 2001; Heinlin 2011).

Quality of the evidence
We completed GRADE assessments for the results included in all four summary of findings tables. We did not rate the evidence for any of the results at moderate or high certainty. We considered the evidence to be of either low or very low certainty. We downgraded for serious or very serious risk of bias and imprecision.
In the comparison NB-UVB versus placebo, we rated the evidence for all outcomes as low certainty. We downgraded by one level due to serious imprecision (small sample sizes), and one level due to serious risk of bias. We either had some concerns or considered the studies at high risk of bias. This was usually due to missing outcome data, or concerns with the selection of reported results (e.g. no protocol available to make an assessment).
In the comparison NB-UVB versus UVA1, we judged the evidence for all outcomes as very low certainty. We downgraded all results by two levels due to very serious risk of bias, as we judged two out of the three included studies at high risk of bias overall. We also downgraded by one or two levels for serious or very serious imprecision (small sample size or wide 95% CI).
In the comparison NB-UVB versus PUVA, we downgraded physician- assessed changes in clinical signs, Investigator Global Assessment, and safety (withdrawals due to adverse events) by one level due to serious risk of bias (some concerns in all domains, apart from measurement of the outcome). We downgraded them all by a further two levels due to very serious imprecision (small sample size); Investigator Global Assessment also had a very wide 95% CI.
In the comparison UVA1 versus PUVA, evidence was only available for physician-assessed changes in clinical signs. We considered it to be very low certainty due to a serious risk of bias (some concerns in three domains), and very serious imprecision (small sample size and wide 95% CI).
The decision whether to downgrade by one or two levels for imprecision was influenced by the width of the confidence interval; the effect of different results within the confidence intervals on the clinical interpretation of effectiveness or safety; the absolute effect size and number of events, participants, and studies contributing to both the reported effect measure and to other relevant outcome data, which could not be combined in meta-analyses with the reported effect measure.

Potential biases in the review process
We attempted to conduct a comprehensive search for studies, but the four Studies awaiting classification may be a potential source of bias. Review authors independently assessed

eligibility of studies to minimise bias in the study selection process. There were some minor deviations from the original protocol, as we became aware of certain factors within the studies as the review progressed, such as the use of the Leicester sign score as an outcome measurement instrument in one of the included studies. Bias may have been introduced by the time points chosen for some of our outcomes. For example, when faced with outcome data with a range of time points, we had to make a decision on which time point to include for the different comparisons. We attempted to minimise this bias by coming to a consensus among all the review authors as to what should be the best time point to include. The decision was made to select a time point (one short-term and one long-term outcome measure) based on what was most commonly reported in trials.

The interventions used in included trials varied in their details. This led to difficulty in classification of the intervention for the purpose of subgroup analysis. For example, the studies described as UVA had to be reclassified as broadband UVA, others reclassified to UVA1 based on the frequency of light given. The regimens used also varied, as well as the machines used. We took advice from the phototherapy experts in our group (JF, SI, RD). We acknowledge that other groups may have classified the interventions differently.

While there was a set list of pre-defined outcomes outlined in the protocol, due to the nature of the trials, we had to deviate from the protocol and include other outcome measures not specified, such as Leicester sign score and disease severity scores that did not fit into one of the validated scores. We discussed these scoring criteria with the lead authors, and decided on the validity of these outcome measures depending on the parameters they included. We decided to include these, as an exclusion would lead to a significant amount of missing data, using the risk of bias tool to mitigate this as far as possible.

We estimated that the potential bias introduced by small deviations from the protocol was not of considerable impact.

Agreements and disagreements with other studies or reviews

Three previously published systematic reviews have evaluated the evidence on phototherapy for atopic eczema. The first systematic review evaluating phototherapy in the treatment of atopic eczema was published in 2007, and did not include PUVA (Meduri 2007). The authors of this review included nine studies, and concluded that UVA1 should be used for acute flares of atopic eczema, and chronic forms of atopic eczema should be treated with NB-UVB. Meduri 2007 found most of their evidence for UVA1 in trials including participants with acute atopic eczema flares, compared to UVAB. As for chronic atopic eczema, they found more evidence on UVAB and NB-UVB compared to UVA or UVA1. Eight out of nine trials included in Meduri 2007 are also included in our systematic review. We excluded one trial from our review because it was a non- randomised controlled trial (non-RCT) study design. We did not focus on the same investigational theme addressed by Meduri 2007. Many of our included studies did not specify whether their studied population had acute or chronic atopic eczema, and did not report baseline atopic eczema duration and severity, so little data were available to affirm these conclusions. In general, our findings are in line with the findings of Meduri 2007, i.e. we found that most evidence on efficacy was available for NB-UVB and UVA1, compared to other types of phototherapy in the treatment of atopic eczema.

Two other systematic reviews evaluating the efficacy of phototherapy for atopic eczema, published in 2014 and 2015, also highlighted that the best-quality evidence on effectiveness was available for the use of NB-UVB and UVA1 (Garritsen 2014; Pérez-Ferriols 2015). Garritsen

2014 used GRADE methodology, and developed a treatment algorithm for the use of phototherapy for atopic eczema, based on their findings. They suggested that both medium dose UVA1 and NB-UVB should be considered first-choice phototherapeutic treatments.
Regarding the dosing regimen of UVA1, Garritsen 2014 noted that they found little to no difference in efficacy between medium dose UVA1 and high dose UVA1. When we compared medium dose versus high dose UVA1, our analysis showed that physician- assessed clinical signs were slightly more reduced with high dose UVA1 (short-term). Evidence from our included studies found that low dose UVA1 was less effective than medium dose and high dose UVA1. However, it should be taken into account that higher doses of UVA1 are associated with photodamage and carcinogeneses.
Unlike Meduri 2007, Garritsen 2014 and Pérez-Ferriols 2015 did include PUVA; and they found that evidence evaluating the use of PUVA in atopic eczema was scarce. Our findings confirmed this. We only identified and included two trials comparing bath and oral PUVA to either NB-UVB or UVA1, and we are uncertain if there is a difference between treatments, because the evidence was very low certainty. Interestingly, a recent survey among 238 dermatologists from 30 European countries found that PUVA was the most frequently prescribed choice of phototherapy for atopic eczema after NB-UVB, despite that fact there is only scant evidence for PUVA.
Garritsen 2014 found that UVAB was more effective at reducing clinical signs than BB-UVB and UVA, but less effective than UVA1, when assessed by physicians. Another study showed that ciclosporin was more effective than UVAB at reducing clinical signs (Granlund 2001). Garritsen 2014 stated that they would not recommend BB-UVB, UVA, and full-spectrum light for the treatment of atopic eczema, due to the small size and low quality of these studies.
Recommendations about other phototherapy modalities included in our review, including balneophototherapy, excimer laser, and Saalmann SUP cabin, were not made by any of these previous reviews. As we identified only single studies assessing each of these phototherapy types, we could not give more than a summary of the results of these studies either.
Our findings are in line with the recommendations in the atopic eczema guidelines from the European Dermatology Forum (EDF), which are currently being updated (Wollenberg 2018). The guidelines' preliminary recommendations state that NB-UVB and medium dose UVA1 are first-line treatment options in adults with atopic eczema who do not respond to topical therapy. The EDF guidelines also made recommendations about treatment cycles and maintenance regimens; stating that prolonged or repeated treatment cycles and maintenance regimens should be avoided in all phototherapy modalities.
Studies included in our review used various treatment schedules, but phototherapy was administered two to three times a week in most trials. Dose increments were generally made using a fixed percentage, and an erythema threshold was used by the majority of included studies. No previous reviews made recommendations about dose increments during phototherapy treatment. We included two studies that assessed a dosing regimen of NB-UVB; they compared a standard increasing dose with a fixed dose, and a fixed dose regimen of NB-UVB with an optimised regimen (Hoey 2006; Selvaag 2005). However, these studies reported incomplete data, on which further analysis was not possible.
Both Garritsen 2014 and Pérez-Ferriols 2015 recognised that little information was available on duration of remission, long-term safety, efficacy in children, or in acute versus chronic atopic eczema. Unfortunately, we were unable to include new data from RCTs that tackled these shortcomings in the evidence. We could only analyse data on long-term control from

four studies, and none of the included studies mentioned a separate evaluation of paediatric participants.

AUTHOR'S CONCLUSIONS

Implications for practice

We found little evidence for our key comparisons, each of which were assessed by a range of only one to four studies that we were often unable to pool. Furthermore, our key results were based on very low- to low-certainty evidence. This means we cannot draw firm conclusions about the effectiveness and safety of phototherapy for atopic eczema.

Reported adverse events associated with phototherapy included phototoxic reaction, severe irritation, ultraviolet-induced erythema, bacterial superinfection, exacerbation of disease, and eczema herpeticum. However, rates of occurrence were low, and did not differ between different phototherapy modalities.

However, lack of high quality RCT evidence does not mean lack of effectiveness of these treatments. Besides, the included studies did not provide the data needed to determine how the interventions differ according to age, Fitzpatrick skin type, AE phenotype, or HIV/AIDS co-morbidity, which limits external validity. The studies assessed our outcomes in the short-term (less than 16 weeks), which does not align with AE as a long-term condition. The vast majority of studies did not report long-term control or duration on remission after the phototherapy treatment course has ended.

We found no studies assessing coal tar plus UVB radiation (Goeckerman therapy), oral trimethylpsoralen with UVA, oral or topical khellin in combination with UV, heliotherapy and excimer lamp. Only two trials investigated PUVA, so there is a lack of evidence to assess this treatment, while it's frequently prescribed in Europe (Vermeulen 2020). Studies in psoriasis showed that there are indications for an increased incidence of actinic keratoses and skin malignancies after systemic PUVA treatment and a positive correlation is seen with the cumulative UVA dose/number of PUVA exposures (Archier 2012; Stern 1998; Henseler 1987; Stern 1994). A Swedish study assessing the risk of skin malignancies in people with AE treated with PUVA did not find any increased risk for melanoma, but confirmed previous reports of an increased incidence of cutaneous squamous cell carcinoma (Lindelöf 1991; Lindelöf 1999). This information should be taken into account when prescribing PUVA.

Our primary outcome physician-assessed changes in clinical signs was reported by almost all studies (compared to patient-reported changes in symptoms, which was assessed by just less than half); however, the tools used to measure these outcomes were not HOME core instruments and were very heterogeneous. Safety data related to withdrawals were limited.

Implications for research

Currently, only very low- to low-certainty evidence is available on the efficacy of narrowband ultraviolet B (NB-UVB) versus no treatment or placebo, NB-UVB versus UVA1, and PUVA versus UVA1 or NB-UVB. We found no studies evaluating the other main comparisons of our review (UVA1 versus no treatment or placebo and psoralenUVA (PUVA) versus no treatment or placebo), so future studies are needed to assess these and our other main comparisons, focusing on NB-UVB, UVA1, and PUVA. Information on duration of remission and long-term efficacy and safety (especially skin cancer risk) of phototherapy for atopic eczema is scarce, and more research is needed to investigate these outcomes. Collecting data on (long-term)

safety of combinations of phototherapy with other systemic or topical treatments (e.g. tacrolimus) or certain treatment sequences (e.g. phototherapy after systemic immunomodulating treatment) would also be of interest, as people with moderate to severe atopic eczema receive numerous treatment modalities and sequences.

Studies evaluating the efficacy of phototherapy for atopic eczema use a wide variation of outcome measurements and study parameters. Future studies should use outcome measures that reflect the core outcomes (including core outcome instruments) of the Harmonising Outcome Measures for Eczema (HOME) initiative in order to compare and pool data. As we found that previous studies evaluating the efficacy of phototherapy in atopic eczema reported very little data on (skin specific) quality of life and other self-reported outcomes, these outcomes should be assessed in future studies.

Trials used different methods for participant selection (including atopic eczema diagnosis), phototherapy dosing regimens, and administration. Future studies should include participants who were diagnosed with atopic eczema using validated criteria, and longer follow-up periods (≥ six months). More homogeneous study designs, with standardised treatment procedures and cumulative doses should also be used, so that they can be pooled in future systematic reviews. Researchers investigating the effectiveness of phototherapy in trials in which participants are treated with concomitant topical corticosteroids are advised to keep track of the amount of topicals that are used.

Correctly designed randomised controlled trials (RCT) should be used to evaluate the effectiveness and safety of phototherapy for atopic eczema in the future, as insufficient reporting of study methodology may lead to biased assessment of treatment effects (Schulz 1995). Future RCTs should include power calculations to establish that adequate participant numbers are included. We recommend that investigators of future (parallel-group) RCTs assessing the effectiveness and safety of phototherapy for atopic eczema consult the CONSORT statement (Schulz 2010).

Data on the effectiveness and safety of phototherapy in certain populations, such as children or people with particular skin types are lacking, and should be considered for future research. We emphasise the need of future studies to investigate the effectiveness and safety of phototherapy in people with skin of colour. Phototherapy for acute versus chronic atopic eczema and other phenotypes should be further investigated. Home phototherapy should also be considered in future studies.

In addition to the results of this systematic review evaluating the existing evidence on phototherapy assessed through RCTs, cohort data of clinical daily practice could be useful. Real-world data on the (long-term) efficacy of phototherapy, for example from the European TREatment of ATopic eczema (TREAT) Registry Taskforce, could be beneficial to develop recommendations and inform clinical guidelines.

As the costs of atopic eczema per person are rising, due to the introduction of new systemic treatments, such as monoclonal antibodies and Janus kinase (JAK) inhibitors, high-quality research into the effectiveness, safety, and cost-effectiveness of skin- directed alternatives, like phototherapy, is of great importance.

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SUPPLEMENTARY MATERIAL

Supplementary material 1. Characteristics of included studies, excluded studies, studies awaiting classification and ongoing studies.

Supplementary material 2. Risk of bias.

Supplementary material 3. Data and analyses (Comparison 1-28, Analysis 1.1-28.1)

Supplementary material 4. Additional tables: correspondence with investigators, RoB 2 assessments of narrative data.

Supplementary material 5. Appendices: search strategies.

A digital version of Supplementary material 1-5 can be found at:

PART III

INTERNATIONAL COLLABORATION THROUGH THE TREATMENT OF ATOPIC ECZEMA (TREAT) REGISTRY TASKFORCE: GENERATING REAL-WORLD DATA ACROSS COUNTRY BORDERS

CHAPTER 4

MAPPING EXERCISE AND STATUS UPDATE OF EIGHT ESTABLISHED REGISTRIES WITHIN THE TREATMENT OF ATOPIC ECZEMA (TREAT) REGISTRY TASKFORCE

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ABSTRACT

Background
The TREatment of ATopic eczema (TREAT) Registry Taskforce is a collaborative international network of registries collecting data of atopic eczema (AE) patients receiving systemic and phototherapy with the common goal to provide long-term real-world data on the effectiveness, safety and cost-effectiveness of therapies. A core dataset, consisting of domains and domain items with corresponding measurement instruments, has been developed to harmonize data collection.

Objectives
We aimed to give an overview of the status and characteristics of the eight established TREAT registries, and to perform a mapping exercise to examine the degree of overlap and pooling ability between the national registry datasets. This will allow us to determine which research questions can be answered in the future by pooling data.

Methods
All eight registries were asked to share their dataset and information on the current status and characteristics. The overlap between the core dataset and each registry dataset was identified (according to the domains, domain items and measurement instruments of the TREAT core dataset).

Results and conclusions
A total of 4,702 participants have been recruited in the 8 registries as of 1st of May 2022. Of the 69 core dataset domain items, data pooling was possible for 69 domain item outcomes in TREAT NL (the Netherlands), 61 items in A-STAR (UK and Ireland), 38 items in TREATgermany (Germany), 36 items in FIRST (France), 33 items in AtopyReg (Italy), 29 items in Biobadatop (Spain), 28 items in SCRATCH (Denmark) and 20 items in SwedAD (Sweden). Pooled analyses across all registries can be performed on multiple important domain items, covering the main aims of analyzing data on the (cost-)effectiveness and safety of AE therapies. These results will facilitate future comparative or joint analyses.

INTRODUCTION

Atopic eczema (AE, syn. 'atopic dermatitis'), is a chronic inflammatory skin condition that affects up to 20% of children and adolescents and up to 10% of adults.[1, 2] Patients with moderate-to-severe AE may require systemic immunomodulating medication or photo(chemo)therapy, when topical treatments including corticosteroids and emollients, prove insufficient for symptom control. A recent survey among 238 dermatologists from 30 European countries conducted by the TREatment of ATopic eczema (TREAT) Registry Taskforce has shown that these therapies are frequently prescribed off-label in both children and adults.[3] Currently, the European Medicines Agency has approved ciclosporin, tralokinumab, baricitinib, upadacitinib and abrocitinib or adults and dupilumab for both adults and children from the age of 6 years for the treatment of AE. Although there is some evidence on the short-term effectiveness of systemic immunomodulating therapies and phototherapy prescribed in patients with moderate-to-severe AE, a clear knowledge gap about the long-term safety, effectiveness and cost-effectiveness of these therapies remains.

The TREAT Registry Taskforce is a collaborative international network of registries collecting data of AE patients receiving systemic and phototherapy.[4] Patients included are followed during treatment and after treatment discontinuation. The registries established within the TREAT Registry Taskforce have the common goal to provide long-term comparative real-world data on the effectiveness, safety and cost-effectiveness of AE therapies. These data are currently lacking for many commonly prescribed systemic treatments.[5, 6] Previous work of the TREAT Registry Taskforce has been to develop a core dataset, consisting of domains and domain items with corresponding measurement instruments, to be captured in AE research registries, to harmonize data collection.[7, 8] The aim of developing this core dataset was to increase the interoperability, direct comparability and pooling of data, and to reduce heterogeneity in data collection across country borders. The TREAT core dataset is aligned with the Harmonising Outcome Measures for Eczema (HOME) recommendations (www.homeforeczema.org). The HOME initative developed a consensus-based core outcome set for clinical trials and is developing one for clinical practice. Heterogeneity of outcomes used in disease registries has been demonstrated to hinder comparing results and pooling of data between centers and countries. A need to harmonize outcomes has been identified within similar collaborative initiatives for other diseases, for instance the Psonet initiative (an European surveillance network to monitor the long-term effectiveness and safety of systemic agents in the treatment of psoriasis).[9]

The TREAT core dataset consists of 19 core domains and 69 domain items, counting 49 baseline items and 20 follow-up items (defining 'what to measure').[7] As a final step in the harmonization process, the outcome measurement instruments, consisting of a total of 118 measurement instruments for all 69 domain items, and follow-up frequency and visit window were determined (defining 'how to measure' and 'when to measure').[8] All affiliated TREAT registries are encouraged to collect data in accordance with this core dataset.

Several registries from different countries have joined the TREAT Registry Taskforce over the past years, currently including the A-STAR registry (The UK-Irish Atopic Eczema Systemic Therapy Register; United Kingdom and Ireland), Biobadatop registry (Spain), TREATgermany

registry (Germany), TREAT NL registry (the Netherlands and Belgium), SCRATCH registry (Severe and ChRonic Atopic dermatitis Treatment CoHort, Denmark), FIRST registry (French atopIc deRmatitiS cohorT, France), AtopyReg registry (Italy) and SwedAD registry (Sweden). These registries concern prospective observational cohorts and offer a platform to conduct cross-border research. A framework to conduct studies within the taskforce has been published previously.[10]

Despite the use of a core dataset, differences in data collection are expected due to several reasons, including the use of different data entry platforms. Potential differences may also arise due to variability in interpretation of the core dataset and the selection of (optional) core dataset items (in the context of feasibility). Furthermore, patient in- and exclusion criteria may differ per country, for example due to discrepancies in treatment reimbursement and differences in prescribing practices.

Therefore, we aimed to give an overview of the status and characteristics of the established TREAT registries and to perform a mapping exercise. The main objective was to examine the data pooling ability between the registries by evaluating the degree of overlap between the registry datasets. Ultimately, this will allow us to determine which research questions can be answered in the future by pooling data and how such joint analyses can be approached.

METHODS

The following eight established registries in the TREAT registry Taskforce were included in this study: the A-STAR, TREAT NL, TREATgermany, Biobadatop, SCRATCH, FIRST, SwedAD and AtopyReg.

Status and characteristics of the registries

To investigate the current status and a description of the characteristics of each registry, we requested the following information (as of 1st of May 2022): status of recruitment, month and year of first patient inclusion, number of recruited patients, number of participating centers, countries involved in each registry, website address, data capture platform/modality, funding sources, language of the database and included therapies (conventional systemic therapies, biologicals, phototherapy and other systemic therapies). In addition, we requested the inclusion and exclusion criteria of each registry. Furthermore, information was collected on the follow-up frequency and visit windows for follow-up, to allow comparison with the defined 'when to measure'. The results were compiled descriptively in tables.

Mapping exercise

All registries were asked to share their dataset (e.g. the (electronic) case report forms ((e)CRFs) used) for the purpose of the mapping exercise. If more than one CRF was used for different timepoints within one registry, multiple CRFs were received. The use of the core dataset and the overlap between the core dataset and the registry dataset was identified according to the domains (n=19), domain items (n=69; 'what to measure') and measurement instruments (n=118; 'how to measure') of the TREAT core dataset.[8] We scored positive (1) if the dataset item was completely in accordance with the core dataset, negative (0) if the item

was not captured and partially positive (2) if the item was only partly corresponding. The mapping exercise was conducted as follows:

- **Core dataset domain items ('what to measure', n=69)**: we scored the presence of core dataset domain items in each registry dataset.

- **Core dataset measurement instruments ('how to measure', n=118):** we scored the use of core dataset instruments in each registry dataset, of which usually more are included per domain item (for example: the core dataset domain item 'how diagnosis AE is established' is measured by two measurement instruments: 1) 'clinically Y/N' and 2) 'histopathology Y/N'). We considered an instrument partially positive (2) if at least one part or category of the core dataset instrument was used (for example: if the answer categories for topical treatment in a registry were: '<30 g | 30-60 g | > 60 g'; instead of the predefined categories in the core dataset: '<30 g | 30-60 g | 60-100 g | >100 g', this instrument would be scored partially positive (2)).

- **Pooling ability of domain item outcomes**: the ability to pool outcomes of the domain items was scored positive (1) if pooling of at least one of the corresponding measurement instruments was deemed possible (for example, when a registry collects data on the domain item 'how diagnosis AE is established' using the measurement instrument 'clinically Y/N', but not 'histopathology Y/N', data pooling on the domain item 'how diagnosis AE is established' was scored positive). Otherwise, pooling ability of the domain items was scored negative (0). We considered the pooling ability of domain item outcomes as the main outcome of interest, because ultimately this will provide information on which cross-border analyses can be performed.

Uncertainties in data collection were resolved through discussion or e-mail correspondence with the corresponding registry investigators. Analyses were performed by using descriptive statistics to summarize the results, using Microsoft Excel version 16.54.

RESULTS

Status and characteristics of the registries

The status and characteristics of the registries are summarized in Table 1. All eight registries are currently recruiting. In total 4,702 participants have been recruited to the eight registries, ranging from 57 to 1,484 participants per registry (as of 1st of May 2022). The therapies included in the registries are methotrexate (in 7 of the registries (n=7)), ciclosporin (n=7), azathioprine (n=7), mycophenolate mofetil/mycophenolic acid (n=7), systemic corticosteroids (n=5), dupilumab (n=8), omalizumab (n=6), baricitinib (n=8) and phototherapy (n=4). Three registries also include patients on drugs that are or were investigational at the time like tralokinumab, upadacitinib or abrocitinib, and one registry includes patients treated with montelukast and apheresis (plasmapheresis). Each registry is a separate entity. Funding sources comprise governmental and pharmaceutical as well as charity support, academic support or a combination of these. The in- and exclusion criteria of each registry are shown in Table 2.

In context of the defined 'when to measure', the follow-up frequency and visit windows of all TREAT registries are shown in Table 3. Although the taskforce had reached consensus on the follow-up frequency and visit window to be applied, differences still exist between the registries. A baseline visit is conducted in all registries, but not all registries have specified a follow-up frequency and visit window. When specified, the first follow-up visit after inclusion ranges from 4 weeks to 12 months after baseline. The next follow-up visits during treatment are scheduled ranging from every 3 to (at least) every 12 months. The follow-up frequency after treatment discontinuation varies from no follow-up at all to at least every 6 months. Five registries have the option for extra visits, for example in case of switch of therapy or disease flares. If specified, the visit window ranges from 2 weeks to 1 month.

Mapping exercise

The complete results of the mapping exercise with the assessment of the presence of core dataset domain items and measurement instruments, and the pooling ability of measurement instruments and domain items can be found in Supplementary Table 1.

Of the 69 core dataset domain items, data pooling was possible for 69 items in TREAT NL (the Netherlands), 61 domain items in A-STAR (UK and Ireland), 39 items in TREATgermany (Germany), 36 items in FIRST (France), 34 items in AtopyReg (Italy), 29 items in Biobadatop (Spain), 28 items in SCRATCH (Denmark) and 20 items in SwedAD (Sweden). The specific results on the pooling ability per domain items are displayed in Table 4. This concerns a condensed part of Supplementary Table 1. In Table 4 it is shown that dataset domain items with the ability to pool data from all eight registry datasets include: 'date of birth', 'date of enrolment into registry', 'gender' (domain: demographics), date of onset of AE (domain: AE diagnosis), 'systemic therapy' (domain: current AE treatments), 'family history of AE or allergic diseases' (domain: family history of AE or allergic diseases), 'asthma', 'allergic rhinoconjunctivitis' (domain: allergic co-morbidities), 'physician-assessed clinical signs', 'patient-reported symptoms', 'skin-specific quality of life score' (domain: baseline physician- and patient-reported domains), physician-assessed clinical signs', 'patient-reported symptoms', 'skin-specific quality of life score' (domain: follow-up physician- and patient-reported domains). The number of domain items that scored positive for pooling ability according to the number of registries can be found in Fig. 1.

The HOME core outcome set consists of clinical signs (EASI), patient-reported symptoms (POEM and NRS-11 for peak itch over past 24 hours), quality of life (DLQI (adults), CDLQI (children), IDQoL (infants)) and long-term control (Recap of Atopic Eczema (RECAP) or Atopic Dermatitis Control Test (ADCT)). We found that all eight registries collect data on EASI, POEM, DLQI, CDLQI and IDQoL. NRS-11 peak itch over past 24 hours was fully or partially collected by five registries. The long-term control item has recently been introduced to the outcome set. Data collection on this item using RECAP and/or ADCT is currently implemented or planned to be implemented by most TREAT registries.

Table 1. Description and status of the TREAT registries, as of 1st of May 2022

	Registry name, country							
	A-STAR, United Kingdom and Ireland	**TREAT NL, the Netherlands and Belgium**	**TREATgermany, Germany**	**Biobadatop, Spain**	**SCRATCH, Denmark**	**FIRST, France**	**SwedAD, Sweden**	**AtopyReg, Italy**
Status	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Month and year of first inclusion	October 2018	November 2017	June 2016	April 2020	October 2017	October 2020	September 2019	June 2020
N included patients (May 1, 2022)	283	597	1.484	198	493	57	637	953
N participating centers	20	7	57	10	6	1	39	12
Countries involved	United Kingdom and Ireland	The Netherlands and Belgium	Germany	Spain	Denmark	France	Sweden	Italy
Website	https://astar-register.org	www.treatregister.nl	www.treatgermany.org	https://aedv.es/investigacion/proyectos-de-investigacion/	https://naed.zitelab.eu/	-	www.swedAd.nu	www.atopyreg2.it
Data capture modality	A-STAR (eCRF)	Castor (eCRF)	REDCap (eCRF)	RedCap (eCRF)	Zitelabs own software and platform (eCRF)	Epiconcept (Healthcare data host), Voozanoo 4 Software (eCRF)	Carmona, dermareg (eCRF)	Patient chart (eCRF)
Language of database	English	English	German	Spanish	Danish	French	Swedish	Italian
Funding	Government, pharma, charity	Government, pharma, academic support	Pharma	Pharma	Pharma	Academic support	Government, pharma	Pharma, academic support
Conventional systemic therapies included:								
Methotrexate	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Ciclosporin	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Azathioprine	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Mycophenolate mofetil/acid	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
Systemic corticosteroids	Yes	Yes	Yes	Yes	No	No	No	Yes
Biologicals included:								
Dupilumab	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Omalizumab	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Baricitinib	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Tralokinumab	Yes	Yes	Yes	No	Yes	Yes	No	No
Upadacitinib	Yes	Yes	Yes	No	Yes	Yes	No	No
Abrocitinib	Yes	Yes	Yes	No	Yes	Yes	No	No
Phototherapy included:								
BB-UVB	No	Yes	Yes	Yes	No	No	No	No
NB-UVB	No	Yes	Yes	Yes	No	No	No	Yes
UVA	No	Yes	Yes	Yes	No	No	No	No
UVA1	No	Yes	Yes	Yes	No	No	No	Yes
UVAB	No	Yes	Yes	Yes	No	No	No	No
PUVA	No	Yes	Yes	Yes	No	No	No	Yes
Other systemic therapies included (so far):								
								Montelukast, Apheresis (plasmapheresis)

A-STAR, The UK-Irish Atopic Eczema Systemic Therapy Register; FIRST, French atopIc deRmatitiS cohort; TREAT, TREatment of ATopic eczema; SCRATCH, Severe and ChRonic Atopic dermatitis Treatment CoHort.

Table 2. Inclusion and exclusion criteria of the TREAT registries

Registry name, country	Inclusion criteria	Exclusion criteria
A*STAR, UK and Ireland	- Paediatric and adult patients with AE of any age who due to the severity of their disease and/or impact on quality of life are commencing on or switching to another systemic immuno-modulatory agent (e.g. CsA, AZA, MTX or biologic treatments); - Written informed consent for study participation obtained from the patient or parents / legal guardian, with assent as appropriate by the patient, depending on the level of understanding; - Participants consent to participate in long-term follow up and access to all medical records, including hospital admission records and linkage to data held by NHS bodies or other national providers of healthcare data; - Diagnosis of AE in keeping with the U.K. Working Party's Diagnostic Criteria; - Willingness to comply with all study requirements; - Competent use of English language, according to patient's age (capable of understanding patient questionnaires).	- Insufficient understanding of the study by the patient and/or parent/guardian; - Patients who are currently participating in a randomised clinical trial.
TREAT NL, the Netherlands	- Patient has a diagnosis of AE, based on the U.K. Working Party's Diagnostic Criteria; - Starts with any type of phototherapy (e.g. UVB) or systemic immunomodulating therapy (e.g. CsA, systemic glucocorticosteroids, AZA, MTX, MPA, dupilumab);	- Patient uses only (systemic) antibiotics or antihistamines; - Patient starts with systemic immunomodulating therapy for another indication than AE; - Insufficient understanding of the study by the patient or parent/legal representative.

	- Has voluntarily signed and dated an informed consent prior to any study related procedure or has a legal representative to do so and is willing to comply with the requirements of this study protocol.	
TREATgermany, Germany	- AD according to the U.K. Working Party's Diagnostic Criteria: moderate-to-severe AE; - Age ≥ 18 years; - Objective SCORAD > 20 or currently anti-inflammatory systemic treatment for AE or previous anti-inflammatory systemic treatment for AE within past 24 months.	Not defined
Biobadatop, Spain	- Any age; - First time use of systemic treatment.	- Unable to provide consent, current participation in a clinical trial, intention to move in the next three months.
SCRATCH, Denmark	- Adults (>18 years) with moderate-to-severe AE (one or more of the following EASI>16, BSA>10%, DLQI>10 or POEM>16), who have not responded adequately to relevant topical treatment and at least one traditional systemic treatment or are not considered to be candidates for traditional systemic treatment. - Patients aged 12-17 years with moderate-to-severe AE, who have not responded adequately to relevant topical treatment and one traditional systemic treatment or are not considered to be candidates for traditional systemic treatment. - Patients aged 12-17 years with severe AE, who are candidates for systemic ciclosporin, where there is a need for rapid onset of action of the systemic treatment due to severe flare-up of AE. - Children (6-11 years) with severe AE after at least one previous traditional systemic treatment.	Not defined
FIRST, France	- Adult patients ≥ 18 year old (amendment for inclusion of adolescents and children ≥ 6 year-old is ongoing); - With AD according to the U.K. Working Party's Diagnostic Criteria; - Who due to the severity of their disease and/or impact on quality of life are commencing on or switching to a systemic treatment (e.g. CsA, MTX, biologic treatments, JAK inhibitors); - With written informed consent for study participation obtained from the patient (consent to participate in long-term follow up and for access to all medical records, including hospital admission records and linkage to data held by national providers of healthcare data); - Willingness to comply with all study requirements including blood samples dedicated to the biological collection.	- No systemic treatment (other than phototherapy)
SwedAD, Sweden	- Age ≥ 5 years; - Systemic treatment.	Not defined

AtopyReg, Italy	- Age: ≥ 18 years
	- To sign informed consent
	- Diagnosis of moderate or severe AE made by one dermatologist defined on the basis of the following criteria:
	  ○ EASI ≥ 16
	  ○ EASI <16 but with at least one of the following conditions:
	  ▪ Localization in at least one of the following "critical" sites: face, hands, genitalia
		- Patient unable to provide informed consent prior to any data collection procedures
		- data related to the study;
		- Patient unable to complete the procedures required for the study;
		- Patient already participating in another registry for the same condition.

	▪ DLQI > 10 ▪ itch-VAS > 7 ▪ sleep-VAS > 7	

Table 3. Visit schedule and window of the TREAT registries

Registry name, country	Baseline visit	First follow-up visit after baseline	Follow-up while on treatment	Follow up after treatment discontinuation	Visit schedule window (aspired maximum deviation (+/-) from visit schedule)	Extra visits (optional)
A-STAR, UK and Ireland	Baseline	4 weeks	3 months	6 months	First follow-up: 2 weeks Thereafter: 1 month	- Therapy switch (schedule restarts at baseline) - Unscheduled visit (e.g. in case of therapy side-effects or disease flare-ups)
TREAT NL, the Netherlands	Baseline	4 weeks	3 months	6 months	1 month	- (Re)start/switch of therapy (schedule restarts at baseline) - Unscheduled visit (e.g. in case of therapy side-effects or disease flare-ups)
TREATgermany, Germany	Baseline	3 months	6 months (3 months if systemic treatment is initiated or changed)	6 months	2 weeks	- Therapy switch - Therapy side-effects - Disease flare-ups - Extra patient questionnaire (every 2 years)
Biobadatop, Spain	Baseline	3 months	At least every 12 months	At least every 12 months	As indicated by standard clinical practice	- Second follow-up visit (6 months after baseline)
SCRATCH, Denmark	Baseline	Usually 4 weeks (not specifically defined)	Usually 3-6 months (not specifically defined)	None, follow-up ends after treatment discontinuation	Not defined	Not defined
FIRST, France	Baseline	At least in 12 months	At least every 12 months	At least every 12 months	1 month	Not defined
SwedAD, Sweden	Baseline	Usually 1 month (not specifically defined)	3-6 months (not specifically defined)	3-6 months (not specifically defined)	Not defined	- Therapy side-effects - Therapy switch

AtopyReg, Italy	Baseline	6 months	6 months	6 months	1 month	Not defined

Table 4. Pooling ability of the TREAT core dataset domain items for each registry

		Registry name, country							
Domain	**Domain item**	**A-STAR, UK and Ireland**	**TREAT NL, the Netherlands**	**TREATgermany, Germany**	**Biobadatop, Spain**	**SCRATCH, Denmark**	**FIRST, France**	**SwedAD, Sweden**	**AtopyReg, Italy**
Demographics	*Date of birth*	✓	✓	✓	✓	✓	✓	✓	✓
	Date of enrolment into registry	✓	✓	✓	✓	✓	✓	✓	✓
	Gender	✓	✓	✓	✓	✓	✓	✓	✓
	Ethnicity	✓	✓						✓
	Educational status	✓	✓	✓		✓	✓	✓	✓
	Current occupation or education	✓	✓	✓				✓	
AE diagnosis	How diagnosis AE is established	✓	✓			✓	✓		
	Use of validated diagnostic criteria	✓	✓	✓	✓		✓	✓	
	Date of onset AE	✓	✓	✓	✓	✓	✓	✓	✓
Past AE treatments	Phototherapy	✓	✓	✓	✓		✓		✓
	Systemic therapy	✓	✓	✓	✓	✓	✓		✓
	Topical treatments for AE	✓	✓	✓	✓		✓		✓
	Day hospital care treatments for AE (outpatient)		✓						
	Hospitalisation for AE	✓	✓						
Current AE treatments	Phototherapy	✓	✓	✓	✓		✓	✓	✓
	Systemic therapy	✓	✓	✓	✓	✓	✓	✓	✓
	Topical treatments for AE	✓	✓	✓	✓	✓	✓		✓
	Amount of topical creams/ointments used per week		✓						

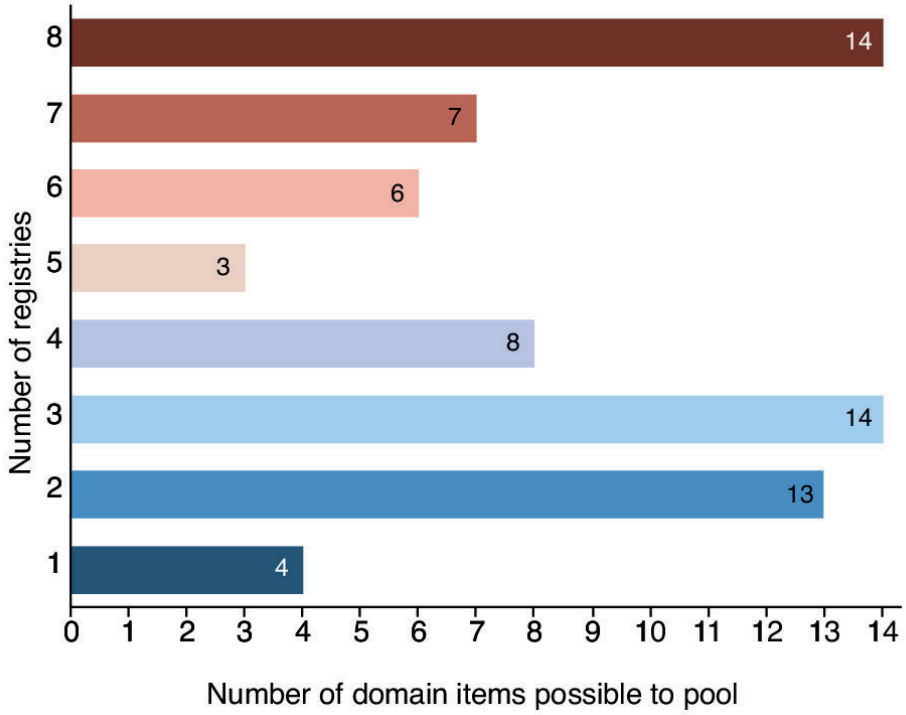
Family history of AE or allergic diseases	*Family history of AE or allergic diseases*	✓	✓	✓	✓	✓	✓	✓	✓
Allergic co-morbidities	*Asthma*	✓	✓	✓	✓	✓	✓	✓	✓
	Allergic rhinoconjunctivitis	✓	✓	✓	✓	✓	✓	✓	✓
	Atopic eye disease	✓	✓		✓	✓	✓		✓
	Eosinophilic oesophagitis	✓	✓		✓				✓
	Food allergies	✓	✓	✓		✓	✓		✓
	Contact allergies	✓	✓		✓				
Other past and current co-morbidities	Malignancies	✓	✓	✓	✓	✓	✓		✓
	Serious infections	✓	✓	✓	✓		✓		
	Other significant illnesses	✓	✓	✓	✓	✓	✓		✓
Current concomitant medication (i.e. other than specific AE medication)	Antihistamines	✓	✓	✓					✓
	Antibiotics	✓	✓	✓					
	Other medication relevant for AE treatment response	✓	✓						✓
	Immunosuppressives for other inflammatory diseases	✓	✓						
Baseline general AE questions	Exposures that trigger disease flares	✓	✓			✓	✓		
	Episodes of skin infection	✓	✓				✓		
	Days lost from usual activities (e.g. work, study)	✓	✓						
Baseline physical examination	Fitzpatrick skin type	✓	✓				✓		
	Skin examination	✓	✓				✓		✓
Baseline physician- and patient-reported domains	*Physician-assessed clinical signs*	✓	✓	✓	✓	✓	✓	✓	✓
	Investigator/physician global assessment	✓	✓	✓			✓		✓
	Patient-reported symptoms	✓	✓	✓	✓	✓	✓	✓	✓

	Patient global assessment		✓				✓		✓
	Generic quality of life score	✓	✓	✓					
	Skin-specific quality of life score	✓	✓	✓	✓	✓	✓	✓	✓
	Patient-reported satisfaction with AE care received		✓	✓		✓			
	Impact of AE on the family		✓						
Baseline investigations	Full blood count	✓	✓						
	Liver function	✓	✓						
	Kidney profile	✓	✓						
	Evaluating TPMT level prior to azathioprine use	✓	✓						
Baseline management	Main reasons for choosing specific treatment (systemic or phototherapy)	✓	✓	✓					
	Relative contraindication(s) for selected treatment	✓	✓						
Follow up general AE questions	Days lost from usual activities	✓	✓	✓		✓			
	Change in diagnosis after enrolment	✓	✓						
	Date of death and relation to AE	✓	✓	✓					
Follow up physical examination	Skin examination	✓	✓				✓		✓
Follow up physician- and patient-reported domains	*Physician-assessed clinical signs*	✓	✓	✓	✓	✓	✓	✓	✓
	Investigator/physician global assessment	✓	✓	✓			✓		✓
	Patient-reported symptoms	✓	✓	✓	✓	✓	✓	✓	✓
	Patient global assessment		✓				✓		
	Generic quality of life score	✓	✓	✓					
	Skin-specific quality of life score	✓	✓	✓	✓	✓	✓	✓	✓
	Patient-reported satisfaction with AE care received		✓	✓		✓			

	Impact of AE on the family		✓						
Follow up investigations	Full blood count	✓	✓						
	Liver function	✓	✓						
	Kidney profile	✓	✓						
Follow up adverse events	Severe adverse events	✓	✓	✓	✓	✓		✓	
Follow up management	Reason for switching therapy	✓	✓		✓				
	Reason for discontinuation of therapy	✓	✓	✓	✓	✓		✓	✓
Total number domain items scored positive on pooling ability		61	69	39	29	28	36	20	34

The domain items displayed in *italics* are deemed possible to pool across all eight registries.

Figure 1. Pooling ability of domain item outcomes according to the number of registries



Dark red bar – the following 14 domain items are deemed possible to pool across eight registries: 'date of birth', 'date of enrolment into registry', 'gender', 'date of onset AE', 'systemic therapy (current)', 'family history of AE or allergic diseases', 'asthma', 'allergic rhinoconjunctivitis', 'physician-assessed clinical signs (baseline and follow-up)', 'patient-reported symptoms (baseline and follow-up)', 'skin-specific quality of life score (baseline and follow-up)';
Red bar – the following seven domain items are deemed possible to pool across seven registries: 'educational status', 'systemic therapy (past)', 'phototherapy (current)', 'topical treatments for AE (current)', 'malignancies', 'other significant illnesses', 'reason for discontinuation of therapy';
Pink bar – the following six domain items are deemed possible to pool across six registries: 'use of validated diagnostic criteria', 'phototherapy (past)', 'topical treatments for AE (past)', 'atopic eye disease', 'food allergies', 'severe adverse events';
Light pink bar – the following three domain items are deemed possible to pool across five registries: 'serious infections', 'investigator/physician global assessment (baseline and follow-up)';
Light purple bar – the following eight domain items are deemed possible to pool across four registries: 'current occupation or education', 'how diagnosis AE is established', 'eosinophilic oesophagitis', 'antihistamines', 'exposures that trigger disease flares', 'skin examination (baseline and follow-up)', 'days lost from usual activities (follow-up)';
Light blue bar – the following 14 domain items are deemed possible to pool across three registries: 'ethnicity', 'contact allergies', 'antibiotics', 'other medication relevant for AE treatment response', 'episodes of skin infection', 'Fitzpatrick skin type', 'patient global assessment (baseline)', 'generic quality of life score (baseline and follow-up)', 'patient-reported satisfaction with AE care received (baseline and follow-up)', 'main reasons for choosing specific treatment (systemic or phototherapy)', 'date of death and relation to AE', 'reason for switching therapy';
Blue bar – the following 13 domain items are deemed possible to pool across two registries: 'hospitalisation for AE', 'immunosuppressives for other inflammatory diseases', 'days lost from usual activities (baseline)', 'full blood count (baseline and follow-up)', 'liver function (baseline and follow-up)', 'kidney profile (baseline and follow-up)', 'evaluating TPMT level prior to azathioprine use', 'relative contraindication(s) for selected treatment', 'change in diagnosis after enrolment', 'patient global assessment (follow-up)';
Dark blue bar – the following four domain items are registered in one registry: 'day hospital care treatments for AE (outpatient)', 'amount of topical creams/ointments used per week', 'impact of AE on the family (baseline and follow-up)'.

DISCUSSION

The overview of the status and characteristics presented here provides insight into the current AE treatment registries within the TREAT Registry Taskforce. Since inception, the TREAT Registry Taskforce has aimed to develop an international platform to uniformly collect long-term data on the (cost-)effectiveness and safety of systemic immunomodulating therapies and/or phototherapy in patients with AE. As per May 1, 2022, the established registries participating within the TREAT Registry Taskforce have jointly collected data of over 4,700 patients. The registries have already been publishing their first results on patient characteristics, treatment effectiveness and safety individually.[11, 12] The next step is to increase the power of the data of individual countries by pooling data across registries. As described, the TREAT Registry Taskforce has developed a core dataset to be used in all registries and a protocol to enable this cross-border data pooling.[8, 10] The current study has revealed both similarities and differences regarding the degree of core dataset use and pooling ability between registries within the TREAT Registry Taskforce.

Similarities between the registries cover the main aims of collecting data on the effectiveness, safety and cost-effectiveness of AE therapies. Pooled analyses across all registries can be performed on the following domain items: 'date of birth', 'date of enrolment into registry', 'gender', date of onset of AE, 'systemic therapy', 'family history of AE or allergic diseases', 'asthma', 'allergic rhinoconjunctivitis', 'physician-assessed clinical signs' (e.g. EASI) (baseline and follow-up), 'patient-reported symptoms' (e.g. POEM) (baseline and follow-up) and 'skin-specific quality of life score' (baseline and follow-up). These items cover important effectiveness outcomes. As for safety, six registries collect data on severe and serious adverse events. Cost-effectiveness analyses can be performed using the generic quality of life score EQ-5D. Data collection on EQ-5D is included in three registries. We found that all HOME core outcomes, except from long-term control, were collected by all eight registries within the TREAT Registry Taskforce. As a result, comparative and pooled analyses on effectiveness and pharmacovigilance are feasible.

Despite the aspired use of an uniform core dataset, differences in data collection were identified. These differences may pose potential challenges in data pooling and synthesis. They may have resulted from various factors, including the use of different data entry platforms per registry. Further, countries may have given their own interpretation to core dataset items. Also the high number of domains and domain items included in the core dataset have compromised its feasibility, despite the fact that feasibility aspects were considered in the TREAT core dataset consensus seeking process. This was indicated by the members (n=23) of the taskforce in a survey, held after finalizing the mapping exercise to clarify the use of the core dataset in their registries. Feasibility was the main reason for not including all core dataset items. Fortunately, the majority of the registries have indicated that they are willing to adapt their registry dataset to overcome potential important differences. We suggest that, in addition to the items that are already being collected by all eight registries, every registry should at least also garther information on safety (i.e. the domain item 'severe adverse events') and cost-effectiveness (i.e. the domain items 'generic quality of life score (baseline and follow-up)').

For future international analyses one should not only take differences in registry datasets into consideration, but also differences in prescribing practices (e.g. patient indications), reimbursement restrictions and in- and exclusion criteria, which underlie potential variations in patient populations across the registries. Another factor to consider is that, due to national regulations and preferences, different modalities for data collection (e.g. the data entry platform) and languages are used across countries. Therefore, some challenges for synthesizing data in a network of registries will always remain, leading to potential methodological difficulties. When performing inter-country analyses, these differences should be taken into consideration in the analyses and interpretation of results.

Future perspectives and recommendations

The results of the mapping exercise inform on which data from which registries can be used to answer specific research questions and therefore will facilitate comparative or joint analyses across country borders in the future. While considerable differences between the registries exist, comparative and pooled treatment (cost)effectiveness and pharmacovigilance analyses are feasible. This is in particular important and encouraging, as rare but important adverse events (e.g. malignancies) demand investigation in large numbers of patients. Studies within the taskforce will run as investigator-led projects but we are open to project proposals requested by other researchers, clinicians and stakeholders. As a next step, the technical compatibility of the registry data will be assessed in a separate pooling exercise. In addition, we are currently performing an analysis on baseline demographic and clinical characteristics of patients included in all registries.

The present study informs researchers worldwide who are engaged in similar data harmonization processes in international research groups studying other diseases and who are aiming to perform pooled and comparative analyses in the future. In case a centralized data entry platform across registries and countries is impossible, our strong recommendation is to undertake substantial efforts to align and uniform datasets, preferably before inception of the databases. Feasibility should be a major criterion when a core dataset is developed. Finally, we would like to invite and encourage other national AE treatment registries to join TREAT (treat-registry-taskforce.org).

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SUPPLEMENTARY MATERIAL

Supplementary table 1. The complete results of the mapping exercise with the assessment of the presence of core dataset domain items and measurement instruments, and the pooling ability of measurement instruments and domain items.

A digital version of Supplementary table 1 can be found at:

CHAPTER 5

FIRST CROSS-BORDER ANALYSES OF 5337 ATOPIC ECZEMA PATIENTS TREATED WITH SYSTEMIC IMMUNOMODULATORY TREATMENT, PHOTOTHERAPY AND TOPICAL THERAPIES ENROLLED IN 7 EUROPEAN REGISTRIES UNITED IN THE TREATMENT OF ATOPIC ECZEMA (TREAT) REGISTRY TASKFORCE

On behalf of the A-STAR, AtopyReg, BIOBADATOP, SCRATCH, SwedAD, TREATgermany and TREAT NL/BE registry teams

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Manuscript submitted

ABSTRACT

Background

The TREatment of ATopic eczema (TREAT) Registry Taskforce, comprising international independent multi-center registries, endeavors to generate dependable real-world data on the enduring efficacy, cost-effectiveness, and safety of systemic immunomodulating treatments and phototherapy for patients with atopic eczema (AE).

Objectives

This study seeks to present a comprehensive overview of the demographics, prior systemic treatments, clinical characteristics, and disease severity and burden at baseline among patients enrolled in seven TREAT registries. Moreover, the aim is to gain insight into the differences between the registries and to explore the current prescribing practices of various therapies for patients with AE across Europe.

Methods

Data on sociodemographics, treatment characteristics, and AE severity and burden were collected up to October 31, 2022, from seven prospective observational cohorts within the TREAT Registry Taskforce: A-STAR registry (United Kingdom and Ireland), AtopyReg registry (Italy), Biobadatop registry (Spain), SCRATCH registry (Denmark), SwedAD registry (Sweden), TREATgermany registry (Germany), and TREAT NL/BE registry (the Netherlands and Belgium).

Results

Analysis included 5337 patients (mean age 39.1 years, 6.3% paediatric patients, 54.4% male). Of these, 3775 (84.1%) had a history of systemic treatment, with systemic corticosteroids (58.8%) and ciclosporin (39.0%) being the most commonly prescribed. Phototherapy had been received by 1212 (30.1%) patients prior to enrolment. At enrolment, dupilumab was prescribed most commonly (75.0%), followed by ciclosporin (7.8%). Janus Kinase inhibitors were initiated in 5.9% of patients. Phototherapy was infrequently initiated at baseline (1.7%). Most patients had moderate (41.9%) to severe (30.1%) AE, as assessed by the Validated Investigator Global Assessment (vIGA) scale, with a mean Eczema Area and Severity Index (EASI) score of 17.6 (±12.1). The mean Patient-Oriented Eczema Measure (POEM) score was 17.2 (±7.7), indicating severe disease. The mean Dermatology Life Quality Index (DLQI) score was 13.4 (±8.5), and the Numerical Rating Scale (NRS) for peak pruritus over the past 24 hours was 6.4 (±3.0).

Conclusions

This pooled analysis from the TREAT Registry Taskforce highlights the variability and similarities in data collection across national registries, providing significant insights into the baseline characteristics of the patient population. It establishes a robust foundation for future analyses of key effectiveness and safety outcomes.

INTRODUCTION

Atopic eczema (AE), or atopic dermatitis, is a common chronic inflammatory skin condition which affects both children and adults and inflicts a major burden on patients' quality of life[1–4]. Topical treatment is the first-choice step in the treatment algorithm for most patients, but patients with moderate to severe AE often need additional management with phototherapy or systemic immunomodulatory treatment or to induce sustained disease control[5,6]. Therapeutic options have expanded in recent years, with the introduction of the biologics dupilumab in 2017 and tralokinumab in 2020 as well as three Janus Kinase inhibitors (JAKi) (baricitinib, upadacitinib and abrocitinib) in 2020 and 2021[7–12]. Prior to 2017, ciclosporin was the only systemic treatment for AE that was approved by the European Medicines Agency (EMA). However, recent surveys show that other systemic immunosuppressive therapies such as methotrexate and oral corticosteroids, and phototherapy are frequently prescribed as off-label therapies for AE, albeit increasingly less often than in the past[5,13,14]. Evidence on the long-term safety, effectiveness and cost-effectiveness for most systemic immunomodulating treatments prescribed for AE in a real-world setting is sparse[15,16]. The TREatment of ATopic eczema (TREAT) Registry Taskforce therefore aims to generate reliable real-world data on long-term effectiveness and safety of systemic immunomodulatory treatments and phototherapy in AE patients across country borders[17]. To achieve this, an international network of independent prospective multi-centre registries was set up in 2017. The TREAT Registry Taskforce has developed a core dataset, consisting of domains and domain items with corresponding measurement instruments, to be captured in all registries, to harmonize data collection[18,19]. The Harmonizing Outcome Measures for Eczema (HOME) recommendations were followed to develop the TREAT core dataset[20].

Currently, 8 independent registries from 10 countries are members of the TREAT Registry Taskforce, including the TREAT NL/BE registry (the Netherlands and Belgium), the A-STAR registry (The UK-Irish Atopic Eczema Systemic Therapy Register; United Kingdom and Ireland), TREATgermany registry (Germany), Biobadatop registry (Spain), SCRATCH registry (Severe and ChRonic Atopic dermatitis Treatment CoHort, Denmark), SwedAD registry (Sweden), AtopyReg registry (Italy) and FIRST registry (French atopIc deRmatitiS cohorT, France; unable to participate in this in analysis). Findings of various studies conducted by the individual national TREAT registries have been published[21–31]. However, no cross-border studies including multiple registries have been performed yet.

A recent publication of the TREAT Registry Taskforce provides an overview of the status and characteristics of the eight established TREAT registries[32]. In addition, the results of a mapping exercise are presented, which was performed to examine the degree of overlap between the TREAT core dataset and the registry dataset and pooling ability between the different registry datasets. This mapping exercise has confirmed large alignment of core outcomes but also some differences; importantly, confirming that pooled analyses across all registries can be performed. As a sequel to our previous work, the current study aims to demonstrate the ability to pool data and to perform cross-border analyses between various TREAT registries. The objective of this study is to give an overview of the baseline demographics, treatment characteristics, AE severity and disease burden of patients enrolled in 7 registries participating within the TREAT Registry Taskforce. Moreover, the aim is to gain insight into the differences between the registries and to explore the current prescribing practices of various therapies for children and adults with AE across Europe.

PATIENTS AND METHODS

Study design and population

The current analysis includes data on all patients that were included between the date of first inclusion (varying between registries) and October 31st 2022 in 7 out of 8 established registries in the TREAT registry Taskforce. FIRST registry (France) was unable to participate in this in analysis, since it was in the start-up phase.

The registries that have joined the TREAT Registry Taskforce are ongoing, prospective, observational cohorts including patients with AE who are commencing on or switching to another systemic immunomodulatory treatment and/or phototherapy as well as topical therapies. No wash-out period was implemented. Written informed consent for study participation obtained from the patient (or parents/legal guardian), except from SwedAD which is a national quality registry obtaining oral informed consent. *Table 1* presents a brief summary of the inclusion criteria. A detailed overview of the inclusion and exclusion criteria of the different TREAT registries can be found in our most recent publication[32].

Table 1. Inclusion criteria

Registry name, country	Inclusion criteria
TREAT NL/BE, the Netherlands and Belgium	- Age: all - Treatment: initiating phototherapy or any type of systemic immunomodulating therapy - AE severity: all
A-STAR, UK and Ireland	- Age: all - Treatment: initiating phototherapy or any type of systemic immunomodulating therapy - AE severity: all
TREATgermany, Germany	- Age: ≥ 18 years o Children and adolescents are included in TREATkids - a separate part of TREATgermany. - Treatment: initiating topical treatment, phototherapy or any type of systemic immunomodulating therapy - AE severity: o Moderate-to-severe AE ▪ Objective SCORAD > 20, or; ▪ Currently anti-inflammatory systemic treatment for AE, or; ▪ Previous anti-inflammatory systemic treatment for AE within past 24 months.
Biobadatop, Spain	- Age: all - Treatment: first time use of systemic immunomodulating therapy - AE severity: all
SCRATCH, Denmark	- Age: all - Treatment: initiating advanced systemic therapy - AE severity: moderate-to-severe AE
SwedAD, Sweden	- Age: all - Treatment: initiating phototherapy or any type of systemic immunomodulating therapy - AE severity: all
AtopyReg, Italy	- Age: ≥ 18 years - Treatment: initiating phototherapy or any type of systemic immunomodulating therapy - AE severity: o Moderate-to-severe AE ▪ EASI ≥ 16 ▪ EASI <16 but with at least one of the following conditions: • Localization in at least one of the following "critical" sites: face, hands, genitalia • DLQI > 10 • Itch VAS > 7 • Sleep VAS > 7

Data collection and outcome measures

For this study, only a selection of the domain items of the core dataset were analysed. Baseline sociodemographic data (sex, age, and level of education) was requested from each registry. According to the core dataset, educational status is measured using the International Standard Classification of Education (ISCED)[33]. However, not all registries use the ISCED as a tool to measure level of education[32]. In order to be able to pool data between registries that used other classification systems, the ISCED levels were merged into 3 categories: lower education (ISCED 0-2: early childhood education, primary education, lower secondary education), intermediate education (ISCED 3-4: upper secondary education, post-secondary non-tertiary education, short-cycle tertiary education) and tertiary education (ISCED 5-8: bachelor's or equivalent level, master's or equivalent level, doctoral or equivalent level). Other baseline characteristics included AE treatment before enrolment into the registry and AE treatment started at enrolment into the registry, physician-reported disease severity and patient-reported disease severity and burden of disease.

For baseline physician-reported outcomes, we collected validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD) (number of patients per category: clear, almost clear, mild, moderate, severe) and Eczema Area and Severity Index (EASI) scores (mean [standard deviation (SD)] and number of patients per category: mild [>0 to <6], moderate [6 to <23], severe [23 to 72])[34,35]. Biobadatop (ES), SCRATCH (DK) and SwedAD (SE) did not collect vIGA-AD. For patient-reported outcomes (PROs), the Patient Oriented Eczema Measure (POEM) (mean [SD] and number of patients per category: clear or almost clear [0-2], mild [3-7], moderate [8-16], severe [17-24], very severe [25-28]), quality of life measured with the Dermatology Life Quality Index (DLQI) (adults), Children's Dermatology Life Quality Index (CDLQI) (children) or Infants' Dermatitis Quality of Life Index (IDQOL) (infants) (scale 0-30) (mean [SD]) and Numerical Rating Scale (NRS) peak pruritus (scale 0-10) over the past 24 hours (mean [SD]) were collected[36–40]. SCRATCH (DK) used the NRS peak pruritus over the past 72 hours instead of 24 hours and Biobadatop used VAS pruritus over the past 24 hours instead of NRS pruritus.

Statistical analyses

Descriptive statistics including means and SDs were used for continuous variables. Frequencies and percentages were used for categorical or ordinal data. Analyses were performed using IBM SPSS Statistics version 26 for Windows, and Microsoft Excel version 16.54. Statistical analyses were performed using R Studio software. The means/SDs and associated p-value comparisons were generated using a sampling procedure. This procedure involved determining the means and SDs based on the normal distribution corresponding to the specified number of patients. For each registry, the specified means and SDs were used to sample a specific number of patients, ensuring that the sampled data matched the given statistical parameters. To investigate the differences between registries, we used ANOVA and Chi-squared tests. This method allowed for straightforward comparison of the means between cohorts.

RESULTS

Table 2 shows the number of participating academic and non-academic centres and included patients between the date of first inclusion and October 31st 2022 in the 7 different registries.

Baseline socio-demographics

Baseline socio-demographics of patients included in the registries are summarized in *Table 3.* Between June 2016 and October 31st 2022, a total of 5337 patients were enrolled in the 7 TREAT registries, ranging from 256 (Biobadatop, ES) to 1587 (TREATgermany, DE) patients per registry. Patients had a mean (SD) age of 39.1 years (17.8) ($p<0.01$), ranging from 26.0 years in A-STAR (UK/IE) to 43.0 years in AtopyReg (IT). Five registries included children, with a total number of 335 (6.3%) paediatric patients. A slight majority of patients were male (54.4%), and this male predominance is seen in all registries ($p<0.05$). 15.8% of patients had followed lower education (ISCED 0-2), 52.0% intermediate education (ISCED 3-4) and 32.2% tertiary education (ISCED 5-8) ($p<0.01$). Biobadatop (ES) did not collect data on level of education. Differences can be seen regarding education level between countries, for instance, the majority (56.3%) of the patients in SCRATCH (DK) have tertiary education levels, while in other registries this was not the case.

Table 2. Number of participating centres and included patients between the date of first inclusion and October 31st 2022

	TREAT NL/BE, the Netherlands and Belgium	A-STAR, United Kingdom and Ireland	TREATgermany, Germany	Biobadatop, Spain	SCRATCH, Denmark	SwedAD, Sweden	AtopyReg, Italy	All registries
Month and year of first inclusion	Nov 2017	Oct 2018	Jun 2016	Apr 2020	Oct 2017	Sep 2019	Jun 2020	
Number of inclusions	617	394	1587	256	460	850	1173	**5337**
Number of participating centres	9	24	65	8	5	39	25	**175**
n (%) academic centers	4 (44.44)	20 (83.33)	17 (26.15)	8 (100)	5 (100)	12 (30.77)	25 (100)	91 (52.00)
n (%) inclusions in academic centers	584 (94.65)	374 (94.92)	1041 (65.60)	256 (100)	460 (100)	637 (74.94)	1173 (100)	4525 (84.79)
n (%) non-academic centers	5 (55.56)	4 (16.67)	48 (73.85)	0 (0.00)	0 (0.00)	27 (69.23)	0 (0.00)	84 (48.00)
n (%) inclusions in non-academic centers	33 (5.35)	20 (5.08)	546 (34.40)	0 (0.00)	0 (0.00)	213 (25.06)	0 (0.00)	812 (15.21)

Table 3. Baseline socio-demographics

		TREAT NL/BE, the Netherlands and Belgium	A-STAR, United Kingdom and Ireland	TREATgermany, Germany	Biobadatop, Spain	SCRATCH, Denmark	SwedAD, Sweden	AtopyReg, Italy	All registries	p-value
Baseline socio-demographics										
Sex	*n (%) patients per category:*	**n patients = 617**	**n patients = 394**	**n patients = 1587**	**n patients = 256**	**n patients = 460**	**n patients = 850**	**n patients = 1173**	**n patients = 5337**	*p < 0.05*
	Male	331 (53.65)	232 (58.88)	886 (55.83)	139 (54.30)	274 (59.57)	446 (52.47)	602 (51.32)	2910 (54.53)	
	Female	286 (46.35)	162 (41.12)	701 (44.17)	117 (45.70)	186 (40.43)	404 (47.53)	571 (48.68)	2427 (45.47)	
	Other	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	
Age	*Mean (SD)*	35.59 (16.28)	26.06 (15.70)	40.30 (14.80)	32.60 (16.20)	40.05 (16.60)	41.20 (18.60)	43.00 (20.68)	39.12 (17.84)	*p < 0.01*
	Adult patients	577 (93.52)	258 (65.48)	1587 (100)	207 (80.86)	425 (92.39)	775 (91.18)	1173 (100)	5002 (93.72)	
	Paediatric patients	40 (6.48)	136 (34.52)	0 (0.00)*	49 (19.14)	35 (7.61)	75 (8.82)	0 (0.00)	335 (6.28)	
Level of education	*n (%) patients per category:*	**n patients = 473**	**n patients = 383**	**n patients = 1562**	**n/a**	**n patients = 295**	**n patients = 433**	**n patients = 899**	**n patients = 4048**	*p < 0.01*
	Lower education	84 (17.76)	83 (21.67)	203 (13.00)	n/a	46 (15.59)	38 (8.78)	185 (20.58)	640 (15.81)	
	Intermediate education	220 (46.51)	147 (38.38)	972 (62.23)	n/a	83 (28.14)	198 (45.27)	480 (53.39)	2103 (51.95)	
	Tertiary education	169 (35.73)	153 (39.95)	387 (24.78)	n/a	166 (56.27)	197 (45.50)	234 (26.03)	1305 (32.24)	

n/a = not available

* children and adolescents are included in TREATkids - a separate part of TREATgermany

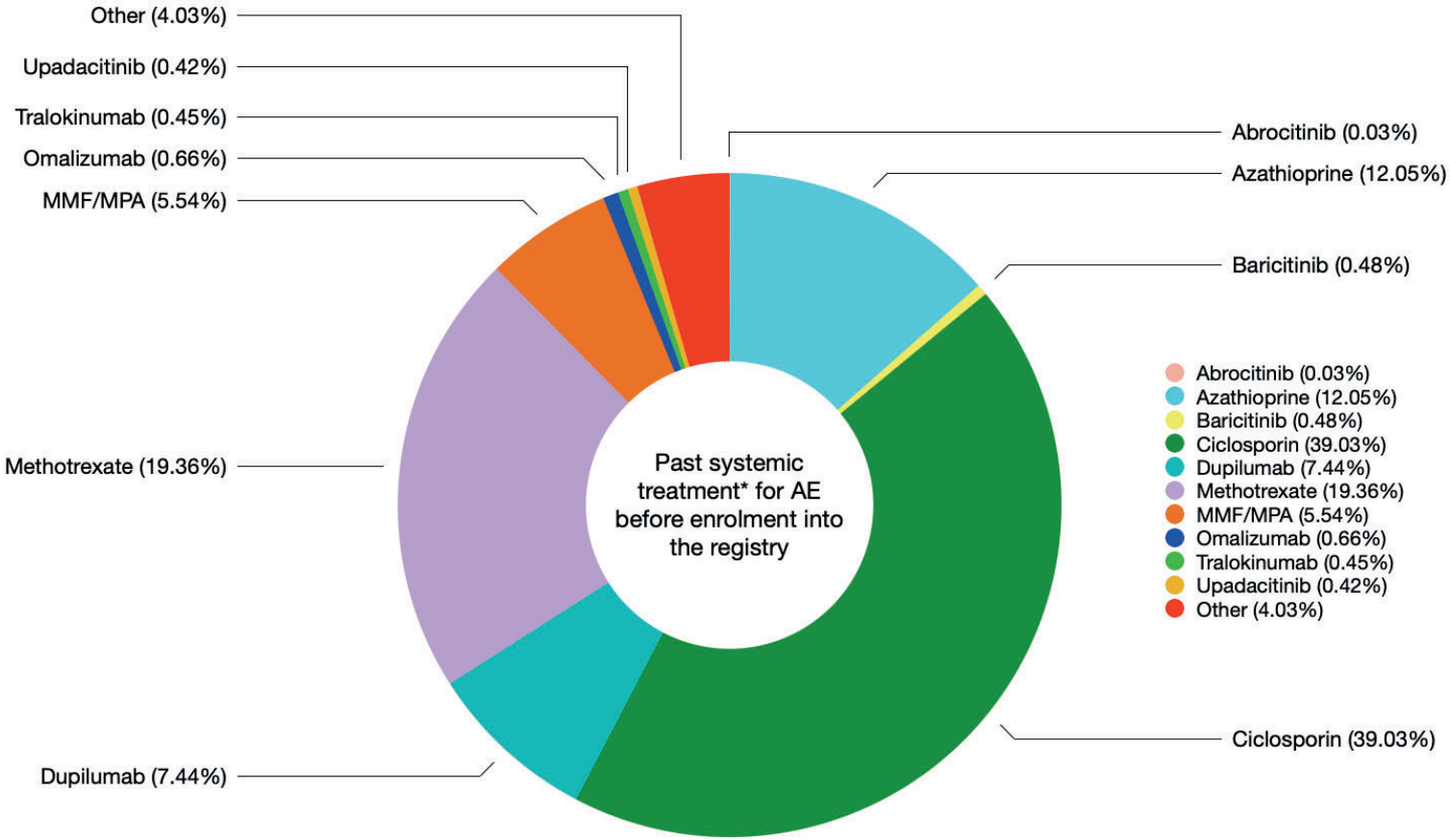
Past treatments before enrolment into the registry

A complete overview of the past AE treatments patients received before their enrolment into the registries is shown in *Table 4* and *Figures 1-2.* Due to the fact that systemic corticosteroids are typically administered as short-term courses to manage flares, the number of patients treated with systemic corticosteroids in the past are not shown in the figures.

3775 (84.1%) patients were treated with any type of systemic treatment before they were enrolled into the registry. Noteworthy, SwedAD (SE) did not collect data on past AE treatment. Patients with prior exposure to systemic medications underwent a cumulative total of 5598 systemic treatment courses, reflecting an average of 1.5 previous systemic treatments per patient. The majority of patients received (short courses of) systemic corticosteroids (58.8%) as a past treatment for their AE, ranging from 25.3% (A-STAR [UK/IE]) to 59.7% (AtopyReg [IT]) of patients. Ciclosporin, methotrexate, azathioprine and mycophenolate mofetil (MMF) or mycophenolic acid (MPA) were administered to 39.0%, 19.4%, 12.1% and 5.5% of patients, respectively. However, substantial differences in the proportions of patients having received certain systemic treatments for their AE in the past exist between the registries ($p<0.01$). For example, in SCRATCH (DK), the majority of patients previously received azathioprine (66.1%), while this percentage is considerably lower in most other registries. Moreover, in TREAT NL/BE (NL/BE), 20.0% of patients received previous treatment with MMF/MPA, while this number is much lower in the other registries. In total, 7.4% of patients received past treatment with dupilumab before enrolment. Past treatments before enrolment with other biologicals (tralokinumab and omalizumab), JAKi (baricitinib, upadacitinib and abrocitinib) and other treatments were only prescribed to a small proportion of patients in the current analysis.

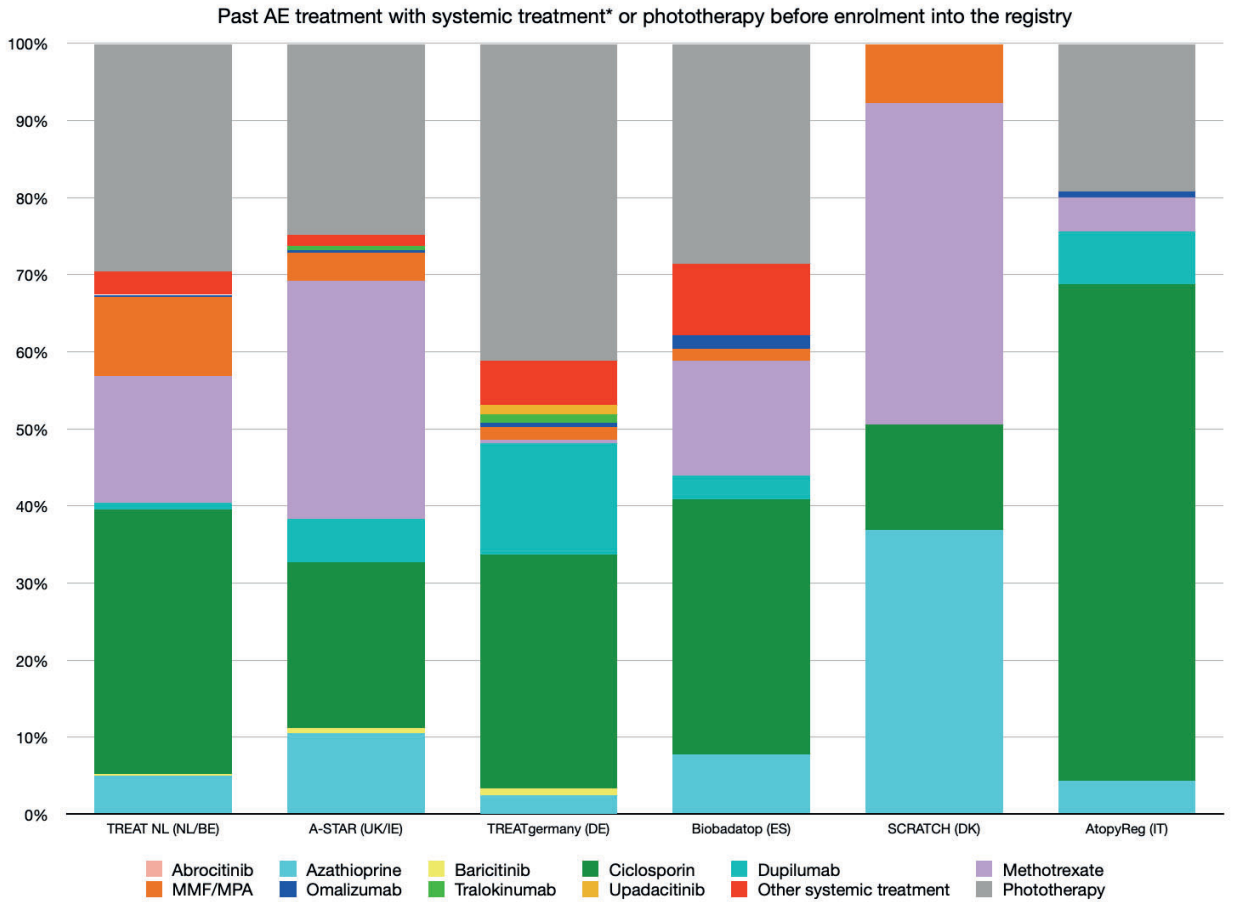
A total of 1212 (30.6%) patients received any type of phototherapy prior to enrolment ($p<0.01$). However, two registries (SCRATCH [DK], SwedAD [SE]) did not collect data on treatment history with phototherapy. Of the registries collecting data on past topical treatment, most patients had some form of topical therapy before enrolment. TREATgermany collects data on topical treatment only for the past year prior to inclusion.

Figure 1. Past systemic treatment for atopic eczema (AE).



3775 patients had previous systemic treatment, with potential for 0 or >1 treatment per patient. *Any systemic treatment besides systemic corticosteroids. SwedAD registry does not collect data on past systemic treatment.

Figure 2. Past atopic eczema (AE) treatment with systemic treatment or phototherapy before enrolment into each registry.



Total number of treatments = 4591. MMF/MPA = mycophenolate mofetil or mycophenolic acid.*Any systemic treatment besides systemic corticosteroids. SwedAD (SE) does not collect data on past systemic treatment. SwedAD (SE) and SCRATCH (DK) do not collect data on past treatment with phototherapy.

Table 4. Past AE treatments before enrolment into the registry

		TREAT NL/BE, the Netherlands and Belgium	A-STAR, United Kingdom and Ireland	TREATgermany, Germany	Biobadatop, Spain	SCRATCH, Denmark	SwedAD, Sweden	AtopyReg, Italy	All registries	p-value
Past AE treatments before enrolment into the registry										
Systemic treatment	*n (%) patients per category:*	**n patients*= 534**	**n patients*= 391**	**n patients*= 1063**	**n patients*= 256**	**n patients*= 381**	**n/a**	**n patients*= 1150**	**n patients*= 3775**	*p < 0.01*
	Methotrexate	173 (32.40)	184 (47.06)	5 (0.47)	59 (23.05)	285 (74.80)	n/a	25 (2.17)	731 (19.36)	
	Ciclosporin	361 (67.60)	128 (32.74)	390 (36.69)	131 (51.17)	94 (24.67)	n/a	370 (32.17)	1474 (39.03)	
	Azathioprine	53 (9.93)	63 (16.11)	31 (2.92)	31 (12.11)	252 (66.14)	n/a	25 (2.17)	455 (12.05)	
	MMF/MPA#	107 (20.04)	22 (5.63)	21 (1.98)	6 (2.34)	53 (13.91)	n/a	0 (0.00)	209 (5.54)	
	Systemic corticosteroids	306 (57.30)	99 (25.32)	830 (78.08)	125 (48.83)	173 (45.41)	n/a	686 (59.65)	2219 (58.78)	
	Dupilumab	9 (1.69)	34 (8.70)	187 (17.59)	12 (4.69)	0 (0.00)	n/a	39 (3.39)	281 (7.44)	
	Omalizumab	3 (0.56)	2 (0.51)	8 (0.75)	7 (2.73)	0 (0.00)	n/a	5 (0.43)	25 (0.66)	
	Baricitinib	2 (0.37)	4 (1.02)	12 (1.13)	0 (0.00)	0 (0.00)	n/a	0 (0.00)	18 (0.48)	
	Tralokinumab	0 (0.00)	3 (0.77)	14 (1.32)	0 (0.00)	0 (0.00)	n/a	0 (0.00)	17 (0.45)	
	Upadacitinib	1 (0.19)	0 (0.00)	15 (1.41)	0 (0.00)	0 (0.00)	n/a	0 (0.00)	16 (0.42)	
	Abrocitinib	0 (0.00)	0 (0.00)	1 (0.09)	0 (0.00)	0 (0.00)	n/a	0 (0.00)	1 (0.03)	
	Other"	31 (5.81)	9 (2.30)	75 (7.06)	37 (14.45)	n/a	n/a	0 (0.00)	152 (4.03)	
	n missing or unknown	2	0	3	0	0	n/a	0	5	
Phototherapy		**n patients = 311**	**n patients = 148**	**n patients = 530**	**n patients = 113**	**n/a**	**n/a**	**n patients = 110**	**n patients = 1212**	*p < 0.01*
	n missing or unknown	51	7	1	3	n/a	n/a	0	62	
Topical treatment	*n (%) patients per category:*	**n patients = 345**	**n patients = 391**	**n patients = 1586**	**n patients = 258**	**n/a**	**n/a**	**n patients = 1040**	**n patients = 3620**	*p < 0.01*
	Corticosteroids	340 (98.55)	320 (81.84)	n/a^	252 (97.67)	n/a	n/a	n/a	912 (91.75)	
	Calcineurin inhibitors	199 (57.68)	14 (3.58)	n/a^	102 (39.53)	n/a	n/a	n/a	315 (31.69)	
	Tar-ointments	71 (20.58)	53 (13.55)	n/a	n/a	n/a	n/a	n/a	124 (16.85)	
	Other	4 (1.16)	52 (13.30)	n/a	5 (1.94)	n/a	n/a	n/a	61 (6.14)	
	n missing or unknown	277	0	1	0	n/a	n/a	n/a	278	

n/a = not available

* total number of patients who had previous systemic treatment, with potential for 0 or >1 treatment per patient.

mycophenolate mofetil or mycophenolic acid.

" other systemic treatments may include trial medications.

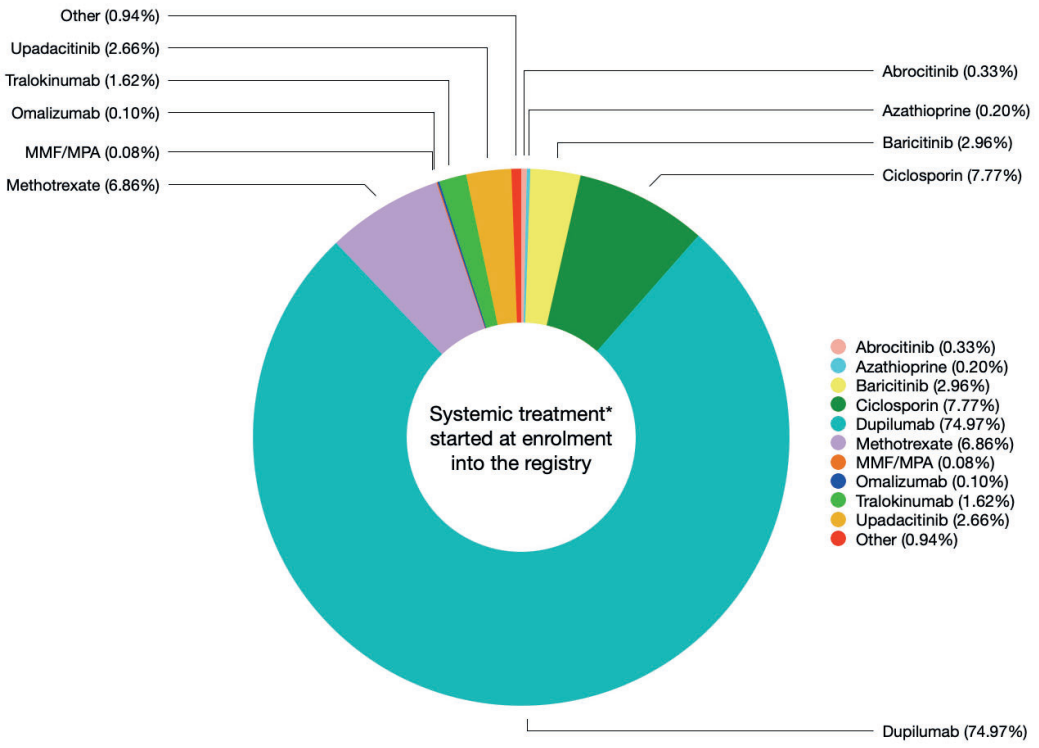
^ a total of 1457 patients were treated with topical corticosteroids and/or calcineurin inhibitors in the past.

Treatments started at enrolment into the registries

Table 5 depicts an overview of the AE treatments that were initiated when patients were enrolled into the registries. The percentage of patients who started a particular systemic treatment (any treatment besides systemic corticosteroids) or phototherapy in the registries are shown in *Figures 3-4*.

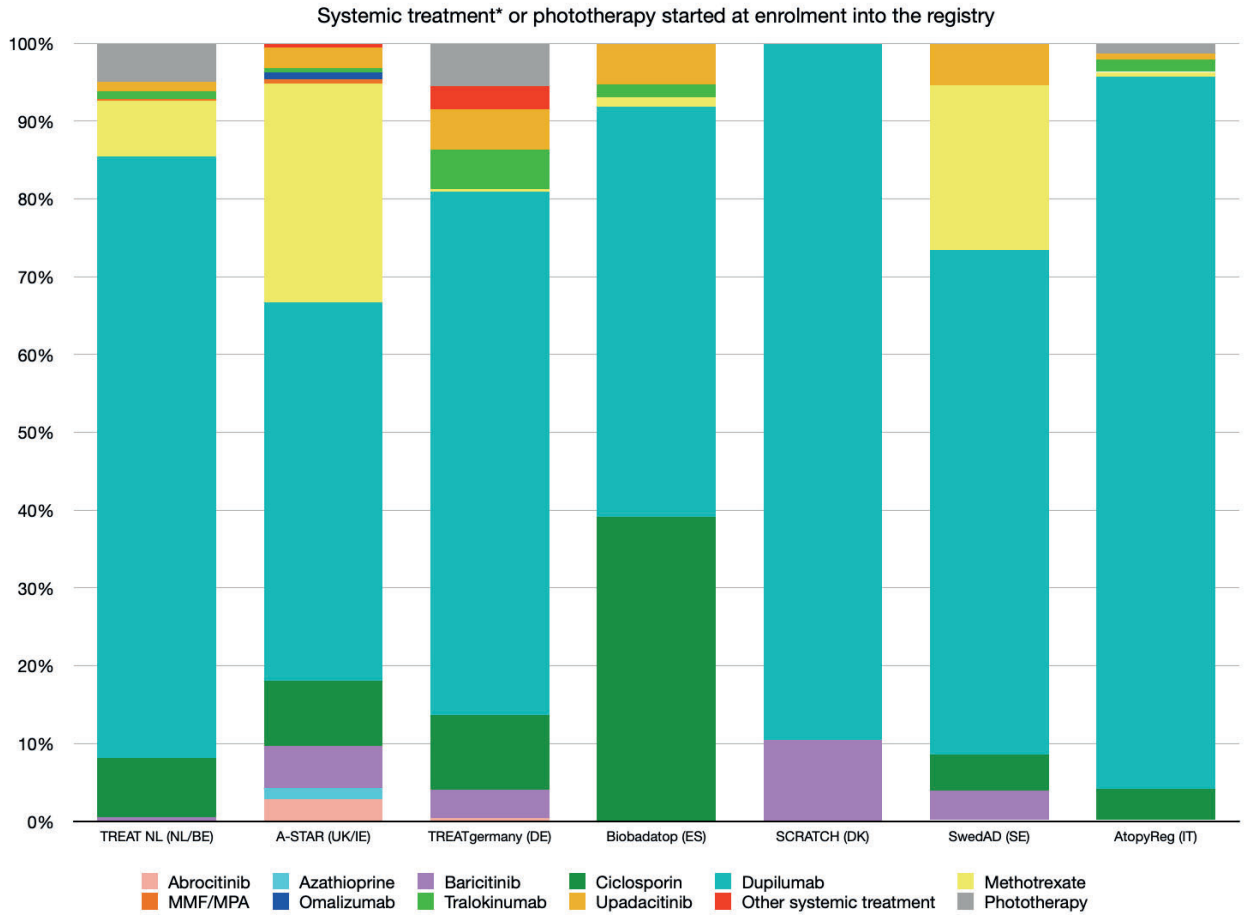
In this analysis, dupilumab was the most frequently prescribed drug at enrolment in all registries (75.0%). Less frequently prescribed therapies at baseline were ciclosporin (7.8%), methotrexate (6.9%), baricitinib (3.0%) and upadactitinib (2.7%). However, SCRATCH (DK) did not include patients starting systemic treatment other than biologicals or JAKi. Noticeable inter-register differences were observed ($p<0.01$). For instance, a substantial proportion of patients started methotrexate treatment at enrolment into A-STAR (UK/IE) and SwedAD (SE) (26.7% and 21.2% of patients, respectively), whereas this number is considerably lower in the other registries. At the time of enrolment in Biobadatop (ES), the prescription rate of ciclosporin was notably higher (38.3%) compared to the other registries. Phototherapy was infrequently initiated at baseline in a total of 82 (1.7%) patients, although three registries (Biobadatop, SCRATCH and SwedAD) do not include patients initiating phototherapy. Finally, a large proportion of patients were prescribed (concomitant) topical treatment at the time of enrolment.

Figure 3. Systemic treatment started at enrolment into the registries.



3952 patients started a specific systemic treatment, with potential for 0 or >1 treatment per patient.
MMF/MPA = mycophenolate mofetil or mycophenolic acid.
*Any systemic treatment besides systemic corticosteroids. SCRACTH (DK) does not include patients on conventional systemic treatments.

Figure 4. Systemic treatment or phototherapy started at enrolment into each registry.



Total number of treatments = 3960. MMF/MPA = mycophenolate mofetil or mycophenolic acid. *Any systemic treatment besides systemic corticosteroids. SCRACTH (DK) does not include patients initiating conventional systemic treatments. Biobadatop (ES), SCRATCH (DK) and SwedAD (SE) do not include patients initiating phototherapy.

Table 5. Treatments started at enrolment into the registry

		TREAT NL/BE, the Netherlands and Belgium	A-STAR, United Kingdom and Ireland	TREATgermany, Germany	Biobadatop, Spain	SCRATCH, Denmark	SwedAD, Sweden	AtopyReg, Italy	All registries	p-value
Treatments started at enrolment into the registry										
Systemic treatment	*n (%) patients per category:*	**n patients*= 585**	**n patients*= 367**	**n patients*= 679**	**n patients*= 251**	**n patients*= 460**	**n patients*= 558**	**n patients*= 1052**	**n patients*= 3952**	*p < 0.01*
	Methotrexate	44 (7.52)	98 (26.70)	2 (0.29)	3 (1.20)	n/a	118 (21.15)	6 (0.57)	271 (6.86)	
	Ciclosporin	47 (8.03)	29 (7.90)	68 (10.01)	96 (38.25)	n/a	26 (4.66)	41 (3.90)	307 (7.77)	
	Azathioprine	0 (0.00)	5 (1.36)	0 (0.00)	0 (0.00)	n/a	1 (0.18)	2 (0.19)	8 (0.20)	
	MMF/MPA#	1 (0.17)	2 (0.54)	0 (0.00)	0 (0.00)	n/a	0 (0.00)	0 (0.00)	3 (0.08)	
	Systemic corticosteroids	2 (0.34)	9 (2.45)	19 (2.80)	6 (2.39)	n/a	0 (0.00)	40 (3.80)	76 (1.92)	
	Dupilumab	474 (81.03)	170 (46.32)	478 (70.40)	129 (51.39)	412 (89.57)	362 (64.87)	938 (89.16)	2963 (74.97)	
	Omalizumab	0 (0.00)	3 (0.82)	0 (0.00)	0 (0.00)	n/a	0 (0.00)	1 (0.10)	4 (0.10)	
	Baricitinib	3 (0.51)	19 (5.18)	26 (3.83)	0 (0.00)	48 (10.43)	21 (3.76)	0 (0.00)	117 (2.96)	
	Tralokinumab	6 (1.03)	2 (0.54)	36 (5.30)	4 (1.59)	0 (0.00)	0 (0.00)	16 (1.52)	64 (1.62)	
	Upadacitinib	8 (1.37)	9 (2.45)	37 (5.45)	13 (5.18)	0 (0.00)	30 (5.38)	8 (0.76)	105 (2.66)	
	Abrocitnib	0 (0.00)	10 (2.72)	3 (0.44)	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)	13 (0.33)	
	Other	0 (0.00)	2 (0.54)	21 (3.09)	0 (0.00)	n/a	0 (0.00)	n/a	23 (0.58)	
	n missing or unknown	0	0	0	0	0	0	0	0	
Phototherapy		**n patients = 30**	**n patients = 0**	**n patients = 39**	**n/a**	**n/a**	**n/a**	**n patients = 13**	**n patients = 82**	*p < 0.01*
	n missing or unknown	0	0	0	n/a	n/a	n/a	0	0	
Topical treatment	*n (%) patients per category:*	**n patients = 338**	**n patients = 62**	**n patients = 345**	**n patients = 258**	**n patients = 227**	**n/a**	**n patients = 1173**	**n patients = 2403**	*p < 0.01*
	Corticosteroids	320 (94.67)	34 (54.84)	254 (73.6)	258 (100)	201 (88.55)	n/a	228 (19.44)	1295 (53.89)	
	Calcineurin inhibitors	125 (36.98)	7 (11.29)	149 (43.2)	26 (10.08)	41 (18.06)	n/a	58 (4.94)	406 (16.90)	
	Tar-ointments	38 (11.24)	0 (0.00)	n/a	n/a	n/a	n/a	0 (0.00)	38 (1.58)	
	Other	4 (1.18)	21 (33.87)	n/a	3 (1.16)	n/a	n/a	421 (35.89)	449 (18.68)	
	n missing or unknown	277	0	0	0	19	n/a	466	762	

n/a = not available. * total number of patients that started with a specific systemic treatment, with potential for 0 or >1 treatment per patient. # mycophenolate mofetil or mycophenolic acid.

Atopic eczema severity and disease burden at the time of enrolment into the registry

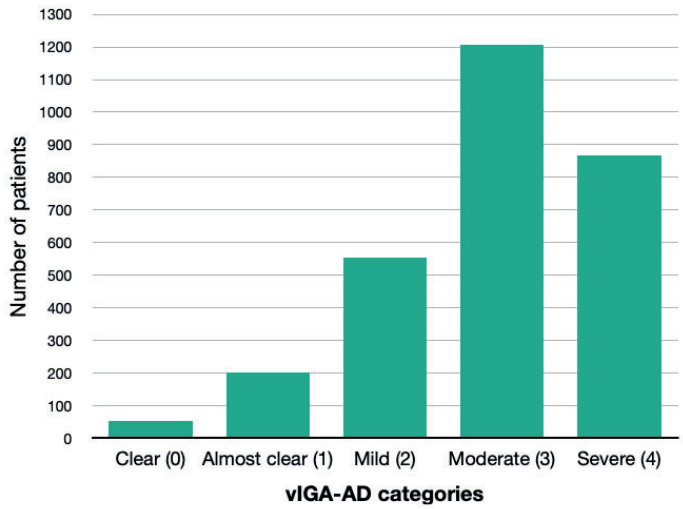
A complete overview of the AE severity and disease burden at the time of enrolment into the registry using physician- and patient-reported outcomes is shown in *Table 6*.

Based on the vIGA-AD, which is a global assessment for clinical signs, most patients were suffering from moderate (41.9%) or severe (30.1%) AE, varying across registries (p<0.01). The combined mean (SD) EASI score was 17.4 (12.1) at baseline and the majority of patients were categorized as having moderate (44.8%) to severe (35.4%) disease, however substantial differences exist between registries (p<0.01). *Figure 5-6* show the total number of patients with clear, almost clear (for vIGA-AD), mild, moderate or severe disease at baseline.

As for patient-reported outcomes, the combined mean (SD) POEM score of all patients included in the registries was 17.2 (7.7), corresponding with severe eczema. Most patients were suffering from moderate (28.3%) to severe (38.0%) eczema, and 18.9% even from very severe eczema at time of enrolment. POEM scores varied between the registries (p<0.01). *Figure 7* shows the total number of patients with clear or almost clear, mild, moderate, severe or very severe eczema measured with POEM. The combined mean (SD) DLQI score was 13.5 (8.4) at baseline, varying across registries ranging from 11.5 (TREATgermany [DE]) to 17.0 (AtopyReg [IT]) (p<0.01). Combined mean (SD) CDLQI and IDLQI scores at baseline were 12.1 (7.2) and 22 (6.7), respectively (p<0.01). Regarding NRS pruritus (past 24 hours), the combined mean (SD) was 6.4 (3.0), ranging from 5.0 (TREATgermany [DE]) to 7.5 (Biobadatop [ES]) (p<0.01). NRS pruritus over the past 72 hours was used by SCRATCH (DK) and VAS pruritus over the past 24 hours was used by Biobadatop (ES).

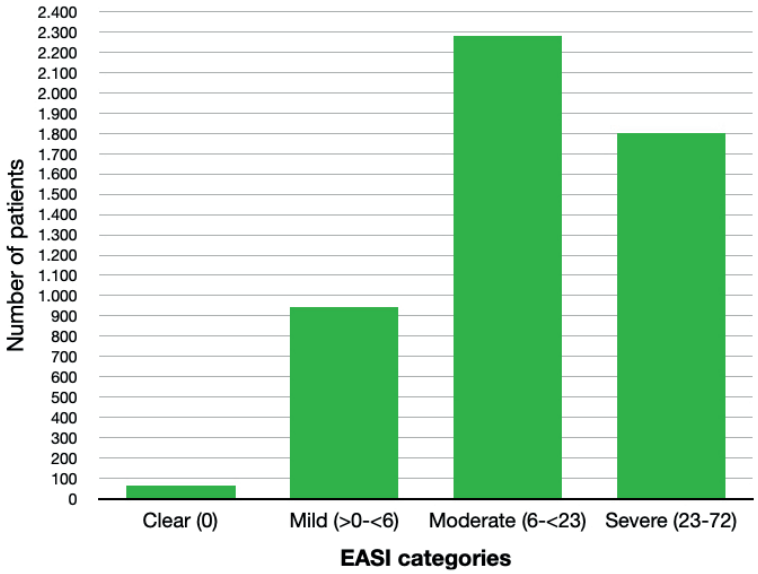
Because no wash-out period is implemented in the registries, patients who are already on systemic therapy and switch to another medication can also be included, which provides an explanation for patients with baseline AE severity and disease burden scores corresponding to clear, almost clear or mild disease.

Figure 5. Total number of patients with clear, almost clear, mild, moderate or severe disease at baseline across all registries, measured with Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD).



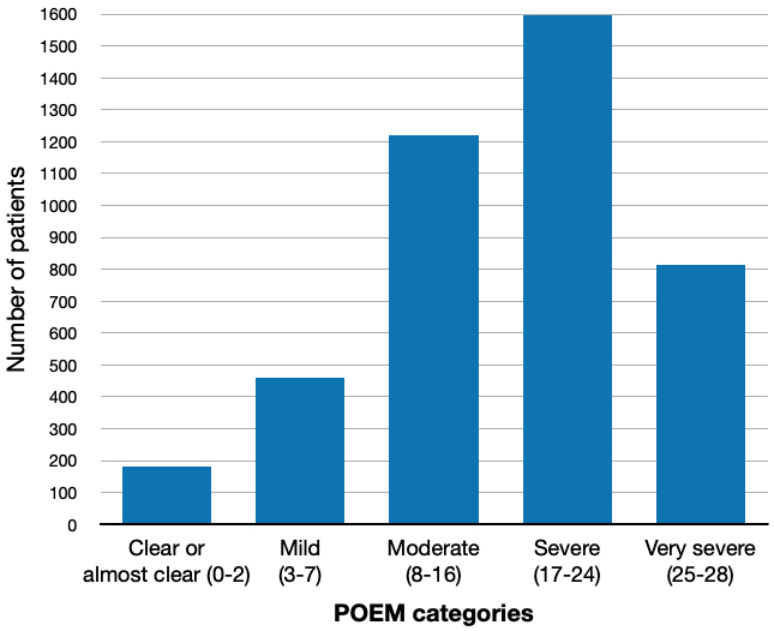
Scale 0-4, n patients = 2884. Biobadatop (Spain), SCRATCH (Denmark) and SwedAD (Sweden) do not collect vIGA-AD.

Figure 6. Total number of patients with clear, mild, moderate or severe disease at baseline, measured with the Eczema Area and Severity Index (EASI) score.



Scale 0-72, n patients = 5089.

Figure 7. Total number of patients with clear or almost clear, mild, moderate, severe or very severe eczema at baseline, measured with Patient Oriented Eczema Measure (POEM).



Scale 0-28, n patients = 4312.

Table 6. Atopic eczema severity and disease burden at the time of enrolment into the registry

		TREAT NL/BE, the Netherlands and Belgium	A-STAR, United Kingdom and Ireland	TREATgermany, Germany	Biobadatop, Spain	SCRATCH, Denmark	SwedAD, Sweden	AtopyReg, Italy	All registries	p-value
Atopic eczema severity and disease burden at the time of enrolment into the registry										
vIGA-AD	*n (%) patients per category:*	**n patients = 374**	**n patients = 350**	**n patients = 1580**	**n/a**	**n/a**	**n/a**	**n patients = 580**	**n patients = 2884**	*p < 0.01*
	Clear (0)	0 (0.00)	1 (0.29)	30 (1.90)	n/a	n/a	n/a	22 (3.79)	53 (1.84)	
	Almost clear (1)	17 (4.55)	12 (3.43)	125 (7.91)	n/a	n/a	n/a	47 (8.10)	201 (6.97)	
	Mild (2)	140 (37.43)	31 (8.86)	227 (14.37)	n/a	n/a	n/a	157 (27.07)	555 (19.24)	
	Moderate (3)	133 (35.56)	175 (50.00)	617 (39.05)	n/a	n/a	n/a	283 (48.79)	1208 (41.89)	
	Severe (4)	84 (22.46)	131 (37.43)	581 (36.77)	n/a	n/a	n/a	71 (12.24)	867 (30.06)	
	n missing or unknown	243	44	7	n/a	n/a	n/a	593	887	
EASI	*n patients*	582	366	1575	245	365	785	1171	5089	
	Mean (SD)	16.06 (11.23)	20.04 (13.14)	15.40 (12.80)	23.40 (11.90)	18.57 (11.44)	13.10 (11.30)	22.00 (9.64)	17.59 (12.09)	*p < 0.01*
	n missing or unknown	35	28	12	11	95	65	2	248	
EASI – categories	*n (%) patients per category:*	**patients = 582**	**n patients = 366**	**n patients = 1575**	**n patients = 245**	**n patients = 365**	**n patients = 785**	**n patients = 1171**	**n patients = 5089**	*p < 0.01*
	Clear (0)	7 (1.20)	0 (0.00)	30 (1.90)	1 (0.41)	0 (0.00)	29 (3.69)	0 (0.00)	67 (1.32)	
	Mild (>0 - <6)	115 (19.74)	41 (11.20)	377 (23.94)	15 (6.12)	48 (13.15)	232 (29.55)	116 (9.91)	944 (18.55)	
	Moderate (6 - <23)	334 (57.42)	203 (55.46)	812 (51.56)	103 (42.04)	203 (55.62)	381 (48.54)	243 (20.75)	2279 (44.78)	
	Severe (23 - 72)	126 (21.64)	122 (33.33)	356 (22.60)	126 (51.43)	114 (31.23)	143 (18.22)	812 (69.34)	1799 (35.35)	
POEM	*n patients*	503	371	1560	173	351	755	599	4312	
	Mean (SD)	19.30 (6.20)	19.27 (6.97)	16.40 (7.80)	19.70 (6.30)	19.49 (6.25)	16.90 (8.40)	14.60 (8.09)	17.21 (7.72)	*p < 0.01*
	n missing or unknown	114	23	27	83	109	95	574	1025	
POEM – categories	*n (%) patients per category:*	**n patients = 503**	**n patients = 371**	**n patients = 1560**	**n patients = 173**	**n patients = 351**	**n patients = 755**	**n patients = 599**	**n patients = 4312**	*p < 0.01*
	Clear or almost clear (0 - 2)	9 (1.76)	3 (0.81)	91 (5.83)	1 (0.58)	3 (0.85)	56 (7.42)	17 (2.84)	180 (4.17)	

	Mild eczema (3 - 7)	27 (5.28)	28 (7.55)	156 (10.00)	5 (2.89)	15 (4.27)	84 (11.13)	144 (24.04)	459 (10.64)	
	Moderate eczema (8 - 16)	146 (28.57)	88 (23.72)	471 (30.19)	43 (24.86)	85 (24.22)	178 (23.58)	211 (35.23)	1222 (28.34)	
	Severe eczema (17 - 24)	240 (46.97)	153 (41.24)	571 (36.60)	75 (43.35)	160 (45.58)	272 (36.03)	166 (27.71)	1637 (37.96)	
	Very severe eczema (25 - 28)	81 (15.85)	99 (26.68)	271 (17.37)	49 (28.32)	88 (25.07)	165 (21.85)	61 (10.18)	814 (18.88)	
DLQI	*n patients*	463	282	1559	164	318	728	1104	4618	
	Mean (SD)	11.89 (7.07)	14.96 (8.28)	11.50 (7.90)	14.62 (7.62)	12.86 (7.17)	12.00 (8.10)	17.00 (9.42)	13.35 (8.51)	*p < 0.01*
	n missing or unknown	132	11	28	72	128	106	69	546	
CLDQI	*n patients*	22	98	n/a	20	14	16	n/a	170	
	Mean (SD)	9.09 (5.26)	13.48 (7.56)	n/a	9.70 (5.58)	15.07 (5.15)	8.31 (6.24)	n/a	12.11 (7.15)	*p < 0.01*
	n missing or unknown	0	0	n/a	0	0	0	n/a	0	
IDLQI	*n patients*	0	3	n/a	0	0	0	n/a	3	
	Mean (SD)	0 (0.00)	22.00 (6.68)	n/a	0 (0.00)	0 (0.00)	0 (0.00)	n/a	22 (6.68)	
	n missing or unknown	0	0	n/a	0	0	0	n/a	0	
NRS pruritus past 24h*	*n patients*	358	382	394	219	361	691	1064	3469	
	Mean (SD)	6.59 (2.21)	6.31 (2.47)	5.00 (3.10)	7.50 (2.10)	7.23 (2.32)	5.30 (3.00)	7.00 (3.20)	6.37 (2.96)	*p < 0.01*
	n missing or unknown	259	12	1193	37	99	159	109	1868	

n/a = not available
vIGA-AD = Validated Investigator Global Assessment scale for Atopic Dermatitis (scale 0-4).
EASI = Eczema Area and Severity Index (scale 0-72).
POEM = Patient Oriented Eczema Measure (scale 0-28).
DLQI = Dermatology Life Quality Index (adults) (scale 0-30).
DLQI = Children's Dermatology Life Quality Index (children) (scale 0-30).
IDLQI = Infants' Dermatitis Quality of Life Index (infants) (scale 0-30).
*SCRATCH (DK) used the NRS peak pruritus over the past 72 hours instead of 24 hours and Biobadatop used VAS pruritus over the past 24 hours instead of NRS pruritus.

DISCUSSION

This pooled analysis provides the first insight in the ability of the TREAT Registry Taskforce to combine forces. This paper highlights the baseline characteristics and reveals the differences that exist between countries, partly reflecting differences in access to systemic immunomodulatory therapies, with some regulatory bodies insisting on other systemic immunosuppressive treatment than biologicals or JAKi as first line.

Prior to enrolment, most patients had received systemic immunomodulatory treatment, primarily corticosteroids and/or methotrexate. Notably, only 39.0% of patients had been prescribed ciclosporin prior to enrolment, although it was the only approved systemic treatment for AE by the EMA until 2017. These findings validate the outcomes of a survey conducted on prescribing practices among dermatologists across 30 European countries, which revealed that off-label therapies and phototherapy were frequently prescribed for moderate-to-severe AE[13].

Because dupilumab was approved by the EMA at the same period as the onset of the TREAT Registry Taskforce, the majority of patients enrolling in the registries started this treatment. The baseline data provided in this study pertains only to treatments initiated at the time of enrolment, excluding any subsequent switch-visits. Consequently, it is likely that the overall current count of patients receiving biological or JAKi treatments is higher than what is reported in the baseline data. Moreover, it is noteworthy that certain countries (the Netherlands, Belgium, Italy, France, Spain, Sweden, and the UK) impose a prerequisite wherein patients must have attempted one or two other systemic treatments before they become eligible for reimbursement of biologicals or JAKi.

Between registries, differences can be observed in baseline physician-assessed AE severity, which may partly be explained by differences between the inclusion criteria with regard to disease severity in the registries. TREATgermany (DE), SCRATCH (DK), and AtopyReg (IT) only include patients with moderate-to-severe AE, whereas TREAT NL/BE (NL/BE), A-STAR (UK/IE), Biobadatop (ES), and SwedAD (SE) include patients initiating systemic treatment and/or phototherapy regardless of their disease severity. Nonetheless, the majority of the included patients suffer from moderate-to-severe AE. Because no wash-out period is implemented in the registries, patients who are already on systemic therapy and switch to another medication can also be included, which provides an explanation for patients with milder baseline AE severity.

It is noteworthy that, in certain cases, physician evaluations of clinical signs using vIGA-AD and EASI indicate milder AE than some patient-reported outcomes. This phenomenon has also been observed in other prospective observational studies in AE, such as the US-Canadian PROSE registry and the Japanese ADDRESS-J, emphasizing the value of PROs in the management of moderate-to-severe AE[41,42]. Compared to PROSE registry, a study of adolescent and adult AE patients initiating dupilumab treatment, baseline AE severity and burden measured in patients included in the TREAT registries were generally similar[41]. Disease severity and burden reported by patients (POEM and DLQI) in our cohort is also comparable to the results from a survey on the burden of illness in adult AE patients from France, Germany, Italy, Spain and the UK[43]. A significant burden on health and health-related quality of life was reported by patients who participated in this questionnaire, particularly by those with uncontrolled AE. Patients included in the TREAT registries reported a mean POEM of 17.0 (severe) and their disease had a very large effect on their quality of life (mean DLQI 13.5).

Moreover, the reported baseline NRS pruritus (past 24 hours) ranged from moderate to severe in the registries, a result typically expected for moderate-to-severe AE[40].

Strengths and limitations

The TREAT Registry Taskforce was established to address questions regarding (cost-)effectiveness and safety of photo- and systemic therapies in AE. This study provides a comprehensive overview of the data collected so far and is crucial for understanding the baseline data and assessing the feasibility of accurately registering and pooling this real-world data. Successful aggregation of such data is a critical step in supporting future research that can pose multiple research questions. This baseline data is considered to be good representation of a real-world AE population as it is collected from daily practice in 175 centres in 9 European countries. Analyses have revealed significant differences across all variables, which is expected given the diverse nature of the registries. These differences are significant by design and reflect the heterogeneity in data collection methodologies and patient populations across the registries. Also, the differences reveal considerable heterogeneity within the patient population as a whole. This heterogeneity underscores the representativeness of our data for the entire population of patients with atopic eczema. The diversity of patients included in the registries enhances the generalizability of our findings and supports the pooling of data from multiple sources. Contrary to concerns about the heterogeneity of the data, we believe that this heterogeneity strengthens the case for data pooling. By including a wide range of patients with varying demographics, treatment characteristics, and disease severities, our datasets capture the complexity of atopic eczema in real-world clinical practice. Pooling such heterogeneous data allows for a more comprehensive understanding of the disease and facilitates robust analyses that can inform clinical decision-making and research priorities.

Our study also has limitations. As charted by our recently published mapping exercise, not all TREAT registries use the core dataset as intended, resulting in missing data[32]. Due to varying eligibility criteria, some registries do not collect data on all the requested systemic immunomodulatory therapies. In addition, registries maintain different inclusion criteria related to disease severity, resulting in differences in baseline AE severity and disease burden scores between registries. Lastly, it is important to consider the potential impact of recruitment bias, as registry studies are susceptible to this type of bias.

Future perspectives

Several single-country studies on treatment effectiveness and other research questions have been conducted by individual TREAT registries[24,25,44–49]. However, it has always been the goal of the TREAT Registry Taskforce to conduct pooled analyses on important safety and (cost)effectiveness outcomes across European countries[50]. With this study we have taken an important step towards future joint analyses. The ability to conduct cross-border analyses has opened the door to answering many other important research questions, in particular for analyses that require large numbers of patients, such as the investigation of malignancy risks. Future research conducted through the TREAT Registry Taskforce will enhance understanding of patients with moderate-to-severe AE and contribute to improved treatment of these patients.

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PART IV

EVALUATING THE SAFETY OF SYSTEMIC TREATMENTS FOR ATOPIC ECZEMA USING REAL-WORLD DATA

CHAPTER 6

REAL-WORLD REPORTED ADVERSE EVENTS RELATED TO SYSTEMIC IMMUNOMODULATING THERAPY IN PATIENTS WITH ATOPIC DERMATITIS: RESULTS FROM THE TREAT NL/BE (TREATMENT OF ATOPIC ECZEMA, THE NETHERLANDS AND BELGIUM) REGISTRY

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ABSTRACT

Background
Evidence on the (long-term) safety of systemic immunomodulating therapies in atopic dermatitis (AD) generated by real-world data is sparse.

Objectives
To describe real-world reported adverse drug reactions (AEs) related to systemic immunomodulating therapy in patients with AD and to compare the incidence rates of AEs with the Summaries of Product Characteristics (SmPCs).

Methods
We conducted an observational prospective multi-centre cohort study, using the TREAT NL registry. All severe AEs, AEs of special interest and serious AEs in adult and paediatric patients on systemic immunomodulating treatment (ciclosporin, methotrexate, azathioprine, mycophenolic acid, dupilumab, tralokinumab, baricitinib and upadacitinib) were assessed. Incidences rates of all (potentially) drug-related AEs were standardized in patient years and compared to the cumulative incidences in the associated SmPCs.

Results
We collected 422 patient years of safety data from 266 patients, of whom 129 (48.5%) reported a total of 224 (potentially) drug-related AEs. Compared to dupilumab's SmPC, higher incidence rates were found for four AEs (reported ≥5 times): eosinophilia, blepharitis, dry eyes and head and neck erythema (i.e. dupilumab facial redness). A higher incidence rate of fatigue was found in patients on oral methotrexate in our cohort compared to the SmPC. Two new drug-related AEs (reported ≥5 times) were found in patients on dupilumab, including non-infectious conjunctivitis and meibomian gland dysfunction.

Conclusions
Real-world reported AEs captured in AD patient registries can add information on the estimated incidence of AEs and benefit clinical decision aids. Future studies using data derived from the TREAT NL registry combined with data from other registries within the TREAT Registry Taskforce will provide more information on (rare) AEs associated with immunomodulating therapy in AD patients.

INTRODUCTION

Evidence on the (long-term) safety of systemic immunomodulating therapies in atopic dermatitis (AD) generated by real-world data (RWD) is sparse[1,2]. Patients and physicians require clear information on the safety profile of these drugs to assess the risk-to-benefit ratio for shared decision making[2,3]. Decision aids to guide patients and physicians on the use of specific treatments are often based on the associated Summary of Product Characteristics (SmPC). However, SmPCs might differ from RWD, as the content is mostly based on spontaneous reports, (pre)clinical trials and post-authorization marketing studies[4].

Most evidence on drug-related AEs is generated by a limited number of randomized controlled trials (RCTs), while a considerable group of AD patients that require systemic therapy is not eligible for clinical trials [2,5]. Moreover, clinical trials often do not include children[6]. On top of this, regulatory agencies rely on post-marketing studies to detect rare AEs, though these studies generally have sample sizes that are too small to improve drug safety surveillance[7]. Consequently, to adequately inform physicians and patients on the safety profile of systemic immunomodulating drugs, discrepancies between RWD and the SmPCs need to be identified. Two recent studies using RWD illustrated new AEs and higher incidences of several AEs compared to the SmPCs in patients with inflammatory bowel disease and rheumatoid arthritis[8,9]. Lastly, numerous systemic therapeutic modalities employed in managing moderate-to-severe AD are prescribed off-label[10]. Consequently, the safety profile of these drugs remains unestablished in the AD population.

Generation of reliable RWD on drug safety and (rare) AEs is one of the main aims of the TREatment of ATopic eczema (TREAT) Registry Taskforce. By means of harmonized data collection in an international network of independent national multi-centre registries, the TREAT Registry Taskforce seeks to better understand effectiveness, safety and cost-effectiveness of systemic immunomodulating therapies for AD[11–14].

The current study aims to assess the incidence rates of AEs in AD patients treated with systemic immunomodulating therapy and to compare these with the corresponding SmPCs, using RWD from the TREAT NL (the Netherlands and Belgium) registry. Hereby, we strive to increase the knowledge on the safety of these drugs in the moderate-to-severe AD population.

METHODS

Study design and patient population

In this registry-based observational prospective cohort study, data was collected between October 2017 and May 2022 in the following TREAT NL centres (the Netherlands and Belgium): Amsterdam University Medical Centres, Huid Medisch Centrum, Leiden University Medical Centre and University Hospital Ghent. We included all adult and paediatric (<18 years) patients with a physician diagnosis of AD based on the U.K. Working Party criteria, who were starting systemic immunomodulating treatment (ciclosporin, methotrexate, azathioprine, mycophenolic acid, dupilumab, tralokinumab, baricitinib or upadacitinib) for their AD[15]. Visits were conducted by trained healthcare professionals and data was collected using the TREAT core dataset consisting of both patient- and physician-reported domains[11,12]. Patients completed visits at baseline, 4 weeks, 12 weeks, followed by every 12 weeks.

Reporting of adverse events

Severe AEs, AEs of special interest (AESIs) and serious AEs (SAEs) were reported during visits. The definition of these terms can be found in *Table 1*. Overlap may exist between these groups: for example, a severe AE may also be an AESI. Drug-relatedness of all reported AEs was assessed by the physician and categorized as: not related, doubtful, possible, probable, very likely or definite. The assessment of causality of AEs was based on physician expertise, existing literature or previous reports and the time of occurrence of the AE. If the drug-relatedness of an AE was missing, it was evaluated independently for each AE by two physicians (PS and AM). Moreover, start and stop date of each AE was reported. If the start date of an AE was missing or unknown, the date of visit in which the AE was reported was used as start date. Also, the action that was undertaken upon the AE (e.g. discontinuation of therapy) and course of the AE were monitored. Persistent AEs were considered solitary events while the second occurrence of an AE was reported as a new event. We collected data on previous or concomitant treatment to identify if an AE was possibly associated with another treatment. For dupilumab, the presence of pre-existent ocular disorders and eosinophilia (>500 cells/mm^3) was assessed. Eosinophilia was only reported as a drug-related AE if it was not pre-existent before treatment initiation. All included patients had eosinophil count measurements at baseline. Information on the presence of pre-existing eye disorders diagnosed by an ophthalmologist was obtained from the medical history. Patients were not routinely evaluated by an ophthalmologist at baseline. When patients complained of eye problems during study visits, they were promptly referred to an ophthalmologist. Diagnosed ocular disorders were then documented and reported as AEs.

All AEs were coded according to Medical Dictionary for Regulatory Activities (MedDRA) codes, version 25[16]. In this study, Preferred Terms were used to distinct AEs. Subsequently, Preferred Terms were bundled into an organ class, for example, the Preferred Term “blepharitis” belongs to the organ class “eye disorders”[16,17].

Table 1. Definition of severe adverse events, serious adverse events and severe advere events of special interest collected in the TREAT NL registry

Severe adverse events
Any undesirable experience resulting in referral to another specialist, prescription of medication (excl. antihistamines and indifferent treatments), treatment schedule adjustments or discontinuation, or causing considerable interference with usual activities, whether or not considered related to this treatment.
Serious adverse events (SAEs)*
Any experience that results in death; is life threatening; requires in-patient hospitalization (or prolongation); results in persistent or significant disability or incapacity; is a congenital anomaly or birth defect; is a serious infection or needed medical intervention to prevent the above from occurring.
Adverse events of special interest (AESIs)
Acne
Arthralgia
Blood and lymphatic system disorders (including eosinophilia)
Cardiovascular disorders
Central nervous system disorders
Dupilumab-induced head and neck erythema
Embolic and thrombotic events
Eye disorders
Gastrointestinal disorders
Hypersensitivity reactions
Lipid disorders
Liver function disorders
Malignancies (including skin-cancer)
Serious chronic or relapsing infections (including herpes infections)

***Definition according to the Council for International Organizations of Medical Sciences guidelines[59].

Data analysis

Patient characteristics, treatment aspects and an overview of AEs related to each drug were summarized using descriptive statistics. Normality was tested using Shapiro-Wilk tests and Q-Q plots.

Because of differences in size and duration of the different treatment groups, we standardized incidence rates of AEs in patient years. This enabled us to directly compare incidence rate between the different treatment groups. Treatment duration was defined as the time between start and stop date (or last visit date). Patient years are the sum of treatment durations for all patients in years. Incidence rates of each AE are expressed in number of events per patient year. We chose to compare the incidence rates of AEs in our study with the cumulative incidence of AEs in the associated SmPCs, as this is a standardized measure that is independent of the study duration and size, and provides transparency. We assume that the expected risk of AEs remains constant over time. Statistical analyses were performed using SPSS (version 28)[18].

Data presentation

The incidence rates of all AEs that were possibly, probably, very likely and definitely drug-related were compared with the cumulative incidences in the most recent versions of the corresponding SmPCs which were derived from the online database of the Dutch Medicine evaluation board[19–29]. Every SmPC contains a section (4.8) 'undesirable effects' where the known AEs and corresponding cumulative incidences are described per organ class, ranging

from 'very common' (≥10%) to 'very rare' (≤0.01%)[4]. AEs that were doubtfully or not-drug related were not compared to the SmPCs. AEs (reported ≥5 times) with higher incidences compared to the SmPC and new drug-related AEs (reported ≥5 times) were demonstrated in a separate table.

RESULTS

Patient characteristics

A total of 266 patients (55.6% male, median age 33 years, 10.5% paediatric) were included. Baseline characteristics are summarized in *Table 2*. At the time of enrolment, the majority of patients initiated dupilumab treatment (60.9%), followed by methotrexate (14.2%) and ciclosporin (13.9%).

Table 2. Baseline patient characteristics

	TREAT NL cohort (n=266) *n (%) or median (IQR)*
Gender	
Male	148 (55.6)
Female	118 (44.4)
Age at enrolment, y	33 (22.8-49.3)
Adult patients (≥18 y)	238 (89.5)
Paediatric patients (<18 y)	28 (10.5)
Body mass index (kg/m²)*	24.2 (22.8-27.1)
Fitzpatrick skin type^	
I	15 (5.6)
II	141 (53.0)
III	50 (18.8)
IV	19 (7.1)
V	27 (10.2)
VI	13 (4.9)
Ethnicity#	
White	192 (72.2)
Asian	26 (9.8)
Black	22 (8.3)
Other	16 (6.0)
Centre of enrolment	
Amsterdam University Medical Centres	216 (81.2)
Huid Medisch Centrum	21 (7.9)
Leiden University Medical Centre	7 (2.6)
University Hospital Ghent	22 (8.3)
Previously used systemic therapies for AD	
Ciclosporin	167 (33.1)
Systemic corticosteroids	156 (30.9)
Methotrexate	92 (18.2)
Azathioprine	19 (3.8)
Mycophenolic acid	33 (6.5)
Dupilumab	7 (1.4)
Omalizumab	2 (0.4)
Investigational medication	21 (4.2)
Other	8 (1.6)
Systemic therapy started at baseline or restart/switch visit	
Ciclosporin	47 (13.9)

Systemic corticosteroids	2 (0.6)
Methotrexate	48 (14.2)
Azathioprine	1 (0.3)
Mycophenolic acid	4 (1.2)
Dupilumab	206 (60.9)
Tralokinumab	7 (2.1)
Baricitinib	10 (3.0)
Upadacitinib	13 (3.8)

*12 missing, ^ 1 missing, # 10 missing, ◊ 3 missing

Severe adverse events, adverse events of special interest and serious adverse events

In total, we collected 422 patient years of safety data. Follow-up time ranged from 0.2 (azathioprine) to 335.5 (dupilumab) patient years. 170 (57.0%) patients reported ≥1 AE(s) (severe AEs, AESIs or SAEs). Of those, 129 patients (59.7% male, median age 40 years, 3.9% paediatric) reported a total of 224 AEs that were categorized as possibly, probably, very likely or definitely drug-related (*Table 3*). A high treatment discontinuation rate (63.2%) due to AEs was found in patients with AEs related to oral methotrexate. Dosage change due to AEs was more often initiated in patients with AEs related to ciclosporin (18.8%) and oral methotrexate (15.8%) compared to dupilumab (9.7%). Overall, most AEs (58.9%) were still ongoing at the time of the last study visit. None of the AEs were fatal or left residual symptoms.

A total of 177 AESIs were reported, of which 151 were possibly, probably, very likely or definitely drug-related and 26 were doubtful or not drug-related. The vast majority of AESIs included eye disorders ([potentially] related to dupilumab [n=75]) and blood and lymphatic system disorders (eosinophilia; [potentially] related to dupilumab [n=40], ciclosporin [n=1] and oral or subcutaneous methotrexate [n=4]). Malignancies (breast cancer [n=1], cutaneous T-cell lymphoma [n=1], oesophageal adenocarcinoma [n=1], transitional cell carcinoma [n=3]) were reported in four patients on dupilumab and were categorized as doubtfully or not drug-related.

In total, 41 (11.0%) AEs were categorized as SAEs, of which 2 were possibly or probably drug-related. These drug-related SAEs included a Campylobacter infection leading to hospitalization in a patient on subcutaneous methotrexate, and a toxic reaction (drug hypersensitivity) leading to discontinuation of treatment in a patient on oral methotrexate. However, this toxic reaction may have occurred due to concomitant use of allopurinol.

Table 3. Overview of possibly, probably, very likely or definitely drug-related AEs, age and sex distribution among patients with AEs, action upon on AEs, course of AEs, time between start of treatment and occurrence of AEs and follow-up duration, per treatment.

	CsA	MTX, oral	MTX, sc	MMF	Dupi	Tralo	Bari	Upa
Follow-up, patient years	32.6	37.1	4.7	3.2	335.5	1.9	3.9	3.1
Number of patients	47	44	4	4	206	7	10	13
Patients with AEs, n	13	14	4	1	91	1	1	4
Male patients, n (%)	7 (53.8)	8 (57.1)	2 (50.0)	1 (100)	56 (61.5)	0 (0.0)	1 (100)	2 (50.0)
Female patients, n (%)	6 (46.2)	6 (42.9)	2 (50.0)	0 (0.0)	35 (38.5)	1 (100)	0 (0.0)	2 (50.0)
Age at time of first AE, years, median (IQR)	25.0 (31.0)	27.0 (44.0)	31.0 (34.0)	61	43.3 (27.6)	61	32	25.5 (30.0)
Adult patients, n (%)	13 (100)	14 (100)	4 (100)	1 (100)	86 (94.5)	1 (100)	1 (100)	4 (100)
Paediatric patients, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)
Total reported AEs, n	16	36	8	1	154	3	1	5
Very likely or definitely drug-related, n (%)	5 (31.3)	2 (5.3)	0 (0.0)	0 (0.0)	8 (5.2)	0 (0.0)	0 (0.0)	3 (60.0)
Possible or probably drug-related, n (%)	11 (68.8)	36 (94.7)	8 (100)	1 (100)	146 (94.8)	3 (100)	1 (100)	2 (40.0)
Severe AEs, n (%)	11 (68.8)	29 (80.5)	5 (62.5)	1 (100)	23 (14.9)	1 (33.3)	0 (0.0)	1 (20.0)
AEs of special interest, n (%)	5 (31.2)	6 (16.7)	2 (25.0)	0 (0.0)	131 (85.1)	2 (66.7)	1 (100)	4 (80.0)
Serious AEs, n (%)	0 (0.0)	1 (2.8)	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Action upon on AE[*], n (%)								
Treatment discontinuation	1 (6.3)	24 (63.2)	0 (0.0)	1 (100)	15 (9.7)	0 (0.0)	0 (0.0)	2 (40.0)
Change in dosage	3 (18.8)	6 (15.8)	0 (0.0)	0 (0.0)	15 (9.7)	0 (0.0)	0 (0.0)	0 (0.0)
None	10 (62.5)	2 (5.3)	6 (75.0)	0 (0.0)	115 (74.7)	3 (100)	0 (0.0)	3 (60.0)
Course of AE[#], n (%)								
Recovered/resolved	5 (31.3)	8 (21.1)	1 (12.5)	0 (0.0)	21 (13.6)	0 (0.0)	0 (0.0)	1 (20)
Recovered/resolved with sequelae	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Recovering/resolving	1 (6.3)	1 (2.6)	0 (0.0)	0 (0.0)	13 (8.4)	0 (0.0)	0 (0.0)	2 (40.0)
Not recovered/resolved	5 (31.3)	15 (39.5)	5 (62.5)	0 (0.0)	102 (66.2)	3 (100)	0 (0.0)	2 (40.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (100)	4 (2.6)	0 (0.0)	1 (100)	0 (0.0)
Time-to-onset of first AE^, weeks, median (IQR)	4.0 (10)	10.0 (49)	7.5 (83)	8.0	12.0 (20)	2.0	7.0	7.5 (9)

CsA = ciclosporin, MTX = methotrexate, MMF = mycophenolate mofetil, dupi = dupilumab, tralo = tralokinumab, bari = baricitinib, upa = upadacitinib.

* 2 missing for ciclosporin, 4 missing for oral methotrexate, 2 missing for subcutaneous methotrexate, 9 missing for dupilumab, 1 missing for baricitinib.

5 missing for ciclosporin, 12 missing for oral methotrexate, 2 missing for subcutaneous methotrexate, 14 missing for dupilumab.

^ 1 missing for ciclosporin, 1 missing for oral methotrexate, 3 missing for dupilumab.

Comparison with the SmPC

Table 4 provides an overview of AEs reported ≥5 times in the TREAT NL registry with a higher incidence rate compared to the associated SmPC. This table also includes new AEs (reported ≥5 times) that are not mentioned in the SmPCs. Compared to the SmPC of dupilumab, higher incidence rates were found in the TREAT NL cohort for eosinophilia (11.9% vs ≥1%-<10%), blepharitis (3.0% vs ≥0.1%-<1%), dry eyes (3.6% vs ≥0.1%-<1%) and head and neck erythema (i.e. 'dupilumab facial redness') (1.5% vs ≥0.1%-<1%). Of the patients with eosinophilia, hypereosinophilia (≥1500/mm³) occurred in 17 patients during dupilumab treatment (1500-4050 eosinophils/mm³), giving an incidence rate of 5.1%. In addition, we found a higher incidence rate of fatigue in patients on oral methotrexate in the TREAT NL cohort compared to the associated SmPC (13.5% vs ≥1%-<10%).

New drug-related AEs (reported ≥5 times) that were not mentioned in the associated SmPC were found in patients receiving dupilumab and included non-infectious conjunctivitis and meibomian gland dysfunction, with incidence rates of 6.0% and 1.5%, respectively.

A complete overview of AEs related to the various treatments and comparison with the SmPCs are shown in *Table 5*.

Table 4. Drug-related AEs (reported ≥5 times) and a higher incidence rate compared to the associated SmPC.

Treatment	Adverse drug reaction	Corresponding organ class	Number of cases	TREAT NL incidence rate (per patient year)	SmPC incidence
Dupilumab	Eosinophilia*	Blood and the lymphatic system disorders	40	11.9%	≥ 1% to < 10%
Dupilumab	Blepharitis#	Eye disorders	10	3.0%	≥ 0.1% to < 1%
Dupilumab	Dry eyes	Eye disorders	12	3.6%	≥ 0.1% to < 1%
Dupilumab	Meibomian gland dysfunction^	Eye disorders	5	1.5%	*Not in SmPC*
Dupilumab	Non-infectious conjunctivitis◊	Eye disorders	20	6.0 %	*Not in SmPC*
Dupilumab	(Head and neck) erythema	Skin and subcutaneous tissue disorders	5	1.5%	≥ 0.1% to < 1%
Methotrexate (oral)	Fatigue	General disorders and administration site conditions	5	13.5%	≥ 1% to < 10%

* Eosinophilia is defined by an eosinophil count of >500 cells/mm3.

Blepharitis is defined as inflammation of the eyelid margins.

^ Meibomian gland dysfunction is defined as a condition with structural and functional abnormalities of the meibomian glands, often resulting in altered tear film composition and stability.

◊ Conjunctivitis is characterized by conjunctival mucosal inflammation and can be classified as non-infectious (allergic, toxic or non-specific) or infectious (bacterial or viral infections).

Table 5. AEs possibly, probably, very likely or definitely related to systemic immunomodulating drugs (dupilumab, methotrexate, ciclosporin, mycophenolate mofetil, tralokinumab, baricitinib and upadacitinib) and incidence rates of AEs in the TREAT NL cohort compared to the incidence mentioned in the corresponding SmPCs.

Ciclosporin					
	Total reported AEs	**Very likely or definite drug-related**	**Possible or probable drug-related**	**TREAT NL incidence rate (per patient year)**	**SmPC incidence**
Total number of AEs	16	5	11		
Type of severe AE					
Blood and lymphatic system disorders	1		1		
Eosinophilia	1		1	3.1%	*Not in SmPC*
Gastrointestinal disorders	2	1	1		
Abdominal pain	2	1	1	3.1%	≥ 1% to < 10%
General disorders and administration site conditions	1		1		
Pyrexia	1		1	3.1%	≥ 1% to < 10%
Immune system disorders	1	1			
Gout	1	1		3.1%	
Infections and infestations	2		2		
Eczema herpeticum	1		1	3.1%	*Not in SmPC*
Epididymitis	1		1	3.1%	*Not in SmPC*
Musculoskeletal and connective tissue disorders	1		1		
Myalgia	1		1	3.1%	≥ 1% to < 10%
Nervous system disorders	4		4		
Headache	3		3	9.2%	≥ 10%
Paraesthesia	1		1	3.1%	≥ 1% to < 10%
Skin and subcutaneous tissue disorders	2	2			
Body hair increased	2	2		6.1%	≥ 1% to < 10%
Vascular disorders	2	1	1		
Hypertension	2	1	1	3.1%	≥ 10%
Methotrexate (oral)					
	Total reported AEs	**Very likely or definite drug-related**	**Possible or probable drug-related**	**TREAT NL incidence rate (per patient year)**	**SmPC incidence**
Total number of AEs	36	2	34		
Type of AE					
Blood and lymphatic system disorders	3		3		
Eosinophilia	3		3	8.1%	< 0.01%
Gastrointestinal disorders	14		14		
Abdominal pain	3		3	8.1%	≥ 10%
Diarrhoea	3		3	8.1%	≥ 10%
Flatulence	1		1	2.7%	*Not in SmPC*
Nausea	4		4	10.8%	≥ 10%
Vomiting	2		2	5.4%	≥ 10%
General disorders and administration site conditions	6		6		
Fatigue	5		5	13.5%	≥ 1% to < 10%

Malaise	1		1	2.7%	*Not in SmPC*
Hepatobiliary disorders	2	1	1		
Alanine aminotransferase increased	1		1	2.7%	≥ 10%
Raised liver function tests	1	1		2.7%	≥ 10%
Immune system disorders	1		1		
Drug hypersensitivity	1		1	2.7%	≥ 0.1% to < 1%
Infections and infestations	2	1	1		
Erysipelas	1		1	2.7%	≥ 1% to < 10%
Acute tonsillitis	1	1		2.7%	≥ 1% to < 10%
Metabolism and nutrition disorders	3		3		
Abnormal loss of weight	1		1	2.7%	*Not in SmPC*
Decreased appetite	2		2	5.4%	≥ 10%
Nervous system disorders	3		3		
Headache	2		2	5.4%	≥ 10%
Dizziness	1		1	2.7%	≥ 10%
Reproductive system and breast disorders	1		1		
Erectile dysfunction	1		1	2.7%	< 0.01%
Skin and subcutaneous tissue disorders	1		1		
Skin ulcer	1		1	2.7%	*Not in SmPC*
Vascular disorders	1		1		
Hypertension	1		1	2.7%	*Not in SmPC*

Methotrexate (subcutaneous)

	Total reported AEs	Very likely or definite drug-related	Possible or probable drug-related	TREAT NL incidence rate (per patient year)	SmPC incidence
Total number of AEs	8	0	8		
Type of AE					
Blood and lymphatic system disorders	2		2		
Eosinophilia	1		1	21.2%	*Unknown*
Anaemia	1		1	21.2%	≥ 1% to < 10%
Gastrointestinal disorders	4		4		
Diarrhoea	2		2	42.5%	≥ 1% to < 10%
Nausea	2		2	42.5%	≥ 10%
Infections and infestations	1		1		
Campylobacter infection* *Captured as 'infections' in the SmPC	1		1	21.2%	≥ 1% to < 10%
Nervous system disorders	1		1		

Mycophenolate mofetil

	Total reported AEs	Very likely or definite drug-related	Possible or probable drug-related	TREAT NL incidence rate (per patient year)	SmPC incidence
Total number of AEs	1		1		
Type of AE					
Gastrointestinal disorders	1		1		
Nausea			1	31.0%	> 10%

Dupilumab

	Total reported AEs	Very likely or definite drug-related	Possible or probable drug-related	TREAT NL incidence rate (per patient year)	SmPC incidence

Total number of AEs	154	8	146		
Type of AE					
Blood and lymphatic system disorders	40		40		
Eosinophilia	40		40	11.9%	≥ 1% to < 10%
Eye disorders	75	2	73		
Blepharitis	10		10	3.0%	≥ 0.1% to < 1%
Conjunctivitis allergic	9	1	8	2.7%	≥ 1% to < 10%
Dry eye	12		12	3.6%	≥ 0.1% to < 1%
Ectropion	2		2	0.6%	*Not in SmPC*
Eye irritation	2		2	0.6%	*Not in SmPC*
Eye pruritus	3		3	0.9%	≥ 0.1% to < 1%
Eyelid ptosis	1		1	0.3%	*Not in SmPC*
Eyelid skin dryness	1		1	0.3%	*Not in SmPC*
Lacrimation increased	2		2	0.6%	*Not in SmPC*
Meibomian gland dysfunction	5		5	1.5%	*Not in SmPC*
Meibomianitis	2		2	0.6%	*Not in SmPC*
Non-infectious conjunctivitis	20	1	19	6.0%	*Not in SmPC*
Ocular hyperaemia	3		3	0.9%	*Not in SmPC*
Photophobia	1		1	0.3%	*Not in SmPC*
Refraction disorder	1		1	0.3%	*Not in SmPC*
Trichiasis	1		1	0.3%	*Not in SmPC*
Gastrointestinal disorders	2		2		
Mouth ulceration			1	0.3%	*Not in SmPC*
Nausea	1		1	0.3%	*Not in SmPC*
General disorders and administration site conditions	4	1	3		
Fatigue	2		2	0.6%	*Not in SmPC*
Injection site reaction	2	1	1	0.6%	≥ 1% to < 10%
Immune system disorders	2		2		
Drug hypersensitivity	1		1	0.3%	≥ 0.01% to < 0.1%
Vaccination complication	1		1	0.3%	*Not in SmPC*
Infections and infestations					
Conjunctivitis	5	3	2	1.5%	≥ 1% to < 10%
Fungal skin infection	1		1	0.3%	*Not in SmPC*
Herpes zoster	2		2	0.6%	*Not in SmPC*
Herpes virus infection	1		1	0.3%	*Not in SmPC*
Sinusitis	1		1	0.3%	*Not in SmPC*
Oral herpes	2		2	0.6%	≥ 1% to < 10%
Metabolism and nutrition disorders	1		1		
Abnormal loss of weight	1		1	0.3%	*Not in SmPC*
Musculoskeletal and connective tissue disorders	6	1	5		
Arthralgia	6	1	5	1.8%	≥ 1% to < 10%
Nervous system disorders	1		1		
Migraine	1		1	0.3%	*Not in SmPC*
Psychiatric disorders	1		1		
Depressed mood	1		1	0.3%	*Not in SmPC*
Skin and subcutaneous tissue disorders	10		10		
Alopecia	1		1	0.3%	*Not in SmPC*
Eczema	1		1	0.3%	*Not in SmPC*
Perioral dermatitis	2		2	0.6%	*Not in SmPC*

(Head and neck) erythema	5		5	1.5%	≥ 0.1% to < 1%
Skin irritation	1		1	0.3%	*Not in SmPC*
Tralokinumab					
	Total reported AEs	**Very likely or definite drug-related**	**Possible or probable drug-related**	**TREAT NL incidence rate (per patient year)**	**SmPC incidence**
Total number of AEs	3		3		
Type of AE					
Eye disorders	2		2		
Lacrimation increased	1		1	53.9%	*Not in SmPC*
Ocular hyperaemia	1		1	53.9%	*Not in SmPC*
Infections and infestations	1		1		
Urinary tract infection	1		1	53.9%	*Not in SmPC*
Baricitinib					
	Total reported AEs	**Very likely or definite drug-related**	**Possible or probable drug-related**	**TREAT NL incidence rate (per patient year)**	**SmPC incidence**
Total number of AEs	1		1		
Type of AE					
Nervous system disorders	1		1		
Headache	1		1	25.7%	≥ 1% to < 10%
Upadacitinib					
	Total reported AEs	**Very likely or definite drug-related**	**Possible or probable drug-related**	**TREAT NL incidence rate (per patient year)**	**SmPC incidence**
Total number of AEs	5	4	1		
Type of AE					
Infections and infestations	3	3			
Herpes virus infection	3	3		32.2%	≥ 1% to < 10%
Nervous system disorders	1		1		
Headache	1		1	32.2%	≥ 1% to < 10%
Respiratory, thoracic and mediastinal disorders	1	1			
Asthma (exacerbation)	1		1	32.2%	*Not in SmPC*

Dupilumab-related ocular AEs

The reported AEs in the organ class 'eye disorders' related to dupilumab use are summarized in *Table 6*. These AEs are highlighted due to incidence rates and discrepancy to the corresponding SmPC. In total, 80 ocular AEs related to dupilumab treatment were reported in 30 unique patients (76.7% male). Pre-existent ocular complaints (assessed by a physician) before dupilumab treatment were present in 6 patients, who later reported 5 cases of non-infectious conjunctivitis and 2 cases of conjunctivitis (infectious; bacterial or viral) under dupilumab treatment. In 5 patients (6.3%) dupilumab treatment was discontinued because of ocular complaints, while in 12 cases (15.0%) the dose was adjusted.

Non-infectious conjunctivitis, dry eyes and blepharitis were most frequently reported, with incidence rates of 6.0%, 3.6% and 3.0%, respectively. Corresponding to the SmPC, allergic conjunctivitis and conjunctivitis were commonly observed in the TREAT NL registry, with incidence rates of 2.6% and 1.5%, respectively. In total, non-infectious, infectious and allergic conjunctivitis associated to dupilumab treatment was reported 34 times, giving an incidence rate of 10.1%.

Table 6. Incidence rates of ocular AEs in the TREAT NL cohort that are possibly, probably, very likely, definitely related to dupilumab treatment, compared to the incidence mentioned in the SmPC.

	Number of cases	TREAT NL incidence rate (per patient year)	SmPC incidence
Total number of ocular AEs	80		
Eye disorders			
Blepharitis	10	3.0%	≥ 0.1% to < 1%
Conjunctivitis allergic	9	2.7%	≥ 1% to < 10%
Dry eyes	12	3.6%	≥ 0.1% to < 1%
Ectropion	2	0.6%	*Not in SmPC*
Eye irritation	2	0.6%	*Not in SmPC*
Eye pruritus	3	0.9%	≥ 0.1% to < 1%
Eyelid ptosis	1	0.3%	*Not in SmPC*
Eyelid skin dryness	1	0.3%	*Not in SmPC*
Lacrimation increased	2	0.6%	*Not in SmPC*
Meibomian gland dysfunction	5	1.5%	*Not in SmPC*
Meibomianitis	2	0.6%	*Not in SmPC*
Non-infectious conjunctivitis	20	6.0%	*Not in SmPC*
Ocular hyperaemia	3	0.9%	*Not in SmPC*
Photophobia	1	0.3%	*Not in SmPC*
Refraction disorder	1	0.3%	*Not in SmPC*
Trichiasis	1	0.3%	*Not in SmPC*
Infections and infestations			
Conjunctivitis	5	1.5%	≥ 1% to < 10%

DISCUSSION

In this registry-based observational prospective cohort study we found 5 drug-related AEs with higher incidence rates compared to the corresponding SmPCs. These AEs included eosinophilia, blepharitis, dry eyes and head and neck erythema related to dupilumab, and fatigue related to oral methotrexate. In addition, we found 2 new drug-related AEs associated to dupilumab that were not mentioned in the SmPC, including non-infectious conjunctivitis and meibomian gland dysfunction.

Our findings indicate that the incidence of eosinophilia associated with dupilumab treatment could be underestimated in the SmPC. The TREAT NL registry only reports eosinophilia as a drug-related AE if it was not pre-existent before treatment initiation. In our study, the incidence rate of eosinophilia was 11.9% (n=40), implying that eosinophilia is a 'very common' (≥10%) undesirable effect instead of 'common' (≥1%-<10%). This is in line with the findings of two multicentre retrospective cohort studies that found that dupilumab-related eosinophilia was more common in real-life compared to phase III trials[30,31]. In our study, only 5 cases of eosinophilia were reported in patients using other therapies than dupilumab, suggesting that the high rate of eosinophilia found in patients on dupilumab is indeed caused by the drug itself rather than active AD. It has been found that dupilumab-induced eosinophilia is often transient without clinical consequences and hypereosinophilia only occurs in a minority of patients[32]. In the TREAT NL cohort, the incidence rate of hypereosinophilia was 5.1%, resulting into treatment discontinuation in one patient. More research into dupilumab-induced (hyper)eosinophilia in AD patients is needed to provide recommendations on its management.

Ocular complaints arising during dupilumab treatment have been increasingly reported since its approval in 2017, with conjunctivitis being the most frequently described ocular AE[33–35]. However, studies often do not specify the type of conjunctivitis[36]. Similarly, the SmPC only mentions allergic conjunctivitis and infectious conjunctivitis. It is unclear whether dupilumab associated conjunctivitis (DAC) is clinically captured by allergic conjunctivitis. Since DAC is not a MedDRA Preferred Term, we believe non-infectious conjunctivitis is the most suitable Preferred Term. Due to the use of unspecific terms, comparing ocular events to literature and the SmPC is challenging. Using more specific terms to describe ocular events associated with dupilumab can prompt early diagnosis. This is of importance, since ocular AEs can lead to discontinuation of treatment and sometimes to long-term sequelae[37]. If, however, the Preferred Term allergic conjunctivitis is maintained for DAC, the resulting incidence rate of conjunctivitis related to dupilumab in our study is 10.1% (consisting of a total of 34 cases of conjunctivitis, allergic conjunctivitis and non-infectious conjunctivitis), equivalent to 'very common' (>10%). This indicates the incidence mentioned in the SmPC could be an underestimation of the actual real-life incidence, as it is grouped under 'common' (≥1%-<10%). Another study reports an even higher incidence of 26.1% for DAC[38].

Other dupilumab-induced ocular AEs with higher incidence rates in the TREAT NL cohort compared to the SmPC included dry eyes and blepharitis. Various retrospective studies showed incidences of dupilumab-associated dry eyes ranging from 3.9% to 10% [39–41]. For blepharitis, even higher incidences of up to 22% have been reported[42,43]. Moreover, we found that meibomian gland dysfunction was a 'common' dupilumab-related AE, however it is not mentioned in the SmPC. A recent study reported that meibomian gland dysfunction occurred in 25% of dupilumab users[44]. We believe that describing this AE in the SmPC of dupilumab would lead to more awareness and early therapeutic intervention prospects.

Ocular complaints including (blepharo-)conjunctivitis, dry eyes, eye pruritus, blurry vision, keratitis, meibomian gland dysfunction, limbus nodules and cicatricial ectropion can be covered under the umbrella term dupilumab-induced ocular surface disease (DIOSD)[1,45–47]. A systematic review that included 2883 AD patients on dupilumab reports that DIOSD occurred in 13% of patients[46]. Supporting these findings, we found that DIOSD was reported in 15% of patients. Interestingly, DIOSD is not reported in asthma, chronic sinusitis or nasal polyps patients receiving dupilumab, suggesting that a disease-specific interaction exists[48–50]. Since ocular diseases such as conjunctivitis are more common in AD patients, pre-existent ocular disease could predispose to higher rates of DIOSD[47,51]. As the risk of development of ocular comorbidities is disease severity-dependent, this is especially true for patients suffering from severe AD[52]. In our study, 1 patient with conjunctivitis and 5 patients with non-infectious conjunctivitis already experienced ocular complaints before treatment initiation, so these might be considered as dupilumab-exacerbated rather than dupilumab-induced.

Dupilumab-induced head and neck erythema (i.e. dupilumab facial redness) has been reported in 5.4-29% of patients by other studies[53,54]. This supports our finding that dupilumab-induced head and neck erythema has a higher real-life incidence compared to the SmPC. The pathogenesis is still unclear and despite several speculations, further studies are indicated to investigate this AE[55,56].

Lastly, we found a higher incidence rate of fatigue related to methotrexate (oral) treatment than mentioned in the SmPC ('very common' vs 'common'). However, as fatigue is also a common symptom of AD itself, due to active disease and sleep-loss, it may be challenging to distinguish its cause. This AE has not yet been extensively studied in AD patients, but a recent

prospective study on patient-reported fatigue and nausea related to methotrexate in rheumatoid- and psoriatic arthritis patients found even higher rates of fatigue, reported by 46% of patients, suggesting the incidence may indeed be underestimated in the SmPC of methotrexate[57].

The major strength of this study is the use of RWD derived from daily practice of 266 AD patients on various treatments, with a total follow-up of 422 patient years. The external validity is likely to be high, considering the fact the TREAL NL registry consists of both adult- and paediatric patients, including those with comorbidities. However, the small number of patients on treatments other than dupilumab, oral methotrexate and ciclosporin can be considered as a limitation, as the calculated incidence rates of AEs related to these treatments may be an over- or underestimate and cannot be adequately compared to the corresponding SmPCs. Furthermore, due to the prominent enrolment of patients treated with dupilumab, there is a possibility that an unintentional exaggeration of dupilumab's adverse effects in comparison to other agents may have been depicted.
Moreover, the fact that only AEs of severe nature were reported might as well be a limitation of this study. This likely caused the estimated incidence rates of the reported AEs to be an underestimation of the actual incidences. This does not apply to dupilumab-related eosinophilia and ocular AEs, as these are AESIs and were always reported, independent of their severity. However, baseline eosinophil count was not determined in patients starting dupilumab in University Hospital Ghent, which could have led to an underestimation of the incidence of dupilumab-induced eosinophilia in this centre. In addition, mild ocular AEs might not always be adequately diagnosed, since these patients did not always visit an ophthalmologist.
Another limitation might be that relatedness to treatment of AEs was assessed by a physician at the moment of occurrence. As recent safety studies on more novel treatments, like dupilumab, have provided new insights not present at the time of study initiation, relatedness may have been misinterpreted or interpreted incompletely among physicians during earlier study visits. Moreover, due to these new insights, the list of AESIs collected in the TREAT NL registry has changed over time, which may have led to underreporting of AESIs.
To standardize the assessment of drug-relatedness of AEs in the future, we will start using the Naranjo Scale (the AE Probability Scale)[58].

This study illustrates that real-world reported AEs captured in AD patient registries can potentially add information on the estimated incidence of AEs to the SmPC, and can subsequently benefit clinical decision aids. Current SmPCs might need an update which will contribute to safer pharmacotherapy. Results from this study will be shared with the Netherlands Pharmacovigilance Centre Lareb. Subsequently, data can be retrieved by third parties and possibly shared with databases from the EMA (Eudravigilance) and World Health Organisation VigiBase. More collection of RWD is needed to provide new insights on the safety of treatments that are underrepresented in this study, including tralokinumab, baricitinib, upadacitinib and abrocitinib. Future studies using data derived from the TREAT NL registry combined with RWD from other registries within the TREAT Registry Taskforce will provide even more information on (rare) AEs associated with immunomodulating therapy in AD patients.

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CHAPTER 7

DUPILUMAB-ASSOCIATED (HYPER)EOSINOPHILIA IN PATIENTS WITH ATOPIC DERMATITIS: A SINGLE-CENTER COHORT STUDY OF THE TREAT NL/BE (TREATMENT OF ATOPIC ECZEMA, THE NETHERLANDS AND BELGIUM) REGISTRY

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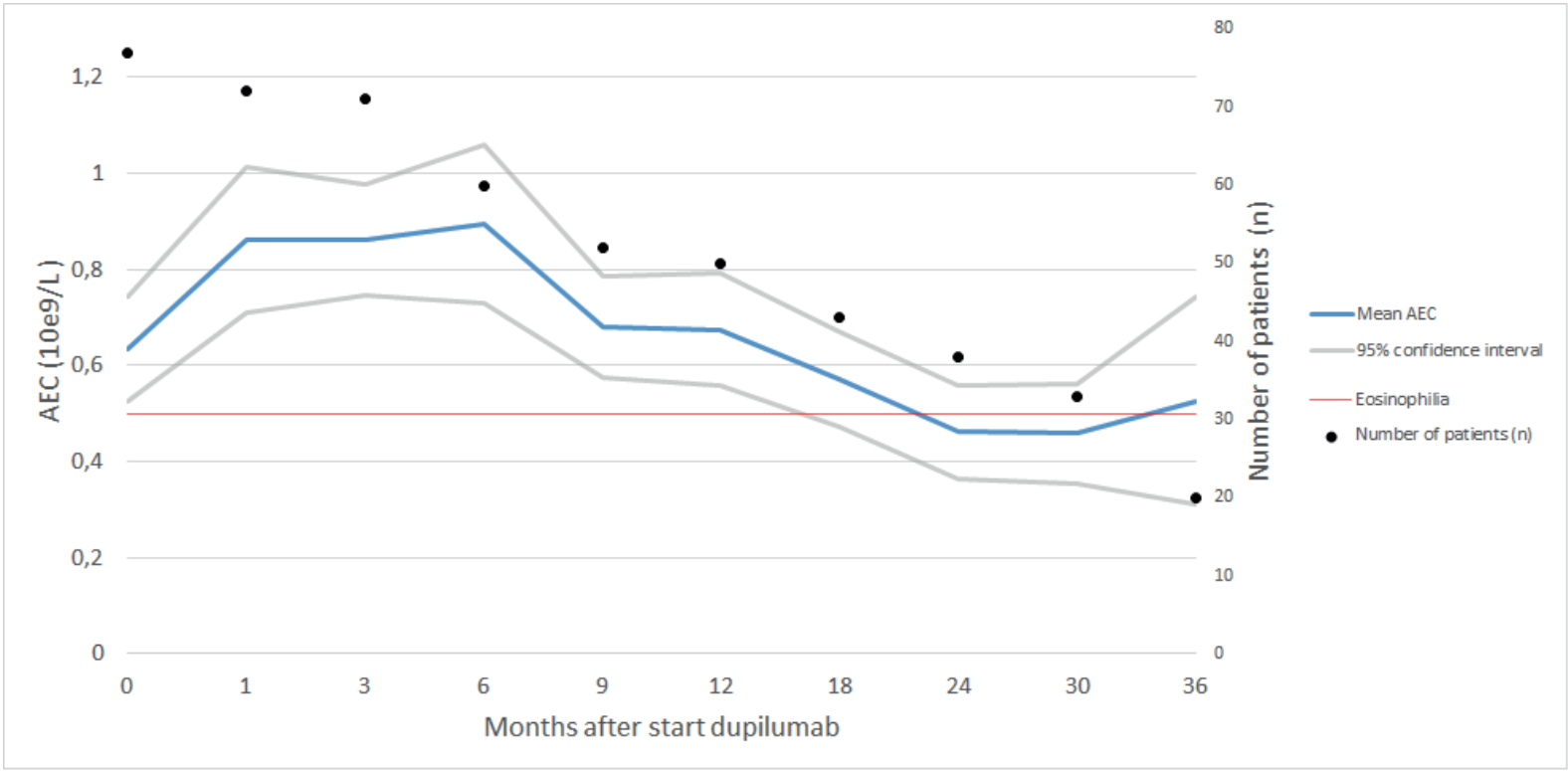
RESEARCH LETTER

Dupilumab, a human monoclonal antibody inhibiting IL-4 and IL-13 signaling, has been proven highly effective as a treatment for atopic dermatitis (AD). However, dupilumab may cause transient peripheral (hyper)eosinophilia due to blocking eosinophilia migration into tissue but not from bone marrow into the peripheral blood[1-3]. This phenomenon has been studied in severe asthma, but not extensively in AD[4]. Our study examines the incidence, progression, and clinical outcomes of (hyper)eosinophilia in AD patients undergoing dupilumab treatment to provide management guidance.

Data was collected from September 2017 to December 2022 using the TREatment of ATopic eczema, the Netherlands/Belgium (TREAT NL/BE) registry cohort at Amsterdam University Medical Center. Three included patients did not participate in the registry. Adults and children with AD, defined by the U.K. Working Party's Criteria, undergoing dupilumab treatment and having at least one (hyper)eosinophilia measurement at baseline or during therapy, were included in the study. Data was collected using the TREAT core dataset at baseline, 4 weeks, 12 weeks, followed by every 12 weeks, and biannually after one year[5, 6]. Dupilumab dosing commenced with 600 mg intramuscularly, followed by biweekly 300 mg. Eosinophilia and hypereosinophilia were defined as an absolute eosinophil count (AEC) of ≥0.5*10^9/L and ≥1.5*10^9/L, respectively.

A total of 200 patients initiated dupilumab treatment, with 77 (38.5%) experiencing (hyper)eosinophilia, either at baseline (n=43 [55.8%]) or during the treatment period (n=35 [44.2%]). The mean age of patients with (hyper)eosinophilia was 39.5 (±17.6) years, predominantly male (62.3%), with a median dupilumab treatment span of 21 months (IQR 8-36, range 1-58 months).
Baseline mean AEC was 0.63*10^9/L (±0.48). After dupilumab initiation, the mean AEC of all patients rose, peaking at 0.89*10^9/L by the sixth month, and declined to normal levels again between 18 and 24 months, as shown in *Figure 1*.

Figure 1. Changes in the mean absolute eosinophil count (AEC) of patients with (hyper)eosinophilia at baseline and/or during dupilumab treatment (n=77) over time. Eosinophilia is defined as an AEC of >0.5*10^9/L. Hypereosinophilia is defined as an AEC of >1.5*10^9/L.



Patients with baseline eosinophilia (n=38) and hypereosinophilia (n=5) had a baseline mean AEC of 0.92*10^9/L (±0.45), which increased to 1.03*10^9/L within a month of treatment and normalized after 30 months. Patients without initial (hyper)eosinophilia (n=34) had a mean baseline AEC of 0.27*10^9/L (±0.15) which increased to 0.83*10^9/L within six months, declining to normal levels by 18 months. The mean time to (hyper)eosinophilia onset was 2.53 months. We observed four cases of late-onset eosinophilia (i.e. after 6 months), with AEC of 1.35, 0.6, 0.76 and 0.56*10^9/L at month 6, where baseline, month 1, and months 3 AEC were <0.5*10^9/L.

A total of 15 patients developed hypereosinophilia during treatment, of which one patient had to discontinue dupilumab due to hypereosinophilia. In this patient (male, 43 years old) an elevated AEC with a maximum of 2.57*10e9/L was observed in week 205 of dupilumab treatment. The patient reported symptoms of night sweats and shortness of breath, possibly related to hypereosinophilia. No evidence of parasitic infection, hypereosinophilic syndrome, or malignancy were. Hematology was consulted and dupilumab was ceased, leading to a reduction in the AEC to 0.93*10^9/L and resolution of symptoms after a 16-week period without treatment. When treatment was resumed, hypereosinophilia was noted again after 16 weeks. Eventually, the AEC normalized (0.48*10^9/L) 30 weeks after reintroduction of dupilumab.

For the remaining 14 patients who experienced hypereosinophilia during their treatment, no potentially associated symptoms were reported, leading to a decision for a watchful waiting approach. In all these patients, AEC levels decreased to below 1.5*10^9/L during the course of treatment.
Patients treated with dupilumab experienced a transient initial eosinophil surge, which was not clinically significant for most, regardless of their baseline eosinophilia status. One case of persistent hypereosinophilia led to the discontinuation of dupilumab, but generally, eosinophilia did not impact the therapeutic course. Our findings assume that dupilumab treatment is viable for AD patients irrespective of baseline eosinophilia, with observed eosinophilia being temporary. These findings align with previous trials, highlighting a consistent eosinophil response pattern across different patient populations [7, 8]. Limitations of this study include a variable cohort size over time and a small sample size, which might conceal rare adverse events and limit the generalizability of the results. Future research should focus on longer follow-up periods to further elucidate the safety and effectiveness of dupilumab, particularly in relation to eosinophil levels and treatment response.

Continuous routine monitoring is not recommended. However, an AEC check in the first six months is advised. If AEC exceeds 5*10^9/L or 3*10^9/L twice, consultation with an internist/hematologist or pediatrician is advised. Clinicians should inquire about symptoms of hyper-eosinophilic organ damage due to eosinophil accumulation in organs, which can include cardiac dysfunction, stroke, thromboembolic events, vasculitis, neurological symptoms in extremities, and shortness of breath.

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CHAPTER 8

THE EFFECTS OF SYSTEMIC IMMUNOMODULATORY TREATMENTS ON COVID-19 OUTCOMES IN PATIENTS WITH ATOPIC DERMATITIS: RESULTS FROM THE GLOBAL SECURE-AD REGISTRY

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ABSTRACT

Background

Limited data are available on the effects of systemic immunomodulatory treatments on COVID-19 outcomes in patients with atopic dermatitis (AD).

Objective

To investigate COVID-19 outcomes in patients with AD treated with or without systemic immunomodulatory treatments, using a global registry platform.

Methods

Clinicians were encouraged to report cases of COVID-19 in their patients with AD in the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Atopic Dermatitis (SECURE-AD) registry. Data entered from April 1st 2020 to October 31st 2021 were analyzed using multivariable logistic regression. The primary outcome was hospitalization from COVID-19, according to AD treatment groups.

Results

442 AD patients (mean age 35.9 years, 51.8% male) from 27 countries with strongly suspected or confirmed COVID-19 were included in analyses. 428 (96.8%) patients were treated with a single systemic therapy (n=297[67.2%]) or topical therapy only (n=131[29.6%]). Most patients treated with systemic therapies received dupilumab (n=216). 14 patients (3.2%) received a combination of systemic therapies. 26 patients (5.9%) were hospitalized. No deaths were reported. Patients treated with topical treatments had significantly higher odds of hospitalization, compared to those treated with dupilumab monotherapy (odds ratio (OR) 4.65[95%CI 1.71-14.78]), including after adjustment for confounding variables (adjusted OR (aOR 4.99[95%CI 1.4-20.84]). Combination systemic therapy which did not include systemic corticosteroids was associated with increased odds of hospitalization, compared to single agent non-steroidal immunosuppressive systemic treatment (OR 8.09[95%CI 0.4-59.96], aOR 37.57[95%CI 1.05-871.11]). Hospitalization was most likely in patients treated with combination systemic therapy which included systemic corticosteroids (OR 40.43[95%CI 8.16-207.49], aOR 45.75[95%CI 4.54-616.22]).

Conclusions

Overall, the risk of COVID-19 complications appears low in patients with AD, even when treated with systemic immunomodulatory agents. Dupilumab monotherapy was associated with lower hospitalization than other therapies. Combination systemic treatment, particularly combinations including systemic corticosteroids, was associated with the highest risk of severe COVID-19.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), causing Coronavirus Disease 2019 (COVID-19), is associated with a highly variable disease course, ranging from asymptomatic infection to severe disease resulting in hospitalization, intensive care unit (ICU) admission, mechanical ventilation, and death.[1] Older age, male sex, non-white ethnicity, obesity, diabetes and underlying immunosuppression are important factors associated with a more severe and protracted disease course and increased mortality rates.[1, 2]

Atopic dermatitis (AD, also known as atopic eczema) is a complex chronic inflammatory skin disease. Both genetic and environmental factors play a role in AD pathogenesis. AD is characterized by skin barrier dysfunction and altered cell-mediated immunity.[3, 4] Compared to the general population, cutaneous and systemic infections are more common in patients with AD,[5] therefore it is plausible that SARS-CoV-2 infection, as well as the risks associated with COVID-19, could be affected by intrinsic immune dysregulation in AD.

A recent epidemiological study using electronic healthcare records demonstrated that many inflammatory skin diseases, including AD, acne, psoriasis, and cutaneous lupus, were associated with higher risk of COVID-19, even after controlling for age, gender, ethnicity, obesity and deprivation status.[6] However, patients with these inflammatory skin diseases had an overall lower odds of mechanical ventilation.[6]

Patients with moderate-to-severe AD are often treated with systemic immunomodulatory therapy, including systemic corticosteroids and conventional systemic therapies, such as ciclosporin, methotrexate, azathioprine and mycophenolate mofetil. More recently, biologics such as dupilumab and tralokinumab, and small immunomodulatory molecules including the Janus Kinase inhibitors (JAKi) baricitinib, upadacitinib, and abrocitinib,[7-9] have been approved in several countries for the treatment of AD. Clinicians and patients must consider the potentially increased risk of infection associated with immunomodulatory treatments, especially in the context of a global pandemic, as differing mechanisms of action and levels of immunosuppression may impart variable risks of serious infections.[10-14] Contrastingly, some degree of immunomodulation may have beneficial effects on the rate of SARS-CoV-2 infection,[15] and targeting of specific immune pathways could reduce the development of a hyper-inflammatory state in severe COVID-19[16-19] a hypothesis supported by the recent World Health Organization recommendation for using baricitinib in the treatment of severe or critical COVID-19.[20]

Responding to the urgent need to better understand the determinants of COVID-19 outcomes and whether immunomodulatory treatments for AD affect the risk of morbidity and mortality, the SECURE-AD (Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion – Atopic Dermatitis) Physician Registry was launched in April 2020. The primary aim of the SECURE-AD study was to evaluate the effects that different systemic immunomodulatory AD treatments have on COVID-19 outcomes.

METHODS

Study design, setting and patients

The SECURE-AD Physician Registry is a global web-based registry, launched through international collaboration between clinicians, researchers, and patients with AD (https://www.covidderm.org/). The study was promoted by national and international

dermatology and patient partner organizations (see Acknowledgements). Clinicians were encouraged to report all cases of COVID-19 in patients with AD, and were required to register using their name, email and hospital affiliation. Ethical approval was granted by the Leeds Research Ethics Committee (20/YH/0135) and by the Irish National Research Committee for COVID-19-related Health Research (NREC COVID-19).
AD patients of all ages and any AD severity with suspected or confirmed COVID-19 (including asymptomatic patients detected through public health screening) were eligible for inclusion. Clinicians were asked to allow sufficient time to pass to observe disease progression, experience partial or complete recovery, hospitalization or death. Patients with AD taking immunomodulatory medication for an indication other than AD were excluded.

Data collection and outcomes
Anonymized observational data were collected using a web-based case report form (CRF), hosted on the OpenAppIT Clinical Insight platform (Dublin, Ireland). A single CRF was completed for each patient which included demographics (age, sex, ethnicity, country of residence), patient characteristics (body mass index (BMI), smoking status, co-morbidities, concomitant medications), date of diagnosis and AD disease activity (prior to and during COVID-19), and details of AD treatments. Although additional ethnicity options were pre-specified, ethnicity data were condensed (White, South Asian, Other, Unknown) for the regression analysis due to sample sizes.
Clinicians reported COVID-19 disease course and outcomes (duration of symptoms, persistence of COVID-19 symptoms at the time of reporting, death due to COVID-19, Emergency Department (ED) attendance, hospitalization, length of hospital stay, intensive care unit (ICU) admission, ventilation requirement, and flare (exacerbation) of AD during COVID-19). Hospitalization due to COVID-19 was selected as the primary measure of severe COVID-19 in our cohort due to low numbers of reported ICU admissions or mechanical ventilation. The web-based CRF was not altered since it was launched on April 1st 2020, so data on COVID-19 vaccination status were not collected.
CRFs were carefully designed to avoid traceability and only anonymized data were submitted to SECURE-AD. In line with the Declaration of Helsinki (1975, revised 2013), written consent from patients was not required.[21] All data were collected and processed exclusively for the promotion of scientific and medical research, carried out in the public interest.
Data collection was harmonized with concurrent efforts studying other immune-mediated inflammatory diseases (IMIDs), for example SECURE-Alopecia, SECURE-IBD, PsoProtect, and the Global Rheumatology Alliance.[22-24]

Statistical analysis
Based on data availability, drug class and mechanisms of action, we created immunomodulatory treatment groups. We summarized demographics and clinical characteristics and COVID-19 outcomes of the study population using descriptive statistics.
To minimize the risk of over-fitting logistic regression models for hospitalization by including each comorbidity as an individual variable, we created a cohort-specific “comorbidity score”, using each patient’s comorbidities and Body Mass Index (BMI). Presence or absence of comorbidities (asthma, other lung diseases including COPD, cardiovascular disease, hypertension, diabetes and stroke) and BMI were used to model the risk of hospitalization from COVID-19. This model gives a higher coefficient to the comorbidities that better predict

hospitalization (irrespective of AD treatments) and these coefficients are used as the weights in our comorbidity score.

We report two main analyses to evaluate the effects of immunomodulatory therapies on COVID-19 outcomes. Firstly, to evaluate the effects of individual systemic treatments, patients receiving topical therapy only or a single systemic therapy for AD (i.e. systemic monotherapy) were analyzed separately to those receiving systemic therapies in combination. Treatment groups in the monotherapy analysis were: topical treatment only, dupilumab, methotrexate, ciclosporin, systemic corticosteroids, other conventional immuno-suppressant treatments (azathioprine and mycophenolate mofetil), JAKi, and other systemic treatments (including tralokinumab and other biologic and small molecule treatments (omalizumab and apremilast)). 95% confidence intervals (95%CI) associated with percentages experiencing COVID-19 outcomes were calculated by Pearson-Klopper method, using R's binom package v1.1-1.[25] Logistic regression was used to generate odds ratios (OR) and 95%CI for hospitalization according to immunomodulatory treatment groups, using dupilumab monotherapy as the reference group. Regression models were then adjusted for age, sex, ethnicity and each patient's comorbidity score.

Secondly, we evaluated the effect of systemic therapies used in combination, stratified according to whether the combination included systemic corticosteroids. The following systemic treatment groups were created: any non-steroidal immunosuppressive systemic treatment (NSISS) as monotherapy (reference group), systemic corticosteroids as monotherapy, combination treatment not including systemic corticosteroids, and combination treatment including systemic corticosteroids. Patients receiving topical therapies only were excluded from the combination treatment analysis. Adjusted OR (aOR) and 95%CI for hospitalization due to COVID-19 were calculated, adjusted as per the monotherapy analysis.

Patients reported in the registry from April 1st 2020 to October 31st 2021 were included in this analysis. All analyses were performed using R (Vienna, Austria), version 4.1.1. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for cross-sectional studies was used.[26]

RESULTS

452 patients with AD and a COVID-19 diagnosis from 27 countries were registered in the SECURE-AD Physician Registry. Ten patients were excluded from further analysis: 3 receiving systemic immunomodulation for conditions other than AD, 3 participating in blinded clinical trials, and 4 who had an unknown COVID-19 outcome. One patient receiving tofacitinib for rheumatoid arthritis, in combination with dupilumab, was retained in the analysis due to presumed similar mechanism of action of JAKi used in AD.

Demographics, clinical characteristics and COVID-19 outcomes

Table 1 provides a summary of demographics and clinical characteristics of the study subjects (n=442), as well as full details of AD therapies used and the observed variation between immunomodulatory treatment groups. All combinations of systemic immunomodulatory treatments are summarized together in Table 1, and the number of patients receiving each specific combination of treatments is listed in the accompanying footnote. Further details of the doses of systemic treatments used are available in Supplementary Table 1 (single agent

systemic therapy, i.e. systemic monotherapy) and Supplementary Table 2 (systemic treatments used in combination). Table 2 outlines the overall proportions of patients with pre-defined COVID-19 outcomes. Hospitalization was reported in 26 patients (5.9%). ICU admissions (n=8, 1.8%) and mechanical ventilation were infrequent (n=6, 1.4%) and there were no reported deaths.

Table 1. Demographics and clinical characteristics

	Overall	Topical treatments only	Dupilumab	Methotrexate	Ciclosporin	Systemic cortico-steroids	Other conventional immuno-suppressants	JAK inhibitors	Other biologic/small molecule treatments	Combination treatments	p-value
COVID-19 cases	442	131	216	30	22	7	6	12	4	14	
Sex (%)											0.661
Female	213 (48.2)	58 (44.3)	108 (50.0)	15 (50.0)	8 (36.4)	3 (42.9)	5 (83.3)	6 (50.0)	2 (50.0)	8 (57.1)	
Male	229 (51.8)	73 (55.7)	108 (50.0)	15 (50.0)	14 (63.6)	4 (57.1)	1 (16.7)	6 (50.0)	2 (50.0)	6 (42.9)	
Age, mean (SD)	35.93 (18.00)	28.58 (18.10)	40.38 (16.92)	38.73 (19.78)	29.95 (13.15)	63.43 (18.31)	30.00 (9.94)	37.00 (22.79)	40.75 (17.80)	41.64 (15.79)	<0.001
Age category (%)											<0.001
<2 years	5 (1.1)	5 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
2-9 years	20 (4.5)	17 (13.0)	1 (0.5)	0 (0.0)	2 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
10-19 years	60 (13.6)	24 (18.3)	19 (8.8)	7 (23.3)	2 (9.1)	1 (14.3)	1 (16.7)	3 (25.0)	1 (25.0)	2 (14.3)	
20-39 years	168 (38.0)	47 (35.9)	86 (39.8)	10 (33.3)	12 (54.5)	4 (57.1)	4 (66.7)	3 (25.0)	0 (0.0)	2 (14.3)	
40-59 years	145 (32.8)	32 (24.4)	79 (36.6)	9 (30.0)	6 (27.3)	1 (14.3)	1 (16.7)	5 (41.7)	3 (75.0)	9 (64.3)	
60-79 years	40 (9.0)	6 (4.6)	30 (13.9)	2 (6.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.1)	
≥80 years	4 (0.9)	0 (0.0)	1 (0.5)	2 (6.7)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Ethnicity (%)											<0.001
White	286 (64.7)	54 (41.2)	175 (81.0)	17 (56.7)	11 (50.0)	2 (28.6)	3 (50.0)	9 (75.0)	3 (75.0)	12 (85.7)	
South Asian	60 (13.6)	36 (27.5)	8 (3.7)	5 (16.7)	7 (31.8)	2 (28.6)	0 (0.0)	1 (8.3)	1 (25.0)	0 (0.0)	
Asian - Chinese	2 (0.5)	1 (0.8)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Asian - other	4 (0.9)	4 (3.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Hispanic or Latino	14 (3.2)	4 (3.1)	4 (1.9)	1 (3.3)	1 (4.5)	1 (14.3)	1 (16.7)	1 (8.3)	0 (0.0)	1 (7.1)	
Afro Caribbean	8 (1.8)	2 (1.5)	5 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Black-African	5 (1.1)	2 (1.5)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Other	6 (1.4)	2 (1.5)	0 (0.0)	2 (6.7)	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	
Unknown	57 (12.9)	26 (19.8)	20 (9.3)	5 (16.7)	3 (13.6)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (7.1)	
Country of residence (%)											<0.001
Italy	138 (31.2)	9 (6.9)	112 (51.9)	1 (3.3)	4 (18.2)	2 (28.6)	0 (0.0)	3 (25.0)	2 (50.0)	5 (35.7)	
India	64 (14.5)	41 (31.3)	2 (0.9)	8 (26.7)	10 (45.5)	2 (28.6)	0 (0.0)	0 (0.0)	1 (25.0)	0 (0.0)	
United Kingdom	61 (13.8)	7 (5.3)	26 (12.0)	13 (43.3)	2 (9.1)	0 (0.0)	2 (33.3)	4 (33.3)	1 (25.0)	6 (42.9)	

France	36 (8.1)	17 (13.0)	16 (7.4)	2 (6.7)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)	
The Netherlands	31 (7.0)	7 (5.3)	21 (9.7)	1 (3.3)	1 (4.5)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	
United States	20 (4.5)	14 (10.7)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	0 (0.0)	1 (7.1)	
Europe (other)	61 (13.8)	20 (15.3)	26 (12.0)	4 (13.3)	4 (18.2)	2 (28.6)	2 (33.3)	2 (16.7)	0 (0.0)	1 (7.1)	
South America	16 (3.6)	5 (3.8)	6 (2.8)	1 (3.3)	1 (4.5)	1 (14.3)	1 (16.7)	0 (0.0)	0 (0.0)	1 (7.1)	
Asia (other)	9 (2.0)	9 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Middle East	4 (0.9)	0 (0.0)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
North America (other)	2 (0.5)	2 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Dose of systemic treatment, median (IQR)	NA	NA	See sTable 1	12.5mg (10 - 15mg) per week*	100mg (100mg - 150mg) per day**	See sTable 1	See sTable 1	See sTable 1	See sTable 1	See sTable 2	
Dose by weight, median (IQR)	NA	NA	NA	0.18mg/kg (0.16 - 0.23mg/kg) per week*	2.86mg/kg (2.22 - 3.15mg/kg) per day**	NA	NA	NA	NA	NA	
Method of COVID-19 diagnosis (%)											0.008
Positive test	305 (69.0)	103 (78.6)	137 (63.4)	20 (66.7)	20 (90.9)	5 (71.4)	4 (66.7)	4 (33.3)	3 (75.0)	9 (64.3)	
Presumptive diagnosis based on typical features	135 (30.5)	28 (21.4)	77 (35.6)	10 (33.3)	2 (9.1)	2 (28.6)	2 (33.3)	8 (66.7)	1 (25.0)	5 (35.7)	
Unknown	2 (0.5)	0 (0.0)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
BMI (median (IQR)) - patients aged 16+ only	24.05 (21.92, 26.51)	23.15 (21.63, 25.31)	24.54 (22.22, 26.83)	23.84 (22.04, 26.47)	22.49 (21.08, 24.24)	23.77 (21.32, 26.07)	25.44 (23.83, 29.26)	22.95 (21.71, 24.98)	24.73 (22.74, 27.57)	25.9 7(23.51, 31.20)	0.059
BMI categories (%) - patients aged 16+ only											0.239
BMI < 19	11 (2.8)	2 (2.2)	7 (3.4)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	1 (8.3)	0 (0.0)	0 (0.0)	
BMI 19 - 25	206 (53.4)	54 (58.7)	104 (50.0)	15 (55.6)	12 (63.2)	3 (50.0)	2 (40.0)	8 (66.7)	2 (50.0)	6 (46.2)	
BMI 25 - 30	100 (25.9)	17 (18.5)	64 (30.8)	6 (22.2)	4 (21.1)	3 (50.0)	1 (20.0)	2 (16.7)	1 (25.0)	2 (15.4)	
BMI > 30	38 (9.8)	4 (4.3)	22 (10.6)	4 (14.8)	0 (0.0)	0 (0.0)	1 (20.0)	1 (8.3)	1 (25.0)	5 (38.5)	
Unknown	31 (8.0)	15 (16.3)	11 (5.3)	2 (7.4)	2 (10.5)	0 (0.0)	1 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	
AD activity prior to COVID-19 infection (%)											<0.001

Remission	211 (47.7)	38 (29.0)	63 (29.2)	6 (20.0)	1 (4.5)	1 (14.3)	2 (33.3)	5 (41.7)	1 (25.0)	1 (7.1)	
Mild	76 (17.2)	62 (47.3)	113 (52.3)	10 (33.3)	5 (22.7)	1 (14.3)	4 (66.7)	6 (50.0)	3 (75.0)	7 (50.0)	
Moderate	118 (26.7)	20 (15.3)	25 (11.6)	13 (43.3)	11 (50.0)	5 (71.4)	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.1)	
Severe	29 (6.6)	7 (5.3)	11 (5.1)	1 (3.3)	5 (22.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (35.7)	
Unknown	8 (1.8)	4 (3.1)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Comorbidities (%)											
Asthma	143 (32.4)	35 (26.7)	71 (32.9)	11 (36.7)	8 (36.4)	3 (42.9)	1 (16.7)	5 (41.7)	3 (75.0)	6 (42.9)	0.446
COPD or other lung disease	14 (3.2)	5 (3.8)	6 (2.8)	2 (6.7)	0 (0.0)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.624
Allergic rhinitis	52 (11.8)	3 (2.3)	37 (17.1)	4 (13.3)	1 (4.5)	1 (14.3)	1 (16.7)	1 (8.3)	1 (25.0)	3 (21.4)	0.008
Cardiovascular disease	19 (4.3)	3 (2.3)	11 (5.1)	2 (6.7)	0 (0.0)	0 (0.0)	1 (16.7)	1 (8.3)	0 (0.0)	1 (7.1)	0.593
Hypertension	40 (9.0)	9 (6.9)	25 (11.6)	3 (10.0)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	0 (0.0)	2 (14.3)	0.45
Stroke	4 (0.9)	0 (0.0)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.836
Diabetes	22 (5.0)	8 (6.1)	11 (5.1)	0 (0.0)	1 (4.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	0.645
Chronic liver disease	7 (1.6)	3 (2.3)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (14.3)	0.032
Chronic kidney disease	5 (1.1)	1 (0.8)	4 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.972
Cancer	2 (0.5)	0 (0.0)	1 (0.5)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0.6
Other	66 (14.9)	8 (6.1)	44 (20.4)	5 (16.7)	0 (0.0)	1 (14.3)	2 (33.3)	0 (0.0)	0 (0.0)	6 (42.9)	<0.001
None	174 (39.4)	77 (58.8)	62 (28.7)	12 (40.0)	12 (54.5)	2 (28.6)	1 (16.7)	6 (50.0)	0 (0.0)	2 (14.3)	<0.001
Smoking status (%)											0.39
Current smoker	63 (14.3)	15 (11.5)	39 (18.1)	2 (6.7)	2 (9.1)	1 (14.3)	0 (0.0)	2 (16.7)	1 (25.0)	1 (7.1)	
Former smoker	44 (10.0)	8 (6.1)	29 (13.4)	2 (6.7)	2 (9.1)	1 (14.3)	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.1)	
Never smoked	314 (71.0)	102 (77.9)	139 (64.4)	25 (83.3)	16 (72.7)	4 (57.1)	5 (83.3)	9 (75.0)	2 (50.0)	12 (85.7)	
Unknown	21 (4.8)	6 (4.6)	9 (4.2)	1 (3.3)	2 (9.1)	1 (14.3)	1 (16.7)	0 (0.0)	1 (25.0)	0 (0.0)	

The category 'other conventional immuno-suppressants' includes patients on azathioprine (n=4), and mycophenolate mofetil (n=2). The category 'JAK inhibitors' includes patients on upadacitinib (n=7), abrocitinib (n=4), and an unspecified JAK inhibitor (n=1). The category 'other biologic/small molecule treatments' includes patients on omalizumab (n=2), tralokinumab (n=1), and apremilast (n= 1). The category 'combination treatments' includes patients on dupilumab + systemic corticosteroids (n=6), dupilumab + ciclosporin (n=2), dupilumab + methotrexate (n=1), dupilumab + tofacitinib (n=1), azathioprine + systemic corticosteroids (n=1), ciclosporin + systemic corticosteroids (n=1), ciclosporin + methotrexate (n=1), and mycophenolate mofetil + omalizumab (n=1).

* Median weekly dose, and median weekly dose by weight of methotrexate calculated from n=29 patients receiving MTX weekly, and excluding n=1 receiving methotrexate on alternate weeks. ** One patient was reported to be taking ciclosporin 100mg twice per week, but this was likely to be a typographical error and the median daily dose, and median dose by weight were calculated under the assumption this dose was 100mg twice per day.

SD = Standard Deviation; IQR = Interquartile range; sTable 1 = Supplementary Table 1; sTable 2 = Supplementary Table 2.

Table 2. COVID-19 outcomes

	Overall	Topical treatments only	Dupilumab	Methotrexate	Ciclosporin	Systemic corticosteroids	Other conventional immuno-suppressants	JAK inhibitors	Other biologic/ small molecule treatments	Combination treatments
Cases of COVID-19	442	131	216	30	22	7	6	12	4	14
Duration of COVID-19 symptoms in days (median (IQR))	7.0 (3.0, 14.0)	6.0 (0.0, 11.0)	7. 0 (4.0, 14.0)	10.0 (3.0, 15.5)	12.0 (6.0, 15.0)	14.0 (3.0, 14.0)	6.0 (5.0, 24.25)	8.0 (7.0, 13.0)	10.0 (8.25, 11.75)	19.0 (11.0, 42.0)
Complete resolution of COVID-19 (%)										
Yes	302 (68.3)	101 (77.1)	122 (56.5)	24 (80.0)	22 (100.0)	5 (71.4)	5 (83.3)	10 (83.3)	4 (100.0)	9 (64.3)
No	34 (7.7)	9 (6.9)	17 (7.9)	4 (13.3)	0 (0.0)	0 (0.0)	1 (16.7)	2 (16.7)	0 (0.0)	1 (7.1)
Unknown	106 (24.0)	21 (16.0)	77 (35.6)	2 (6.7)	0 (0.0)	2 (28.6)	0 (0.0)	0 (0.0)	0 (0.0)	4 (28.6)
Died of COVID-19 (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
ED attendance (%)										
Yes	55 (12.4)	20 (15.3)	18 (8.3)	2 (6.7)	4 (18.2)	1 (14.3)	1 (16.7)	0 (0.0)	2 (50.0)	7 (50.0)
No	373 (84.4)	109 (83.2)	189 (87.5)	28 (93.3)	17 (77.3)	5 (71.4)	4 (66.7)	12 (100.0)	2 (50.0)	7 (50.0)
Unknown	14 (3.2)	2 (1.5)	9 (4.2)	0 (0.0)	1 (4.5)	1 (14.3)	1 (16.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hospitalized (%)	26 (5.9)	13 (9.9)	5 (2.3)	1 (3.3)	1 (4.5)	1 (14.3)	0 (0.0)	0 (0.0)	0 (0.0)	5 (35.7)
Median length of hospital stay in days (IQR)	8.0 (4.0, 11.0)	6.0 (4.0, 10.0)	11.0 (9.0, 12.0)	2.0 (2.0, 2.0)	10.0 (10.0, 10.0)	4.0 (4.0, 4.0)	NA	NA	NA	33.0 (5.0, 42.0)
Admitted to ICU (%)	8 (1.8)	3 (2.3)	2 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (21.4)
Required ventilation (%)	6 (1.4)	0 (0.0)	3 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (21.4)
AD flare during COVID-19 (%)										
Yes	100 (22.6)	43 (32.8)	30 (13.9)	7 (23.3)	7 (31.8)	1 (14.3)	2 (33.3)	4 (33.3)	2 (50.0)	4 (28.6)
No	317 (71.7)	82 (62.6)	171 (79.2)	22 (73.3)	15 (68.2)	5 (71.4)	4 (66.7)	7 (58.3)	2 (50.0)	9 (64.3)
Unknown	25 (5.7)	6 (4.6)	15 (6.9)	1 (3.3)	0 (0.0)	1 (14.3)	0 (0.0)	1 (8.3)	0 (0.0)	1 (7.1)

The category 'other conventional immuno-suppressants' includes patients on azathioprine (n=4), and mycophenolate mofetil (n=2). The category 'JAK inhibitors' includes patients on upadacitinib (n=7), abrocitinib (n=4), and an unspecified JAK inhibitor (n=1). The category 'other biologic/small molecule treatments' includes patients on omalizumab (n=2), tralokinumab (n=1), and apremilast (n= 1). The category 'combination treatments' includes patients on dupilumab + systemic corticosteroids (n=6), dupilumab + ciclosporin (n=2), dupilumab + methotrexate (n=1), dupilumab + tofacitinib (n=1), azathioprine + systemic corticosteroids (n=1), ciclosporin + systemic corticosteroids (n=1), ciclosporin + methotrexate (n=1), and mycophenolate mofetil + omalizumab (n=1). Median length of stay calculated amongst hospitalized patients only.

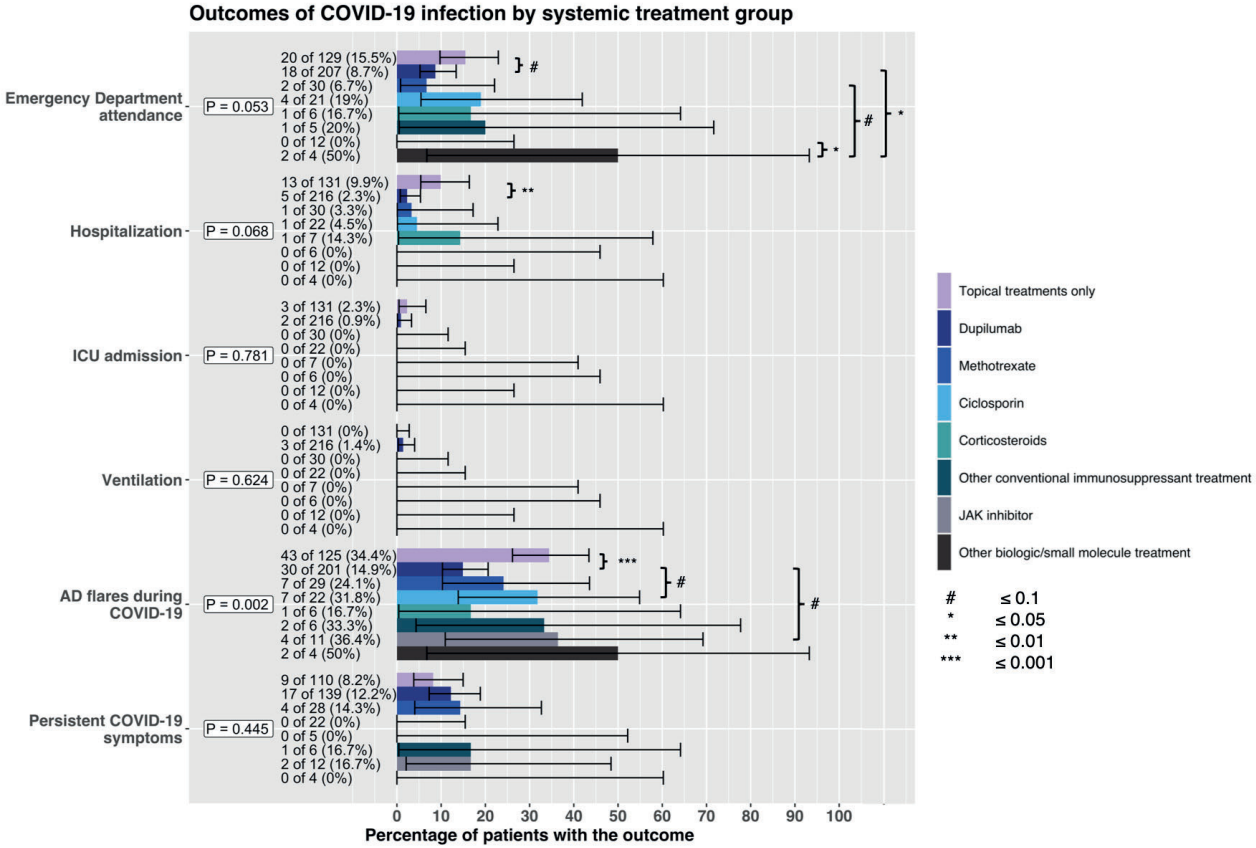
COVID-19 outcomes in patients treated with topical or single agent systemic immunomodulatory therapy (monotherapy analysis)

Figure 1 depicts the proportions of patients with pre-specified COVID-19 outcomes, according to their immunomodulatory treatment group. 48 patients in the monotherapy analysis attended the Emergency Department (ED). ED attendance rates differed between treatment groups (p=0.053) and was higher in those treated with topical treatments compared to dupilumab (15.5% vs 8.7%, p=0.075). Overall, hospitalization because of COVID-19 was infrequent (n=21 [5.2%]), but the proportions of hospitalized patients varied between the treatment groups (p=0.068) and was highest in those treated with systemic corticosteroids (14.3%). Patients treated with topical treatments were more likely to be hospitalized than those treated with dupilumab (9.9% vs 2.3%, p=0.004). Compared to dupilumab (14.9%), patients treated with topical treatments (34.4%), ciclosporin (31.8%) and JAKi (36.4%) were more likely to experience a flare (exacerbation) of AD during COVID-19 (p<0.001, p=0.065, p=0.08 respectively). Supplementary Table 3 presents the p-values for between group comparisons for each pre-specified COVID-19 outcome.

Regression analysis of hospitalization rates according to topical or single agent systemic immunomodulatory treatment group

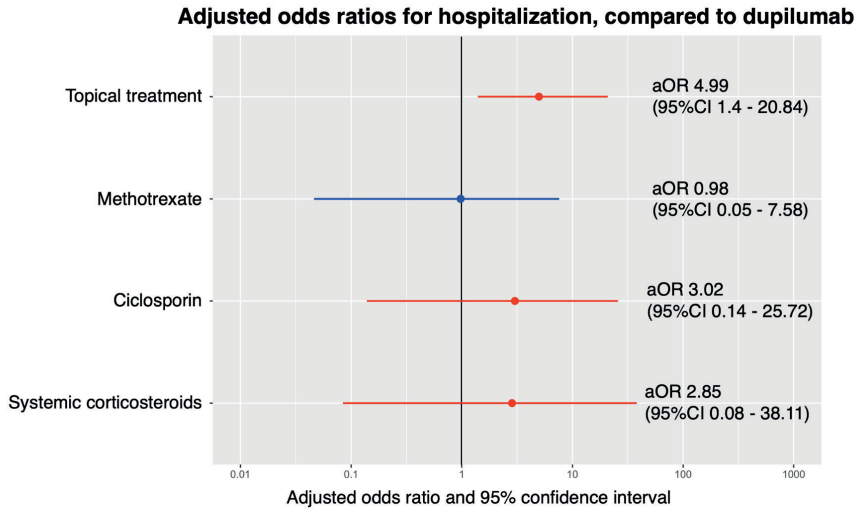
To further explore the differences in hospitalization rates observed between systemic treatments identified in the monotherapy analysis (Figure 1, Supplementary Table 3), a multivariable logistic regression model was fitted, adjusting for confounding variables (age, sex, ethnicity, comorbidity score). No hospitalizations were reported in patients treated with JAKi (n=12), other conventional immunosuppressant treatments (n=6), or other biologic/small molecule treatments (n=4), so these treatment groups were excluded from regression analysis. An additional 41 patients with missing BMI data were excluded, leaving 365 patients to assess the association between hospitalization and topical treatments and systemic monotherapy (Figure 2). Compared to patients prescribed dupilumab, patients treated with topical treatments had significantly higher rates of hospitalization from COVID-19 (OR 4.65 [95%CI 1.71-14.78]), including after adjusting for age, sex, ethnicity and comorbidity score (aOR 4.99 [95%CI 1.4-20.84]). Compared to dupilumab, hospitalization was more frequently reported in patients receiving systemic corticosteroids (OR 7.03 [95%CI 0.34-53.86], aOR 2.85 [95%CI 0.08-38.11]), or ciclosporin (OR 2.01 [95% 0.1-13.25], aOR 3.02 [95%CI 0.14-25.72]), however, these findings were not statistically significant. After adjustment for confounding variables, patients treated with methotrexate and dupilumab had equivalent odds of hospitalization (OR 1.46 [95%CI 0.07-9.45], aOR 0.98 [95%CI 0.05-7.58]).

Figure 1. Barchart demonstrating the proportions of patients and their pre-specified COVID-19 outcomes, according to the immunomodulatory treatment groups.



Patients receiving topical therapy (n=131) or a single systemic therapy for atopic dermatitis (n=297) were included. 95% confidence intervals around the percentage of each outcome were calculated using the Pearson-Klopper method. P-values were calculated using Fisher's exact test for differences across all groups (boxed P-values). Asterix notation shows statistically significant differences between bracketed pairs of treatments (P-values>0.1 are not shown but are available in *Supplementary Table 3*). AD = atopic dermatitis, ICU = intensive care unit, JAK inhibitor = Janus Kinase inhibitor.

Figure 2. Forest plot demonstrating adjusted odds ratios (aOR) and associated 95% confidence intervals (95%CI) for hospitalization from COVID-19, in patients with atopic dermatitis (AD) treated with topical therapies or a single systemic therapy, compared to those patients receiving dupilumab for their AD.

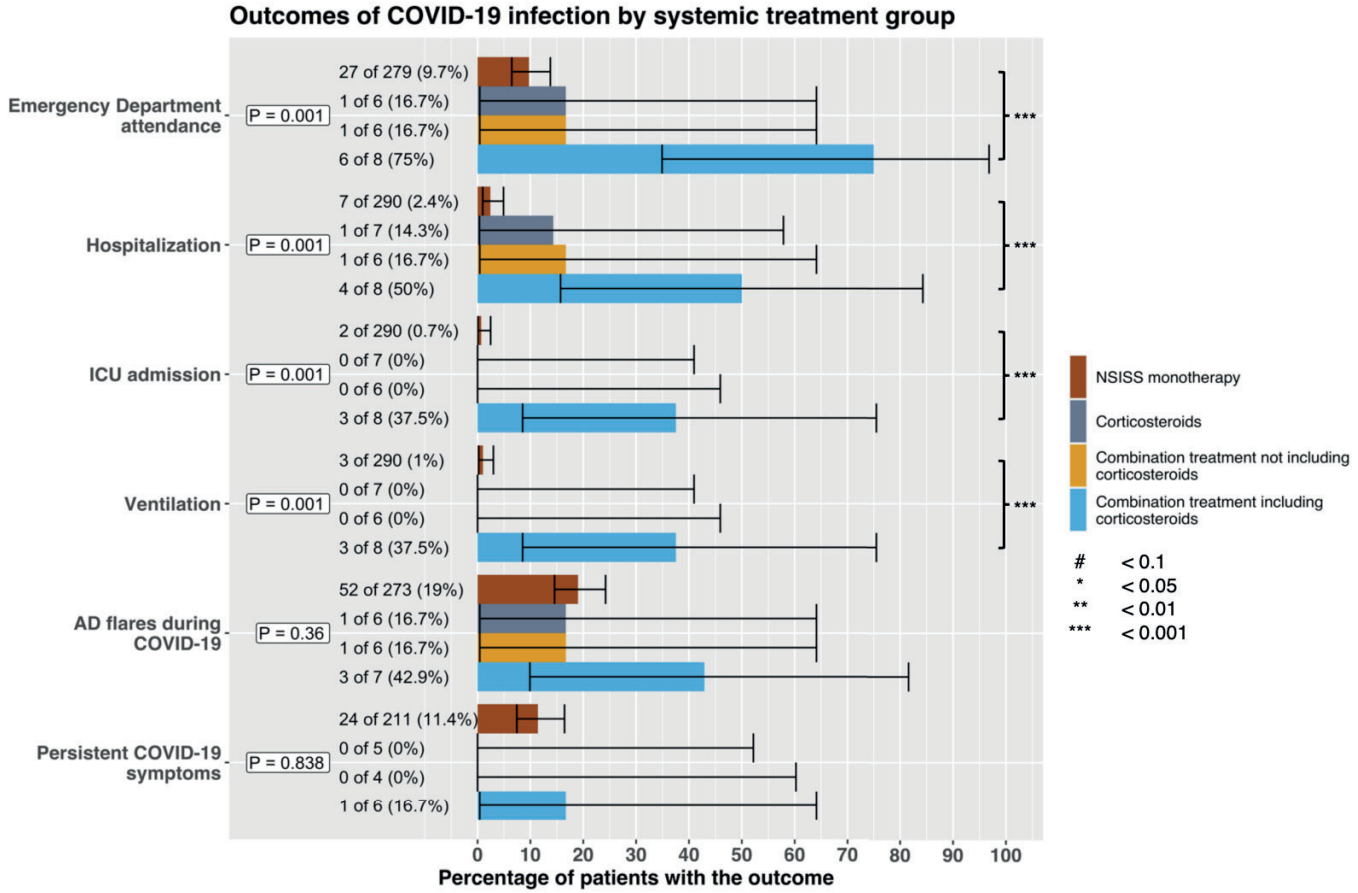


OR were adjusted for age, sex, ethnicity and comorbidity score. aORs less than 1 are in blue, while aORs greater than 1 are in red.

Exploring the effects of combination systemic therapy on COVID-19 outcomes in patients with AD (combination treatment analysis)

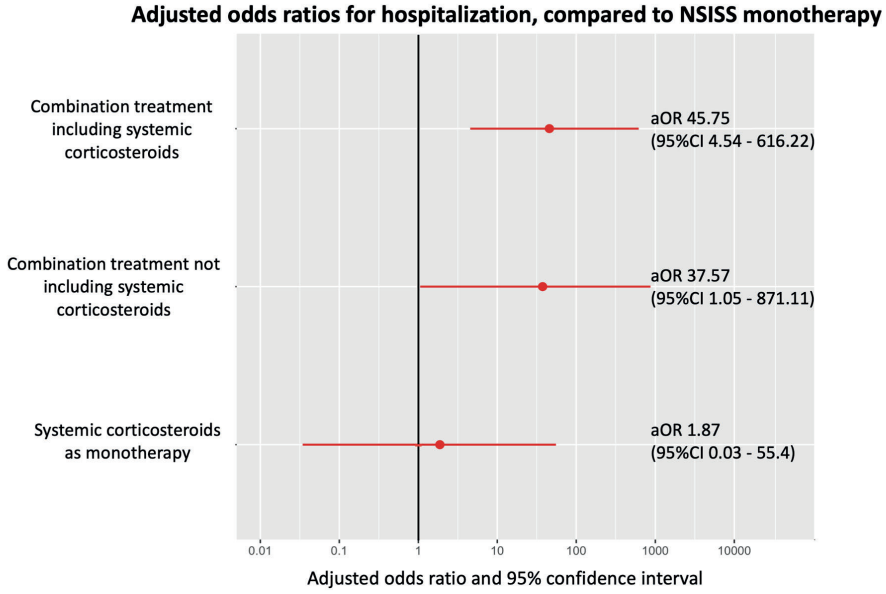
To evaluate the effects of systemic treatments used in combination, a subgroup analysis including patients treated with systemic monotherapy (n=297) or combination systemic therapy (n=14) was performed. Patients were prescribed systemic corticosteroids as monotherapy (n=7), NSISS as monotherapy (n=290), combination treatments not including systemic corticosteroids (n=6) and combination treatments including systemic corticosteroids (n=8). Figure 3 depicts the proportions of patients in each treatment group with each pre-specified COVID-19 outcome. Patients prescribed combination treatments including systemic corticosteroids had the highest rates of ED attendance, hospitalization, ICU admission, ventilation, AD flares (exacerbations) and persistent COVID-19 symptoms. Statistically significant comparisons between treatment groups are highlighted in Figure 3, and p-values for all comparisons are presented in Supplementary Table 4. The effects of combination systemic therapy on hospitalization from COVID-19 was investigated further using multivariable logistic regression, adjusted for confounding variables (age, sex, ethnicity, comorbidity score (Figure 4)). Compared to patients treated with any NSISS as monotherapy, significantly higher rates of hospitalization from COVID-19 were reported in patients treated with combination therapy including systemic corticosteroids (OR 40.43 [95%CI 8.16-207.49], aOR 45.75 [95%CI 4.54-616.22]), and in patients treated with combination therapy not including systemic corticosteroids (OR 8.09 [95%CI 0.4-59.96], aOR 37.57 [95%CI 1.05-871.11]). Compared to single agent NSISS, systemic corticosteroid monotherapy was associated with higher rates of hospitalization (OR 6.74 [95%CI 0.33-47.64], aOR 1.87 [95%CI 0.03-55.4]), although the difference was not statistically significant.

Figure 3. Barchart demonstrating the proportions of patients and their pre-specified COVID-19 outcomes, according to systemic treatment groups.



Patients receiving topical therapy (n=131) were excluded to allow comparison of single agent vs combination systemic therapy for atopic dermatitis. 95% confidence intervals around the percentage of each outcome were calculated using the Pearson-Klopper method. P-values were calculated using Fisher's exact test for differences across all groups (boxed P-values). Asterix notation identifies statistically significant differences between bracketed pairs of treatments (P-values > 0.1 are not shown but are available in *Supplementary Table 4*). AD = atopic dermatitis, ICU = intensive care unit, NSISS = non-steroidal immunosuppressive systemic treatment.

Figure 4. Forest plot demonstrating adjusted odds ratios (aOR) and associated 95% confidence intervals (95%CI) for hospitalization from COVID-19, in patients with atopic dermatitis (AD) treated with systemic corticosteroids (as monotherapy), combination therapy not including systemic corticosteroids, and combination therapy including systemic corticosteroids, compared to those patients receiving a non-steroidal immunosuppressive systemic treatment (NSISS) for AD.



OR were adjusted for age, sex, ethnicity and comorbidity score. aORs greater than 1 are in red.

DISCUSSION

In this global registry study of AD patients from 27 countries, we found important differences in COVID-19 outcomes between different treatment modalities, even if hospitalization rates overall (5.9% of all SECURE-AD patients) did not appear higher than would be expected in the general population.[27] Compared to other IMID registries, hospitalization rates in SECURE-AD patients were lower than reported in patients with inflammatory bowel disease (IBD, 31%), rheumatic diseases (46%) or psoriasis (21%). Fatality rates were also higher in the comparable studies (3%, 10.5% and 2% respectively, vs 0% in the SECURE-AD physician registry).[22-24, 28]

Among those treated with systemic monotherapy, the highest rates of hospitalization were seen in those receiving systemic corticosteroids (14.3%). This finding is consistent with results reported for patients with rheumatic diseases, where ≥10mg prednisolone/day (or equivalent) was associated with higher COVID-19-related mortality, compared to patients prescribed methotrexate.[28]

Compared to dupilumab, topical treatments were associated with significantly higher rates of hospitalization from COVID-19, even after adjusting for confounding variables (aOR 4.99 [95%CI 1.4-20.84]). Compared to dupilumab, patients on methotrexate had equivalent odds

of hospitalization, and dupilumab was associated with lower odds of hospitalization than ciclosporin, or systemic corticosteroids, although these findings did not reach statistical significance.

Dupilumab targets interleukin (IL)-4 and IL-13 which are not activated for viral infections, therefore inhibition is not expected to significantly affect rates of SARS-CoV-2 infection. COVID-19 is characterized by an exaggerated Th1/Th17 immune response and can be associated with a cytokine storm in severe disease.[29] Emerging evidence suggests that expression of Th2 cytokines, including IL-4 and IL-13, may also be increased during COVID-19.[30-34] Our data reinforces the established safety profile of dupilumab from clinical trials and case series during the COVID-19 pandemic.[35-38] In an electronic health record analysis, dupilumab exposure (for any indication) was associated with a lower risk of ventilation and death from COVID-19 (risk of death in dupilumab-treated cohort: 0% vs 1.98% in those not receiving dupilumab [95%CI 1.94-2.03%]).[33] Using the COVID-19 Research Database, Wu et al. compared the risk of contracting SARS-CoV-2 in patients prescribed different AD treatments.[15, 39] Patients on dupilumab were at lower risk of infection, compared to patients on prednisone, ciclosporin, azathioprine and patients not on systemic medication. In contrast to our work, this study did not examine the severity of COVID-19 in relation to AD treatments. Ungar et al. reported a prospective, single-center case series of patients with moderate-severe AD (n=1237), of whom 87 experienced a COVID-19 episode, and reported no deaths or ICU admissions, and only 4 hospitalizations due to COVID-19.[16] In contrast to our study, which used hospitalization as the primary outcome of severe COVID-19, Ungar et al. created a custom COVID-19 symptom severity score and found that patients treated with dupilumab experienced fewer and less severe COVID-19 symptoms, compared to patients on other systemic treatments (including phototherapy), and topical or no treatments. While their study provides useful insights into COVID-19 symptoms in patients with AD treated with systemic therapies, the generalizability of this study's findings is limited by low rates of laboratory-confirmed COVID-19 (7%, compared to 69% in our study) and the use of a COVID-19 symptom score, rather than more objective measures of COVID-19 severity, such as hospitalization or ICU admission.

Our subgroup analysis including patients treated with either a single systemic agent or combination systemic therapy showed that patients treated with combination therapy including systemic corticosteroids had the highest rates of ED attendance, hospitalization, ICU admission, ventilation, AD flares (exacerbations) and persistent COVID-19 symptoms. Compared to patients on NSISS monotherapy, patients on combination treatment with or without systemic corticosteroids had significantly higher odds of hospitalization, after adjusting for confounding variables (aOR 45.75 [95%CI 4.54-616.22]) and aOR 37.57 [95%CI 1.05-871.11]) respectively). The numbers of patients receiving combination systemic therapy was small, reflected in wide confidence intervals, and further research is warranted to validate these findings in a larger sample.

Risk of COVID-19 in patients treated with combination systemic therapy has previously been evaluated in other IMID registries.[40] In a pooled analysis of 6077 patients with IMIDs (IBD, inflammatory arthritis, psoriasis) and COVID-19, TNFi in combination with thiopurines (azathioprine/6-mercaptopurine) was associated with significantly higher odds of hospitalization or death compared with TNFi monotherapy (aOR 1.74 [95%CI 1.17-2.58]), whereas TNFi combined with methotrexate was not associated with significantly higher odds of severe COVID-19 (defined as hospitalization or death) (aOR 1.18 [95%CI 0.85-1.63]).

Interestingly, the use of both methotrexate and thiopurines as monotherapy was associated with higher odds of severe COVID-19 than TNFi monotherapy, highlighting the importance of evaluating the risks of specific combinations of treatments. This study adjusted for systemic corticosteroid use, rather than analyzing systemic therapy in combination with corticosteroid use, and found a dose-dependent relationship with corticosteroid use (aOR per 1 mg increase prednisolone-equivalent, 1.07 [95%CI 1.05-1.08]). While systemic corticosteroids are sometimes used in severe or refractory AD, they are immunosuppressive and can cause hyperglycemia, a strong risk factor for severe COVID-19 and mortality, independent of pre-morbid diabetic status.[41] In contrast to poorer outcomes in those on systemic corticosteroids prior to contracting COVID-19, the RECOVERY trial demonstrated that dexamethasone significantly improves survival in hospitalized patients with severe COVID-19 requiring supplemental oxygen or ventilation.[42] The benefit was not seen across all COVID-19 severity strata, and in hospitalized patients not requiring supplemental oxygen, dexamethasone was associated with numerically higher rates of death than usual care (17.8% vs 14.0%), although the finding was not statistically significant (rate ratio 1.19 [95%CI 0.92-1.55]). Thus, it is likely that pre-existing treatment with systemic corticosteroids increases the risk of COVID-19, whereas the hyper-inflammatory state seen in severe COVID-19 can be attenuated by systemic corticosteroids when they are administered during the course of severe illness.

Strengths and limitations

Strengths of our study include the geographically and ethnically diverse sample of patients, and a detailed description of the COVID-19 disease course in patients with AD. We included cases from 27 countries, making our findings more generalizable than single-centre, regional or national studies. Utilization of physician-reported data on AD treatments and comorbidity status reinforce the validity of the SECURE-AD data.

Our data are drawn from mostly secondary and tertiary care dermatology centres, and the sample is mostly adults. Therefore, this cohort is unlikely to be representative of the whole population of people with AD, the majority of whom are children and at overall lower risk of severe COVID-19. Thus, our conclusions should only be applied in the appropriate context.

Our study also has weaknesses. An important limitation is the absence of vaccination status of the included patients. We considered utilizing a binary timepoint cut-off, to identify patients, before and after which time, were likely to have received COVID-19 vaccination. A significant limitation of this approach would be the multitude of approaches to vaccination prioritization, provision/administration and up-take across different jurisdictions, and we felt that there was no accurate way to define a binary time-point for such a sensitivity analysis. However, one aspect of our analysis which reassures us of the validity of our findings, despite inability to control for vaccination status, is that our adjusted analysis controlled for age, sex, BMI and comorbidity status, which in many jurisdictions, were the variables used to prioritize patients for vaccination. Therefore, it is likely that we have already (at least partially) adjusted for likelihood of vaccination by proxy, in our adjusted analysis.

A further limitation, is the selection bias inherent in registry studies. Physicians may be more likely to report patients on systemic therapy, or with more severe COVID-19 infections. The absence of any reported deaths is therefore reassuring. Patients receiving systemic immunomodulatory medications may be more likely to access testing, report COVID-19 to

their clinician, or come to the attention of SECURE-AD collaborating clinicians whilst hospitalized due to perceived risks associated with immunomodulation.
Because of the relatively small numbers of patients on some individual treatments, some analyses were at aggregate level. This is particularly important when interpreting findings from the combination therapy analysis, where numbers are small and the groups contain a variety of combination treatments. Data collection is ongoing and larger patient numbers will provide more power to detect differences in COVID-19 outcomes between immunomodulatory treatments. Although we have adjusted for variables such as age, gender, comorbidities and BMI, unmeasured confounding remains a possibility. Despite our global sample, numbers of patients from individual countries varied widely (median n=4, range 1-139). With infrequent hospitalization, and in some countries no hospitalizations, we were thus unable to adjust for country-level differences in hospitalization rates, or country-level factors such as socioeconomic factors, background rates of COVID-19 or availability and frequency of use of systemic treatments for AD. Due to the size of our cohort, we were unable to adjust for dosage of systemic immunomodulatory treatments, including corticosteroids, or changes in the management of COVID-19 over the course of the pandemic, including vaccination.

Future perspectives
As the global COVID-19 pandemic goes on, we continue to collect data to investigate the determinants of COVID-19 outcomes in patients with AD using our web-based SECURE-AD registry. To help us better understand the effects on patients with AD, we set up a second self-report registry platform, the SECURE-AD Patient Registry, launched globally in June 2020. Co-operation with patient organizations and the involvement of all patients is crucial,[43] and will support further data analyses, including the impact of COVID-19 vaccination on patients with AD. Beyond our own initiatives, we strongly advocate for collaboration with and harmonization of data across COVID-19 registries to facilitate comparative analyses to gain a broad understanding of the impact of COVID-19 on patients treated with various immunomodulatory therapies. Consensus on harmonization has been reached among the leaders of the COVID-19 dermatology registries.[44] Collaboration between registries, including non-dermatological diseases, has been crucial for the rapid generation of knowledge and can serve as an example for the prospective harmonization of data collection in the future.[45]

CONCLUSIONS

The overall risk of COVID-19 complications appears to be low in patients with AD treated with immunomodulatory treatments. Compared to topical treatment, patients on dupilumab monotherapy were less likely to be hospitalized. Systemic monotherapy with either dupilumab or methotrexate was associated with similar odds of hospitalization. An increased rate of hospitalization was seen in patients treated with combination systemic therapy, particularly patients treated with combinations including systemic corticosteroids. Risks and benefits need to be considered by physicians who treat patients with AD using systemic therapies. We will examine the risk associated with individual immunomodulatory treatments in more detail in future analyses.

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SUPPLEMENTARY MATERIAL

Supplementary table 1. Number of patients receiving different doses of systemic treatments (used as a single agent systemic therapy, i.e. systemic monotherapy)

Supplementary table 2. Number of patients receiving different doses of systemic treatments (when used as combination systemic therapy)

Supplementary table 3. Comparison of COVID-19 outcomes in those treated with topical treatment or a single systemic therapy (monotherapy analysis)

Supplementary table 4. Comparison of COVID-19 outcomes in those treated with systemic monotherapy vs combination therapy

A digital version of Supplementary table 1-4 can be found at:

CHAPTER 9
DISCUSSION

DISCUSSION

The aim of this thesis is to contribute to a unified and effective international approach to managing atopic eczema, emphasizing the significance of international collaboration and the use of real-world data. This chapter summarizes the main conclusions of the studies and discusses its findings.

Part I: Diagnosing atopic eczema

Despite the availability of various validated diagnostic criteria for atopic eczema, many new sets of criteria are still being developed and a lack of uniformity in the use of diagnostic criteria remains.[1,2] In **Chapter 2**, we conducted a systematic review to summarize existing evidence on the diagnostic accuracy of physician-assessed and patient-assessed (questionnaire-based) diagnostic criteria for atopic eczema, and to identify valid diagnostic criteria that can be used per research setting. 39 studies on the diagnostic accuracy of various criteria for atopic eczema were included. The U.K. Working Party (UKWP) criteria were the most extensively studied, followed by the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire and Hanifin and Rajka (H&R). The review found that while the UKWP criteria had the highest specificity, the H&R criteria exhibited the highest sensitivity and combined summary estimates for sensitivity and specificity, likely due to their comprehensive minor criteria addressing the heterogeneous presentation of atopic eczema. The quality of evidence varied, with the quality regarding the UKWP and H&R criteria rated as low and the ISAAC criteria as very low, using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.

Our review also highlights that numerous new patient-reported diagnostic criteria have been proposed. These studies were largely similar in terms of sensitivity and specificity. This observation reflects the prevailing situation where novel diagnostic criteria have been proposed, aiming to improve the sensitivity and specificity in various population settings, but with insufficient evidence validating their performance in different settings.

Overall, atopic eczema diagnostic criteria were found to be more specific than sensitive, with physician-administered criteria showing higher specificity than patient-assessed ones. Differences in sensitivity and specificity between hospital-based and population-based studies were noted but were not statistically significant. In the diagnosis of atopic eczema, the preference for higher sensitivity or specificity varies with the context. Higher sensitivity is crucial in clinical settings for early detection and timely management, as well as in epidemiological research for accurate disease prevalence data. In contrast, higher specificity is vital to ensure accurate diagnosis and avoid unnecessary treatments in clinical settings, while in clinical trials it ensures that participants truly have the disease, maintaining study validity. Balancing these metrics is key, with high sensitivity prioritized for broad screening and high specificity for precise diagnosis and research accuracy.

Gaps in the data were identified, particularly concerning diagnostic accuracy across different population groups and age demographics. Few studies included non-White patients, limiting subgroup analysis based on ethnicity. Most studies focused on children, addressing the challenges of atopic eczema diagnosis in adults, where recall bias and differing clinical features are considerations.[3] Our review found many newly proposed patient-reported diagnostic

criteria. However, these require validation in multiple studies before definitive conclusions can be drawn about their diagnostic utility.
In large-scale epidemiological studies, especially in low-resource settings, the availability of dermatologists and feasibility of physical examinations are limited. Questionnaire-based diagnostic criteria, while potentially less accurate than physical examinations, provide a practical alternative in settings where clinical resources are scarce. However, it is important to acknowledge and report their limitations, particularly their tendency to underestimate disease prevalence. Efforts should be made to standardize the approach for identifying atopic eczema cases in electronic health records to improve the reliability of large-scale epidemiological studies.
Adding to the complexity of diagnostic criteria variability, atopic eczema is recognized as a heterogeneous disease with numerous phenotypes that may have implications for prognosis and treatment. The classification of these phenotypes is crucial as it can inform more precise diagnostic criteria and tailored therapeutic approaches. A systematic review of the literature on atopic eczema phenotypes identified a wide range of phenotypic classifications, with significant variation in their associated characteristics.[4] This underscores the lack of uniform and consistent use of atopic eczema phenotypes, highlighting the need for standardized definitions and methodologies in future research to enhance the accuracy and applicability of diagnostic criteria. Moving forward, we recommend the standardization of diagnostic criteria and to identify various diagnostic criteria that can be used per research setting, to improve the clarity and comparability of study findings.[5,6]

Part II: Phototherapy for atopic eczema

In **Chapter 3**, we assessed the efficacy of phototherapy as a treatment option for atopic eczema, as it is commonly prescribed for patients with atopic eczema.[8] We conducted a systematic review which provided a comprehensive summary of the clinical efficacy and safety of various forms of phototherapy, identified gaps in the existing evidence, and suggested future research directions[9]. The systematic review included 32 randomized controlled trials (RCTs) with a total of 1219 participants, focusing primarily on narrow-band ultraviolet B (NB-UVB), which was the most frequently studied therapy. In comparisons of NB-UVB versus no treatment or placebo, four studies involving 89 participants indicated that NB-UVB might improve clinical signs and reduced itch more effectively than placebo after 12 weeks. The rate of withdrawals due to adverse effects was minimal. However, the certainty of the evidence of the comparison of NB-UVB versus no treatment or placebo was low. When comparing NB-UVB with ultraviolet A1 (UVA1), three studies involving 66 participants provided very low-certainty evidence. No significant differences in clinical outcomes, self-reported itch, or quality of life were observed after six weeks of treatment. In the comparison of NB-UVB with psoralen plus UVA (PUVA), one study of 10 participants showed no substantial differences in clinical outcomes after six weeks, and the evidence was again of very low certainty with no reported patient-reported symptoms. In a study comparing UVA1 with PUVA involving 40 participants, there was uncertainty regarding differences in clinical outcomes after three weeks of treatment, with very low-certainty evidence. Adverse events reported were infrequent, including phototoxic reactions, irritation, ultraviolet burns, and infections. Overall, NB-UVB was the most studied form of phototherapy, with approximately 40% of studies focusing on it. Other types such as broadband UVB and UVA1 were also examined, and fewer studies assessed PUVA. Most studies included very small numbers of patients, affecting the

generalizability of the findings. The evidence for phototherapy in treating atopic eczema remained of low to very low certainty, highlighting significant gaps in long-term efficacy, safety, and direct comparisons of different therapies.

Further research is needed, particularly on the effects of various phototherapy types in diverse populations and different eczema phenotypes. Although phototherapy is commonly used as a treatment for atopic eczema, the existing evidence remains limited. High-quality research is crucial, with future studies adopting standardized methodologies, evaluating long-term effects, and investigating home phototherapy options. Furthermore, more robust data on the safety and cost-effectiveness of phototherapy in clinical practice is needed.

As a result of this review, two RCTs were set up to evaluate the efficacy, cost-effectiveness and safety of phototherapy for atopic eczema. The first, the UPDATE Trial (Uvb Phototherapy in Dermatology for ATopic Eczema), is comparing the efficacy and cost-effectiveness of NB-UVB with optimal topical therapy versus optimal topical therapy alone over 3 months in adults with poorly controlled atopic eczema.[10] The second, the BRONTE (BROadband vs Narrowband photoTherapy for Eczema) trial, aims to determine which phototherapy, broadband-UVB or NB-UVB, is more effective for treating atopic eczema.[11] These trials are crucial in addressing gaps in the current evidence for phototherapy in atopic eczema. Their outcomes are expected to provide valuable insights into the efficacy, safety, and cost-effectiveness of phototherapy, informing guidelines and thereby guiding better clinical decision-making and improving patient care.[12] Additionally, several registries within the TREatment of ATopic eczema (TREAT) Registry Taskforce are gathering real-world data on the (cost-)effectiveness and safety of phototherapy.

Beyond assessing the efficacy of phototherapy, it is essential to address existing knowledge gaps in its implementation. Current guidelines do not provide specific recommendations on determining the correct starting dose or on how to progressively increase exposure times. An evidence-based elaboration of these details seems unlikely in the near future. Therefore, the next best approach is to establish a consensus on implementing phototherapy for patients with atopic eczema. To achieve this, an international e-Delphi survey on NB-UVB phototherapy for atopic eczema is currently being conducted, aiming to develop an experience-based treatment standard.

Part III: International collaboration through the TREAT Registry Taskforce: generating real-world data across country borders

The TREAT Registry Taskforce aims to systematically collect long-term real-world data on the effectiveness, safety, and cost-effectiveness of systemic immunomodulating therapies and phototherapy for atopic eczema.[13] By May 1, 2022, data from over 4.700 patients had been gathered across 8 individual registries from within the TREAT Registry Taskforce. These registries individually began publishing results on patient demographics, treatment effectiveness and safety. To strengthen outcomes, the next step is to pool data across registries. The TREAT Registry Taskforce has created a core dataset and protocol, aligned with Harmonizing Outcome Measures for Eczema (HOME) recommendations, to facilitate this cross-border pooling.[14–16] A mapping exercise identified both similarities and differences in how registries use the core dataset and their ability to pool data, presented in **Chapter 4.**[17] Registries demonstrated similarities in collecting data on treatment effectiveness, safety, and cost-efficiency, including patient demographics, therapy details, clinical assessments, and patient-reported outcomes. Most also tracked severe adverse events and collected data for

cost-effectiveness analysis. Despite the goal of a uniform dataset, variations in data collection were identified, potentially challenging data pooling and synthesis. Various factors, including different data entry platforms and countries interpreting core dataset items differently, have led to inconsistencies. Despite considering feasibility in the TREAT core dataset consensus process, the high number of domains and domain items compromised its feasibility. A survey of TREAT Registry Taskforce members revealed feasibility as the main reason for not including all core dataset items. However, most registries showed a willingness to adapt their datasets to overcome important differences.
Future efforts will emphasize technical data compatibility assessments to support comparative and pooled studies, benefiting other international research groups seeking harmonized data collection and analysis across various diseases. In this context, five registries within the TREAT Registry Taskforce are currently working to align their databases and encoding standards, using the technological solution DataSHIELD (datashield.org) to enable secure international analysis through a central server.

As a continuation of our previous work described in Chapter 4, a study featured in **Chapter 5** sought to investigate the ability to pool data and perform cross-border analyses among various TREAT registries. The objective was to provide an overview of the baseline demographics, treatment characteristics, atopic eczema severity, and disease burden of patients enrolled in seven registries within the TREAT Registry Taskforce. Additionally, the study aimed to investigate the ability to pool data, gain insights into the similarities and differences between the registries, and to explore current prescribing practices for therapies in children and adults with atopic eczema across Europe. The analysis included data from between the date of first inclusion (varying between registries) and October 31, 2022. Involving 5.337 atopic eczema patients from nine European countries, it revealed significant variations in baseline socio-demographics, disease severity and treatment characteristics. Differences in treatment characteristics partly reflect the variations in access to certain systemic immunomodulatory therapies between countries. The diversity found in the study population highlights heterogeneity, underscoring the representativeness of the data for the entire atopic eczema patient population.
By including patients with a wide range of demographics, treatment histories, and disease severities, the study's findings are highly generalizable, thus supporting the integration of data from multiple sources. Rather than being a limitation, this variability strengthens the rationale for data pooling, as pooling such heterogeneous data provides a more nuanced understanding of atopic eczema, enabling robust analyses that can guide clinical decision-making and establish research priorities. However, limitations of the study included missing data due to inconsistent use of the core dataset and potential recruitment bias. This study marks a significant step forward in enabling cross-border analyses, which are essential for exploring research questions that necessitate large patient cohorts, such as malignancy risk investigations. The TREAT Registry Taskforce's future research will deepen our understanding of moderate-to-severe atopic eczema and contribute to the advancement of more effective treatments for these patients.
The TREAT Registry Taskforce has also acted as a model for other dermatology patient registries, illustrating the potential for successful data pooling and cross-border analyses in diverse dermatological conditions. Notable examples inspired by the TREAT Registry include the Global Registry of Alopecia Areata Disease Severity and Treatment Safety (GRASS), the

International Laser Treatment Dermatology (LEAD) registry, and the Vitiligo International Task force for an Agreed List of core data (VITAL).[18–20] These initiatives have adopted similar methodologies, emphasizing the importance of comprehensive data collection and international collaboration. This trend underscores the significant impact of the TREAT Registry Taskforce in shaping the future of dermatology research and patient care globally.

Part IV: Evaluating the safety of systemic treatments for atopic eczema using real-world data
One of the primary goals of the TREAT Registry Taskforce is to generate reliable real-world data on drug safety and (rare) adverse events. The study presented in **Chapter 6**, assessed the incidence rates of adverse events in atopic eczema patients treated with systemic immunomodulating therapy, comparing these rates to those listed in Summary of Product Characteristics (SmPC) using real-world date from the TREAT NL/BE registry in the Netherlands and Belgium.[21] Five drug-related adverse events with higher incidence rates than those reported in the SmPCs were identified: eosinophilia, blepharitis, dry eyes, and head and neck erythema related to dupilumab, and fatigue related to oral methotrexate. Additionally, it found two new dupilumab-related adverse events not mentioned in the SmPC: non-infectious conjunctivitis and meibomian gland dysfunction.
Recent studies have further expanded on the ocular side effects of dupilumab, shedding light on the various manifestations and management strategies of dupilumab-related ocular conditions.[22–27] Ocular surface disease refers to a spectrum of disorders affecting the surface of the eye, including the cornea, conjunctiva, and eyelids. Dupilumab-associated ocular surface disease specifically refers to these ocular symptoms arising in patients undergoing treatment with dupilumab, and is characterized by conjunctivitis, dry eye symptoms, and inflammation of the ocular surface, possibly linked to changes in the tear film and goblet cell density, which are essential for maintaining ocular surface health.

The strength of our study was its use of real-world data from 266 atopic eczema patients with a total follow-up of 422 patient years, providing high external validity, but limitations included a small number of patients on other treatments than dupilumab, oral methotrexate and ciclosporin and a possible underreporting of mild adverse events. Moreover, adverse events were assessed for treatment-relatedness at occurrence, and newer safety insights might have led to incomplete or misinterpreted assessments. The changing list of adverse events of special interest in the TREAT NL/BE registry over time may have also resulted in underreporting. To standardize future adverse event assessments, the Naranjo Scale will be utilized.[28] This scale, also known as the Adverse Drug Reaction Probability Scale, evaluates the likelihood of a causal relationship between a drug and an adverse clinical event. It utilizes a straightforward questionnaire to assign probability scores to this relationship.
Concluding, our study demonstrated that real-world adverse events reported in atopic eczema patient registries could enhance the accuracy of adverse event incidence estimates in SmPCs, benefiting clinical decision-making. Integrating real-world reported adverse events into European Medicines Agency (EMA) pharmacovigilance enhances adverse event incidence estimates in SmPCs. The EMA incorporates real-world data from patient registries into pharmacovigilance through the EudraVigilance database, Risk Management Plans, Periodic Safety Update Report, Post-Authorization Safety Studies and through the EMA-HMA (Heads of Medicine Agencies) Big Data Workplan. This integration enhances signal detection, benefit-

risk assessment, and updates to safety profiles, ensuring more comprehensive and current safety information for clinical decision-making and patient outcomes.

Continued real-world data collection is essential for understanding the safety of less-represented treatments in our analysis, including tralokinumab, baricitinib, upadacitinib, and abrocitinib. To further enhance our understanding, future analyses should delve into specific subgroups, such as patients with a history of liver disease, renal function impairment, hepatitis, tuberculosis, or malignancies. Additionally, examining diverse age groups, including children, the elderly, and those on multiple medications, will provide a richer, more nuanced picture of treatment safety and efficacy. By focusing on these distinct populations, we can uncover vital insights and ensure that our findings are comprehensive and inclusive, ultimately leading to better care. The TREAT Registry Taskforce's commitment to long-term prospective observational safety studies is further exemplified by a protocol developed for assessing the safety of systemic immunomodulating therapies, such as dupilumab.[29] By leveraging standardized methodologies across various national registries, this protocol aims to provide robust safety evidence applicable to routine clinical care and regulatory frameworks.
Future studies combining data from the TREAT NL/BE registry and other TREAT Registry Taskforce registries will also provide further insights into rare adverse events associated with immunomodulating therapies in atopic eczema patients.

In **Chapter 7**, we delved into a specific adverse event, dupilumab-associated (hyper)eosinophilia, by examining its incidence, progression, and clinical outcomes in atopic eczema patients within a single-center cohort study from the TREAT NL/BE registry. Dupilumab, a human monoclonal antibody that inhibits IL-4 and IL-13 signalling, has been proven highly effective in treating atopic eczema. However, it may cause transient peripheral (hyper)eosinophilia by blocking eosinophil migration into tissues. While this effect is known in severe asthma, it had not been thoroughly examined in atopic eczema. Our study assessed the incidence, progression, and clinical outcomes of this condition in atopic eczema patients treated with dupilumab. Data from 200 atopic eczema patients treated with dupilumab at the Amsterdam University Medical Center between September 2017 and December 2022 showed that 38.5% developed (hyper)eosinophilia, with a peak in absolute eosinophil count (AEC) at six months post-treatment, normalizing between 18 and 24 months. Fifteen patients developed hypereosinophilia, one of whom discontinued treatment due to related symptoms, which resolved upon cessation. The remaining cases were managed with observation, as their AEC levels decreased during treatment. These findings suggested that dupilumab-induced eosinophilia was generally transient and clinically insignificant for most patients, aligning with previous studies in different patient populations. Only one case of persistent hypereosinophilia required treatment discontinuation, indicating that dupilumab remains a viable option for atopic eczema patients regardless of baseline eosinophilia. The study's limitations included a variable cohort size and small sample, which might obscure rare adverse events and limit generalizability. Future research should include longer follow-up periods to better understand the long-term safety concerning eosinophil levels. Continuous monitoring of eosinophil levels was not deemed necessary, but checking AEC within the first six months was recommended. High AEC values should prompt consultation with specialists. Clinicians should also be vigilant for symptoms of hyper-eosinophilic organ damage, which can include

thromboembolic events, vasculitis, neurological symptoms in extremities, shortness of breath, cardiac dysfunction, and stroke.

With the global outbreak of the coronavirus SARS-CoV-2 (COVID-19) pandemic in March 2020, there was an urgent need to understand whether immunomodulatory treatments for atopic eczema affected the risk of COVID-19 outcomes, including morbidity and mortality. In response, the SECURE-AD (Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion - Atopic Dermatitis) Physician Registry was launched in April 2020, presented in **Chapter 8.**[30] The primary aim of the SECURE-AD study was to evaluate the effects of different systemic immunomodulatory treatments for atopic eczema on COVID-19 outcomes. In this global registry study, involving 442 atopic eczema patients from 27 countries, differences in COVID-19 outcomes (duration of COVID-19 symptoms, persistence of symptoms at the time of reporting, death due to COVID-19, emergency department attendance, hospitalization, length of hospital stay, intensive care unit admission, ventilation requirement, and flare (exacerbation) of atopic eczema during COVID-19) were observed across various treatment modalities. Overall hospitalization rates (5.9%) were not higher than in the general population and compared to other immune-mediated inflammatory disease (IMID) registries, hospitalization rates in atopic eczema patients were lower than in those with inflammatory bowel disease, rheumatic diseases, or psoriasis. Patients on systemic corticosteroids had the highest hospitalization rates (14.3%), consistent with findings in other IMID patients. Dupilumab monotherapy was associated with lower hospitalization rates compared to topical treatments, even after adjusting for confounding variables. Moreover, dupilumab was associated with lower odds of hospitalization compared to ciclosporin or systemic corticosteroids. Dupilumab targets IL-4 and IL-13, which are not activated in viral infections, thus not significantly affecting SARS-CoV-2 infection rates. Our data supports the established safety profile of dupilumab from clinical trials and case series during the COVID-19 pandemic.[31–33] In our cohort, combination therapies, especially those including systemic corticosteroids, had higher hospitalization rates, which also has been seen in other IMID registries. The study's strengths include a diverse sample and detailed COVID-19 disease course description. However, limitations such as variable cohort sizes, lack of vaccination status, and potential selection bias were noted.
Overall, the risk of severe COVID-19 complications in atopic eczema patients on immunomodulatory therapies appeared to be low. These findings emphasized the importance of careful risk-benefit analysis when prescribing systemic therapies for atopic eczema patients during the COVID-19 pandemic.

Strengths and limitations of registries collecting real-world data

Precisely during the COVID-19 pandemic, it was evident that registries could be established rapidly and effectively.[34] Despite their benefits, patient registries face challenges like data security, privacy regulations, and poor harmonization across regions.[35] This lack of interoperability can lead to valuable information being lost, especially during pandemics. However, several COVID-19 dermatology patient registries were established rapidly, showing remarkable collaboration and data sharing.[36–38] To enhance the utility of patient registries, a proposed international federation of dermatology registries could standardize data sets and streamline development processes.[36] This federation would foster global collaboration, ensuring rapid deployment during future pandemics and improving overall registry quality and

efficiency. The pandemic underscored the importance of having robust, adaptable registries ready to address urgent healthcare needs.

This brings us to a critical analysis of the strengths and limitations of patient registries in collecting real-world data. Patient registries play a crucial role in evidence-based medicine by capturing real-world data that offers a comprehensive and representative view of patient populations. Unlike RCTs, which have stringent inclusion and exclusion criteria, registries include a diverse range of patients, including children and those with comorbidities. This broader inclusion enhances the external validity of the data, making the findings more applicable to general clinical practice.

One of the key strengths of patient registries is their ability to detect rare adverse events and long-term safety issues that RCTs might miss due to limited sample sizes and shorter follow-up periods. The European Psonet network, which links psoriasis registries across multiple countries, exemplifies the value of international collaboration in tracking treatment outcomes and ensuring patient safety.[39] Another example highlighting how registry data can lead to significant improvements in patient outcomes and healthcare (cost-)efficiency is how the Swedish Hip Arthroplasty Register's data helped avoid approximately 7,500 hip revisions by identifying best clinical practices and the most suitable implants.[40] Furthermore, patient registries are generally more feasible and acceptable to patients compared to RCTs. Patients are often more willing to participate in observational studies since these do not involve randomization and potential allocation to what they perceive as inferior treatments. This willingness to participate can lead to richer and more extensive data collection over time. Governmental support also underscores the importance of registries. Initiatives by the U.S. Department of Health and Human Services and the European Union aim to standardize and harmonize data across registries, enhancing their utility for improving patient care and health service planning. Projects like the PAtient Registries iNiTiative (PARENT) joint action received substantial funding from the European Union's Horizon programme to establish best practices for registry development.[35]

Despite their strengths, patient registries have inherent limitations primarily due to their observational nature. The absence of randomization and blinding introduces various biases, including information bias, selection bias, and confounding factors. For example, patients included in registries might be selected based on specific eligibility criteria for treatment, leading to selection bias. Moreover, the lack of controlled environments means that co-medications, noncompliance, and unintended dosing deviations can influence the outcomes. The internal validity of registry data is often questioned due to these biases. Unlike RCTs, registries do not typically involve wash-out periods, standardized follow-up schedules, or strict monitoring of dosing and compliance. Patients starting new treatments might have previously failed multiple systemic therapies, adding another layer of complexity to the data. The feasibility and resource intensity of maintaining high-quality registries also pose significant challenges. Increasing data security and privacy regulations require careful attention and substantial resources. Furthermore, registries often develop independently, resulting in poorly harmonized datasets across different regions. This lack of interoperability can hinder the utility of registry data, making it difficult to compare and combine information from different sources. Efforts to address these issues include statistical models that account for

variable follow-up times and initiatives to standardize data collection across regions. The harmonization of datasets and international collaboration are critical to maximizing the value of registry data.

In conclusion, patient registries are invaluable for capturing real-world data that RCTs cannot provide, offering insights into the long-term safety and effectiveness of treatments across diverse patient populations. While they come with challenges such as potential biases and the need for significant resources, the benefits they offer in terms of external validity and applicability to clinical practice are substantial. Future efforts should focus on enhancing data harmonization and collection, improving interoperability, and ensuring to fully leverage the potential of improving patient care and health outcomes.

Future perspectives

Aiming to improve care for atopic eczema, it's important to recognize that no detail is too small. Every aspect of data collection and analysis can significantly impact our understanding and management of this condition.

The future of reliable diagnosis of atopic eczema requires a unified and precise approach to determine accurate diagnostic criteria, in order to enhance patient care and research. Despite the availability of various sets of validated criteria, we found many studies proposing new criteria. The atopic eczema research community should critically assess the need for any new diagnostic criteria and strive to reach a consensus on widely validated standards, rather than creating additional criteria. Without standardized criteria per study setting, research comparability and clinical practices will remain fragmented, leading to inefficiencies and missed opportunities. Therefore, achieving international agreement on diagnostic criteria is essential, potentially led by initiatives such as the HOME group or the BIOMarkers in Atopic dermatitis and Psoriasis (BIOMAP) consortium.

Phototherapy is commonly prescribed for treating atopic eczema, yet its full potential remains untapped. Future research must focus on standardizing phototherapy treatment protocols, determining optimal dosing regimens and tailoring treatments for subpopulations, such as patients with skin of colour. Studies should investigate phototherapy for both acute and chronic atopic eczema, as well as other phenotypes, and evaluate the efficacy and safety of home phototherapy. Ongoing RCTs will shed light on these aspects, while real-world data from registries will help assess long-term safety and the feasibility of phototherapy.

The potential for international collaboration in pooling real-world data is immense. However, without harmonized datasets and standardized inclusion criteria, valuable information remains underutilized. Future efforts should prioritize technical compatibility and the standardization of data collection methodologies. The TREAT Registry Taskforce's work in this area is a crucial step forward. For future pooled analyses, it is essential to consider differences in registry datasets, prescribing practices, reimbursement criteria, and national regulations, all of which could affect patient population variations and data synthesis. By facilitating robust cross-border analyses, we can gain comprehensive insights into atopic eczema, guiding clinical decision-making and establishing global research priorities. Failure to do so would result in a significant waste of data, perpetuating gaps in knowledge and impeding progress.

The extensive collection of long-term data from patients in real-world settings to evaluate the (cost-) effectiveness of systemic immunomodulating therapies and phototherapies by the TREAT Registry Taskforce will underpin numerous future studies, enhancing our understanding of atopic eczema treatment.[13] Looking ahead, it is urgent to generate real-world data on the novel therapies arriving on the market for atopic eczema, as these are not yet investigated in daily practice. As the costs per patient rise with the introduction of these new systemic treatments, it also becomes increasingly important to conduct high-quality research into the effectiveness, safety, and cost-effectiveness of alternative treatments such as phototherapy and older systemics (often prescribed off-label), like methotrexate.[41] Introducing new expensive treatments makes it crucial to investigate and compare them to guarantee optimal cost-effectiveness. Strategies such as therapeutic drug monitoring and dose reduction should be explored. An RCT on dupilumab dose reduction, embedded in the TREAT NL/BE registry, is currently being conducted.[42]

Working towards personalized medicine will eventually guide the determination of the best treatment for each patient. Ensuring diversity in research is crucial to develop treatments effective across a diverse population, addressing current underrepresentation and improving the relevance of findings for all patient groups. The BIOMAP initiative aims to identify biomarkers that predict disease course and treatment response, enabling more tailored and effective treatment strategies. Embracing this future will not only enhance patient outcomes but also increase the efficiency of healthcare delivery, avoiding unnecessary treatments and focusing on those most likely to benefit each patient.

Safety is another critical area where continued real-world data collection is essential. Understanding the safety profile of systemic treatments requires ongoing monitoring, as spontaneous reporting often falls short. Not properly recording side effects will lead to an incomplete understanding of treatment safety, potentially compromising patient health. Special topics of interest, often not covered in RCTs, include pregnancy data, malignancies, and safety data in children. Future studies combining data from TREAT Registry Taskforce will provide deeper insights into rare adverse events. In pharmacoepidemiology, accurate and complete reporting of research is a necessity. Adhering to guidelines such as RECORD-PE (REporting of studies Conducted using Observational Routinely collected Data - for non-interventional pharmacoepidemiological research) for accurate and complete reporting of pharmacoepidemiological studies is necessary to ensure the reliability of these findings.[43]

To better deal with future pandemics, we need robust and adaptable patient registries. The COVID-19 pandemic showed that registries could be rapidly established despite challenges like data security, privacy, and regional harmonization. A proposed international federation of dermatology registries could streamline processes and standardize datasets, ensuring quick and efficient deployment during health crises.[36]

In conclusion, attention to every detail, from accurate diagnosis and data collection methods to rigorous safety monitoring, will lead to better health outcomes and more effective treatment of atopic eczema. By focusing on every aspect of the research process, we aim to improve the care and management of this condition.

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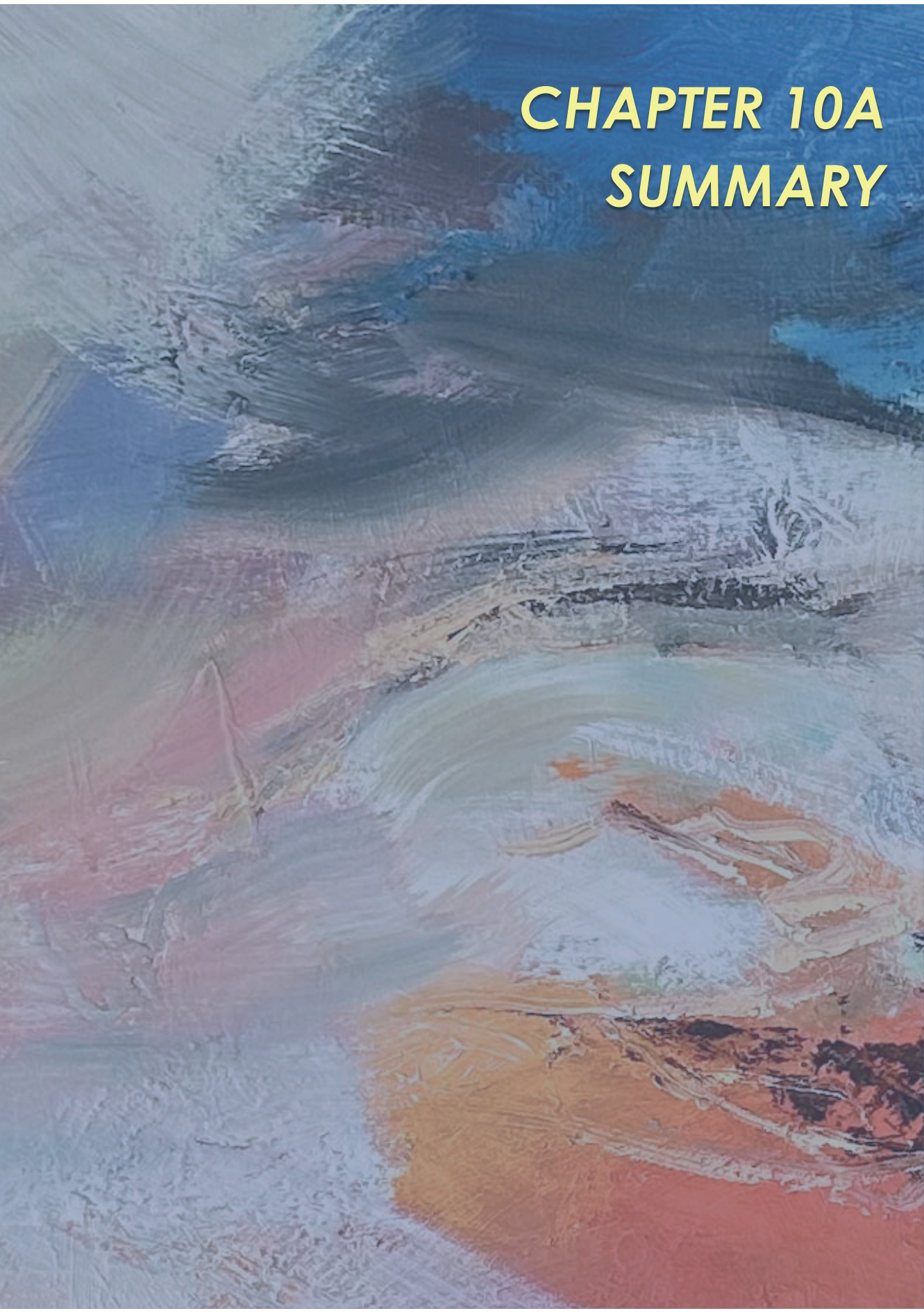

CHAPTER 10A SUMMARY

SUMMARY: IMPROVING ATOPIC ECZEMA CARE THROUGH INTERNATIONAL COLLABORATION - IN A MAJOR MATTER, NO DETAILS ARE SMALL

This thesis aimed to improve the diagnosis and management of atopic eczema by establishing a robust framework for international collaboration. It focused on several areas to achieve this goal. First, it examined the evidence on the diagnostic accuracy of various diagnostic criteria for atopic eczema, striving to standardize diagnostic practices. Second, it assessed the efficacy of phototherapy as a treatment option for atopic eczema. Third, it highlighted the significance of international collaboration in standardizing real-world data collection through global registries assessing the (long-term) efficacy and safety of phototherapy and systemic immunomodulating treatments and for atopic eczema. Lastly, it evaluated the safety of systemic treatments based on real-world data.

Part I: Diagnosing atopic eczema

Chapter 2 presented a systematic review that updated and synthesized the existing evidence on the diagnostic accuracy of physician-assessed and patient-assessed (questionnaire-based) diagnostic criteria for atopic eczema, and to identify valid diagnostic criteria that can be used per research setting. Despite the existence of several validated diagnostic criteria, there remains a lack of consensus on which diagnostic criteria are most accurate for atopic eczema and there is inconsistency in the application of these criteria.

The search identified 2071 articles, resulting in the inclusion of 39 studies with 99,822 patients from 25 countries. The UK Working Party (UKWP) criteria had a pooled sensitivity of 56.8% and specificity of 96.4%. The Hanifin and Raijka (H&R) criteria showed a pooled sensitivity of 83.9% and specificity of 92.3%. The International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire demonstrated a pooled sensitivity of 54.9% and specificity of 85.0%. The UKWP criteria were the most extensively studied, followed by the ISAAC questionnaire and H&R criteria. The quality of evidence was rated as low for the UKWP and H&R criteria and very low for the ISAAC criteria using the GRADE approach. Moreover, many studies (n=23) assessing other (newly proposed) diagnostic criteria were evaluated, yet these require validation in multiple studies before definitive conclusions can be drawn about their diagnostic utility.

Overall, diagnostic criteria for atopic eczema were more specific than sensitive, with physician-administered criteria being more specific than patient-assessed ones. Differences in sensitivity and specificity between hospital-based and population-based studies were observed but were not statistically significant.

Concluding, the review found that while the UKWP criteria had the highest specificity, the H&R criteria exhibited the highest sensitivity and combined summary estimates, likely due to their comprehensive minor criteria addressing the heterogeneous presentation of atopic eczema. This review highlighted the need for consensus on diagnostic criteria for atopic eczema to improve research comparability and clinical diagnosis reliability.

Part II: Phototherapy for atopic eczema

Chapter 3 presented a Cochrane systematic review synthesizing current evidence on phototherapy for atopic eczema, assessing the clinical efficacy and safety of various forms of phototherapy and identifying gaps in existing evidence.

The systematic review included 32 randomized controlled trials (RCTs) with 1,219 participants, primarily focusing on narrowband UVB (NB-UVB) therapy. Four RCTs with 89 participants comparing NB-UVB to no treatment or placebo indicated that NB-UVB might improve clinical signs and reduce itch more effectively than placebo after 12 weeks, with minimal adverse effects. However, the certainty of this evidence was low. Comparisons of NB-UVB with UVA1 and psoralen plus UVA (PUVA) provided very low-certainty evidence, showing no significant differences in clinical outcomes, itch, or quality of life. Adverse events reported were infrequent and included phototoxic reactions, irritation, ultraviolet burns, and infections.
Overall, NB-UVB was the most extensively studied form of phototherapy, with about 40% of studies focusing on this form of phototherapy. Other forms, such as broadband UVB and UVA1, were also examined, but fewer studies assessed psoralen plus UVA (PUVA). The evidence for phototherapy in treating atopic eczema remained of low to very low certainty, highlighting significant gaps in knowledge about long-term efficacy, safety, and direct comparisons of different therapies.
While phototherapy is commonly used to treat atopic eczema in daily practice, existing evidence is limited. This review highlighted that more research is needed, focusing on standardizing phototherapy treatment protocols, determining optimal dosing regimens and tailoring treatments for subpopulations, such as patients with skin of colour.

Part III: International collaboration through the TREAT Registry Taskforce: generating real-world data across country borders

This part focused on enhancing international collaboration and standardization of data collection through the TREatment of ATopic eczema (TREAT) Registry Taskforce.

Chapter 4 presented a mapping exercise examining the overlap and pooling potential of data across eight established TREAT registries to facilitate comprehensive research on the effectiveness and safety of therapies for atopic eczema.
The TREAT Registry Taskforce aims to systematically collect long-term real-world data on the effectiveness, safety, and cost-effectiveness of systemic immunomodulating therapies and phototherapy for atopic eczema. To facilitate this cross-border pooling, the TREAT Registry Taskforce has created a core dataset and protocol, aligned with Harmonizing Outcome Measures for Eczema (HOME) recommendations.
By May 1st, 2022, data from over 4.700 patients had been gathered across eight individual registries. These registries had already published individual results on patient demographics, treatment effectiveness, and safety. To strengthen outcomes, the next step is to pool data across registries. A mapping exercise identified similarities and differences in how registries used the core dataset and their ability to pool data. Registries demonstrated similarities in collecting data on treatment effectiveness, safety, and cost-efficiency, including patient demographics, therapy details, clinical assessments, and patient-reported outcomes. Most also tracked severe adverse events and collected data for cost-effectiveness analysis. Despite the goal of a uniform dataset, variations arose due to differences in data entry platforms and interpretations, potentially complicating data synthesis. However, most registries showed a willingness to adapt their datasets. Future efforts will emphasize technical data compatibility assessments and demographic analyses to support comparative and pooled studies, benefiting other international research groups seeking harmonized data collection and analysis across various diseases.

Chapter 5 featured the first cross-border analyses of patients treated with various therapies across seven European TREAT registries, providing insights into patient demographics, disease severity, and prescribing practices, and highlighting differences and commonalities across Europe. This study demonstrated the ability to pool data and perform cross-border analyses among seven TREAT registries. The analysis included data from the date of first inclusion (varying between registries) to October 31st, 2022. Involving 5.337 atopic eczema patients from nine European countries, it revealed significant variations in baseline socio-demographics, disease severity and treatment characteristics and partly reflecting variations in access to systemic immunomodulatory therapies between countries.
Most patients had received prior systemic treatment, primarily systemic corticosteroids, methotrexate, and ciclosporin. However, each registry showed varying proportions of patients with certain treatment histories, reflecting differences in prescribing practices. The majority of patients enrolling in the registries initiated dupilumab treatment. The baseline data reflected treatments at enrolment, suggesting that the current use of biological or JAK inhibitors could be higher than reported. Differences in atopic eczema severity across registries can be attributed to varying inclusion criteria, with some registries including only moderate-to-severe cases, while others include patients regardless of severity.
The diversity found in this analysis underscored the representativeness of the data for the entire atopic eczema patient population. By including patients with diverse demographics, treatment histories, and disease severities, the findings are highly generalizable, supporting the integration of data from multiple sources. Despite limitations such as missing data and potential recruitment bias, the study marked a significant step forward in enabling cross-border analyses, acting as a model for other dermatology patient registries. These pooled analyses are essential for exploring research questions requiring large patient cohorts, such as malignancy risk investigations. The TREAT Registry Taskforce's future research will deepen the understanding of atopic eczema and contribute to more effective treatments.

Part IV: Evaluating the safety of systemic treatments for atopic eczema using real-world data
The safety of various systemic treatments for atopic eczema using real-world data were examined in part IV.

Chapter 6 focused on adverse drug reactions associated with systemic immunomodulatory therapy using data from the TREAT NL/BE registry, comparing real-world incidence rates with official summaries of product characteristics (SmPCs). This chapter provided a clearer picture of the safety profile of these treatments, identifying five drug-related adverse events with higher incidence rates than reported in the SmPCs: eosinophilia, blepharitis, dry eyes, and head and neck erythema related to dupilumab, and fatigue related to oral methotrexate. Two new adverse events related to dupilumab, non-infectious conjunctivitis, and meibomian gland dysfunction, were also discovered. The study emphasized the importance of incorporating real-world adverse event data into pharmacovigilance to enhance clinical decision-making.

Chapter 7 delved into dupilumab-associated (hyper)eosinophilia, examining its incidence, progression, and clinical outcomes in atopic eczema patients using data from the a single-center cohort of the TREAT NL/BE registry. Data from 200 patients treated with dupilumab at the Amsterdam University Medical Center between September 2017 and December 2022

showed that 38.5% developed (hyper)eosinophilia, peaking at six months and normalizing between 18 and 24 months. Most cases were transient and clinically insignificant, with only one patient discontinuing treatment due to hypereosinophilia-related symptoms. The study recommended measuring eosinophil levels at least once within the first six months of treatment. Clinicians are advised to watch out for symptoms of hyper-eosinophilic organ damage, which can include thromboembolic events, vasculitis, neurological symptoms in extremities, shortness of breath, cardiac dysfunction, and stroke.

Chapter 8 investigated the impact of systemic immunomodulatory therapies on COVID-19 outcomes in atopic eczema patients using data from the global Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion - Atopic Dermatitis (SECURE-AD) registry. COVID-19 outcomes included the duration of COVID-19 symptoms, persistence of symptoms at the time of reporting, death due to COVID-19, emergency department attendance, hospitalization, length of hospital stay, intensive care unit admission, ventilation requirement, and flare (exacerbation) of atopic eczema during COVID-19. The study included 442 patients from 27 countries and found that hospitalization rates for COVID-19 among atopic eczema patients were not higher than in the general population. Patients on systemic corticosteroids had the highest hospitalization rates, while those on dupilumab had lower hospitalization rates compared to those on topical treatments. Patients on combination therapies, especially those including systemic corticosteroids, also had higher hospitalization rates. The study supported the safety profile of dupilumab during the COVID-19 pandemic and emphasized careful risk-benefit analysis when prescribing systemic therapies during such times.

In conclusion, attention to every detail, from accurate diagnosis and data collection techniques to robust safety monitoring, will lead to better health outcomes and more effective treatments for atopic eczema, ultimately improving its care and management.

CHAPTER 10B
SAMENVATTING

SAMENVATTING: VERBETERING VAN DE ZORG VOOR ATOPISCH ECZEEM DOOR INTERNATIONALE SAMENWERKING - IN BELANGRIJKE KWESTIES ZIJN GEEN DETAILS TE KLEIN

Dit proefschrift had als doel de diagnose en behandeling van atopisch eczeem te verbeteren door een robuust kader voor internationale samenwerking op te zetten. Om dit doel te bereiken, werden verschillende aspecten onderzocht. Ten eerste werd de diagnostische accuratesse van verschillende diagnostische criteria voor atopisch eczeem onderzocht, met als doel om valide diagnostische criteria te identificeren die per onderzoekssetting kunnen worden toegepast. Ten tweede werd de effectiviteit van lichttherapie als behandeloptie voor atopisch eczeem beoordeeld. Ten derde werd het belang van internationale samenwerking benadrukt bij het standaardiseren van gegevensverzameling door middel van wereldwijde registers die de (lange termijn) werkzaamheid en veiligheid van lichttherapie en systemische immunomodulerende behandelingen voor atopisch eczeem evalueren. Ten slotte werd de veiligheid van systemische behandelingen geëvalueerd op basis van praktijkgegevens.

Deel I: Diagnostiek van atopisch eczeem

Hoofdstuk 2 presenteerde een systematische review die de bestaande bewijzen over de diagnostische accuratesse van zowel door artsen als door patiënten toegepaste diagnostische criteria voor atopisch eczeem onderzocht. Het doel was om valide diagnostische criteria te identificeren die per onderzoekssetting kunnen worden toegepast. Ondanks het bestaan van verschillende gevalideerde diagnostische criteria, ontbreekt er een consensus over welke criteria het meest nauwkeurig zijn voor atopisch eczeem en is er inconsistentie in de toepassing van deze criteria.

De zoekopdracht leverde 2071 artikelen op, wat resulteerde in de opname van 39 studies met 99.822 patiënten uit 25 landen. De UK Working Party (UKWP) criteria hadden een gepoolde sensitiviteit van 56.8% en specificiteit van 96.4%. De Hanifin en Raijka (H&R) criteria toonden een gepoolde sensitiviteit van 83.9% en specificiteit van 92.3%. De vragenlijst van de International Study of Asthma and Allergies in Childhood (ISAAC) had een gepoolde sensitiviteit van 54.9% en specificiteit van 85.0%. De UKWP criteria waren het meest uitgebreid bestudeerd, gevolgd door de ISAAC vragenlijst en de H&R criteria. De kwaliteit van het bewijs werd beoordeeld als laag voor de UKWP en H&R criteria en zeer laag voor de ISAAC criteria volgens de GRADE benadering. Verder werden veel studies die andere (nieuw voorgestelde) diagnostische criteria beoordeelden geëvalueerd. Deze nieuw voorgestelde diagnostische criteria moeten echter in meerdere studies worden gevalideerd, voordat definitieve conclusies getrokken kunnen worden over hun diagnostische bruikbaarheid.

Over het algemeen waren de diagnostische criteria voor atopisch eczeem meer specifiek dan sensitief, waarbij de door artsen toegepaste criteria specifieker waren dan de door patiënten toegepaste criteria (vragenlijsten). Verschillen in sensitiviteit en specificiteit tussen ziekenhuis-gebaseerde en populatie-gebaseerde studies werden waargenomen, maar waren niet statistisch significant.

Concluderend bleek uit deze review dat hoewel de UKWP criteria de hoogste specificiteit hadden, de H&R criteria de hoogste sensitiviteit en gecombineerde sensitiviteit en specificiteit vertoonden, waarschijnlijk vanwege hun uitgebreide secundaire criteria die rekening houden met de heterogene presentatie van atopisch eczeem. Deze review benadrukte de noodzaak van het bereiken van internationale consensus over de toepassing van diagnostische criteria

voor atopisch eczeem om de vergelijkbaarheid van onderzoek en de betrouwbaarheid van klinische diagnoses te verbeteren.

Deel II: Lichttherapie voor atopisch eczeem

Hoofdstuk 3 presenteerde een Cochrane systematische review die het huidige bewijs over lichttherapie als behandeling voor atopisch eczeem onderzocht. De review beoordeelde de klinische effectiviteit en veiligheid van verschillende vormen van lichttherapie en identificeerde hiaten in het bestaande bewijs.

De systematische review omvatte 32 gerandomiseerde gecontroleerde onderzoeken (RCT's) met in totaal 1.219 deelnemers. De studies waren voornamelijk gericht op smalband (narrowband) UVB (NB-UVB) lichttherapie. Vier RCT's met in totaal 89 deelnemers vergeleken NB-UVB met placebo of geen behandeling. Deze vier RCT's lieten zien dat NB-UVB de klinische tekenen van eczeem en jeuk na 12 weken effectiever verminderde dan placebo, waarbij slechts minimale bijwerkingen optraden. De zekerheid van dit bewijs was echter laag. In de studies die NB-UVB met UVA1 en psoraleen plus UVA (PUVA) vergeleken werden geen significante verschillen in klinische uitkomsten, jeuk of kwaliteit van leven gevonden. De bewijskracht van deze studies was van zeer lage kwaliteit. In alle studies werden weinig bijwerkingen gerapporteerd, en deze omvatten fototoxische reacties, irritatie, verbranding en infecties.

Over het algemeen was NB-UVB de meest uitgebreid bestudeerde vorm van lichttherapie. Ongeveer 40% van de geïncludeerde studies richtten zich op NB-UVB. Andere vormen van lichttherapie, zoals breedband UVB en UVA1 werden tevens door een aantal studies onderzocht. Weinig studies evalueerden de effectiviteit van PUVA. Het bewijs voor lichttherapie bij de behandeling van atopisch eczeem bleek van lage tot zeer lage zekerheid. Dit benadrukte de significante hiaten in kennis over de lange termijn effectiviteit en de veiligheid van verschillende vormen van lichttherapie als behandeling voor atopisch eczeem. Hoewel lichttherapie in de dagelijkse praktijk veel wordt toegepast voor atopisch eczeem is het bestaande bewijs beperkt. Deze review benadrukte dat verder onderzoek nodig is, gericht op het standaardiseren van lichttherapiebehandelingsprotocollen, het bepalen van optimale doseringsschema's en het op maat maken van behandelingen voor bepaalde subpopulaties, zoals patiënten met een gekleurde huid.

Deel III: Internationale samenwerking door de TREAT Registry Taskforce: genereren van praktijkgegevens over landsgrenzen heen

Dit deel richtte zich op het verbeteren van internationale samenwerking en standaardisatie van dataverzameling door de TREatment of ATopic eczema (TREAT) Registry Taskforce.

In **hoofdstuk 4** werd een studie beschreven die de overlap en het potentieel voor het samenvoegen van data van acht verschillende TREAT registers onderzocht, met als doel om uitgebreid onderzoek naar de effectiviteit en veiligheid van therapieën voor atopisch eczeem te faciliteren. De TREAT Registry Taskforce streeft ernaar om systematisch lange termijn data uit de dagelijkse praktijk te verzamelen over de effectiviteit, veiligheid en kosteneffectiviteit van systemische immuunmodulerende therapieën en lichttherapie voor atopisch eczeem. Om het samenvoegen van data te vergemakkelijken, heeft de TREAT Registry Taskforce een kerndataset en protocol ontwikkeld, in overeenstemming met de aanbevelingen van de Harmonizing Outcome Measures for Eczema (HOME) groep.

Op 1 mei 2022 waren gegevens van meer dan 4700 patiënten verzameld in acht afzonderlijke registers. Deze registers hadden al individuele resultaten gepubliceerd over de demografie van patiënten, de effectiviteit van behandelingen en de veiligheid daarvan. De volgende stap is het samenvoegen van de gegevens uit de verschillende registers om de onderzoeksresultaten te versterken.
Deze studie identificeerde overeenkomsten en verschillen in hoe registers de kerndataset gebruikten en evalueerde daarmee hun vermogen om data samen te voegen. De registers verzamelden allemaal data over de effectiviteit, veiligheid en kostenefficiëntie van behandelingen, inclusief informatie over demografische kenmerken, therapiegegevens, klinische beoordelingen en patiënt-gerapporteerde uitkomsten. De meeste registreerden ook ernstige bijwerkingen en verzamelden data voor analyses van de kosteneffectiviteit. Hoewel gestreefd wordt naar een uniforme dataset, werden er variaties gezien door verschillen in data-invoer systemen en interpretaties van de data, wat het samenvoegen van data in de toekomst mogelijk lastig maakt. De meeste registers waren echter bereid hun datasets aan te passen. In de toekomst zal de focus liggen op het beoordelen van de technische compatibiliteit van data en demografische analyses om vergelijkende en gecombineerde studies te ondersteunen. Dit zal ook andere internationale onderzoeksgroepen helpen die streven naar geharmoniseerde dataverzameling en analyse.

Hoofdstuk 5 presenteerde de eerste gepoolde analyses van patiënten die behandeld werden met verschillende therapieën uit zeven TREAT-registers. Dit gaf inzicht in demografische kenmerken van de patiënten, ernst van de ziekte en het voorschrijfgedrag van artsen, en benadrukte de verschillen en overeenkomsten in Europa. Deze studie toonde aan dat het mogelijk is om data te bundelen en gepoolde analyses uit te voeren onder zeven TREAT-registers. De analyse omvatte data vanaf het moment van inclusie (varieert per register) tot 31 oktober 2022. Bij deze studie waren 5.337 patiënten met atopisch eczeem uit negen Europese landen betrokken, en liet aanzienlijke variaties zien in de demografische kenmerken van patiënten, de ernst van het atopisch eczeem en voorgeschreven behandelingen. Dit weerspiegelde deels de verschillen in toegang tot systemische immunomodulerende therapieën tussen landen.
De meeste patiënten hadden eerder een systemische behandeling gehad voordat ze werden geïncludeerd in het register. Patiënten waren voornamelijk behandeld met systemische corticosteroïden, methotrexaat en ciclosporine. Elk register toonde verschillende aantallen van patiënten met een bepaalde therapeutische voorgeschiedenis, wat de verschillen in voorschrijfgedrag weerspiegelde. De meerderheid van de patiënten startte met dupilumab ten tijde van inclusie in de registers. De gegevens zijn een weergave van de behandeling ten tijde van inclusie, wat suggereert dat de huidige aantallen patiënten die behandeld worden met biologicals of JAK-remmers mogelijk hoger zouden kunnen zijn dan gerapporteerd. Verschillen in de ernst van het atopisch eczeem tussen de registers kunnen worden toegeschreven aan variërende inclusiecriteria, waarbij sommige registers alleen patiënten includeren met matig tot ernstig eczeem.
De diversiteit die gevonden werd benadrukte de mate van representativiteit van de data voor de gehele patiëntenpopulatie van atopisch eczeem. Door patiënten te includeren met verschillende demografische kenmerken, therapeutische voorgeschiedenis en ernst van atopisch eczeem, zijn de bevindingen zeer generaliseerbaar, wat de integratie van data uit meerdere bronnen ondersteunt. Ondanks limitaties van de studie, zoals missende data en

mogelijke wervingsbias, was deze studie een belangrijke stap voorwaarts in het mogelijk maken van gepoolde analyses, wat als model kan dienen voor andere patiëntenregisters in de dermatologie. Deze gepoolde analyses zijn essentieel voor het beantwoorden van onderzoeksvragen waarvoor grote patiëntencohorten nodig zijn, zoals bijvoorbeeld onderzoeken naar het risico op maligniteiten. Het toekomstige onderzoek van de TREAT Registry Taskforce zal het onderzoek naar atopisch eczeem verbeteren en bijdragen aan effectievere behandelingen.

Deel IV: Evaluatie van de veiligheid van systemische behandelingen voor atopisch eczeem met behulp van data uit de dagelijkse praktijk
De veiligheid van verschillende systemische behandelingen voor atopisch eczeem werd onderzocht in deel IV.

Hoofdstuk 6 richtte zich op bijwerkingen van systemische immunomodulerende therapie met gebruik van data uit het TREAT NL/BE register, waarbij de incidentie van bijwerkingen in de dagelijkse praktijk werd vergeleken met de officiële samenvattingen van de productkenmerken (SmPC). Dit hoofdstuk gaf een duidelijker beeld van het veiligheidsprofiel van deze behandelingen en identificeerde vijf geneesmiddel gerelateerde bijwerkingen met een hogere incidentie dan gerapporteerd in de SmPC's: eosinofilie, blefaritis, droge ogen en hoofd-hals erytheem gerelateerd aan dupilumab, en vermoeidheid gerelateerd aan oraal methotrexaat. Er werden daarnaast twee nieuwe bijwerkingen van dupilumab aan het licht gebracht die niet beschreven staan in de SmPC: non-infectieuze conjunctivitis en meibomklierdysfunctie. Het onderzoek benadrukte het belang van het opnemen van data uit de dagelijkse praktijk over bijwerkingen in de geneesmiddelenbewaking om de klinische besluitvorming te verbeteren.

Hoofdstuk 7 ging in op dupilumab-geassocieerde (hyper)eosinofilie, waarbij de incidentie, progressie en klinische uitkomsten bij patiënten met atopisch eczeem werden onderzocht aan de hand van gegevens uit het single-center cohort van het TREAT NL/BE register. Uit gegevens van 200 patiënten die tussen september 2017 en december 2022 werden behandeld met dupilumab in Amsterdam Universitair Medische Centra, bleek dat 38,5% (hyper)eosinofilie ontwikkelde, met een piek na zes maanden behandeling en normalisatie van de eosinofiel spiegels tussen 18 en 24 maanden. De meeste gevallen van (hyper)eosinofilie waren van voorbijgaande aard en hadden geen klinische betekenis. Slechts één patiënt moest de behandeling met dupilumab stoppen vanwege symptomen gerelateerd aan hypereosinofilie. In het onderzoek wordt aanbevolen om de eosinofiel spiegel ten minste één keer binnen de eerste zes maanden van de behandeling te meten. Artsen worden geadviseerd om alert te zijn op symptomen van hypereosinofiele orgaanschade, zoals trombo-embolische events, vasculitis, neurologische klachten in de extremiteiten, kortademigheid, hartfunctiestoornissen en herseninfarct.

Hoofdstuk 8 onderzocht de invloed van systemische immunomodulerende therapieën op COVID-19-uitkomsten bij patiënten met atopisch eczeem met behulp van gegevens van het internationale Surveillance Epidemiology of Coronavirus (COVID-19) Under Research Exclusion - Atopic Dermatitis (SECURE-AD) register. COVID-19-uitkomsten omvatten de duur van COVID-19-symptomen, het persisteren van symptomen op het moment van rapportage,

sterfte ten gevolge van COVID-19, bezoeken aan de spoedeisende hulp, ziekenhuisopname, opnameduur, opname op de intensive care, beademingsbehoeftigheid en toename van de ernst van het eczeem tijdens COVID-19-infectie.
Het onderzoek omvatte 442 patiënten uit 27 landen en toonde aan dat het aantal ziekenhuisopnames vanwege COVID-19 onder patiënten met atopisch eczeem niet hoger was dan in de algemene bevolking. Patiënten die behandeld werden met systemische corticosteroïden werden het vaakst opgenomen in het ziekenhuis. Patiënten behandeld met dupilumab werden minder vaak opgenomen in het ziekenhuis dan patiënten die alleen topische therapie gebruikten. Patiënten op systemische combinatietherapie, vooral combinaties die systemische corticosteroïden bevatten, hadden eveneens hogere hospitalisatiecijfers. Het onderzoek ondersteunde het veiligheidsprofiel van dupilumab tijdens de COVID-19 pandemie en benadrukte een zorgvuldige risico-batenanalyse bij het voorschrijven van systemische therapieën tijdens dergelijke perioden.

Concluderend kan worden gesteld dat aandacht voor elk detail, van nauwkeurige diagnose en accurate dataverzameling tot robuuste veiligheidsbewaking, zal leiden tot betere gezondheidsuitkomsten en effectievere behandelingen voor atopisch eczeem. Hierdoor zal de zorg voor patiënten met atopisch eczeem steeds verder verbeteren.

APPENDICES

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Diagnostic accuracy of physician- and patient-assessed diagnostic criteria for atopic dermatitis: a systematic review

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Mapping exercise and status update of eight established registries within the TREatment of ATopic eczema (TREAT) Registry Taskforce

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First cross-border analyses of 5337 atopic eczema patients treated with systemic immunomodulatory treatment, phototherapy and topical therapies enrolled in 7 European registries united in the TREatment of ATopic eczema (TREAT) Registry Taskforce, on behalf of the A-STAR, AtopyReg, BIOBADATOP, SCRATCH, SwedAD, TREATgermany and TREAT NL/BE registry teams

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Real-world reported adverse events related to systemic immunomodulating therapy in patients with atopic dermatitis: results from the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry

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Dupilumab-associated (hyper)eosinophilia in patients with atopic dermatitis: a single-center cohort study of the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry

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The effects of systemic immunomodulatory treatments on COVID-19 outcomes in patients with atopic dermatitis: results from the global SECURE-AD registry

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- **Musters AH**, Mashayekhi S, Flohr C, Drucker AM, Gerbens L, Ferguson J, Ibbotson S, Dawe RS, Garritsen F, Brouwer M, Limpens J, Lax SJ, Harvey J, Spuls PI. Phototherapy for atopic eczema.* Cochrane Database of Systematic Reviews 2021, Issue 2. Art. No.: CD013870. DOI: 10.1002/14651858.CD013870. *protocol (intervention).

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- **Musters AH**, van Lookeren FL, van der Gang LF, Middelkamp-Hup MA, Bosma AL, Jessurun NT, Lapeere H, Nguyen AL, Ouwerkerk W, de Schepper S, Gerbens LAA, Spuls PI. Real-world reported adverse events related to systemic immunomodulating therapy in patients with atopic dermatitis: Results from the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry. J Eur Acad Dermatol Venereol. 2024 Mar;38(3):530-542. doi: 10.1111/jdv.19643. Epub 2023 Nov 29. PMID: 38031478.

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PHD PORTFOLIO

PhD candidate: A.H. Musters
PhD period: February 2020 - November 2024
Promotor: prof. dr. P.I. Spuls
Co-promotores: dr. M.A. Middelkamp Hup, dr. L.A.A. Gerbens

1. PhD training

General courses	**Year**	**ECTS**
Project Management	2020	0.6
Basic Course Regulations and Organization for Clinical Investigators (eBROK)	2021	1.5
Research Integrity	2022	2.0
The Amsterdam UMC World of Science	2022	0.7
	Total	**4.8**

Presentations	**Year**	**ECTS**
American Academy of Dermatology (AAD) Annual Meeting 2022, Boston, United States. *Oral presentation: Outcomes after COVID-19 infection in patients with atopic dermatitis - Results from the global SECURE-AD registry.*	2022	0.6
Society for Eczema Studies (SES) webinar 2022, India and South East Asia (virtual meeting). *Oral presentation: Outcomes after COVID-19 infection in patients with atopic dermatitis - Results from the global SECURE-AD registry.*	2022	0.4
7th congress of the Skin Inflammation and Psoriasis International Network (SPIN), Paris, France. *Oral presentation: SARS-CoV-2 vaccinations in patients with immune-mediated inflammatory disorders on immunosuppressants.*	2022	0.6
7th congress of the Skin Inflammation and Psoriasis International Network (SPIN), Paris, France. *Oral presentation: Diagnostic criteria for atopic dermatitis.*	2022	0.6
12th Georg Rajka International Symposium on Atopic Dermatitis (ISAD), Montréal, Canada (virtual meeting). *Poster presentation: Phototherapy for atopic eczema.*	2022	0.4
31st European Academy of Dermatology and Venereology (EADV) Congress, Milan, Italy. *Oral presentation: Outcomes after COVID-19 infection in patients with atopic dermatitis - Results from the global SECURE-AD registry.*	2022	0.6
31st European Academy of Dermatology and Venereology (EADV) Congress, Milan, Italy. *Poster presentation: Phototherapy for atopic eczema.*	2022	0.4
32nd European Academy of Dermatology and Venereology (EADV) Congress, Berlin, Germany. *Poster presentation: First cross-border analyses of 5337 atopic eczema patients treated with systemic immunomodulatory treatment, phototherapy and topical therapies enrolled in 7 European registries united in the TREatment of ATopic eczema (TREAT) Registry Taskforce.*	2023	0.4

Skin Inflammation & Psoriasis International Network (SPIN) World Tour 2024 webinar series (virtual meeting). *Oral presentation: Diagnostic criteria for atopic dermatitis.*	2024	0.4
	Total	**4.5**

(Inter)national conferences	**Year**	**ECTS**
American Academy of Dermatology (AAD) Annual Meeting 2022, Boston, United States.	2022	1.5
Society for Eczema Studies (SES) webinar 2022, India and South East Asia (virtual meeting).	2022	0.1
7th congress of the Skin Inflammation and Psoriasis International Network (SPIN), Paris, France.	2022	1.5
12th Georg Rajka International Symposium on Atopic Dermatitis (ISAD), Montréal, Canada (virtual meeting).	2022	0.5
31st European Academy of Dermatology and Venereology (EADV) Congress, Milan, Italy.	2022	1.5
32nd European Academy of Dermatology and Venereology (EADV) Congress, Berlin, Germany.	2023	1.5
Skin Inflammation & Psoriasis International Network (SPIN) World Tour 2024 webinar series (virtual meeting).	2024	0.1
33rd European Academy of Dermatology and Venereology (EADV) Congress, Amsterdam, The Netherlands.	2024	1.5
	Total	**8.2**

Other	**Year**	**ECTS**
Weekly meeting 'klinische wetenschappelijke bespreking', Department of Dermatology, Amsterdam University Medical Centers.	2020 - 2023	3.2
Werkgroep Leidraad Lichttherapie	2020	2.0
Wetenschappelijke vergadering Nederlandse Vereniging voor Dermatologie en Venereologie, Department of Dermatology, Amsterdam University Medical Centers.	2024	0.5
Deelname aan duo-intervisie patiënten participatie, top 10 kennisvragen medisch specialistische zorg 2020, Zorgevaluatie en Gepast Gebruik (ZE&GG) (UPDATE trial).	2021	2.0
	Total	**7.7**

2. Teaching

Lecturing	**Year**	**ECTS**
Lecture on ‘Lichttherapie voor atopisch eczeem’, during 'klinische wetenschappelijke bespreking', Department of Dermatology, Amsterdam University Medical Centers.	2021	0.3
Lecture on ‘Leidraad Lichttherapie’, education for dermatology residents, Department of Dermatology, Amsterdam University Medical Centers.	2023	0.3
Lecture on ‘Real-world reported adverse events related to systemic immunomodulating therapy in patients with atopic dermatitis’, during 'klinische wetenschappelijke bespreking', Department of Dermatology, Amsterdam University Medical Centers.	2023	0.3

Lecture on ‘Bijwerkingen van systemische medicatie bij atopisch eczeem’, education for dermatology residents, Department of Dermatology, Amsterdam University Medical Centers.	2023	0.3
	Total	**1.2**

Supervising	**Year**	**ECTS**
Supervising master thesis student Manja Bloem	2020	2.0
Supervising master thesis student Lian van der Gang	2021-2022	2.0
Supervising master thesis student Emilie de Monchy	2021	2.0
Supervising master thesis student Nina Buter	2022	1.0
Supervising master thesis student Florine van Lookeren	2022	2.0
Supervising master thesis student Jasper van Hoek	2022	2.0
	Total	**11.0**

DANKWOORD

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ABOUT THE AUTHOR

Annelie Hanna Musters was born on July 19, 1993, in Haren. She began her education at Maartens College Haren, where she completed her VWO in Nature & Health in 2011, following a bilingual program and earning an International Baccalaureate Middle Years Programme certificate in 2009.

In 2011, Annelie moved to Groningen and began her studies in Medicine at the University of Groningen, obtaining her Bachelor's degree in 2015. During the gap between her Bachelor's and Master's studies, she became a board member of the International Student Congress of (bio)Medical Sciences (ISCOMS), where she helped organize a large 5-day international medical congress.

From 2016 to 2019, Annelie pursued her Master's in Medicine at the University of Groningen. As part of her training, Annelie completed junior internships at the University Medical Center Groningen, followed by senior internships at Ziekenhuisgroep Twente. It was during these internships that her interest in dermatology was sparked. In her final year, she focused entirely on dermatology, completing internships at both Amsterdam University Medical Centers and Onze Lieve Vrouwe Gasthuis, alongside a research internship under the supervision of Prof. Dr. P.I. Spuls. This experience ultimately led her to pursue a PhD under the guidance of Prof. Dr. P.I. Spuls, Dr. M.A. Middelkamp Hup and Dr. L.A.A. Gerbens.

In 2020, Annelie began her PhD as a physician-researcher at Amsterdam UMC's Dermatology Department. Under the supervision of her promotors, she helped coordinating the TREAT NL registry and served as a trial physician. During this period, she also worked as a physician at the BIO AD clinic, treating atopic eczema patients receiving systemic treatments.

In March 2023, Annelie began her dermatology residency at the Department of Dermatology at Amsterdam UMC.