UNDERSTANDING TREATMENT RESPONSE IN REAL-WORLD PATIENTS WITH ATOPIC ECZEMA

ANGELA LEIGH-ANN BOSMA

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INTRODUCTION AND THESIS OUTLINE AND AIMS

INTRODUCTION

Atopic eczema

Atopic eczema, also known as atopic dermatitis, is a common and chronic inflammatory skin disorder that is characterized by the presence of pruritic lesions on the skin.[1] Excluding mortality, skin diseases were shown to be the fourth leading cause of disability worldwide.[2] Of all skin diseases, atopic eczema has the highest non-fatal health burden.[3,4] Atopic eczema can have a large negative impact on the quality of life of patients and their families.[5] It is associated with other atopic diseases, such as asthma and allergic rhinitis.[1] Furthermore, atopic eczema is also associated with sick leave, change or loss of work and productivity impairment.[6-8]

In 2019, there were an estimated 394,600 patients, of which 178,000 men and 216,600 women, with atopic eczema in the Netherlands who received care for their disease from their general practitioner or of whom the general practitioner knew that the patient was receiving care in secondary care (care prevalence).[9] This corresponds to 20.7 per 1,000 men and 24.8 per 1,000 women. Over time, the prevalence of atopic eczema has increased from 2011 to 2019, for both men (increase of 10%) and women (increase of 17%).[9] Globally, the 1-year prevalence of physician-diagnosed atopic eczema in adults has been demonstrated to range from 1.2% in Asia and Europe to 17.1% in Europe, and in children from 1.0% to 22.6% in Asia and from 1.8% to 17.0% in Europe.[10]

Two major models exist to explain the pathogenesis of atopic eczema. Atopic eczema can be considered both an immunological and skin barrier disorder.[11,12] Traditionally, atopic eczema is seen as primarily an immune function disorder in which allergen specific T-cells in the skin are activated.[11] The other model describes atopic eczema as a result of an intrinsic defect in epidermal barrier in which a mutation of filaggrin has a central role.[12] The disorder is influenced by endogenous factors, i.e. a genetic predisposition, as well as by exposure to environmental factors.[1] There is increasing recognition that atopic eczema is a highly complex syndrome with multiple causes and mechanistic pathways.[13]

Within the population of patients with atopic eczema, many subgroups of patients (i.e. phenotypes) can be identified based on several features. Atopic eczema affects people from all ethnic groups and ages, including patients of reproductive age, children and elderly. It a heterogeneous disease with a wide spectrum in clinical presentation, leading to various morphological phenotypes, as shown in Figure 1. Atopic eczema is known to present differently in patients with dark compared to light skin types.[14-16] Phenotypes can also be identified based on patterns of disease onset, persistence and resolution over time (i.e. disease trajectory), and based on their susceptibility to triggers, including

allergens, of which pollen have been demonstrated to be one of the most relevant aeroallergens.[17,18] Other phenotypes include subgroups based on gender, presence of comorbidities, serum IgE or genetic mutations. As a last example, subgroups based on disease severity can also be considered phenotypes.

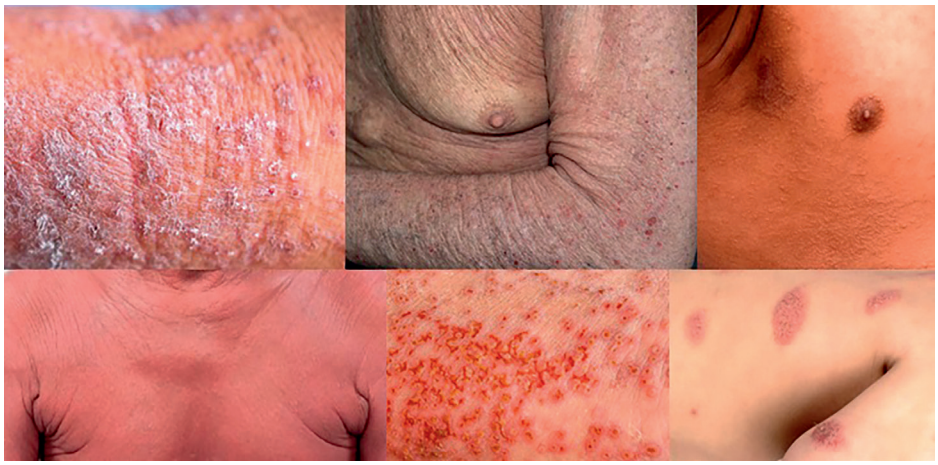

Figure 1. Examples of phenotypes of atopic eczema based on morphology[19]
From left to right: flexural eczema, lichenified eczema, follicular eczema, erythroderma, eczema herpeticum, nummular eczema

Systemic therapies

The majority of patients with atopic eczema have a mild disease severity and can be treated effectively with emollients, topical anti-inflammatory agents and avoidance of potential triggers that may worsen the disease. However, about 15% of patients are considered to have moderate-to-severe disease.[20,21] These patients are potential candidates for systemic immunomodulating therapies. In this specific subset of patients, topical therapies, including indifferent emollients and topical corticosteroids or calcineurin inhibitors, and phototherapies are deemed not effective enough to induce sufficient disease control.

At the moment, various systemic therapies are available for atopic eczema. Conventional systemic therapies, such as ciclosporin, have been available for decades.[22] Many conventional therapies are prescribed off-label, including methotrexate, azathioprine, mycophenolic acid, mycophenolate mofetil and systemic corticosteroids. Mycophenolic acid and mycophenolate mofetil can be prescribed in adults. All of the other treatments can be prescribed in both adults and children from the age of two.[23] More recently, biologics (-mabs) and JAK inhibitors (-nibs) have entered the treatment arsenal. Dupilumab has been available since the end of 2017 and can now be prescribed in adults and children from the age of six months.[24,25] Baricitinib, tralokinumab, upadacitinib

and abrocitinib have been approved by the European Medicines Agency (EMA) and became available in 2021 and 2022.[26-29] Upadaticinib and tralokinumab are available for adults and adolescents (≥ 12 years).[27,30,31] The other JAK inhibitors are only prescribed in adults. Dupilumab, baricitinib, tralokinumab, upadacitinib and abrocitinib are the only treatments approved for atopic eczema by both the EMA and the U.S. Food and Drug Administration. There is a lack of knowledge regarding many aspects of the treatments that are available for atopic eczema.

In the Netherlands, dupilumab, baricitinib, tralokinumab, upadacitinib and abrocitinib are currently prescribed in patients who have shown insufficient effectiveness, side-effects or contraindications for conventional therapies. Our national criteria as determined by the Dutch Society for Dermatology and Venereology (NVDV) stipulate a treatment episode of at least 4 months with 1 or more conventional systemic therapies in an adequate dose.[30-33] As for the available treatments, patients are prescribed a treatment that often depends on the experience and preference of the prescriber, and the availability of treatments in countries or centers, rather than specific patient characteristics. However, we know that it concerns a heterogeneous population in both pathophysiology and clinical appearance. No specific criteria exist for prescribing systemic therapies and no clear-cut treatment algorithm is available to facilitate this, as displayed in Figure 2.[23] The limited guidance results in variation in prescribing practices. This variation between countries and dermatologists has been identified in a European survey.[34] Before the introduction of dupilumab, ciclosporin was the preferred treatment of choice by the majority of dermatologists, followed by systemic corticosteroids and methotrexate.

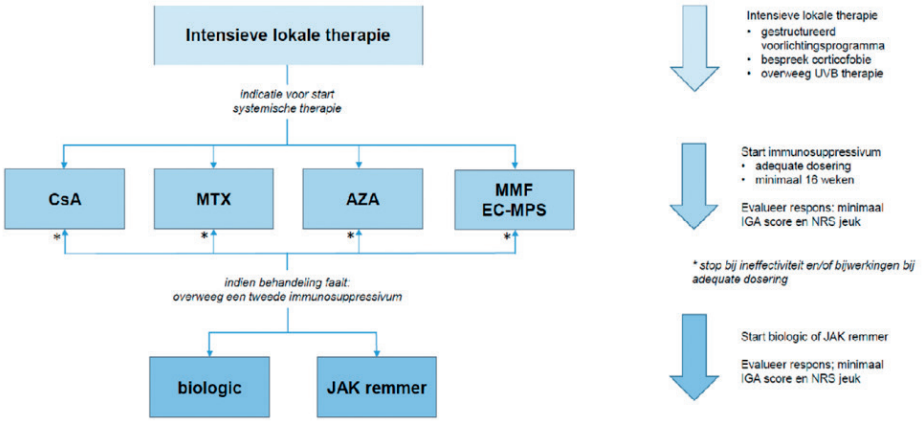

Figure 2. Treatment algorithm for systemic therapy, NVDV[35]
CsA: ciclosporin A (start: 4-5 mg/kg/dag 3-6 weeks; maintenance: 2-3 mg/kg/day); MTX: methotrexate (15-22,5 mg/week); AZA: azathioprine (2-3 mg/kg/day); MMF: mycophenolate mofetil (2000 mg/day) / mycophenolic acid (1440 mg/day); biologic: dupilumab, tralokinumab; JAK inhibitor: abrocitinib, baricitinib, upadacitinib.

The current evidence to guide clinical management for moderate-to-severe atopic eczema is based on a small body of short-term placebo-controlled randomized controlled trials (RCTs) and observational studies. Few studies have been conducted directly comparing treatments or investigating long-term outcomes of treatment. Treatment response outcomes comprise both effectiveness and safety. To answer questions about safety, large numbers of patients with a long follow-up duration are required to investigate rare adverse events, such as malignancies. There are at the moment no long-term, prospective and comparative data on the effectiveness and safety of systemic therapies in children or adults from large-scale multicenter cohort studies.

A systematic review from 2014 on the efficacy and safety of systemic therapies for moderate-to-severe atopic eczema states that more large long-term head-to-head studies are required.[36] Years later, we can draw the same conclusions based on two updated systematic reviews with network meta-analyses.[37,38] These recent network meta-analyses both showed that there is a lack of head-to-head studies on systemic treatments of good quality.[37,38] The first network meta-analysis concluded that dupilumab and ciclosporin may be more effective for up to 16 weeks of treatment than methotrexate and azathioprine for treating adult patients with atopic eczema.[37] In the second network meta-analysis, the authors reported that their findings indicate that dupilumab is the most effective biological treatment and that evidence for the efficacy of most other immunosuppressive treatments for moderate-to-severe atopic eczema is of low or very low certainty.[38] In a recent systematic review of observational studies, only two studies were identified that investigate the safety of systemic therapies in older adults with atopic eczema and both were considered to be of low quality.[39] All in all, the present evidence on systemics to inform therapeutic management in clinical practice is limited.

Due to the lack of evidence and the resulting lack of clear therapeutic management guidance, consensus statements have been written by various initiatives to guide in which cases prescribing certain treatments should be considered. Examples are the position paper of the European Task Force on Atopic Dermatitis for the treatment of atopic eczema during pregnancy and lactation,[40] and the consensus statement for systemic therapy and systemic corticosteroids of the International Eczema Council.[41,42] In addition, to guide shared decision-making on systemic treatment continuation, modification, or discontinuation, treat-to-target- oriented recommendations have been developed.[43]

The relevance of investigating therapies for atopic eczema is increasingly recognized. This knowledge gap is highlighted by the inclusion of the research question “What is the effectiveness of different treatments in patients with atopic eczema?” in the knowledge agenda of the Dutch Society for Dermatology and Venereology in 2019.[44]

This agenda comprises the top 10 highest prioritized knowledge gaps within the field of dermatology and was selected out of more than 1300 research questions. Investigating the (cost) effectiveness of treatments that are part of existing care is also called health care evaluation ('zorgevaluatie'). The abovementioned research question has also been selected by the program 'Zorgevaluatie en Gepast Gebruik' as part of the top 10 research questions that require health care evaluation research within all medical specialties.[45] Further, the 'Hoofdlijnenakkoord medisch-specialistische zorg' includes that health care evaluation should become an integral part of daily practice over the next 5 years.[46]

We have entered an era of new promising systemic therapies, such as biologics and small molecules. Various biologics and small molecules are currently being investigated in RCTs.[47] More new treatments will become available for atopic eczema in the future. Over the past years, biologics have become the best-selling drugs in the pharmaceutical market and the expected global revenue generated by these therapies are expected to increase steadily.[48] Comparative studies are of interest, by comparing these treatments to conventional systemic therapies, which generally have more well-known safety profiles, lower costs and a wider availability. New treatments are initially only studied in healthy patients with a relatively short follow-up duration. If new treatments enter the market, data on long-term outcomes and subgroups can be collected in registries.

Real-world data

By means of observational research registries, data can be collected prospectively from patients in daily practice to answer research questions in relation to various aspects of treatments, including questions that cannot be properly investigated through RCTs. Awareness of the importance of research registries is growing, also shown by the development of a guideline for registry-based studies by the EMA.[49] As guidance for a registry population, this document states that a registry should be representative of the complete target population and ideally should cover a broad patient population covering all disease aspects and patient characteristics.

Patients included in RCTs are not representative of the entire population. Relevant phenotypes are often not included in RCTs, due to strict inclusion and exclusion criteria that are applied in these studies. While atopic eczema has shown to be more prevalent in patients with dark skin,[14,50-52] studies investigating treatments are predominantly conducted in patients with light skin types.[53] Study participants in RCTs are usually white, middle-aged men.[53] However, in daily practice we treat patients of all ethnic backgrounds and ages, patients may have comorbidities, wish to have children, use co-medication and so on. In addition, combination treatment may be deemed necessary. A classic RCT does not lend itself sufficiently to take this patient heterogeneity into

account. The generalizability of the findings of RCTs to the context of routine daily clinical practice is relatively limited. The psoriasis literature has indicated that approximately 30% of patients eligible for registries are not eligible for participation in clinical trials,[54] further highlighting the lack of external validity of RCTs. In addition, it will not be feasible to perform long-term RCTs to investigate all potentially relevant subgroups of patients and all comparisons between treatments.

In general, post-marketing studies funded by pharmaceutical companies have not been found to improve drug safety surveillance, because sample sizes are too small to allow the detection of rare adverse events and due to strict obligations of confidentiality towards the sponsors.[55] Like described earlier, investigating safety pre-eminently also requires large participant numbers and long-term follow-up in order to detect rare drug adverse events. Registries have the potential to provide these data. Also generally speaking, clinical trials have relatively short follow-up durations for feasibility reasons. Registries can provide effectiveness and safety data beyond the confines of short-term RCTs.

In the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry, long-term observational data is collected from patients with moderate-to-severe atopic eczema, both children and adults, who start treatment with systemic therapies (e.g., dupilumab, ciclosporin, methotrexate) and phototherapies (e.g., UVB) in daily practice (*treatregister.nl*). At the moment, participating centers include Amsterdam UMC, Huid Medisch Centrum, Centrum Oosterwal, Leids Universitair Medisch Centrum, Medisch Centrum Leeuwarden, Dijklander Ziekenhuis, Onze Lieve Vrouwe Gasthuis, Erasmus MC, Rijnstate Ziekenhuis, Flevoziekenhuis and Universitair Ziekenhuis Gent. Patients are followed during treatment and after treatment discontinuation. The treatments that are investigated in the TREAT NL registry concern phototherapy and systemic therapies that are part of existing routine clinical care. With this registry, we aim to investigate the (cost-)effectiveness and safety of these treatments for atopic eczema on the long term. The TREAT NL registry was established in 2017 and is part of the TREAT Registry Taskforce, an international network of registries within Europe that collect the same data using a core dataset, to ensure uniformity in data collection (*treat-registry-taskforce.org*).[56,57]

The development of the TREAT core dataset was a global initiative, including an eDelphi exercise among more than 400 participants from over 30 countries and several consensus meetings.[57,58] The aim of developing this core dataset was to increase interoperability, direct comparability and pooling of data, and to reduce heterogeneity in data collection across country borders. Harmonization of data collection, both at a national and international level, is key in order to pool data and subsequently study large numbers of patients. A preceding psoriasis registry initiative had highlighted the difficulty of pooling data when it is not collected in the exact same way.[59] The core dataset is aligned with HOME (Harmonizing Outcome Measures for Eczema)

recommendations and comprises both investigator- and patient-reported outcome measures, including the scores based on skin severity assessment, symptom scores and quality of life scores, and also consists of a diverse variety of demographic patient characteristics.

In addition to the international TREAT core dataset, additional data is collected in the TREAT NL registry on sleep loss, work-related quality of life, work ability, pregnancy (paternal/maternal use), intoxications and height and weight. A uniform comprehensive dataset is collected from all patients, and some dataset items are only collected if applicable. The time points of data collection are: at start of treatment (baseline), 4 weeks, 12 weeks/3 months, every 12 weeks/3 months thereafter during treatment and every 6 months after discontinuation of treatment. It is aspired to collect follow-up data with a duration of at least 5 years per patient, even after they may have discontinued treatment.

In the long term, we hope that recommendations and analyses from registries like the TREAT NL registry will supplement the shorter-term results of RCTs, to enable working towards treatment algorithms based on personalized medicine, ultimately resulting in improvement of the care for patients with atopic eczema in the future.

THESIS OUTLINE AND AIMS

The overall aim of this thesis is to gain more understanding on treatment response (i.e. both effectiveness and safety) in real-world patients with atopic eczema. To answer this aim, several studies were conducted. The focus was set on increasing international standardization and cooperation to investigate treatments for atopic eczema (**Part I**), gaining real-world evidence on dupilumab in atopic eczema (**Part II**) and increasing the knowledge on phenotypes of atopic eczema (**Part III**).

Part I: The TREAT Registry Taskforce and the TREAT NL registry

This part of the thesis reflects the aim of increasing international standardization and cooperation to enable research on the effectiveness and safety of therapies for atopic eczema. For this purpose, we used the TREAT Registry Taskforce as a basis. In **Chapter 2** we aimed to design a protocol for conducting a long-term safety study comparing dupilumab with other systemic therapies in patients with atopic eczema. This protocol can be used as a framework for conducting other studies within the taskforce and beyond. The aim of **Chapter 3** was to perform an exercise of mapping the individual registry datasets to the TREAT core dataset and to give an overview of the status and characteristics of the eight established TREAT registries, in order to facilitate future analyses within the taskforce. **Chapter 4** aims to provide guidance on the process of selecting a web-based application to measure patient-reported outcomes, which was conducted for the TREAT NL registry, to facilitate researchers worldwide in their decision making.

Part II: Real-world experience with dupilumab in atopic eczema

The aim of gaining real-world evidence on dupilumab in atopic eczema is covered in this part. Studies investigating several aspects of systemic treatment with dupilumab in daily practice using data from the TREAT NL registry are set out here. In **Chapter 5** we aimed to investigate the daily practice effectiveness and safety of dupilumab treatment up to 16 weeks, and in **Chapter 6** on the long term, i.e. up to 84 weeks of treatment. **Chapter 7** concerns an elaboration of the methods used in these studies, with the aim to advocate that methods applied in RCTs do not necessarily lend themselves well for real-world research. In **Chapter 8** the aim was to investigate the work ability and quality of working life of atopic eczema patients and how this is affected by dupilumab treatment. The aim of **Chapter 9** was to get insight into the clinical relevance (i.e. the influence on both effectiveness and safety) of serum drug levels of dupilumab. As patients requiring systemic therapies include patients of reproductive age, **Chapter 10** aims to report on four patients treated with dupilumab wishing to conceive child and to provide a review of the literature on this topic.

Part III: Phenotypes of atopic eczema

The aim of this part is to increase the knowledge on phenotypes of atopic eczema. In **Chapter 11** we aimed to provide an extensive overview of the literature of phenotypic subgroupings in patients with atopic eczema. In **Chapter 12** we aimed to investigate which characteristics best describe the phenotype of children flaring in the pollen season, including an analysis on the influence of skin type (skin colour). In **Chapter 13** the focus is also on skin type with the aim of identifying potential differences in patient characteristics, including morphological phenotype, and differences in treatment outcome between skin type groups.

In **Chapter 14** and **Chapter 15** the findings of this thesis are discussed and summarized.

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PART I

THE TREAT REGISTRY TASKFORCE AND THE TREAT NL REGISTRY

TREATMENT OF ATOPIC ECZEMA (TREAT) REGISTRY TASKFORCE: PROTOCOL FOR A EUROPEAN SAFETY STUDY OF DUPILUMAB AND OTHER SYSTEMIC THERAPIES IN PATIENTS WITH ATOPIC ECZEMA

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ABSTRACT

Background

A long-term prospective observational safety study is essential to fully characterize the safety profile of systemic immunomodulating therapies for patients with atopic eczema. The TREatment of ATopic eczema (TREAT) Registry Taskforce offers a large platform to conduct such research using national registries that collect the same data using a predefined core dataset.

Objectives

We present a protocol for a safety study comparing dupilumab with other systemic immunomodulating therapies in children and adults with moderate-to-severe atopic eczema to assess the long-term safety risk of these therapies in a routine clinical care setting.

Methods

We describe a registry-embedded international observational prospective cohort study. Adult and paediatric patients who start treatment with dupilumab or another systemic immunomodulating agent for their atopic eczema will be included. The primary endpoint is the incidence of malignancies (excluding non-melanoma skin cancer) compared between the treatment groups. Secondary endpoints include other serious adverse events and adverse events of special interest, such as eye disorders and eosinophilia.

Conclusions

This protocol delineates a safety study for dupilumab in adult and paediatric patients with atopic eczema, using a standardized methodological approach across several national registries. The protocol could also be used for other novel systemic immunomodulating therapies and could provide licensing and reimbursement authorities, pharmaceutical companies and clinicians with safety evidence from a routine clinical care setting.

INTRODUCTION

In a substantial number of patients with atopic eczema systemic immunomodulating therapies are required because the disease is not sufficiently controlled with topical therapies.[1] Ciclosporin was until recently the only systemic treatment approved in Europe and only in adults with severe disease.[2] The frequency and duration of the use of ciclosporin is limited due to the risk of renal toxicity and hypertension. In addition, neurological symptoms, fatigue or gastrointestinal symptoms, next to treatment failure are reasons for patients to discontinue their treatment.[3] Ciclosporin has many potential contraindications and drug interactions. Alternative systemic immunomodulating therapies are used off-label and include methotrexate, mycophenolic acid, mycophenolate mofetil and azathioprine.[4] These treatments are frequently prescribed for atopic eczema.[5,6] Methotrexate has limitations due to potential liver toxicity and teratogenicity.[7] Azathioprine and ciclosporin have been associated with an increased risk of incident cancer.[8-11] However, the relative contribution of the diseases themselves and disease-related risk factors are difficult to separate from treatment-related factors.

Dupilumab, a monoclonal antibody binding to the alpha subunit of the interleukin-4 receptor (IL-4Rα), has recently been approved by both the Food and Drug Administration (FDA) in the U.S.A. and European Medicines Agency (EMA) for the treatment of adult patients with moderate-to-severe atopic eczema. Regarding short-time safety, clinical trials on dupilumab have shown no significant difference in the proportion of patients with at least one adverse event in comparison to placebo, nor were there serious adverse events related to dupilumab. Injection-site reactions and conjunctivitis were the most commonly reported adverse events.[12,13] Eosinophilia has been reported in trials investigating dupilumab treatment in patients with asthma, with symptomatic hypereosinophilia being observed in rare cases.[14,15] In atopic eczema studies asymptomatic eosinophilia has been observed.[12,16] In addition, conflicting evidence exists about the role of IL-4 in tumor promotion.[17,18] The long-term safety of dupilumab has not yet been investigated.

In order to fully characterize the safety profile of the long-term use of dupilumab and mostly off-label systemic treatments among patients with atopic eczema, a long-term, prospective, observational safety study is essential and often stipulated by the licensing body, such as the EMA. Clinical registries can provide such data.

The TREatment of ATopic eczema (TREAT) Registry Taskforce is an international network of research registries which collect observational data of adult and paediatric patients with atopic eczema in a harmonized fashion.[19] Consensus was reached on a core dataset based on an international Delphi exercise among over 400 stakeholders from over 20 countries.[20,21] Recently, recommendations for measurement instruments have

been added to this core dataset.[22] Currently, TREAT registries are being established in different European countries and in North America. Countries participating in the TREAT registry initiative are the U.K., Ireland, the U.S.A., Germany, the Netherlands, Denmark, Sweden, France, Italy, Spain and Portugal.

Data collected in a harmonized and standardized fashion across the TREAT registries can be used for the purpose of conducting a long-term safety study and here we present a study protocol for such an approach. The main objective of this study is to characterize the long-term safety profile of dupilumab compared to other systemic immunomodulating therapies for the treatment of atopic eczema in a routine clinical care setting.

PATIENTS AND METHODS

Study design

A registry-embedded long-term international prospective cohort study is conducted, aiming to recruit adult and paediatric patients with atopic eczema who start treatment with dupilumab and to compare the adverse event rates in this cohort with a cohort starting treatment with other systemic immunomodulating therapy (e.g. ciclosporin, methotrexate, mycophenolic acid, mycophenolate mofetil and/or azathioprine). The study has an observational nature where interventions are initiated by the treating physician and not determined by the study. Coordinating centres of this study are the sites that coordinate the atopic eczema registries of the TREAT Registry Taskforce, each with a network of recruiting sites. Our European initiative has been registered as a research network with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCEPP).[23]

Patient population

The study population consists of patients with a physician diagnosis of atopic eczema, who are starting on or switching to a systemic immunomodulating treatment for their atopic eczema that they have not received before. We aim to include as many dupilumab-treated patients as those treated with other systemic immunomodulating therapies as contemporaneous comparator. Participants need to be willing to comply with all study requirements and provide consent to participate in long-term follow-up for the collection of observational data during their visits, including adverse event recording and disease severity assessments. Written informed consent is obtained from each patient before participation.

Patients will not be allowed to be enrolled in the study if they are concurrently participating in an interventional study of systemic therapy for atopic eczema. The

study participants can be enrolled in clinical trials prospectively. We will record if participants are participating in an investigational trial and include this as a variable in our analysis. If possible, follow-up visits for this safety study will be continued during the investigational trial. Participants can also be co-enrolled in other observational studies.

Study schedule

During the observation period, participants will be assessed on at least a 6 monthly basis while on therapy and at least annually off systemic immunomodulating treatment to collect data on adverse events and reasons for potential changes in therapy. A +/-2 months visit window will be applied. The study aims to monitor patients for as long as possible, aiming for at least 5 years of follow-up for each participant.

Study endpoints

Primary endpoint:

- Incidence rate ratios of cancer (any pathology-confirmed malignant tumour or cancer excluding non-melanoma skin cancer (NMSC)) within the follow-up period comparing the group receiving dupilumab and the group receiving other systemic immunomodulating treatments.

Secondary endpoints:

- Incidence rate ratios of serious adverse events (any untoward medical occurrence that results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect, including serious infections (e.g pneumonia, septicaemia, bone, joint and opportunistic infections)[24]) within the follow-up period comparing the groups.
- Incidence rate ratios of other adverse events of special interest in the groups: eosinophilia (an absolute eosinophil count of ≥500/µl), eye disorders (e.g. conjunctivitis, blepharitis, and other eye disorders as diagnosed by an ophthalmologist if appropriate), skin cancer (including both melanoma and NMSC), cardiac disorders (e.g. myocardial infarction), central nervous system disorders (e.g. demyelination, peripheral neuropathy, seizures), and haematological disorders (e.g. aplastic anaemia, pancytopaenia).
- Discontinuation rate of dupilumab due to adverse events, compared to the discontinuation of the other systemic treatments.

Sample size

The definite power calculation will be based on the anticipated frequency of the outcomes. Under the assumption of 80% power and 5% alpha error (2-sided), a hazard ratio (HR) of 2 and 1:1 ratio of patients exposed vs. non-exposed to dupilumab

(primary exposure) requires 66 events in the study.[25] Due to non-random allocation of patients between the groups a R2 (r-squared) of exposure to dupilumab explained by other covariates = 0.2 is considered. Assuming an annual incidence rate of any cancer (excluding NMSC) of 33 per 10,000 patients,[26] this results in 82 events.[27] There would be less power to detect the rare cancer specific subtypes, such as lymphoma and melanoma, unless the risk difference is very large. Our assumed HR for this power calculation is in line with the standard EMA requirements for a post-marketing safety study focused on cancer. A safety study should be large enough to detect a two folded increases risk for cancer (without NMSC). If the risk is higher than a HR of 2 the desired 82 cancer events would happen earlier in time and if the risk is smaller than a HR of 2 a larger sample size would be required.

Furthermore, a dropout rate of 20% including those with only limited exposition to dupilumab (exposure to dupilumab < 4 weeks) or other possible future biologicals is assumed. To achieve these 82 events, we are dependent on the number of recruited patients, the speed of recruiting and the time the patients are under observation in the registry. Table 1 gives an overview about possible scenarios if recruitment is uniformly distributed over the recruitment period. By recruiting 1000 patients (N_y) per year over three years (Y_rec) the desired number of 82 events will appear in the 9th year of the study. By recruiting 800 patients per year over four years the desired number of 82 events will also appear in the 9th year of the study but require overall 3200 instead of 3000 patients to be included in the study.

Table 1. Distribution of follow-up time in years for different recruitment scenarios to achieve estimated event numbers at the end of the year, assuming recruitment is uniformly distributed over the recruitment period with 20% dropout and a background incidence of 33 per 10.000 person years.

N_y	Y_rec	3y	4y	5y	6y	7y	8y	9y	10y	11y	12y	13y	14y
600	3	11	18	25	32	39	45	52	59	66	73	79	86
800	3	14	24	33	42	51	61	70	79	88	97	106	115
1000	3	18	29	41	53	64	76	87	99	110	121	132	143
600	4	11	19	28	38	47	56	65	74	83	92	101	110
800	4	14	25	38	50	62	75	87	99	111	123	135	147
1000	4	18	31	47	63	78	93	109	124	139	154	169	184
600	5	11	19	29	41	53	64	76	87	99	110	121	132
800	5	14	25	39	55	70	86	101	116	131	147	162	176
1000	5	18	31	49	69	88	107	126	145	164	183	202	221

N_y: number of recruited patients per year; Y_rec: duration of recruitment.

Exposure to dupilumab and other systemic immunomodulating treatments for atopic eczema will vary over time. It is expected that many patients will be exposed to more than one systemic immunomodulating agent within the study period. Differences in previous exposure to systemic immunomodulating atopic eczema treatments also have to be considered as potential confounders in the analysis. Additionally, a certain lag time has to be assumed between relevant exposures and detection of incident cancer. Long latency adverse events, like cancer, will be linked to a drug if patients were ever exposed to the drug. Short latency adverse events, like eye disorders, will be linked to a drug if they took place while the patient was using the drug or within 90 days after the end of exposure.

Statistical analysis

The data from each participating registry will be analysed separately at first. A descriptive analysis of baseline patient characteristics and medical history will be presented. Categorical variables will be summarized by number and percentage in each category. Missing data will be displayed as a separate category where appropriate. Both cumulative incidence and incidence rates of malignancies, including 95% two-sided confidence intervals, will be estimated for the treatment groups.

The data from each registry will then be pooled and a comparative analysis will be performed on the pooled data to estimate if there is a difference in the incidence rates for malignancies or serious infections and the other adverse events of interest between the treatment groups. In the primary confirmatory analysis exposure to dupilumab will be handled as a binary variable, i.e. patients are classified as exposed if they received dupilumab at least once within the study period; otherwise as non-exposed. The log-rank test will be used followed by cox proportional hazard models. Potential confounders and effect modifiers (age, sex, previous treatments (including previous phototherapy), malignancy history, smoking, family history, co-treatments, socioeconomic position, country etc.) will be tested and included in the cox model if they improve the model fit according to the Bayesian information criterion. Primary population for analysis will be all patients up to the point when 82 cancer events appear. The analyses will take into account switching from one drug to another as well as medical (therapeutic) history, such that the person-years of follow-up switch to the new drug when this is initiated.

Sensitivity analyses will:

- Consider history of malignancy
- Include analyses stratified by cancer type (including NMSC)
- Consider lag time of exposure and cancer incidence of 12 months
- Explore a potential dose-response effect of cumulative dupilumab exposure

The same methods as described above will be applied to analyse secondary outcomes.

Data collection

Each country will use a purpose-built online data entry platform to prospectively collect the study data. All data will be pooled across countries for the final analyses. The pseudonymised data of each national registry will be hosted on secure servers. All data will be additionally stored on a backup server in case of data loss. Only registered local investigators and delegated study members will have access to the data entry platform and only to the data of their own patients.

Data capture includes a case record form (CRF) based on the TREAT core dataset.[21,22] A variety of parameters will be collected during the study visits. Concerning safety, data on the predefined adverse events, including severity, seriousness, and relatedness to therapy as part of pharmacovigilance will be recorded at each follow-up visit and entered into the CRF. All predefined malignancy and other pre-defined adverse event categories will be recorded using MedDRA (Medical Dictionary for Regulatory Activities) data dictionary coding. Where possible, the use of data from national cancer registries will be explored. In case of loss to follow-up, every effort will be made to collect information on the reason for this, including data on a potential (serious) adverse event related to this.

Study governance structure

The safety study will be governed by a Steering Committee (SC), consisting of the Chair (Study Lead Investigator), the Co-Chair (Deputy Lead Investigator) and all country Principal Investigators (PI) and Co-PIs. The SC will be responsible for the running and management of the study and will meet regularly, at least six monthly, either in person or via teleconference. In addition, there will be a Data Monitoring Committee (DMC), an independently formed committee with responsibility for monitoring the patient safety. The DMC safeguards the interests of the patients participating in the study. It is the job of the DMC to monitor the comparative data and make recommendations to the SC on whether there are any ethical or safety reasons why the study should not be continued. They can also advise on modifications to the protocol. Apart from its Chair, the DMC will have at least one statistician and at least two clinicians not directly involved in the study, with an interest in pharmacovigilance.

DISCUSSION

The current evidence to inform clinical management for moderate-to-severe atopic eczema stems from a small body of randomized controlled trials.[28-33] The psoriasis literature indicates that approximately 30% of patients entered into registries would be ineligible for clinical trials.[34] In addition, procedures differ between trials and routine clinical practice which impairs the generalizability of the findings. There is no long-term, comparative

and observational data on effectiveness and safety of systemic immunomodulating therapies for atopic eczema from a large-scale multicenter international cohort study. Several guidelines and a systematic review highlight these gaps.[35-37]

The overall aim of the described study is to provide data on the long-term safety of dupilumab compared with other systemic immunomodulating therapies for the treatment of atopic eczema in adults and children. The observational nature of the study, using the platform of registries of the TREAT Registry Taskforce, guarantees the collection of data from patients in a routine clinical care setting. The described standardized methodological approach across registries will allow data pooling, in order to obtain the large number of patients required to acquire the power to detect rare events like malignancies.

A limitation of the study is that although the severity of disease requiring dupilumab treatment or another novel systemic agent is likely to be closely comparable to that of those exposed to another systemic immunomodulating drug intervention, the decision to start dupilumab treatment will most frequently be based on access to these novel systemic agents and a lack of suitability of or responsiveness to other immunomodulating therapies rather than on disease severity. This is likely to result in differences between treatment groups, for example in the responsiveness to standard agents, which cannot be quantified other than by fully documenting previous systemic treatments for atopic eczema and then adjust for such confounders in statistical analysis.

Individuals commencing novel systemic treatments have often received multiple systemic therapies in the past. Limiting the study only to new users of such therapies would restrict the dupilumab group to patients with contraindications for many other therapies. This approach would undermine the scope of evidence from the routine clinical care setting and introduce bias.[38] Our data will take into account sequential treatment switching decisions that typically take place in routine clinical practice and that are almost impossible to study in clinical trials.

The need for long-term safety studies for other therapies will increase, as many other novel therapies are currently being assessed in clinical trials. The described study protocol primarily concerns a comparison between dupilumab and other systemic therapies. However, this protocol can be used as a framework for similar studies for other novel systemic immunomodulating therapies across both adult and paediatric populations within the TREAT Registry Taskforce. The described study could be adapted to include and collect on any drug and adverse event of interest. While the presented protocol is focused on dupilumab, we will also collect similar adverse event data on all other systemic therapies the participants are on. This will allow safety comparisons

between all other systemic immunomodulating therapies, provided that the number of treated patients and power is adequate.

This study will run as an investigator-led project but is open to receive financial support from charities, governments as well as pharmaceutical companies, who might want to task the study team with the follow-up of patients on their agents. This approach could provide pharmaceutical companies post-authorization safety data on their systemic therapies as requested by licensing and regulatory bodies.

Next to the countries that have already started, several other countries have shown their interest in joining in the TREAT Registry Taskforce (*treat-registry-taskforce.org*) and establishing a TREAT registry. This offers opportunities for expansion of this and similar studies for other systemic therapies in the future.

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APPENDIX

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Conflicts of interest

AI is a consultant to Abbvie, Sanofi-Genzyme, Regeneron, Novartis and a PI to Abbvie and Regeneron. AM is co-investigator of the UK-Irish Atopic eczema Systemic Therapy Registry – A-STAR and member of the Technology Appraisal Committee of the National Institute for Health and Care Excellence (NICE) for England and Wales. CA has received consultancy fees from Dr. Wolff GmbH and Sanofi Genzyme and institutional funding from Dr. Wolff GmbH. CF is Chief Investigator of the UK-Irish Atopic eczema Systemic Therapy Registry – A-STAR and his department has received funding from Sanofi for investigator-led microbiome research. CV has advised and given lectures for AbbVie, GlaxoSmithKline, LEO Pharma, Novartis and Sanofi-Genzyme, and has been involved in the PO-SCORAD development. DW has acted in a consultancy capacity for Janssen & Novartis. EB has been a speaker for Sanofi, Almirall, Pierre-Fabre dermatology, an investigator for Pfizer, Abbvie and Pierre_Fabre and an advisor for Sanofi-Genzyme and Pierre-Fabre Dermatology. FV was involved as sub-investigator in clinical trials for Abbvie, Novartis, LEO Pharma, Lilly and Regeneron. IGD has received institutional funding from Sanofi. JSc has received institutional funding for investigator-initiated research from ALK, Novartis, Pfizer and Sanofi, and is co-principal investigator of the German atopic eczema registry – TREATgermany. JSe has received and has been speaker for Sanofi and Pierre Fabre dermatology. JT has been a speaker for Sanofi-Genzyme and LEO Pharma, an investigator for Sanofi-Genzyme, Eli Lilly & Co, Abbvie and LEO Pharma, and an advisor for Sanofi-Genzyme and Eli Lilly & Co, and Union Therapeutics. LE has served as a consultant to Allergan, Anacor/Pfizer, Dermavant, Dermira, DS Biopharma, Forte, Galderma Labs, Glenmark, Incyte, LEO Pharma, Lilly, Matrisys, Medimetriks/Otsuka, Menlo Therapeutics, Novan, Novartis, Ortho Dermatologics, Sanofi/Regeneron and TopMD, and has been an investigator for LEO pharma and Sanofi/Regeneron. LK is consultant to Sanofi-Genzyme, and had received funding from Sanofi-Genzyme and

LEO Pharma. LN has been a consultant for Lilly, Novartis and Sanofi. MD has been a speaker for Sanofi-Genzyme, Eli Lilly, Pierre Fabre, and LEO Pharma, an investigator for Sanofi-Genzyme, Eli Lilly, Abbvie and LEO Pharma, and an advisor for Sanofi-Genzyme, Eli Lilly, Pierre Fabre, Meda, Galapagos, La Roche Posay, Pfeizer, and Almirall. MMH is an advisory board member for Sanofi-Genzyme. PMB has worked as a consultant/speaker for AbbVie, Pfizer, Janssen-Cilag, LEO Pharma, Novartis, Sanofi, Teva, L'Oreal, Cantabria Labs and Bayer and has worked as investigator in clinical trials promoted by AbbVie and Novartis. PS has served as a consultant to AbbVie, Anacor, LEO Pharma, Novartis and Sanofi, has received independent research grants from LEO Pharma and Schering-Plough, has been involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of atopic eczema, and is Chief Investigator of the Dutch atopic eczema registry – TREAT NL. SB received research grants from Pierre Fabre Laboratory and Fondation pour la dermatite atopique, personal fees from Bioderma, Laboratoire La Roche Posay, Sanofi-Genzyme, Abbvie and non-financial support from Abbvie, Novartis and Janssen. SW has received institutional research grants from Novartis, Pfizer and L'Oreal, has performed consultancies for Sanofi-Genzyme, Regeneron, LEO Pharma, Incyte and Novartis, has lectured at educational events sponsored by Sanofi-Genzyme, Regeneron, LEO Pharma, Abbvie and Galderma, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for e.g. the treatment of psoriasis and atopic eczema and is co-principal investigator of the German atopic eczema registry - TREATgermany. TT has served as a consultant to AbbVie, LEO Pharma, Lilly, Novartis, Pfizer and Sanofi.

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3

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 (*homeforeczema.org*). The HOME initiative 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 apherisis (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.

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

Table 1. *(continued)*

	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**
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); - 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.	- 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.
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.

Table 2. *(continued)*

Registry name, country	Inclusion criteria	Exclusion criteria
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: o EASI ≥ 16 o 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	- 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.

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

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

Domain	Domain item	Registry name, country							
		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*	✓	✓	✓	✓	✓	✓	✓	✓

Table 4. *(continued)*

Domain	Domain item	Registry name, country							
		A-STAR, UK and Ireland	**TREAT NL, the Netherlands**	**TREATgermany, Germany**	**Biobadatop, Spain**	**SCRATCH, Denmark**	**FIRST, France**	**SwedAD, Sweden**	**AtopyReg, Italy**
Allergic comorbidities	*Asthma*	✓	✓	✓	✓	✓	✓	✓	✓
	Allergic rhinoconjunctivitis	✓	✓	✓	✓	✓	✓	✓	✓
	Atopic eye disease	✓	✓		✓	✓	✓		✓
	Eosinophilic oesophagitis	✓	✓		✓				✓
	Food allergies	✓	✓	✓		✓	✓		✓
	Contact allergies	✓	✓		✓				
Other past and current comorbidities	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	✓	✓				✓		✓

Table 4. *(continued)*

Domain	Domain item	Registry name, country							
		A-STAR, UK and Ireland	**TREAT NL, the Netherlands**	**TREATgermany, Germany**	**Biobadatop, Spain**	**SCRATCH, Denmark**	**FIRST, France**	**SwedAD, Sweden**	**AtopyReg, Italy**
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	✓	✓	✓					

Table 4. *(continued)*

Domain	Domain item	Registry name, country							
		A-STAR, UK and Ireland	**TREAT NL, the Netherlands**	**TREATgermany, Germany**	**Biobadatop, Spain**	**SCRATCH, Denmark**	**FIRST, France**	**SwedAD, Sweden**	**AtopyReg, Italy**
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.

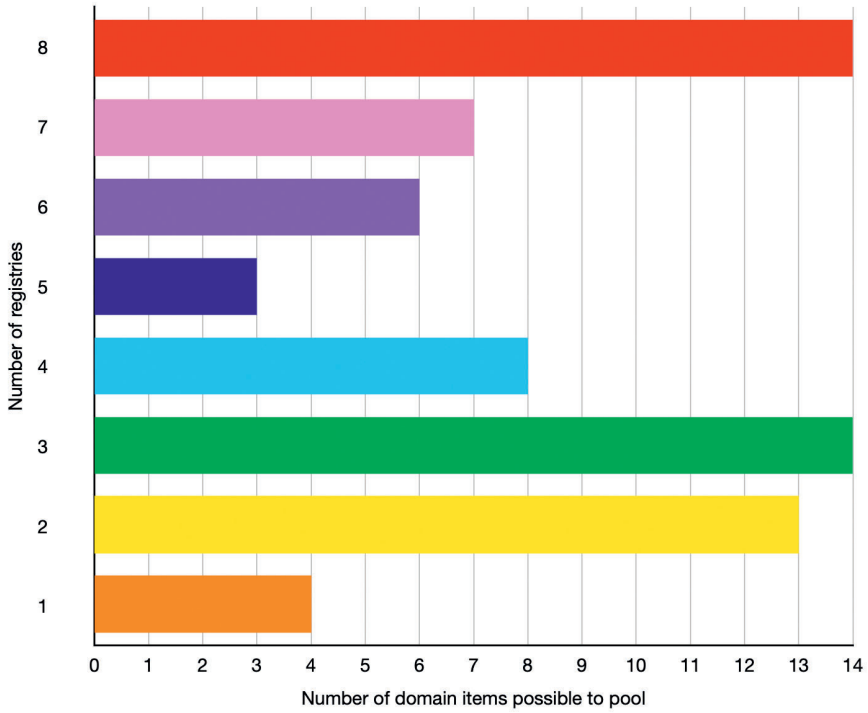

Figure 1. Pooling ability of domain item outcomes according to the number of registries

Red bar – the following 14 domain items are deemed possible to pool across 8 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)';

Pink bar – the following 7 domain items are deemed possible to pool across 7 registries: 'educational status', 'systemic therapy (past)', 'phototherapy (current)', 'topical treatments for AE (current)', 'malignancies', 'other significant illnesses', 'reason for discontinuation of therapy';

Purple bar – the following 6 domain items are deemed possible to pool across 6 registries: 'use of validated diagnostic criteria', 'phototherapy (past)', 'topical treatments for AE (past)', 'atopic eye disease', 'food allergies', 'severe adverse events';

Dark blue bar – the following 3 domain items are deemed possible to pool across 5 registries: 'serious infections', 'investigator/physician global assessment (baseline and follow-up)';

Light blue bar – the following 8 domain items are deemed possible to pool across 4 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)';

Green bar – the following 14 domain items are deemed possible to pool across 3 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';

Yellow bar – the following 13 domain items are deemed possible to pool across 2 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)';

Orange bar – the following 4 domain items are registered in 1 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 gather 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 MATERIALS

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 this supplementary material can be found at:

https://doi.org/10.17632/5yp8wp42ky.1

APPENDIX

Funding sources
None.

Conflicts of interest
P.I. Spuls has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), received a departmental independent research grants from pharmaceutical industries since December 2019 for the TREAT NL registry, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and, is Chief Investigator (CI) of the systemic and phototherapy atopic eczema registry (TREAT NL) for adults and children and one of the main investigators of the SECURE-AD registry. C. Flohr is Chief Investigator of the UK National Institute for Health Research–funded TREAT (ISRCTN15837754) and SOFTER (Clini calTrials.gov: NCT03270566) trials and the UK-Irish Atopic Eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and is a principal investigator in the European Union Horizon 2020–funded BIOMAP Consortium (*biomap-imi.eu*). He is also Chief Investigator of the EU Joint Program Initiative TRANS-FOODS consortium. His department has also received investigator-led funding from Sanofi-Genzyme for skin microbiome work. L.A.A. Gerbens is one of the main investigators of the TREAT NL registry. She has no further conflicts of interest. A. Chiricozzi is advisory board member, consultant, speaker, investigator in clinical trials for AbbVie, Almirall, Biogen, Fresenius Kabi, Leo Pharma, Lilly, Janssen, Novartis, Sanofi Genzyme and UCB Pharma. M.A. Middelkamp-Hup is consultant for Sanofi and Pfizer and one of the main investigators of the TREAT NL registry. E.K. Johansson received speaker honoraria and/or been a consultant for AbbVie, ACO, Galenica, LEO Pharma, Novartis, and Sanofi-Genzyme. E. Haufe is coordinator of TREATgermany; no further conflicts of interest. J. Schmitt is PI of TREATgermany; institutional funding of IITs from Sanofi, Novartis, Pfizer, ALK; consultancies for Sanofi, Lilly, Novartis, ALK. I. García-Doval received financial compensation for talks unrelated to atopic dermatitis from UCB and Novartis, and a travel grant from Janssen. N.J. Reynolds has received, through Newcastle University, research grant funding, funding for lectures and/or travel support from Celgene, Genentech and Sanofi-Genzyme. M.R. Ardern-Jones has acted as a collaborative researcher/consultant/speaker for AbbVie, Pfizer, Sanofi Genzyme, Ducentis, Hosei Septares, Leo Pharma, Novartis. I. Vittrup has received salary from research funding from Sanofi and Regeneron Pharmaceuticals, Inc. S. Barbarot is investigator or speaker for Almirall, Sanofi-Genzyme, Abbvie, Novartis, Janssen, Leo-Pharma, Pfizer, Eli Lilly, UCB Pharma. D. Staumont-Sallé is investigator or speaker or member of advisory board for Abbvie, AstraZeneca, Eli Lilly, Galderma,

Janssen, Leo-Pharma, Novartis, Pfizer, Sanofi-Genzyme, UCB Pharma. J. Seneschal is investigator or speaker or member of advisory board for Abbvie, Eli Lilly, Galderma, Janssen, Leo-Pharma, Novartis, Pfizer, Sanofi-Genzyme. J. Thyssen is advisor, speaker or investigator for Abbvie, Arena, Pfizer, LEO Pharma, Regeneron, Sanofi-Genzyme, Almirall, and Eli Lilly. He has received research grants from Regeneron and Sanofi-Genzyme. C. Vestergaard is Speaker/honorarium for Sanofi, Leo Pharma, Abbvie, Pfizer, Pierre Fabre, AstraZeneca. No other disclosures were reported.

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Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Materials.

THE SELECTION PROCESS FOR A WEB-BASED APPLICATION TO MEASURE PATIENT-REPORTED OUTCOMES FOLLOWING THE EXAMPLE OF THE TREAT NL REGISTRY

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LETTER

Research was conducted on behalf of the TREAT NL (TREatment of Atopic eczema, the Netherlands) registry to select a web-based application for collection of patient-reported outcome measures (PROMs). The registry aims to collect long-term, real-life data from patients with atopic eczema on phototherapy and systemic immunomodulating therapy. The collected PROMs comply with the TREAT core dataset to ensure cross-country data uniformity.[1]

We outline requirements and steps in selecting the most suitable application. With this, we aim to guide researchers in selecting an application for research-oriented collection of PROMs.

The selection process starts with determining must-have initial requirements by the investigators, who will be managers of the selected application. Examples of initial requirements for the TREAT NL registry: the application has to provide or support composition of the designated PROMs, the application has to work on mobile devices, and the costs of the application have to be feasible.

The next step is to identify candidate applications based on their availability. Applications that do not meet the initial requirements are then excluded.

Next, detailed requirements need to be determined. We grouped detailed requirements into these categories based on Volere:[2] investigator, legal, security, patient, feedback, and interoperability requirements. A literature search was conducted in PubMed, Google Scholar and additional relevant sources to find information on conditions regarding legislation, security, patient preferences, feedback (i.e. of results to patients and clinicians), and interoperability (i.e. between systems).

Investigator requirements give insight into preferences of the researchers that will manage the application.

Legal requirements must be met to comply with the General Data Protection Regulation (GDPR), which applies to all organizations that process personal data in the European Union. Performing a privacy impact assessment prior to the data processing can be mandatory and may be required by the research institution.[3] National legislation may also apply.

The International Organization for Standardization (ISO) provides guidelines for security requirements.[4-6] NEN-7510, NEN-7512 and NEN-7513.[7-9] These standards must be met for security. The application should log activity for an audit trail and should have secure connections, with the data being only accessible to patients and researchers.

An overview of potential patient requirements has been presented elsewhere.[10] Surveys should preferably be short and simple. Multiple questions can be presented per survey page, but too much page scrolling should be avoided. In addition, ability to add free text in the survey is appreciated by patients. To facilitate data entry, mobile applications should be considered, as these can be used at any time and on any device. The user experience of software needs to be assessed and optimized.

Feedback requirements relate to the presentation of results after the survey has been completed. Both patients and clinicians consider line graphs as the most useful and easiest to understand.[11] Displaying multiple time points is generally preferred by patients. Scaling should be uniform for all questionnaires. A scale from 0 to 100 is recommended.[11] Depending on the nature of the project, a link between the application and the Electronic Health Record (EHR) of participants can be considered. This may entail requirements to allow interoperability.

The next step is to rank the importance of all the requirements in a template (Supplementary Table 1). This template is based on the work of Lawlis et al., Maiden and Ncube, and Bandor.[12-14] The requirements should be given a weight of importance from 1 to 10. The candidate applications can be scored in the template thereafter. A score of 1 or 0 is given if the application respectively does or does not meet the requirement. A score of 0.5 is given when the requirement is met partly or will be at a later point. Afterwards, a weighted score is calculated for each requirement. The application with the highest total sum score is in theory the best suitable application.

The requirements described above are software requirements. There are also external factors to consider when choosing an application, for example: whether the application can be implemented within the institution, the amount of support or experience from the supplier, as well as the experience or preference within the institution. If the highest scoring application is found to be unsuitable due to one or more of these factors, the next application should be considered as the best alternative.

The completed template guiding the selection process for the TREAT NL registry can be found in Table 1. Eight candidate applications were investigated for the TREAT NL registry. The selection process resulted in the choice for Castor EDC, which scored among the best (percentage score of 90%). We learned that external factors, imposed by institutions, can be crucial in the decision process. An important decisive external factor for us was that at our institution a connection was planned to be established between our EHR system and this application.

Table 1. Requirements established for the TREAT NL registry and the (weighted) score for each considered application.

		Software applications under consideration															
		MonIQ		Clinical Insight		eHEALTH		RoQua		Consult Assistent		Quest Manager		MyChart		Castor EDC	
Requirement[3]	Weight	Score	Weighted	Score	Weighted	Score	Weighted	Score	Weighted	Score	Weighted	Score	Weighted	Score	Weighted	Score	Weighted
INVESTIGATOR REQUIREMENTS																	
Application offers the possibility to fill out questionnaires at all times.	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10
The questionnaires can be linked to a corresponding consultation.	8	1	8	1	8	1	8	0,5	4	1	8	1	8	1	8	0,5	4
Questionnaires can be modified within the application.	9	1	9	1	9	1	9	1	9	1	9	1	9	1	9	1	9
Questionnaires can be completed on mobile devices.	10	1	10	1	10	1	10	1	10	1	10	1	10	0,5	5	1	10
Questionnaires can be sent to the patient automatically before the consultation or the patient can be automatically informed that new questionnaires are available.	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10
The patient can receive a reminder to fill out the questionnaires.	9	1	9		0	1	9	1	9	1	9	1	9	1	9	0	0
Application allows multiple types of inputs to answer questions (e.g. radio buttons, checkboxes, free text).	10	1	10		0	1	10	1	10	1	10	1	10	0,5	5	1	10
The application allows questionnaires to be sent to family members of the patient and results registered in the application.	7	0,5	3,5	0,5	3,5	1	7	1	7	0,5	3,5	1	7	0	0	1	7
Data from the patient must be able to be removed by the healthcare provider.	8	1	8	1	8	1	8	1	8	1	8	1	8	1	8	1	8
PROs can automatically be registered in MyChart (patient portal for EPIC).	8	0	0	0	0	0	0	1	8	0,5	4	0,5	4	1	8	0,5	4
Answers / scores can be adjusted / removed by the healthcare provider.	10	0	0	1	10	1	10	0,5	5	1	10	1	10	1	10	1	10
Images can be shown in a questionnaire.	8	0,5	4		0	1	8	1	8	1	8	1	8	1	8	0,5	4
User interface for patients can show a logo of the hospital and the logo of the project.	8	0,5	4		0	1	8	1	8	1	8	1	8	0	0	1	8
Application is available in Dutch.	10	1	10	0	0	1	10	1	10	1	10	1	10	1	10	1	10
Application is available in English.	10	0,5	5	1	10	1	10	0,5	5	0,5	5	1	10	0,5	5	1	10
Application can be used without or minimal training.	9	1	9	1	9	1	9	1	9	1	9	1	9	1	9	1	9
If the system is unavailable this is no longer than 5 minutes on a working day.	7	1	7	1	7	1	7	1	7	1	7	1	7	1	7	1	7

Table 1. *(continued)*

		Software applications under consideration															
		MonIQ		Clinical Insight		eHEALTH		RoQua		Consult Assistent		Quest Manager		MyChart		Castor EDC	
Requirement[3]	**Weight**	**Score**	**Weighted**	**Score**	**Weighted**	**Score**	**Weighted**	**Score**	**Weighted**	**Score**	**Weighted**	**Score**	**Weighted**	**Score**	**Weighted**	**Score**	**Weighted**
FEEDBACK REQUIREMENTS																	
PROs[1] can be discussed during a consultation[4].	8		0		4,8		7,2		7,2		4		8		2,4		4
1. Application shows outcomes of questionnaires in graphs (with multiple time points) and / or bar charts.	60%	0	60%	1	60%	1	60%	1	60%	0,5	60%	1	60%	0,5	60%	0,5	60%
2. Additional information such as confidence intervals and p-values are shown to healthcare providers.	20%	0	20%	0	20%	0,5	20%	0,5	20%	0,5	20%	1	20%	0	20%	0,5	20%
3. Users can indicate whether they see the data in line charts or bar charts with or without extra information.	20%	0	20%	0	20%	1	20%	1	20%	0,5	20%	1	20%	0	20%	0,5	20%
SECURITY/LEGAL REQUIREMENTS																	
Application is only accessible to healthcare providers and patients.	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10
Patients only have access to their own questionnaires and data.	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10
System meets the security standard (NEN 7510).	10	1	10	1	10	1	10	1	10	0,5	5	1	10	1	10	1	10
System must have secure connections (NEN 7512).	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10	1	10
System logs activity for audit trail (NEN 7513).	9	1	9	1	9	1	9	1	9	1	9	1	9	1	9	1	9
INTEROPERABILITY REQUIREMENTS																	
Application can be linked to the web-based project database	10	0,5	5	1	10	1	10	0,5	5	1	10	1	10	0,5	5	1	10
Application is able to link to EHRs.[2]	10	0	0	1	10	1	10	1	10	0,5	5	1	10	0,5	5	1	10
Application offers possibilities to collaborate on an (inter) national registration. Exchange of data or access to data is possible.	9	0	0	1	9	1	9	0,5	4,5	1	9	1	9	0,5	4,5	1	9
Data can be stored in a standardized manner[5].	10	0	0	1	10	1	10	0	0	0,5	5	1	10	0	0	1	10
Total	**247**		**170,5**		**187,3**		**238,2**		**212,7**		**215,5**		**243**		**186,9**		**222**
Percentage score	**100%**		**69%**		**76%**		**95%**		**86%**		**87%**		**98%**		**76%**		**90%**

[1], PROs: Patient Reported Outcomes; [2], EHR: Electronic Health Record; [3], A limitation of the selection process for the TREAT NL registry was that patient requirements were not included in our template. However, patient requirements are of importance as patients are users of the application, hence we included patient requirements in the selection process recommendations; [4], Specific requirements are the three sub feedback requirements; [5], Application allows data to be saved as SNOMED CT or LOINC code

Testing and monitoring is advised before and directly after the implementation to assess whether the software works as intended and to ensure that users have an optimized user experience.

The proposed process to select an application uses the accompanying template. This provides a systematized overview of requirements that have to be considered and can provide a solid starting point for this process. We aimed for a process that is maximally manageable for researchers who do not have expertise in software engineering. Applying the process contributes to optimize users' expectancies and experiences on performance and effort, which influence the behavioral intention and use of the application.[15]

Learning from the process of selecting an application for the TREAT NL registry, the generalized and systematized selection process is presented to facilitate researchers worldwide in their decision making to find a suitable application to capture PROMs.

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SUPPLEMENTARY MATERIALS

Supplementary table 1. Template for scoring the requirements to select a candidate application.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/cpm93pdrmm.1

APPENDIX

Funding sources
None.

Conflicts of interest
AB: none; RC: none; RG: none; PS has served as a consultant to AbbVie, Anacor, LEO Pharma, Novartis and Sanofi, has been involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of atopic eczema and psoriasis, and is Chief Investigator of the Dutch atopic eczema registry – TREAT NL.

Data availability statement
No datasets were generated or analyzed during the current study.

PART II

REAL-WORLD EXPERIENCE WITH DUPILUMAB IN ATOPIC ECZEMA

5

EFFECTIVENESS OF DUPILUMAB TREATMENT IN 95 PATIENTS WITH ATOPIC DERMATITIS: DAILY PRACTICE DATA

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ABSTRACT

Background

Dupilumab is the first biologic registered for the treatment of moderate-to-severe atopic dermatitis (AD) and efficacy was shown in phase III clinical trials (primary outcome at week 16 was reached in 38% of patients). Currently, there is limited daily practice data on dupilumab available, especially when combined with systemic immunosuppressants.

Objectives

To evaluate dupilumab treatment in daily practice in AD patients.

Methods

In this observational cohort study we prospectively included all adult AD patients treated with dupilumab in two University Hospitals in The Netherlands. Concomitant systemic immunosuppressive treatment was monitored. Physician-reported and patient-reported outcome measures (PROMs) of patients with ≥12 weeks of follow-up were analysed. We used a linear mixed-effects model to determine changes in scores during follow-up.

Results

Ninety-five patients were included of which 62 patients used systemic immunosuppressants at baseline, which were continued during dupilumab treatment in 43 patients. From baseline to 16 weeks of treatment, the estimated mean Eczema Area and Severity Index score (0-72) decreased from 18.6 (95%CI 16.0-21.4) to 7.3 (95%CI 5.4-10.0), and the estimated mean PROMs showed a decrease of 41-66%. Investigator Global Assessment 0 or 1 (clear/almost clear) was reached in 38% of the patients. Five patients discontinued dupilumab treatment due to side effects or ineffectiveness. Eye symptoms and orofacial (non-ocular) Herpes Simplex Virus (HSV) reactivation were reported in 62% and 8% of the patients, respectively.

Conclusions

Dupilumab treatment in daily practice shows a clinically relevant improvement of physician-reported scores and PROMs, which is in line with efficacy data from clinical trials. Besides frequently reported eye symptoms and orofacial (non-ocular) HSV reactivation, there were no apparent safety concerns.

INTRODUCTION

Atopic dermatitis (AD) is a complex and heterogeneous chronic inflammatory skin disease. AD is characterized by severe itch and recurrent eczematous lesions. Up to twenty percent of the worldwide pediatric population and approximately 2-10% of all adults suffer from AD.[1,2] AD can have a profound negative effect on quality of life as it is the skin disease with the highest non-fatal health burden.[1]

Besides avoiding triggers and the use of moisturisers, AD is mostly treated with topical corticosteroids (TCS) and calcineurin inhibitors (TCI). Around 15% of the AD population is considered to suffer from moderate-to-severe disease, requiring photo- or systemic immunosuppressive therapy.[3,4] The use of systemic glucocorticosteroids, phototherapy, and conventional systemic immunosuppressive agents, including cyclosporine A (CsA), azathioprine (AZA), mycophenolic acid (MPA), mycophenolate mofetil (MMF) and methotrexate (MTX) can be effective and is well-tolerated in many patients but may have limitations such as side effects and an unfavorable risk/benefit ratio.[5-7] In addition, most of these treatments are used off-label and there is limited long-term treatment data available.[5,8-10]

Dupilumab, the first biologic for the treatment of moderate-to-severe AD, is a fully human IgG4 monoclonal antibody that targets the IL-4 receptor alpha chain, inhibiting the effects of cytokines IL-4 and IL-13.[11] These cytokines are thought to play a central role in the pathogenesis of AD. Dupilumab has been approved recently, after it was shown a successful treatment for AD in several phase III clinical trials.[11-13] These trials showed improvement of disease severity, itch, sleep disturbance, anxiety, depression and quality of life with dupilumab as monotherapy or in combination with TCS.[3] The most frequently observed side effects were conjunctivitis, herpes infections, and injection-site reactions.[3,11]

However, there may be considerable differences in patient characteristics and treatment responses between clinical trials and daily practice (i.e. efficacy versus effectiveness). This is partly explained by strict in- and exclusion criteria, treatment adherence, and prohibited medication and procedures in clinical trials, which may limit the ability to answer questions related to daily practice.[14] Observational studies in a real-world setting are therefore essential to document benefits and harms of a therapy in a wider patient population. Here, we would like to present and evaluate data of dupilumab treatment, in a subset of patients combined with systemic immunosuppressants, in patients with AD in daily practice.

PATIENTS AND METHODS

Study design and patients

This prospective multicenter observational longitudinal cohort study consecutively included all patients with AD having a history of systemic immunosuppressive treatment, who started dupilumab treatment in the context of standard care from October 2017 to September 2018 at the Erasmus MC University Medical Center (Rotterdam, The Netherlands) and the Amsterdam University Medical Centers (Amsterdam, The Netherlands). There was only 1 patient who refrained from participation.

All patients were aged ≥18 years and fulfilled the criteria for dupilumab treatment set forth by the Dutch Society of Dermatology and Venereology (NVDV) (Appendix 1).[15] Patients visited the outpatient clinic at baseline, week 4, and between 12 and 16 weeks of treatment. In one of the centers data was collected according to the harmonized dataset of the TREAT Registry Taskforce.[16-18]

Treatment

A 600 mg loading dose of dupilumab was injected subcutaneously at baseline, followed by an injection of 300 mg dupilumab every other week.[19] Patients either discontinued systemic immunosuppressive treatment before starting dupilumab treatment, or a shared decision on continuation of the systemic immunosuppressant during dupilumab treatment was made. The (dis)continuation or initiation of systemic immunosuppressants during dupilumab treatment was recorded and monitored. During dupilumab treatment, patients were encouraged to continue the use of moisturizers, TCS, and TCI which was not monitored in specific.

Outcome measures

Patient characteristics and previous and current AD treatment were assessed at baseline. Clinical examinations were conducted by a maximum of 7 trained and proficient raters at each visit. Physician-reported severity was reported using Eczema Area and Severity Index (EASI: 0-72)[20] and Investigator Global Assessment for AD (IGA: 0-4).[21] In addition, Patient Reported Outcome Measures (PROMs) were assessed at every visit, including Numeric Rating Scale (NRS: 0-10) peak pruritus during the past 7 days or past 24 hours (further referred to as 'NRS pruritus 7d' and 'NRS pruritus 24h'),[22] Dermatology Life Quality Index (DLQI: 0-30)[23] and Patient-Oriented Eczema Measure (POEM: 0-28).[24] These outcome measures are in line with the Core Outcome set defined by the global Harmonising Outcome Measures for Eczema (HOME) initiative.[25,26] Furthermore, we calculated the number of days until the minimal clinically important difference (MCID) was reached and the proportion of patients who reached the MCID at follow-up (after

12-16 weeks).[27,28] Patients with a baseline score lower than the MCID, were excluded from this analysis. Collection of blood samples (liver, renal and hematologic tests) and additional safety assessments (i.e. blood pressure measurement and urinalysis) in case of concomitant use of systemic immunosuppressants were conducted to monitor safety. Furthermore, potential drug-related adverse events were recorded.

Evaluation of effectiveness

Treatment effect was evaluated using the estimated mean change of EASI over time in the first 16 weeks of dupilumab treatment and IGA score recorded at baseline and follow-up (period 12 to 16 weeks). Furthermore, the estimated mean change of PROMs (NRS peak pruritus, POEM and DLQI) over time in the first 16 weeks of treatment was analysed. These estimated mean scores were based on our linear mixed-effects (LME) model.

Data analysis

Studying data on patients treated in a real-world setting comes with several challenges, due to variation resulting from less stringent inclusion- and exclusion criteria and follow-up schedules compared to clinical trials. To evaluate the effectiveness of dupilumab we used LME models to describe and present the change of the repeatedly measured, continuous score of interest in time (days since start of treatment). The use of these models allows for analysis of unbalanced repeated measurements, i.e. measurements that are not taken at exactly the same points in time for all patients. The use of this model is more efficient than cross-sectional analyses which only consider a subset of measurements taken at a particular point in time. The use of random effects allows to appropriately take into account that measurements originating from the same patients are not independent. We analyzed measurements performed at visits from start up to and including 17 weeks (16 weeks, visit window of +7 days) of treatment. The use of square root transformations in order to normalize the residuals and improve the model fit was confirmed by evaluation of histograms and Akaike Information Criterion (AIC) (Appendix 2). Predicted values of the (continuous) score of interest which are shown in the figures, are based on the LME models and transformed back to the original scale. Confidence intervals for the predicted values were determined using bootstrap. We used natural cubic splines to model the non-linear association between outcomes and follow-up time. This non-linear association was confirmed and the appropriate number of degrees of freedom were chosen based on AIC.[29,30] Visual evaluation of the trajectories estimated by the spline showed that they could not be approximated by a piece-wise linear fit, which would have the advantage of directly interpretable parameter estimates. Sex, age and concomitant immunosuppressive treatment were included as covariates in our model. We allowed the estimated trajectories over time to differ between treatment groups by including interaction terms. However, since

likelihood ratio test showed that there was no evidence for these interactions, we did not include them in the final model in the interest of interpretability of the parameter.

Analyses were performed using SPSS 24.0 (IBM, Armonk, NY, U.S.A.) and R version 3.4.1 (Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

Our study was exempted from evaluation by the local Medical Research Ethics Committees (MEC-2017-1123; W18_097#18.123). The study conduct was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations.[31]

RESULTS

Population

Table 1 presents the baseline characteristics of the 95 patients (Erasmus MC: n=60, Amsterdam UMC: n=35) included in our analyses. Sixty-two percent (59/95) of the patients were male, with a median age of 42 (IQR 27-52) years. Onset of AD was before the age of 2 years in 72% (68/95) of the patients. Asthma (65%), allergic contact dermatitis (45%), and allergic (rhino)conjunctivitis and/or atopic (kerato)conjunctivitis (72%) were reported. All patients were treated with systemic immunosuppressants prior to dupilumab treatment, of which 72% had used at least 2 different conventional systemic immunosuppressants, mostly CsA (88%) and MTX (58%) (Table 1).

The median IGA score at baseline was 3.0 (IQR 2.0-3.0). Based on the LME model, patients had an estimated mean EASI score of 18.6 (95%CI 16.0-21.4), POEM score of 21.4 (95%CI 19.7-23.3), NRS pruritus 7d of 7.4 (95%CI 6.1-8.6), NRS pruritus 24h of 7.5 (95%CI 6.1-8.9), and DLQI score of 12.5 (95%CI 10.4-14.6) at baseline.

Effectiveness of dupilumab treatment

Figures 1a-d show the changes in the outcome measures over time, until 12 weeks (NRS pruritus 24h) and 16 weeks (EASI, POEM, NRS pruritus 7d) of treatment. The IGA score measured at baseline and follow-up and change in estimated mean DLQI score are shown in Figure S1 and Figure S2 (see Supporting Information). Furthermore, the estimated mean EASI score and PROMs at start and 16 weeks of treatment, which were based on our LME model, are shown in Table 2. The percentage change from baseline to 16 weeks of treatment was: EASI: -61% (95%CI -71-46%), POEM: - 53% (95%CI -63-44%), NRS pruritus 7d: -41% (95%CI -53-30%), and NRS pruritus 24h: -57% (95%CI -99-23%). IGA 0 or 1 (clear or almost clear) was reached in 38% of the patients. Table 3 shows that the MCID for all outcome measures is estimated to be reached within 5 weeks of

treatment. At 12-16 weeks of follow-up, the MCID of EASI, POEM, DLQI, NRS pruritus 7d and 24h was reached in 66%, 86%, 65%, 65% and 70% of the patients, respectively.[27,28]

Table 1. Demographic and Clinical Characteristics of the Patients at baseline (n=95[a])

Characteristic	Daily practice cohort
Age at start of dupilumab, median (IQR) - years	42 (27-52)
Male sex – no. (%)	59 (62)
Race – no. (%)	
White	73 (77)
Black	9 (10)
Asian	11 (12)
Other[b]	2 (2)
Age of onset AD	
Median age of onset (IQR) - year	0 (0.0 – 2.0)[1]
0 - <2 years – no. (%)	68 (72)
2 - <6 years	11 (12)
6 - <18 years	8 (8)
≥18 years	7 (8)
Disease duration until start of dupilumab, mean (SD) – years	35.5 (16.5)[1]
Previous use of conventional systemic immunosuppressants – no. (%)[c,d]	
Cyclosporine A	84 (88)
Methotrexate	55 (58)
Azathioprine	29 (31)
Mycophenolic acid/mycophenolate mofetil	36 (38)
Number of previous used conventional systemic immunosuppressants – no. (%)[c]	
1	27 (28)
2	36 (38)
3	23 (24)
4	9 (10)
Atopic/allergic conditions – no. (%)[e]	
Asthma	62 (65)
Allergic (rhino)conjunctivitis / atopic (kerato)conjuncitvitis[f]	68 (72)
Allergic contact dermatitis[g]	43 (45)
BMI, median (IQR)	25.0 (22.3 – 28.3)[2]

IQR, interquartile range; No, number; AD, atopic dermatitis; SD, standard deviation; BMI, body mass index. Missing data: [1]n=1 (1%), [2]n=3 (3%). [a] Diagnosis AD based on U.K. workings party's diagnostic criteria for atopic dermatitis: n=35. [b] Chinese-Creole (n=1), Dutch-Indonesian (n=1). [c] previous use of systemic glucocorticoids is not reported because of anamnestic inconsistency in short- and long term use. [d] besides conventional systemic immunosuppressants, the following systemic therapies were used: dupilumab, study (n=2); apremilast (n=2); ustekinumab (n=1); omalizumab (n=1); alitretinoin (n=2); lebrikizumab, study (n=2); fevipiprant, study (n=1); upadacitinib, study (n=1); [e] patient-reported (n=60), physician-diagnosed (n=30); [f] merged as one category because of the differences in definition and registration in two University Hospitals; [g] positive patch tests in history; other 55% is tested negative, never tested or unknown.

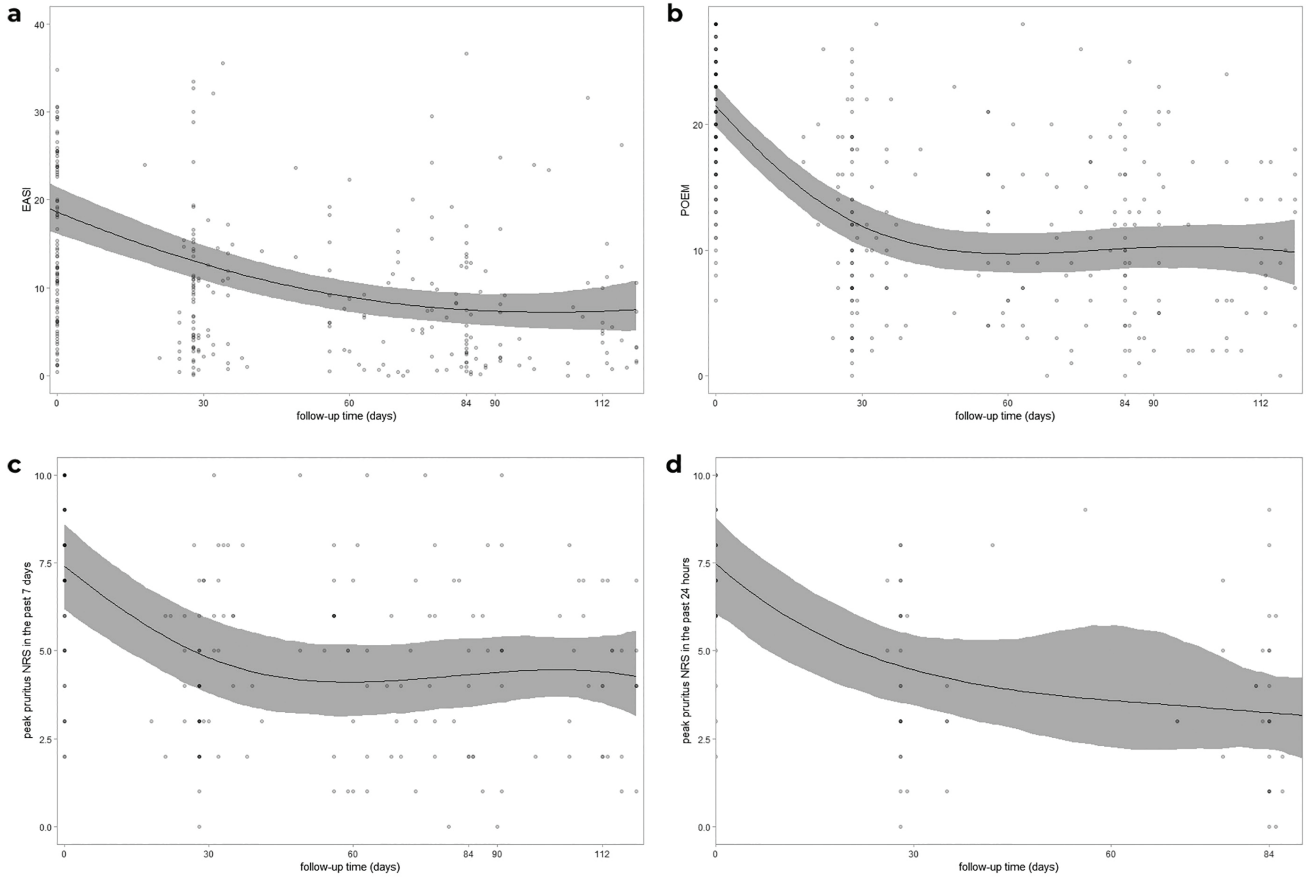

Figure 1a-d. Estimated mean change in (a) Eczema Area and Severity Index (EASI), (b) Patient Oriented Eczema Measure (POEM) and (c-d) Numeric Rating Scale (NRS) peak pruritus scores in patients with atopic dermatitis from start until 16 weeks of dupilumab treatment (n=95)

Figure 1a-d. *(continued)*

A linear mixed-effects model was used to model the changes over time. Higher scores indicate worsened state. The grey area represents the 95% confidence interval. We included measurements from baseline until 16 (visit window: +7 days) weeks of dupilumab treatment in our model. (a) Estimated mean EASI score (0-72) decreased from 18.6 (95%CI 16.0-21.4) at baseline to 7.3 (95%CI 5.4-10.0) at 16 weeks of dupilumab. An outlier presenting with an EASI score of 72 at baseline is not shown in this figure, but included in the model. (b) Estimated mean POEM score (0-28) decreased from 21.4 (95%CI 19.7-23.3) at baseline to 10.1 (95%CI 7.9-12.2) at 16 weeks of dupilumab treatment. (c) Estimated mean NRS pruritus 7d score (0-10) decreased from 7.4 (95%CI 6.2-8.6) at baseline to 4.4 (95%CI 3.6-5.5) at 16 weeks of treatment. NRS itch was registered differently in the two University Hospitals. Analysis of NRS peak pruritus past 7 days scores was based on 60 patients during 16 weeks of follow-up. (d) Estimated mean NRS pruritus 24h score (0-10) decreased from 7.5 (95%CI 6.1-8.9) at baseline to 3.2 (95%CI 2.2-4.3) at 12 weeks of treatment. Analysis of NRS peak pruritus past 24 hours scores was based on observations of 35 patients during 12 weeks of follow-up (outcome measure was recorded in Amsterdam UMC at week 12 only).

Table 2. Effectiveness of dupilumab in daily practice

Outcome measure	n=95
EASI (0-72)	
Score at baseline – estimated mean (95%CI)	18.6 (16.0-21.4)
Score at 16 weeks – estimated mean (95%CI)	7.3 (5.4-10.0)
Change score from baseline to 16 weeks - % (95%CI)	-61% (-71%, -46%)
POEM (0-28)	
Score at baseline – estimated mean (95%CI)	21.4 (19.7-23.3)
Score at 16 weeks – estimated mean (95%CI)	10.1 (7.9-12.2)
Change score from baseline to 16 weeks - % (95%CI)	- 53% (-63%, -44%)
NRS peak pruritus past 7 days (0-10)	
Score at baseline – estimated mean (95%CI)	7.4 (6.2-8.6)
Score at 16 weeks – estimated mean (95%CI)	4.4 (3.6-5.5)
Change score from baseline to 16 weeks - % (95%CI)	-41% (-53%, -30%)
NRS peak pruritus past 24 hours (0-10)	
Score at baseline – estimated mean (95%CI)	7.5 (6.1-8.9)
Score at 12 weeks – estimated mean (95%CI)	3.2 (2.2-4.3)
Change score from baseline to 12 weeks - % (95%CI)	-57% (-99%, -23%)
DLQI (0-30)	
Score at baseline – estimated mean (95%CI)	12.5 (10.5-14.5)
Score at 16 weeks – estimated mean (95%CI)	4.3 (2.8-5.9)
Change score from baseline to 16 weeks - % (95%CI)	-66% (-75%, -47%)

CI, confidence interval; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index. The estimated mean scores in our cohort are based on the used linear mixed-effects model, confidence intervals for the predicted values were determined using bootstrap. Percentage change in our cohort was based on estimated mean baseline score and estimated mean score at 16 weeks of treatment. NRS itch was registered differently in the two University Hospitals (peak score in the past 7 days versus past 24 hours). Analysis of NRS peak pruritus past 7 days scores was based on observations during 16 weeks of 60 patients. Analysis of NRS peak pruritus past 24 hours scores was based on observations of 35 patients during 12 weeks of follow-up.

Table 3. Minimal Clinically Important Difference (MCID)

	EASI	POEM	DLQI	NRS pruritus 7d	NRS pruritus 24h
MCID	6.6	3.4	4	2.7	2.7
Days until MCID is reached[a]	29	9	11	29	21
Percentage of patients reaching MCID after 12-16 weeks of treatment	66%	86%	65%	65%	70%
Number of patients with a baseline score < MCID[b]	20	0	7	2	1

MCID, Minimal Clinically Important Difference, EASI, Eczema Area and Severity Index; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; NRS, Numeric Rating Scale; [a] Estimation based on the Linear Mixed Effects model. [b] We excluded patients with a baseline score lower than the MCID from our MCID analyses.

In our cohort, 62 patients (65%) used systemic immunosuppressants, including systemic glucocorticosteroids, at the start of dupilumab treatment. Systemic immunosuppressive treatment was continued during dupilumab treatment in 43 patients (43/95=45%) (Table 4). Table 4 shows that concomitant immunosuppressants were successfully tapered off and stopped in 34 (34/43=79%) patients in the first 16 weeks of treatment. In 5 patients with flares or insufficient response to dupilumab treatment, systemic glucocorticosteroids were started for periods of 2-8 weeks. Three patients were treated with systemic antibiotics.

Side effects

In our cohort, 59 patients (59/95=62%) reported eye symptoms, including redness, itching, stinging, burning, tearing, scaling, crusting and foreign body sensation. Sixteen patients consulted an ophthalmologist, of which 13 patients were diagnosed with (allergic)(kerato)conjunctivitis (n=9), blepharitis (n=2), or sicca (n=2). Most patients were treated with artificial tears, antihistamine eyedrops, fluorometholone 0.1% eye drops or tacrolimus 0.03% eye ointment. The prevalence of pre-existing ocular comorbidities in our cohort is unknown. In addition, 12 episodes of orofacial Herpes Simplex Virus (HSV)reactivation were reported in 8 (8/95= 8%) patients, with recurrent infections during follow-up in 3 patients (Table S1). None of these patients had HSV infections around the eyes. In addition, none of these patients experienced eye pain, chemosis, or blurred vision, which makes HSV eye infections highly unlikely.[32] There were no clinically significant changes in laboratory parameters or additional safety assessments (i.e. blood pressure measurement and urinalysis) in case of concomitant use of systemic immunosuppressants.

Table 4. Concomitant systemic immunosuppressive treatment (n=95)

Discontinued systemic immunosuppressive treatment prior to or at start of treatment – no. (%) [a]	**52 (55)**
Discontinued systemic immunosuppressive treatment in first 16 weeks of treatment – no. (%)	**29 (31)**
CsA – no. (%); median weeks continued	8 (8); 6
AZA – no. (%); median weeks continued	3 (3); 7
MTX – no. (%); median weeks continued	1 (1); 4
MPA/MMF – no. (%); median weeks continued	2 (2); 10
Prednisone[b] – no. (%); median weeks continued	15 (16); 4
Systemic immunosuppressive treatment > 16 weeks of treatment – no. (%)	**9 (9)**
CsA – no. (%)	3 (3)
AZA – no. (%)	0 (0)
MTX – no. (%)	1 (1)
MPA/MMF – no. (%)	2 (2)
Prednisone – no. (%)	3 (3)
Combination of categories above (multiple systemic immunosuppressants) – no. (%) [b]	**5 (5)**

CsA, cyclosporine A; AZA, azathioprine; MTX, methotrexate; MPA, mycophenolic acid; MMF, mycophenolate mofetil. [a] In this group 19 patients (22%) discontinued their systemic immunosuppressive treatment at start or one day before starting dupilumab treatment. These patients used: CsA: 4 (4%), AZA: 3 (3%), MTX: 11 (12%), Prednisone: 1 (1%). [b] This category contains of the following combinations: Prednisone continued for 4 weeks, MPA was discontinued at start of dupilumab treatment; AZA continued for 4 weeks, prednisone was continued after 16 weeks of dupilumab treatment; Prednisone continued for 16 weeks, apremilast was discontinued at start of dupilumab treatment; AZA continued for 7 weeks, prednisone was discontinued at start of dupilumab treatment; MPA continued for 16 weeks, CsA was discontinued at start of dupilumab treatment.

Discontinuation of dupilumab treatment

Five patients discontinued dupilumab treatment. One patient discontinued dupilumab treatment because of a mono-arthritis in the right ankle starting a few days after the first dupilumab administration. Four patients discontinued because of lack of clinical response after 9, 15, 17 and 18 weeks. No evident common phenotypical characteristics, laboratory markers or other predictors of failure could be detected in these patients.

DISCUSSION

In this observational study dupilumab treatment was evaluated in a daily practice cohort of 95 AD patients, whose eczema could not be adequately controlled with TCS, TCI and conventional systemic immunosuppressants. Dupilumab treatment resulted in a rapid decrease of EASI, IGA, POEM, DLQI, and NRS pruritus score in the first 16 weeks of treatment (Figure 1a-d, S1, S2; Table 2, S2). Overall, dupilumab was well tolerated in most patients, although 62% of the patients reported eye symptoms (Table S1). In contrast to previous clinical trials and limited daily practice literature, dupilumab treatment was combined with concomitant systemic immunosuppressants in 45% (43/95) of the patients in this study.[11,33] Continuation of conventional systemic immunosuppressants in the first weeks of dupilumab treatment seems to be an effective and safe transition

to monotherapy with dupilumab, but needs to be studied in larger numbers of patients. This emphasizes the importance of the introduction of registries such as the national registries of the TREatment of ATopic eczema (TREAT) Registry Taskforce for monitoring systemic treatments in daily practice.[18]

Although methodology and follow-up visits in our study, clinical trials and limited daily practice literature available were different, we tried to compare our results.[11,33-37]

Overall, patients in the current study had lower baseline EASI scores compared to patients in previous dupilumab studies/trials (Table S2).[11] In our study, patients were not asked to discontinue topical steroids nor systemic immunosuppressants before the start of dupilumab treatment, resulting in lower baseline EASI scores compared to clinical trials that required a minimum washout period of 2 and 4 weeks, respectively. Currently available daily practice studies with relatively high EASI scores did not report about presence of systemic treatment at baseline.[34,35] From clinical experience we know that discontinuation of systemic immunosuppressants in AD patients often results in exacerbations of their disease.[38] Therefore, the use of conventional systemic immunosuppressants during dupilumab treatment was continued initially in a subset of patients, in a tapering schedule guided by PROMs. Although it would be interesting to study if dupilumab combined with one of the systemic immunosuppressants used in our patient population would be of particular benefit, we did not perform inter- and intra-group comparisons between patients on different concomitant systemic immunosuppressants because this would lead to non-robust conclusions due to relatively small subsets of patients (Table 4). Interestingly, baseline PROMs, including NRS pruritus, POEM and DLQI in daily practice were comparable to patients clinical trials (Table S2).[11] Even though 65% (62/95) of patients in this study were still treated with a systemic immunosuppressant at baseline, they had relatively poor PROM scores at start of dupilumab treatment. This might be the result of a long history of severe disease in most patients in our cohort compared to patients in previous clinical trials. Although Dutch regulations do not require patients to have a minimum severity score to warrant dupilumab treatment, they do require patients to have failed treatment with at least one systemic immunosuppressant in a sufficient dose for at least four months with intensive guidance and instructions (Appendix 1). The majority of patients in our study (72%) and a similar amount of patients in daily practice studies available, had been treated with at least 2 different conventional systemic immunosuppressants, in contrast to a minority (26-28%) which used at least 1 systemic immunosuppressant in SOLO trials.[11,33-37] This suggests that patients in daily practice are at the end of the 'severity spectrum'. Because a long-term severity measure is not available, surrogate markers such as previous treatment with systemic immunosuppressants may be used. Interestingly, a comparable relative reduction of both physician-reported severity and

PROMs is achieved after at least 12 weeks of treatment (Table 2, S2), although direct comparison of these scores is complicated due to the different study designs used in this study, other daily practice studies and SOLO trials.[11,33-37] The percentage of patients reaching IGA 0/1 in our patient population (38%) and the percentage of patients reaching the primary endpoint in SOLO1/2 trials (38%) is equal (Figure S2). However, in addition to IGA 0/1, an improvement of ≥2 on IGA was required in the SOLO trials.

We observed that the MCIDs for the PROMs (POEM, DLQI, NRS pruritus 24h) were reached prior to the MCID for physician-reported severity score (EASI), which suggests that patients' symptoms improve prior to clinical severity. This corresponds to our clinical observation that in dupilumab-treated patients the itch improves before the eczema disappears.

In our cohort, 62% (59/95) of the patients presented with eye symptoms suggestive for conjunctivitis, sicca and/or blepharitis, whereas conjunctivitis was observed in only 4-5% of the patients in SOLO trials.[11] However, limited daily practice literature available also showed conjunctivitis incidence ranges up to 50% in patients treated with dupilumab.[33-37] Literature on ocular comorbidities in AD shows that several ocular comorbidities are more prevalent among AD patients as compared with the general population.[39] Additionally, Thyssen et al. recently showed that this increased risk and prevalence is disease-severity dependent.[40,41] We hypothesize that the difference between real-world and clinical trials may be explained by differences in (long-term) disease severity in patients in this study, as discussed above. In addition, a reporting bias may have been induced by specifically asking for eye complaints.

We found an incidence of 8% (8/95) of orofacial HSV reactivation in our cohort. The absence of typical HSV infection related eye complaints, make HSV eye involvement in these infections highly unlikely. A recent meta-analysis showed a slightly lower incidence of 6.1% reported in dupilumab clinical trials.[42] This incidence was not significantly different in patients in the placebo groups (5.2%). Possibly, concomitant systemic immunosuppressants which were used in 4 out of 8 patients may have contributed to the higher incidence found in our cohort. Moreover, in the previously mentioned clinical trials it was found that there was a higher incidence of severe, and clinically important herpes infections, including herpes zoster and eczema herpeticum, in the placebo groups.[43] In our cohort, there were no cases of severe, clinically important herpes infections.

Daily practice data were prospectively collected at 2 university medical hospitals in The Netherlands. Although the centers used slightly different visit schedules (visits at 12 weeks versus 16 weeks), different outcome measures (NRS peak pruritus in the past 24 hours versus past 7 days) and assessment of baseline characteristics (allergic

comorbidities; U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis), we were able to analyze the data using a LME model. As a result, we could not retrieve a standard deviation for the outcomes as advised by the reporting guidelines for clinical trials of the HOME initiative.[44]

In addition to short-term follow-up data, continuous collection of real-world and standardized data is important to evaluate the effectiveness and safety of dupilumab treatment in daily practice on the long term. The TREAT Registry Taskforce (*treat-registry-taskforce.org)* is an international network of national registries that aims to collect such data.[18] These registries intend to gather observational real-world data of paediatric and adult patients with AD receiving photo- and systemic therapy, using a harmonized dataset including timepoints.[16,17] The TREAT NL registry is the Dutch TREAT registry and data from this registry was partly used for the current study.

In our daily practice cohort, we confirmed that dupilumab is an effective treatment in the vast majority of patients with moderate-to-severe AD. Furthermore, we report on the concomitant use of conventional systemic immunosuppressive agents in a subset of patients. In the patients reported in this study we found a high reporting rate of eye symptoms, and an apparent increase in orofacial (non-ocular) HSV reactivation. No other safety concerns were reported in the first 16 weeks of dupilumab treatment.

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SUPPLEMENTARY MATERIALS

Supporting Information

Table S1. Patient-reported side effects.

Table S2. Baseline and follow-up scores in our daily practice cohort, limited daily practice literature and clinical trials (dupilumab (Q2W) treatment).

Figure S1. Estimated mean change in Dermatology Life Quality Index (DLQI) scores in patients with atopic dermatitis from start until 16 weeks of dupilumab treatment (n=95).

Figure S2. Investigator Global Assessment (IGA) scores at baseline and follow-up (between 12 and 16 weeks).

Appendix 1 - Criteria for dupilumab treatment set forth by the Dutch Society of Dermatology (NVDV).

Appendix 2 - Histograms, Akaike Information Criterion (AIC) of original and sqrt-transformed scale.

A digital version of this supplementary material can be found at:

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APPENDIX

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LONG-TERM EFFECTIVENESS AND SAFETY OF TREATMENT WITH DUPILUMAB IN PATIENTS WITH ATOPIC DERMATITIS: RESULTS OF THE TREAT NL (TREATMENT OF ATOPIC ECZEMA, THE NETHERLANDS) REGISTRY

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ABSTRACT

Background

Evidence on long-term dupilumab treatment for atopic dermatitis in daily practice is lacking.

Objective

To investigate patient characteristics, treatment aspects, effectiveness and safety of up to 84 weeks of dupilumab treatment.

Methods

An observational prospective cohort study was conducted, including atopic dermatitis patients starting dupilumab in routine clinical care.

Results

Of the 221 included patients, 103 used systemic therapy at baseline. At 84 weeks we found a change of -15.2 (SE 1.7) for EASI, -16.9 (SE 1.4) for POEM, -17.2 (SE 1.6) for DLQI. As for IGA and NRS pruritus, we found a trend for improvement over time. Severe (n=79) including serious (n=11) adverse events were observed in 69 patients. Eye complaints were most frequently reported (n=46). Twenty-one patients adjusted the regular dosing schedule. Fourteen patients discontinued treatment, mainly due to ineffectiveness (n=7).

Limitations

Only adverse events of severe and serious nature were registered for feasibility reasons.

Conclusion

Daily practice dupilumab treatment up to 84 weeks is generally well-tolerated, apart from the reporting of eye complaints. It can be considered a long-term effective treatment for atopic dermatitis in combination with topical and initial concomitant systemic treatment, showing a sustained improvement of signs, symptoms and quality of life.

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a chronic pruritic inflammatory skin disorder which is among the most common dermatological conditions. AD can put a large burden on patients.[1] Most patients can be treated effectively with emollients and topical anti-inflammatory agents. A subgroup of around 15% of patients suffers from moderate-to-severe AD and phototherapy and systemic immunomodulating therapies can be indicated.[2]

High-quality evidence from several randomized controlled trials indicates that dupilumab is superior to placebo in treating AD.[3] However, there is a lack of long-term data from observational studies in daily practice. Patients selected for clinical trials can differ from daily practice patients due to strict in- and exclusion criteria.

We have previously published daily practice results of dupilumab treatment up to 16 weeks.[4] The aim of the present study was to investigate AD treatment with dupilumab in daily practice on the long-term, i.e. up to 84 weeks of treatment.

METHODS

Study design and patient population

We conducted a registry-embedded observational prospective cohort study. Patients with physician-diagnosed AD that started treatment with dupilumab in context of routine clinical care were included from October 2017 to June 2019 at the Amsterdam University Medical Centers (Amsterdam UMC) and the Erasmus MC University Medical Center (EMC) in the Netherlands. Visits were conducted by trained healthcare professionals and aspired to be scheduled at baseline, 4 weeks, 12-16 weeks after starting treatment and every 12 weeks thereafter. A subset of data from the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry was used. The EMC data was also part of the EMC Biological Registry.

All patients met the national criteria for dupilumab as determined by the Dutch Society of Dermatology which stipulate a treatment episode of at least 4 months with 1 or more conventional systemic therapies in an adequate dose.[5] In two patients dupilumab was prescribed off-label, as they were 17 years old at the time. All patients started treatment with 300mg dupilumab injections every two weeks after an initial loading dose of 600mg. Patients were allowed to concomitantly continue using conventional systemic immunomodulating treatment in a tapering schedule and were allowed to use topical treatments (e.g. corticosteroids and calcineurin inhibitors).

In case of dupilumab discontinuation, data collection was aimed every 6 months. Treatment discontinuation therefore did not implicate discontinuation of registry participation.

Study outcomes

Data collection was based on the TREAT (TREatment of ATopic eczema) Registry Taskforce core dataset.[6, 7] The following patient characteristics were collected at baseline and during follow-up: demographics, co-morbidities, past treatments, concomitant medication and treatment aspects.

Effectiveness was analyzed by using both investigator- and patient-reported outcome measures (PROMs). Investigator-reported outcome measurements consisted of Eczema Area and Severity Index (EASI: 0-72)[8] and Validated Investigator Global Assessment scale for Atopic Dermatitis (vIGA-AD: 0-4)[9]. Patients completed the following PROMs: Numerical Rating Scale (NRS: 0-10, NRS peak pruritus past 24 hours, NRS mean pruritus past 7 days)[10], Patient-Oriented Eczema Measure (POEM: 0-28)[11] and Dermatology Life Quality Index (DLQI: 0-30)[12].

Safety was assessed by analyzing severe and serious adverse events (AEs). Severe AEs were defined as any undesirable experience occurring during dupilumab treatment resulting in referral to another specialist, prescription of medication (excluding antihistamines and indifferent treatments), treatment schedule adjustments or discontinuation, or causing considerable interference with usual activities, whether or not considered related to this treatment. Events that resulted in death, were life-threatening, required (prolonging of) hospitalization, resulted in persistent or significant disability, or congenital anomaly or birth defect, were considered serious AEs.[13]

Statistical analyses

The patient characteristics, treatment aspects and safety data were summarized using descriptive statistics.

We analyzed a predefined population of all patients while receiving dupilumab injections every two weeks with a follow-up duration of up to 84 weeks. For each patient, multiple measurements of the outcomes were obtained during follow-up. To deal with the correlation between measurements from the same patient, mixed effect models were fitted. More specifically, we used linear mixed-effects models to analyze EASI, POEM, and DLQI and ordinal logistic mixed-effects models to analyze IGA and NRS pruritus. In all models, follow-up time, gender, age, body mass index (BMI), (Fitzpatrick) skin type and concomitant systemic therapy were added as additive fixed effects. The effect of follow-up time was described by a natural spline function to allow non-linear effects. The knots of the natural spline function were placed at the appropriate percentiles

of the data. Optimal degrees of freedom for the natural spline function were chosen based on the Bayesian Information Criterion. All other variables were assumed to have a linear effect on the outcome. To capture correlation between measurements from the same patient, a random intercept was added to all models. All observations with missing values were excluded from the analyses.

Analyses were performed using SPSS 24.0 (IBM, Armonk, NY, U.S.A.) and R version 3.4.1 (Foundation For Statistical Computing, Vienna, Austria). In all analyses, effects were considered statistically significant if $p<0.05$.

RESULTS

Patient characteristics

In total 221 patients were included (Amsterdam UMC: n=75, EMC: n=146)**.** The baseline characteristics are shown in table 1. The majority of patients was male (n=127/221, 57.5%), white (n=178/221, 80.5%) and had skin type II (n=126/221, 57.0%). In 153 patients (n=153/221, 69.2%) AD occurred before the age of 2 and the median age at start of dupilumab was 41 years (IQR 27-52). Unless contraindicated, all patients were previously treated with other systemic immunomodulating therapies. One hundred three patients (n=103/221, 46.6%) continued their conventional systemic therapy after starting dupilumab, because it was deemed undesirable to discontinue. The majority of these patients used ciclosporin (n=37/221, 16.7%) or systemic corticosteroids (n=36/221, 16.3%). Eighty-three patients discontinued this concomitant therapy after a median of 50 days (supplementary table 1). One patient had a pre-existent type-4 allergy for polysorbate 80 (i.e. one of the excipients of dupilumab) as relative contraindication, yet did not experience complications. One patient had an active malignancy: low-grade recurrent superficial bladder cancer, which remained stable. No patients were lost to follow-up.

Table 1. Patient characteristics at baseline

Patient characteristics	TREAT NL cohort (n=221)[a]
Sex – no. (%)	
Male	127 (57.5)
Female	94 (42.5)
Age at start dupilumab, median (IQR) – years	41 (27-52)
Age of onset AD – years	
Median age (IQR)	0 (0-4)[1]
<2 years – no. (%)	153 (69.2)
≥2-<6 years	19 (8.6)
≥6-<12 years	11 (5.0)
≥12-<18 years	9 (4.1)
≥18 years	28 (12.7)
Ethnicity – no. (%)	
White	178 (80.5)
Black	19 (8.6)
Asian	22 (10.0)
Other[b]	2 (0.9)
Fitzpatrick skin type – no. (%)	
I	9 (4.1)
II	126 (57.0)
III	41 (18.6)
IV	19 (8.6)
V	22 (10.0)
VI	4 (1.8)
BMI – median (IQR)	24.7 (22.1-27.5)[2]
Atopic/allergic conditions (patient-reported/physician-diagnosed) – no. (%)	
Asthma	143 (64.7)[c]
Allergic (rhino)conjunctivitis and/or atopic (kerato)conjunctivitis	179 (81.0)[c]
Eosinophilic esophagitis	0 (0.0)[d,m]
Food allergies	121 (54.8)[e,3]/30 (40.0)[d]
Allergic contact dermatitis	113 (51.1)[f,4]
Family history of atopic diseases[g] - no. (%)	160 (72.4)[5]
Previous use of systemic therapies for AD – no. (%)	
Ciclosporin	197 (89.1)
Azathioprine	46 (20.8)
Methotrexate	103 (46.6)
Mycophenolic acid/mycophenolate mofetil	75 (33.9)
Systemic corticosteroids[h]	136 (61.5)
Other medication[i]	24 (10.9)
Investigational medication[j]	9 (4.1)
Number of previous used systemic immunomodulating therapies[k] – no. (%)	
0	3 (1.4)[l]
1	68 (30.8)
2	90 (40.7)
3	42 (19.0)
≥ 4	18 (8.1)

Table 1. *(continued)*

Patient characteristics	TREAT NL cohort (n=221)[a]
Previous use of phototherapy – no. (%)	
Yes	166 (75.1)
No	33 (14.9)
Unknown	22 (10.0)
Type of previous used phototherapy[m] – no. (%)	
NB-UVB[m]	10 (13.3)
BB-UVB[m]	2 (2.7)
UVB-unspecified[m]	33 (44.0)
UVA[m]	3 (4.0)
UVA1[m]	2 (2.7)
UVAB[m]	0 (0.0)
PUVA[m]	11 (14.7)
Unknown[m]	15 (20.0)
Other[m]	1 (1.3)
Number of previous used phototherapies[m] – no. (%)	
0	12 (16.0)
1	52 (69.3)
2	10 (13.3)
3	1 (1.3)
Immunomodulating therapy at start dupilumab – no. (%)	
None	118 (53.4)
Ciclosporin	37 (16.7)
Azathioprine	8 (3.6)
Methotrexate	10 (4.5)
Mycophenolic acid/mycophenolate mofetil	11 (5.0)
Systemic corticosteroids	36 (16.3)
Omalizumab	0 (0.0)
Other medication[n]	1 (0.5)
Investigational medication	0 (0.0)
Treatment at outpatient daycare treatment unit in the past year[m] – no. (%)	13 (17.3)
Hospitalization for AD in the past year[m] – no. (%)	7 (9.3)

AD, atopic dermatitis; BMI, body mass index; IQR, interquartile range; No., number. Missing data: [1] n=1 (0.5%), [2] n=13 (5.9%), [3] n=14 (9.6%), [4] n=1 (0.5%), [5] n=16 (7.2%). [a] Diagnosis AD based on U.K. workings party's diagnostic criteria for atopic eczema: n=75 (Amsterdam UMC patients), [b] mixed (n=2), [c] patient-reported in EMC and physician-diagnosed in Amsterdam UMC, [d] physician-diagnosed (n=75 (Amsterdam UMC patients)), [e] patient-reported (EMC: 79, Amsterdam UMC: 42), [f] positive patch test: remaining 48.4% is never tested, unknown or tested negative, [g] first degree family member with at least one of the following atopic diseases: AD, asthma or allergic (rhino)conjunctivitis, [h] systemic corticosteroids: usage unknown n=49 (22.2%), no usage n=36 (16.3%), [i] other medication: apremilast (n=2), dupilumab (n=1), omalizumab (n=1), ustekinumab (n=1), dapson (n=1), alitretinoin (n=7), acitretin (n=5), fumaric acid (n=5), dimethyl fumarate (n=1), [j] investigational medication: upadacitinib or placebo (n=2), baraticinib or placebo (n=2), tralokinumab or placebo (n=2), lebrikizumab or placebo (n=2), fevipiprant or placebo (n=1), [k] not including the use of systemic corticosteroids because of anamnestic inconsistency, [l] three patients did not receive any past systemic therapies because of contra-indications: a solitary kidney (n=1), history of poorly-differentiated squamous cell carcinoma of the lip (n=1), renal insufficiency and liver functions abnormalities (n=1), [m] data only available for Amsterdam UMC patients (n=75), [n] other: alitretinoin.

Based on our model, a 'median' patient, i.e. being a 41 year-old man with a BMI of 25 and skin type II without usage of concomitant systemic immunomodulating therapy, had an estimated EASI of 21.4 (standard error (SE) 1.0), POEM of 25.9 (SE 1.0) and DLQI of 19.6 (SE 1.1) at baseline (table 2).

Table 2. Effectiveness of dupilumab, estimated scores over time

Outcomes	**EASI (0-72)**				**POEM (0-28)**				**DLQI (0-30)**			
Time	Est. score	SE	Est. change score from baseline	SE	Est. score	SE	Est. change score from baseline	SE	Est. score	SE	Est. change score from baseline	SE
Baseline	21.4	1.0			25.9	1.0			19.6	1.1		
4 weeks	18.0	0.9	-3.4 (-15.9%)	0.3	21.4	0.8	-4.6 (-17.8%)	0.3	14.9	0.8	-4.8 (-24.5%)	0.5
12 weeks	12.2	0.8	-9.2 (-43.0%)	0.8	13.8	0.7	-12.1 (-46.7%)	0.8	8.1	0.7	-11.5 (-58.7%)	1.2
24 weeks	8.3	0.7	-13.2 (-61.7%)	0.9	9.5	0.7	-16.4 (-63.3%)	0.9	5.8	0.7	-13.8 (-70.4%)	1.0
36 weeks	7.7	0.7	-13.7 (-64.0%)	0.8	9.9	0.7	-16.1 (-62.2%)	0.7	5.5	0.6	-14.1 (-71.9%)	0.9
48 weeks	7.5	0.7	-14.0 (-65.4%)	0.8	10.0	0.7	-15.9 (-61.4%)	0.8	5.5	0.6	-14.2 (-72.4%)	1.0
60 weeks	7.1	0.8	-14.3 (-66.8%)	1.0	9.6	0.8	-16.4 (-63.3%)	0.9	6.1	0.7	-13.5 (-68.9%)	0.9
72 weeks	6.7	0.8	-14.8 (-69.2%)	1.0	9.2	0.8	-16.7 (-64.5%)	0.9	5.1	0.7	-14.5 (-74.0%)	1.0
84 weeks	6.2	1.5	-15.2 (-71.0%)	1.7	9.0	1.3	-16.9 (-65.3%)	1.4	2.4	1.3	-17.2 (-87.8%)	1.6

Scores displayed for 'median' patient: male, 41 years old, BMI 25, Fitzpatrick skin type II, no usage of concomitant medication; Est., estimated; SE, standard error; EASI, Eczema Area and Severity Index; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; Estimated scores and changes in score are based on our linear mixed-effects models.

Treatment effectiveness

The course until 84 weeks of treatment for all 6 outcome measurements is shown in Fig. 1 and Fig. 2. An improvement of all outcome measurements is observed, in particular in the first 12 weeks of treatment. The estimated change in score from baseline till 84 weeks was: -15.2 (SE 1.7) for EASI, -16.9 (SE 1.4) for POEM, -17.2 (SE 1.6) for DLQI (table 2). As for IGA and NRS pruritus, we found a trend for improvement of the scores (supplementary table 2). The daily practice setting resulted in different follow-up durations for each outcome measure (supplementary Fig. 1). The mean follow-up duration for the outcome measurements varied from 28.9 to 31.4 weeks (SD 22.8-23.9, range: 0-85.6 weeks).

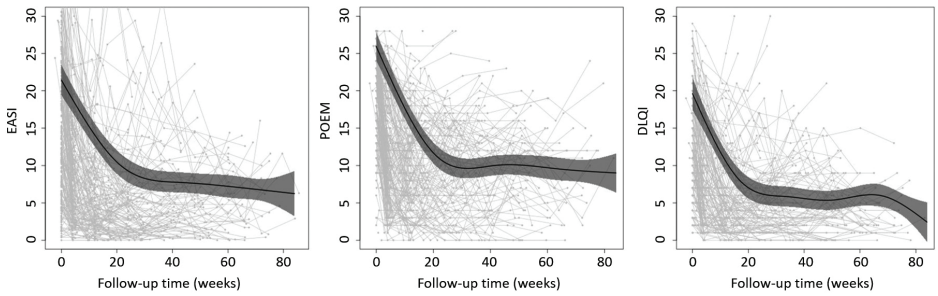

Figure 1. Outcome measures over time until 84 weeks of treatment (Eczema Area and Severity Index (EASI), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI))

Figure 1. *(continued)*

Results based on our linear mixed-effects models. Higher scores indicate higher disease activity and/or burden. The dark grey area surrounding the black line represents the standard error (SE). Estimated scores are based on our 'median' patient (a 41 year-old man with a BMI of 25 and Fitzpatrick skin type II who does not use concomitant systemic therapy). The estimated EASI score (0-72) decreased from 21.4 (SE 1.0) at baseline to 6.2 (SE 1.5) at 84 weeks. EASI observations of > 30 at are not shown in the figure, but are included in the model. The estimated POEM score (0-28) decreased from 25.9 (SE 1.0) at baseline to 9.0 (SE 1.3) at 84 weeks. The estimated DLQI score (0-30) decreased from 19.6 (SE 1.1) at baseline to 2.4 (SE 1.3) at 84 weeks.

In our model we found that females had significantly lower scores of EASI (-3.04 (SE 0.75), p=9.24e-13) and IGA (-1.20 (SE 0.32), p=0.0002) compared to males as fixed effect over time during treatment, whereas patients with skin type IV (n=19) had higher scores for EASI (+2.90 (SE 1.27), p=0.0241), DLQI (+2.56 (SE 1.26), p=0.0439) and IGA (+1.57 (SE 0.55), p=0.0042) compared to skin type II (n=126). In addition, the use of concomitant immunomodulating systemic therapy resulted in lower estimated scores of EASI (change in score: -2.66 (SE 0.69), p=0.0001), IGA (-0.73 (SE 0.26), p=0.0046) and NRS mean pruritus past 7 days (-0.77 (SE 0.34), p=0.0231), in comparison with absence of concomitant therapy (supplementary table 3).

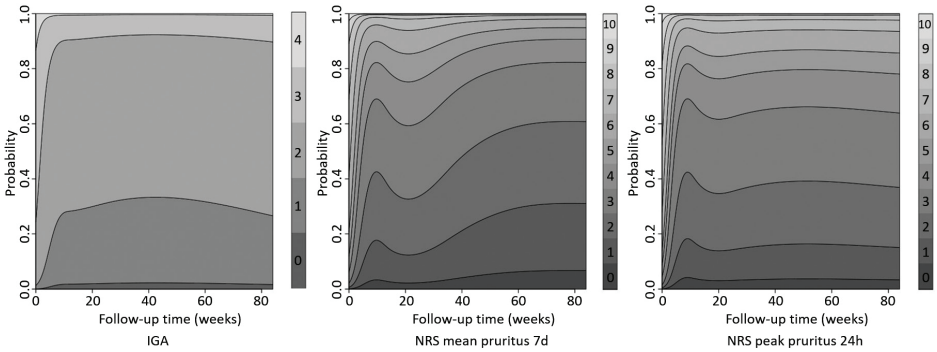

Figure 2. Outcome measures over time until 84 weeks of treatment (Investigator Global Assessment for atopic eczema (IGA), Numerical Rating Scale (NRS) mean pruritus past 7 days, NRS peak pruritus past 24 hours)

Estimated probability ranging from 0 to 1 for the answer categories based on our ordinal logistic mixed-effects models. The probability score illustrates the probability of achieving a specific score at a certain time point. Higher scores indicate higher disease activity and/or burden. Estimated scores are based on our 'median' patient (a 41 year-old man with a BMI of 25 and Fitzpatrick skin type II who does not use concomitant systemic therapy). Over time there is an increase in probability for IGA 1 and IGA 2 and a decrease for IGA 3 and IGA 4. Regarding the NRS measures, there is an increase in lower scores over time at the expense of higher scores. NRS peak pruritus past 24 hours was registered in the Amsterdam UMC only.

Safety of treatment

Seventy-nine severe AEs were registered in 69 patients (n=69/221, 31.2%) (table 3). Sixty-one of these AEs were considered probably and possibly linked to dupilumab. Eye complaints were most frequently reported: 46 events in 46 patients (n=46/221, 20.8%). Forty-five were possibly or probably and 1 doubtfully linked to dupilumab. On average, the ocular severe AEs occurred after 36 days (range: 0-280 days). Of the patients experiencing ocular severe AEs, 39 patients (n=39/46, 84.8%) had more

than one allergic comorbidity. In addition, two-thirds of these patients had an IGA 3 or 4 at baseline (n=28/42, 66.7%) and the mean EASI was 14.6 (SD 10.5), which did not significantly differ from patients without ocular severe AEs (p=0.143 and p=0.853 respectively). Thirty-three patients had eye complaints not classified as severe. Other severe AEs, mainly considered not related or doubtfully related to dupilumab, are described in table 3. The AEs described as peri-oral dermatitis, depressed mood, eczema exacerbation, arthritis, joint/muscle strain complaints, herpes zoster, herpes simplex, hair loss and paradoxical facial erythema were possibly or probably linked to dupilumab. Eleven severe AEs (n=11/79, 13.9%) were accounted as serious AEs. Four of these were considered not and 7 doubtfully related to dupilumab.

Table 3. Overview of severe and serious adverse events, including action, course, relatedness and type

Total number of severe adverse events – no.	79
Action on severe adverse event – no.	
Treatment discontinuation	3
Adjustment of treatment schedule	6
None	70
Course of severe adverse event – no.	
Recovered/resolved	10
Recovered/resolved with sequelae	1
Recovering/resolving	6
Not recovered/resolved	17
Fatal	0
Unknown	45
Relatedness to dupilumab treatment – no.	
Not related	6
Doubtful	12
Possible	19
Probable	42
Very likely	0
Definite	0
Type of severe adverse event[a] – no.	
Eye disorders	
Eye complaints	46
(Kerato)conjunctivitis	24
Sicca complaints	4
Blepharitis	2
Epiphora	1
Combined diagnoses[b]	15
Musculoskeletal and connective tissue disorders	
Joint/muscle strain complaints	6
Arthritis	2
Cardiac disorders	
Angina pectoris	3
Acute coronary syndrome	1
Chest pain, unknown cause	1
Injury, poisoning and procedural complications	
Bone fracture (not spontaneous)	2

Table 3. *(continued)*

Total number of severe adverse events – no.	79
Endocrine disorders	
Adrenal insufficiency[c]	2
Skin and subcutaneous tissue disorders	
Hair loss	2
Perioral dermatitis	1
Panniculitis, unknown cause	1
Exacerbation of eczema	1
(Paradoxical) facial erythema	1
Blood and lymphatic system disorders[d]	
(Increase of) neutropenia	1
Liver function abnormalities	1
Nervous system disorders	
Bell's palsy	1
Psychiatric disorders	
Depressed mood	2
Renal and urinary disorders	
Pyelonephritis	1
Neoplasms benign, malignant and unspecified	
Bladder carcinoma[e]	1
Infections and infestations	
Herpes zoster	1
Herpes simplex	1
Surgical and medical procedures	
Allergenic desensitisation procedure	1
Serious adverse events[f] – no.	11

No., number; [a] subdivided into Medical Dictionary for Regulatory Activities (MedDRA) terminology categories; [b] combined diagnoses: (kerato)conjunctivitis and blepharitis (n=5), (kerato)conjunctivitis and sicca complaints (n=3), (kerato) conjunctivitis and sicca complains and blepharitis (n=2), sicca complaints and blepharitis (n=2), conjunctivitis and (increase of) ectropion (n=2), epiphora and ectropion (n=1); [c] adrenal insufficiency occurred in 2 patients, due to discontinuation of long-term treatment with systemic corticosteroids; [d] no significant laboratory abnormalities were found aside from worsening of a pre-existing neutropenia in one patient and liver function abnormalities due to alcohol abuse in one patient; [e] the bladder carcinoma occurred after treatment discontinuation; [f] four serious adverse events were considered not related to the dupilumab treatment and the relatedness to dupilumab of the other 7 events was considered doubtful.

Treatment schedule adjustments

In 21 patients (n=21/221, 9.5%) the dupilumab dosing was adjusted, either by prolonging or shortening the injection interval. Nine patients (n=9/221, 4.1%) prolonged. Seven of these patients increased the injection interval to once every 3 weeks and 2 patients to once every 4 weeks. Eight out of these 9 patients prolonged due to severe adverse events: eye complaints in 6 patients and depressed mood in 2 patients. Both patients reporting depressed mood had prior history of these symptoms and reported improvement after prolonging. One patient prolonged due to achieving complete disease control. In 2 patients the interval was shortened secondarily (from 4 to 3 weeks after 168 days and from 3 to 2 weeks after 105 days of a prolonged interval, respectively) due to disease flares. In 12 patients (n=12/221, 5.4%) the interval was shortened due to ineffectiveness. Of these patients, 4 were shortened to a 10-day and 8 to a weekly

interval. One of these patients eventually discontinued treatment due to persisting ineffectiveness. In 6 patients there was clinical improvement. One patient did not improve. Follow-up time was not sufficient for this assessment in the other patients.

Treatment discontinuation

Fourteen patients (n=14/221, 6.3%) discontinued dupilumab. In 7 patients treatment was discontinued due to ineffectiveness after 66, 111, 123, 126, 166, 204, 336 days. One patient switched to a weekly interval prior to discontinuation. One patient discontinued as a result of non-adherence and three patients due to severe AEs: mono-arthritis of the ankle days after the first dupilumab injection,[14] paradoxical facial erythema[15] and panniculitis. These complaints resolved after discontinuation. Three patients discontinued based on physician recommendation because of anticipated pregnancy.

DISCUSSION

We analyzed patient characteristics, treatment aspects, the effectiveness and safety of dupilumab treatment in 221 AD patients in daily practice for up to 84 weeks, in combination with topical and initial concomitant systemic treatment. We observed improvement of clinical signs (EASI, IGA), patient-reported symptoms (POEM, NRS pruritus) and quality of life (DLQI) in particular in the first 12 weeks of treatment (Fig. 1, Fig. 2, table 2), followed by a prolonged effect suggesting long-term disease control up to 84 weeks.

Our daily practice study complements long-term clinical trial data of treatment up to 76 weeks.[16] In the latter clinical trial, an off-label dose of dupilumab 300mg/week was used, instead of every two weeks according to the label. Moreover, there are differences between clinical trials and daily practice. Psoriasis literature has shown that approximately 30% of patients who are included into registries would be ineligible for clinical trials.[17] Other studies found higher baseline EASI scores.[18-23] A likely explanation is that in these studies washout periods were applied and/or concomitant therapy was not allowed. Interestingly, our baseline scores for POEM and DLQI were comparable or higher. After 12-24 weeks of treatment we found similar scores of both investigator- as well as patient-reported outcomes.

In the models of our effectiveness analyses we included patients only while receiving the on-label dose of 300mg dupilumab every 2 weeks without a minimum treatment duration. Patients that discontinued treatment or continued in an alternative dosing schedule due to ineffectiveness or substantial side-effects were not included thereafter. Gender, age, BMI, skin type and concomitant systemic therapy were added as additive fixed effects in our models and the same effect size over time during treatment was assumed for these variables. We found significantly lower scores of EASI and IGA for females and for concomitant immunomodulating therapy, whereas patients with skin type IV had

significantly higher scores of EASI, DLQI and IGA. The effectiveness of dupilumab in different racial subgroups has been confirmed in a pooled analyses of three phase 3 trials, although the sample size of Black/African American patients was relatively small.[24]

Conjunctivitis has been a commonly reported AE in clinical trials.[18, 19, 25] Daily practice literature has shown incidences of conjunctivitis ranging from 8.5% to 38.5%.[20-23] Long-term permanent ocular complications, including those persisting after treatment discontinuation, have not been reported in literature. Severe eye complaints indicating conjunctivitis, blepharitis, sicca complaints, epiphora and combined diagnoses were registered in 20.8% of our patients. In accordance with other literature,[26] we found that the majority of patients with eye complaints have allergic co-morbidities (84.8%). We explicitly asked patients about eye complaints, which may have resulted in reporting bias. In both hospitals there was a low threshold for referral to an ophthalmologist in case of (worsening of) eye complaints. Although in none of the patients eye complaints were reason to discontinue treatment, we observed that patients tend to accept these complaints in lack of alternative systemic treatment options.

Several limitations result from the daily practice setting. While there were no reasons to suspect treatment noncompliance during treatment, we cannot rule this out completely, as most patients received treatment at home. Also, bias may have been induced by the non-blinded observational nature of the study. Further, for feasibility reasons only severe AEs are registered as part of the TREAT core dataset.[7] In the EMC AEs were registered by inquiring about side-effects. This insinuates a level of relatedness and may have led to unrelated AEs not being registered.

Further investigation of the safety and future studies comparing dupilumab treatment with other systemic therapies would be of interest.[27] The TREAT NL registry is part of the TREAT Registry Taskforce, which is an international network of research registries that aim to collect these data, while ensuring uniformity in data collection (*treat-registry-taskforce.org*).[28] In addition, research on alternative treatment options for AD is of great importance for the patients for whom dupilumab is not an ideal treatment option due to ineffectiveness and/or side effects.

Conclusion

Long-term dupilumab treatment in a routine clinical setting can be considered an effective treatment in patients with AD in combination with topical treatment and initial systemic therapy, showing a sustained improvement of investigator- and patient-reported outcomes up to 84 weeks. Dupilumab is initially often prescribed in combination with other systemic immunomodulating therapies and is well-tolerated in most patients. Eye complaints are the most frequently reported severe AEs, but did not result in treatment discontinuation. Other severe AEs can lead to treatment discontinuation in rare cases. For various reasons, treatment schedule adjustments are applied or treatment is discontinued in a subset of patients.

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SUPPLEMENTARY MATERIALS

Supplementary table 1. Concomitant immunomodulating therapy.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/rs3t44yj4f.1

Supplementary table 2. Effectiveness of dupilumab, estimated probability over time.

A digital version of this supplementary material can be found at:

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Supplementary table 3. Effectiveness of dupilumab, regression coefficients.

A digital version of this supplementary material can be found at:

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Supplementary figure 1. Follow-up duration per outcome measure (Eczema Area and Severity Index (EASI), Patient-Oriented Eczema Measure (POEM), Dermatology Life Quality Index (DLQI), Investigator Global Assessment for atopic eczema (IGA), Numerical Rating Scale (NRS) mean pruritus past 7 days, NRS peak pruritus past 24 hours).

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APPENDIX

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Conflicts of interest
AB: none; LdW: none; MH: none; BvN: none; LG: none; MAM: consultancies for Sanofi and Pfizer; DJH: investigator for LEO pharma, MedImmune/Astrazeneca, Novartis, Sanofi/Regeneron; consultancies for Regeneron/Sanofi, LEO pharma, MedImmune/AstraZeneca, Novartis, Incyte, Janssen, Pfizer; PS: consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), independent research grants in the past > 5 years ago, contract support: involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis for which we get financial compensation paid to the hospital.

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7

RESPONSE TO "COMMENT ON 'LONG-TERM EFFECTIVENESS AND SAFETY OF TREATMENT WITH DUPILUMAB IN PATIENTS WITH ATOPIC DERMATITIS: RESULTS OF THE TREAT NL (TREATMENT OF ATOPIC ECZEMA, THE NETHERLANDS) REGISTRY'"

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LETTER

We appreciate the comments of Seo et al. with regard to our article "Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: Results of the TREAT NL registry". We support their view that improvement in the Eczema Area and Severity Index (EASI) does not correlate 1:1 with disease improvement. Data collection on various outcome measurements should be considered to fully capture disease improvement by covering signs, symptoms and quality of life. Therefore, we report various investigator- and patient-reported outcomes, including EASI, Investigator Global Assessment (IGA), Numerical Rating Scale (NRS, pruritus peak 24h/mean 7d), Patient-Oriented Eczema Measure (POEM) and Dermatology Life Quality Index (DLQI).

The EASI, POEM and DLQI are validated continuous outcome measurements resulting in numerical scores ranging from 0-72, 0-28 and 0-30, respectively. In our study we use these scores as intended and we report scores at baseline and at each time point, conform reporting guidelines.[1] In addition, we report the percentage change over time. This approach is in accordance with methods in RCTs, with key endpoints including mean percent change from baseline.[2] The reference in the commentary to support a non-linearity of EASI in comparison to other assessments does not provide evidence for non-linearity nor a comparison.[3] When a score range is less broad, such as in case of NRS (0-10) and IGA (0-4), we agree that a non-linear approach is justified, as these could be considered more or less categorical. For that reason specifically we opted for a non-linear approach for these scores by using ordinal logistic mixed-effects models.

We did carefully consider performing EASI-50/75 analyses (50/75% improvement). However, we refrained from this approach due to the observational nature of our study. It is important to realize that this study concerns a real-life study in daily practice. As we also describe in our discussion, factors including absence of washout periods and presence of concomitant therapy have resulted in substantially lower baseline EASI scores in our population compared to other studies. Strict in- and exclusion criteria are applied in RCTs.[2] The lower baseline EASI scores in our study would distort EASI-50/75 analyses without even enabling any meaningful comparison with RCTs. Methods applied in RCTs do not necessarily lend themselves well for daily practice research.

The TREAT NL dataset complies with the international TREAT core dataset that resulted from an eDelphi and consensus exercises.[4, 5] For feasibility reasons consensus was obtained to register severe adverse events only. We describe this and several other limitations of a daily practice setting in the discussion. Our severe adverse event definition implies that an event was severe enough to warrant referral to another specialist, prescription of medication (excluding antihistamines and indifferent treatments), treatment schedule adjustments or discontinuation, or to cause

considerable interference with usual activities. The majority of events were no reason for treatment discontinuation or adjustment and therefore per definition resulted in referral, prescription or interference. Naturally, this definition should be taken into consideration when interpreting the results and by doing so this does not implicate excessive concerns.

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APPENDIX

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WORK ABILITY AND QUALITY OF WORKING LIFE IN ATOPIC DERMATITIS PATIENTS TREATED WITH DUPILUMAB

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ABSTRACT

Atopic dermatitis is associated with work productivity loss. Little is known about how patients perceive their work ability and quality of working life, and how this is affected by treatment. Our primary objective was to investigate work ability and quality of working life at baseline and during treatment in the long term. A registry-embedded prospective observational cohort study was conducted consisting of patients with atopic dermatitis starting dupilumab in routine clinical care. The instruments used were the Work Ability Index (WAI; questions 1, 2 and 3) and the Quality of Working Life Questionnaire (QWLQ). Ninety-three patients were included of which 72 were (self-) employed (77%). From baseline to 48 weeks, the mean WAI-1 score (general work ability, range 0-10) improved from 6.8 (±2.0) to 7.9 (±1.3), WAI-2 (physical work ability, range 1-5) from 3.7 (±0.9) to 4.3 (±0.7) and WAI-3 (mental/emotional work ability, range 1-5) from 3.4 (±0.9) to 3.9 (±0.8) ($p=0.001$, $p=0.005$, $p<0.001$, respectively). The mean QWLQ total score improved from 74.0 (±9.1) to 77.5 (±9.6) and subscale 'Problems due to health situation' improved from 37.4 (±22.3) to 61.5 (±23.1) (range 0-100; $p=0.032$, $p<0.001$, respectively). In conclusion, patients with moderate-to-severe atopic dermatitis starting with dupilumab report a decreased work ability and quality of working life, mainly due to health-related problems. Significant improvement of work ability and quality of working life is observed with dupilumab treatment.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic dermatological condition that is associated with impairment of quality of life and work productivity.[1] Skin diseases were found the 18th leading cause of global disability-adjusted life years. Excluding mortality, skin diseases were the fourth leading cause of disability worldwide.[2] Of all skin diseases, AD has the highest non-fatal health burden.[3, 4] AD is associated with sick leave, change or loss of job and receiving disability pensions.[5] Data from the TREATgermany registry has shown that moderate-to-severe AD has a substantial adverse economic impact with a mean productivity loss of almost 10%.[6] Patients with AD using systemic treatment are found to incur considerable direct costs as well as indirect costs resulting from productivity loss.[7]

Little is known about how AD patients perceive their work ability and quality of working life (QWL). The Work Ability Index (WAI) was developed to investigate how long people are able to work and to what extent they are able to work depending on work content and demands. The WAI is considered reliable and valid, and has become a common tool to investigate work ability in research worldwide.[8, 9] QWL is defined by the experiences and perceptions in the work situation.[10] The Quality of Working Life Questionnaire (QWLQ) was developed to assess subjective work outcomes in employed cancer patients.[10, 11] In contrast to other questionnaires it was not developed for healthy employees or particular occupations.[12] Adequate internal consistency, construct validity and reproducibility, as well as sufficient responsiveness and interpretability were found in cancer survivors.[12,13] To date, WAI or QWLQ have never been used in the AD population.

The aim of this study was to generate new knowledge on work-related outcomes in AD, focusing on work ability and QWL in particular. The primary objective was to investigate the work ability and QWL of AD patients at baseline and during dupilumab treatment using WAI and QWLQ scores. The secondary objectives were to explore associations between change in QWLQ (from baseline to 48 weeks) and baseline characteristics, and to explore the convergent validity of the QWLQ.

METHODS

Study design and patient population

We conducted a registry-embedded prospective observational study in patients with AD based on the UK working party criteria.[14] Patients of the department of Dermatology of the Amsterdam UMC starting treatment with dupilumab in context of routine clinical care, indicating moderate-to-severe disease, were included from November 2017 to

February 2020. Six patients refrained from participation and informed consent was obtained from all participants. Apart from the requirement for informed consent, there were no exclusion criteria. A subset of TREAT NL registry data was used.[15] Patients starting treatment with other systemic immunomodulating therapies or phototherapies, which are also included in the TREAT NL registry, were not included in this study as the numbers were low. At baseline and every 24 weeks thereafter, outcome data was collected (see 'Study outcomes'). The study was exempted from evaluation by our local Medical Research Ethics Committee (W18_097#18.123). The study was carried out in accordance with the provisions of the Declaration of Helsinki.

All patients met the national criteria for dupilumab as determined by the Dutch Society of Dermatology which stipulate a failed treatment episode (ineffectiveness or adverse events) with ≥1 conventional systemic therapy(ies) prior to starting dupilumab.[16] In two patients dupilumab was prescribed off-label at the time, as they were 17 years old. All other patients were adults. Patients started with an initial loading dose of 600mg, followed by 300mg dupilumab injections every two weeks. In our analyses we included patients while receiving dupilumab, regardless of dosing interval deviations and follow-up duration. Conform daily practice, patients were allowed to continue using conventional systemic treatment in a tapering schedule and to use topical treatments (e.g. corticosteroids and calcineurin inhibitors).

Study outcomes

Data collection was based on the TREAT core dataset.[15,17,18] The following baseline characteristics were retrieved: demographics (gender, age, ethnicity, educational status: ISCED (International Standard Classification of Education) classification), health-related characteristics (disease duration, co-morbidities, outpatient daycare treatments and hospitalizations for AD) and work-related characteristics (work status: Eurostat classification (e.g. (self-/un)employed), number of days lost from usual activities (e.g. work, study), problems at work (e.g. fatigue), reasons for not working (e.g. retired)).

As part of this study we implemented the WAI and QWLQ in the Amsterdam UMC dataset (Appendix S1 and S2).[8,12] The first three WAI questions were used (i.e. WAI-1, WAI-2, WAI-3), giving insight into patient-reported general, physical and mental work ability, respectively. General work ability (WAI-1) was assessed in comparison to best work ability ever, on a scale of zero (worst) to ten (best). Five-point Likert scales were applied to assess work ability with respect to physical (WAI-2) and mental/emotional demands of the work (WAI-3). QWLQ is a 23-item questionnaire focusing on five subscales: (1) Meaning of work, (2) Perception of the work situation, (3) Atmosphere in the working environment, (4) Understanding and recognition in the organization and (5) Problems due to the health situation, which are scored on a 6-point Likert scale.

Higher scores correspond with better QWL, ranging from 0 to 100.[12] These subscales are considered to capture the complete scope of QWL and were based on literature and focus group discussions.[12] In cancer survivors improvement of >3.9 of the QWLQ total score after an intervention is considered clinically meaningful.[13] For the WAI, the clinically meaningful change in score is unknown.

Correlation was investigated between QWLQ and patient-reported outcome measurements (PROMs) indicating symptoms and quality of life in AD[18,19], that were also collected every 24 weeks: Numerical Rating Scale (NRS) peak pruritus past 24 hours (0-10)[20], NRS mean pruritus past 7 days (0-10)[21], Visual Analogue Scale (VAS) peak pain past 24 hours (0-10), VAS mean sleep loss past 3 days (0-10), Patient Global Assessment (PGA: 0-4), Patient-Oriented Eczema Measure (POEM: 0-28)[22], Dermatology Life Quality Index (DLQI: 0-30)[23] and EuroQol-5 dimensions-5 level health score (EQ-5D-5L health score: 0-100).[24] All were available in Dutch and English and administered at the same time.

When >15% of patients achieve the lowest or highest possible score on the QWLQ or its subscales, this is considered a floor or ceiling effect.[25,26]

Statistical analyses

Patient characteristics and scores were summarized using descriptive statistics and paired t-tests as appropriate. A linear mixed-effects model, with patients as random effect, was used to model scores over time up to 96 weeks as latest time point.

To explore associations between baseline characteristics and change in QWLQ from baseline to 48 weeks, we first imputed missing values five times using multi-chain Monte Carlo methods Gibbs sampling.[27] Afterwards, we performed multivariable linear regression analysis with stepwise backwards selection using Akaike Information Criterion. The stepwise backward regression uses 1000 bootstrap samples to get a robust selection of important patient characteristics associated with change in QWLQ. We performed the regression analysis in all 5 imputed datasets and only selected patient characteristics if they were selected in all 5 analyses. Patients with missing data on QWLQ at baseline or 48 weeks were excluded in these analyses.

Convergent validity is assessed by means of hypothesis testing: determining whether scores of an instrument correlate with other instruments in a way that one would expect.[28] Hypothesis testing is part of investigating construct validity, as proposed by the COSMIN taxonomy of measurement properties.[29] Our hypothesis was that a correlation (r) >|0.40| exists for EQ-5D-5L health score, POEM, DLQI, PGA, NRS pruritus, VAS pain and sleep loss, indicating moderate-to-strong correlations (|0.20|-|0.39|: weak, |0.40|-|0.59|: moderate, |0.60|-|0.79|: strong).[25] Spearman correlations were

used to assess the correlation between QWLQ total score, subscale 'Problems due to the health situation' and these constructs.

Analyses were performed using SPSS 25.0 (IBM, Armonk, NY, U.S.A.) and R version 4.0.2 (Foundation For Statistical Computing, Vienna, Austria). In all analyses, results were considered statistically significant at $p<0.05$.

RESULTS

This study included 93 patients with baseline characteristics shown in Table I. The majority of patients was male (58%) and white (76%). The average age (±SD) was 43 (±15) years. The mean disease duration was 39 (±15) years. The majority had allergic co-morbidities (up to 68%). Educational status ranged from ISCED 1 (primary education) to ISCED 8 (doctoral level). There were 53 (57%) patients employed, 8 (9%) self-employed, 7 (8%) retired, 1 (1%) student, 2 (2%) unemployed, 4 (4%) both employed and self-employed, 7 (8%) both employed and student, 11 (12%) received a disability pension. Of the 72 working patients (either employed or self-employed), 46 (64%) reported to experience problems at work, with a combination of problems (including pruritus, fatigue, pain and psychological complaints) being most common. In total, 54 patients reported days lost from usual activities in the past 3 months (58%) with a median of 4 days per month (25^{th}-75^{th} percentile (IQR) 1-7). The median days lost from usual activities was 3.5 (IQR 1-5) in working and 16.3 (IQR 2.5-30) in not working patients ($p=0.01$). At baseline, the median EASI was 14.6 (range: 1.2-60.3) and 29% of patients had severe disease according to Investigator Global Assessment (IGA). At 48 weeks, the median EASI improved to 5.4 (range: 0.1-25.2) and none of the patients had severe disease according to IGA.

WAI and QWLQ assessments were completed by 72 patients with a median follow-up of 27.5 weeks (range: 0-100). At 48 weeks, data was available for 37 of the 72 patients. Due to the daily practice setting, 7 visits occurred outside the aspired window, ranging from windows of 5 weeks in 5 patients, 7 weeks in 1 patient, to 8 weeks in 1 patient. No patients were lost to follow-up.

Work ability

WAI scores are shown in Fig. 1. Improvement is observed from baseline, with a slight decrease as time progresses. At baseline mean WAI-1 indicating general work ability was 6.8±2.0. The mean WAI-2 indicating physical work ability was 3.7±0.9. The mean WAI-3 indicating mental/emotional work ability was 3.4±0.9. Compared to baseline, the mean scores at 48 weeks significantly improved to 7.9±1.3, 4.3±0.7 and 3.9±0.8 for WAI-1, WAI-2 and WAI-3 respectively ($p=0.001$, $p=0.005$, $p<0.001$).

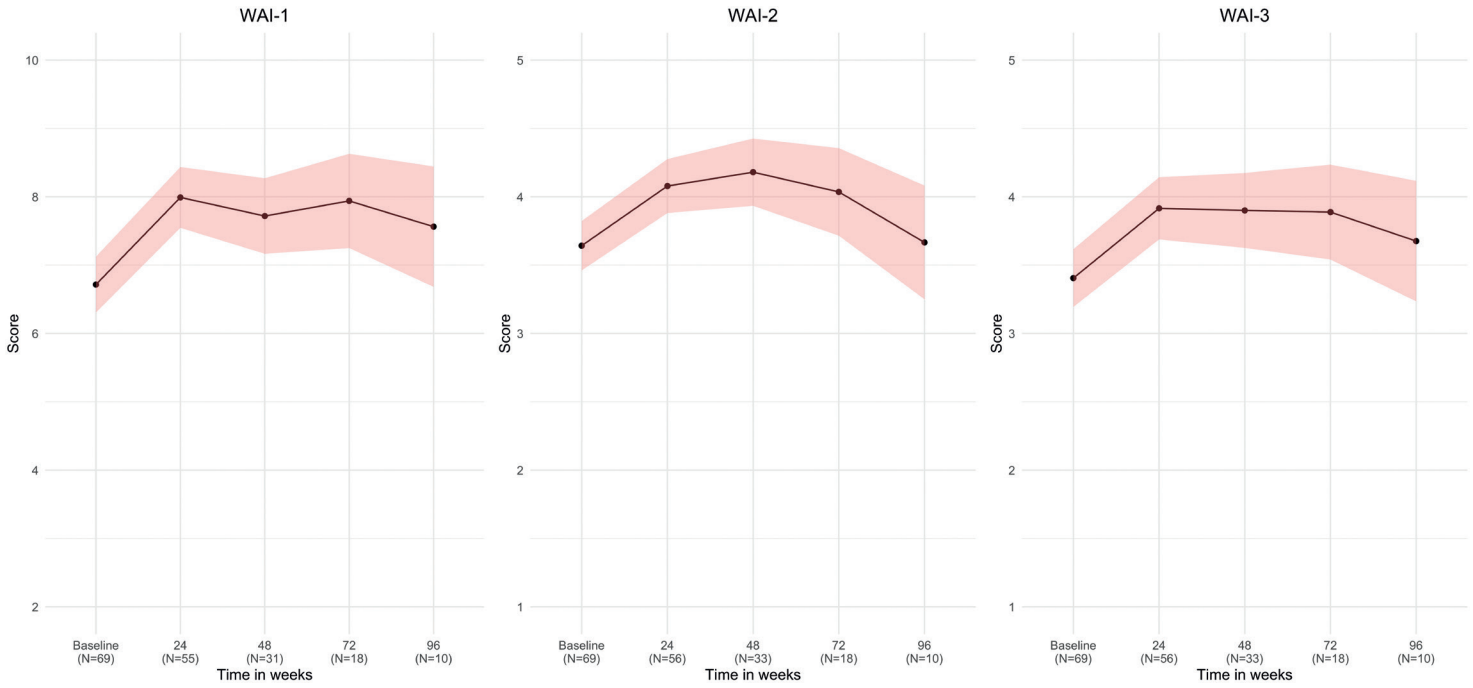

Figure 1. Work Ability Index (WAI) mean scores over time from baseline to 96 weeks of follow-up

Results based on our linear mixed-effects models. Higher scores indicate better patient-reported general (WAI-1), physical (WAI-2) and mental (WAI-3) work ability. The red area surrounding the black line represents the 95% confidence interval. To increase the legibility of this figure, data from the visits at 4 weeks of 3 patients were considered baseline data. Missing data: n=6 at baseline; n=3 for WAI-1, n=2 for WAI-2 and WAI-3 at 24 weeks; n=6 for WAI-1, n=4 for WAI-2 and WAI-3 at 48 weeks; n=1 at 72 weeks. As follow-up duration varied between patients, the number of patients per visit decreases over time.

Table 1. Patient characteristics at baseline

Demographic, health- and work-related characteristics	**TREAT NL cohort (n=93)**
Demographic characteristics	
Gender – no. (%)	
Male	54 (58)
Female	39 (42)
Age in years – mean ± SD	43 ± 15
Ethnicity – no. (%)	
White (Europe, Russia, Middle East, North Africa, USA, Canada, Australia)	71 (76)
African-other, Afro-Caribbean	3 (3)
Afro-American	0 (0)
Asian-Chinese	4 (4)
South-Asian (India, Pakistan, Sri Lanka, Nepal, Bhutan, Bangladesh)	6 (7)
Asian-other (Korea, China north of Huai River)	5 (5)
Japanese	0 (0)
Hispanic or Latino	0 (0)
Mixed[a]	4 (4)
Other	0 (0)
Educational status: ISCED classification – no. (%)	
ISCED 0: Early childhood education	0 (0)
ISCED 1: Primary education	3 (3)
ISCED 2: Lower secondary education	15 (16)
ISCED 3: Upper secondary education	22 (24)
ISCED 5: Short-cycle tertiary education	16 (17)
ISCED 5: Short-cycle tertiary education	4 (4)
ISCED 6: Bachelor's or equivalent level	22 (24)
ISCED 7: Master's or equivalent level	8 (9)
ISCED 8: Doctoral or equivalent level	3 (3)
Health-related characteristics	
Disease duration in years – mean ± SD	39 ± 15
Allergic co-morbidities – no. (%)	
Asthma[b]	54 (58)
Allergic rhinoconjunctivitis[b]	56 (60)
Atopic eye disease[b]	12 (13)
Eosinophilic oesophagitis[b]	0 (0)
Allergic contact dermatitis[1,c]	63 (68)
Food allergy[2,d]	53 (57)
Treatment at outpatient daycare treatment unit in the past year – no. (%)	18 (19)
Treatment at outpatient daycare treatment unit in the past year in cumulative days – median (IQR)[3]	5.5 (3-13.5)
Hospitalization for atopic dermatitis in the past year – no. (%)	7 (8)
Hospitalization for atopic dermatitis in the past year in cumulative days – median (IQR)	7.0 (2-14)

Table 1. *(continued)*

Demographic, health- and work-related characteristics	TREAT NL cohort (n=93)
Work-related characteristics	
Work status: Eurostat classification – no. (%)	
Employed	53 (57)
Self-employed	8 (9)
Disability pension (unable to work)	11 (12)
Retired	7 (8)
Student or pupil	1 (1)
Engaged on home duties	0 (0)
Unemployed	2 (2)
Employed and self-employed	4 (4)
Employed and student or pupil	7 (8)
Working patients – no. (%)[e]	72 (77)
Patients that reported problems at work – no. (%)[4,f]	46 (64)
Combination of problems[g]	15 (21)
Psychological problems	9 (13)
Pain	8 (11)
Fatigue	4 (6)
Pruritus	3 (4)
Receiving insufficient understanding from the working environment	2 (3)
Inconsistent course of illness	1 (1)
Other[h]	4 (6)
Patients that reported days lost from usual activities (e.g. work, study) – no. (%)[i]	54 (58)
Average number of days lost from usual activities per month – median (IQR)[5,j]	4 (1–7)
Working patients that reported days lost from usual activities – no. (%)[k]	43 (60)
Average number of days lost from usual activities per month in working patients – median (IQR)[6]	3.5 (1-5)
Not working patients that reported days lost from usual activities – no. (%)[l]	11 (52)
Average number of days lost from usual activities per month in not working patients – median (IQR)[7]	16.3 (2.5-30)
Patients that reported reasons for not working – no. (%)[l]	15 (71)
Retired	6 (29)
Incapacitated for work because of experienced limitations due to atopic dermatitis	3 (14)
Incapacitated for work because of other reasons	3 (14)
Incapacitated for work because of a combination of atopic dermatitis and other reasons	1 (5)
Unemployed	2 (10)

IQR, interquartile range; No., number of patients; SD, standard deviation. Missing data: [1] n=1, [2] n=1, [3] n=2, [4] n=4, [5] n=2, [6] n=1, [7] n=1.[a] Creole and Dutch (n=1), Chinese and Creole (n=1), Indonesian and Dutch (n=2), [b] physician diagnosis, [c] positive patch test: remaining patients were never tested, unknown or tested negative, [d] patient-reported food allergy, [e] Patients that were employed, self-employed, employed and self-employed or employed and student or pupil at baseline, [f] of the working patients: (self-) employed patients that reported problems at work, [g] pruritus and fatigue (n=1), pruritus, fatigue and pain (n=2), pruritus, fatigue and psychological problems (n=2), pruritus, fatigue, pain and inconsistent course of illness (n=2), pruritus, psychological problems and inconsistent course of illness (n=1), pain and inconsistent course of illness (n=1), pruritus, fatigue and other: eczema flare with stress (n=1), psychological problems and other: visibility of the disease (n=1), pain and other: eczema located on fingertips (n=1), pruritus, fatigue and other: eye complaints (n=1), pruritus, fatigue, pain and other: scaling/flaking skin (n=1), pruritus, fatigue, receiving insufficient understanding from the working environment and other: tingling/burning skin sensation (n=1), [h] concentration problems (n=1), planning of emollient use (n=1), tight feeling of the skin and visibility of the disease (n=1), the use of soap triggers eczema (n=1), [i] average number of days per month in the past 3 months, [j] in patients that reported days lost from usual activities, [k] n=72, [l] n=21.

Quality of working life

QWLQ scores are shown in Fig. 2. The subscale 'Problems due to health situation' was found to have the lowest mean of 37.4±22.3, showing an increase followed by a light decrease over time. The subscale with the highest baseline score was 'Meaning of work' with a mean score of 85.2±13.3, which remained stable over time. The subscale 'Understanding and recognition in the organization' showed a decrease from a baseline score of 78.9±14.9. Both the subscale 'Perception of the work situation' and 'Atmosphere in the working environment' showed a decrease in mean score from baseline (81.3±12.9 and 82.3±11.5, respectively), followed by an increase. The mean QWLQ total score was 74.0±9.1 at baseline, 78.5±9.8 at 24 weeks, 77.5±9.6 at 48 weeks, 72.9±13.1 at 72 weeks and 76.4±13.2 at 96 weeks. When comparing the means at baseline with 48 weeks, we only found significant improvement for total score and subscale 'Problems due to the health situation' (4.1 points with $p=0.032$ and 23.3 points with $p<0.001$, respectively).

Characteristics associated with change in QWLQ from baseline to 48 weeks

Table 2 shows the baseline characteristics significantly associated with change in score from baseline to 48 weeks (complete results shown in Table S1). We found that females reported more improvement of subscales 'Meaning of work' (12.2±4.5, $p=0.018$) and 'Atmosphere in the working environment' (12.0±4.4, $p=0.021$), and QWLQ total score (9.7±4.0, $p=0.038$) compared to males, whereas Asian patients had less improvement of the subscales 'Perception of the work situation' (-12.8±3.1, $p<0.001$) and 'Understanding and recognition in the organization' (-29.5±9.6, $p=0.027$), and the QWLQ total score (-13.2±4.8, $p=0.022$) compared to White patients. In addition, less improvement was observed for patients who experienced days lost from usual activities in subscales 'Meaning of work' (-16.5±6.5, $p=0.029$) and 'Atmosphere in the working environment' (-22.8±6.1, $p=0.004$). Patients with ISCED 2-4 and ISCED 5-6 had higher improvement of subscale 'Atmosphere in the working environment' (36.3±9.5, $p=0.003$ and 29.1±8.3, $p=0.006$, respectively), compared to ISCED 0-1 patients. Patients who reported problems at work had higher improvement of subscale 'Problems due to the health situation' (24.7±9.3, $p=0.016$) in comparison to patients who did not. Patients with allergic rhinoconjunctivitis had higher improvement of 'Perception of the work situation' (9.3±2.8, $p=0.005$). Patients with atopic eye disease, contact dermatitis and food allergy had lower improvement of respectively subscales 'Perception of the work situation' (-12.6±4.2, $p=0.009$), 'Problems due to the health situation' (-33.5±13.0, $p=0.020$) and 'Atmosphere in the working environment' (-17.2±5.9, $p=0.016$).

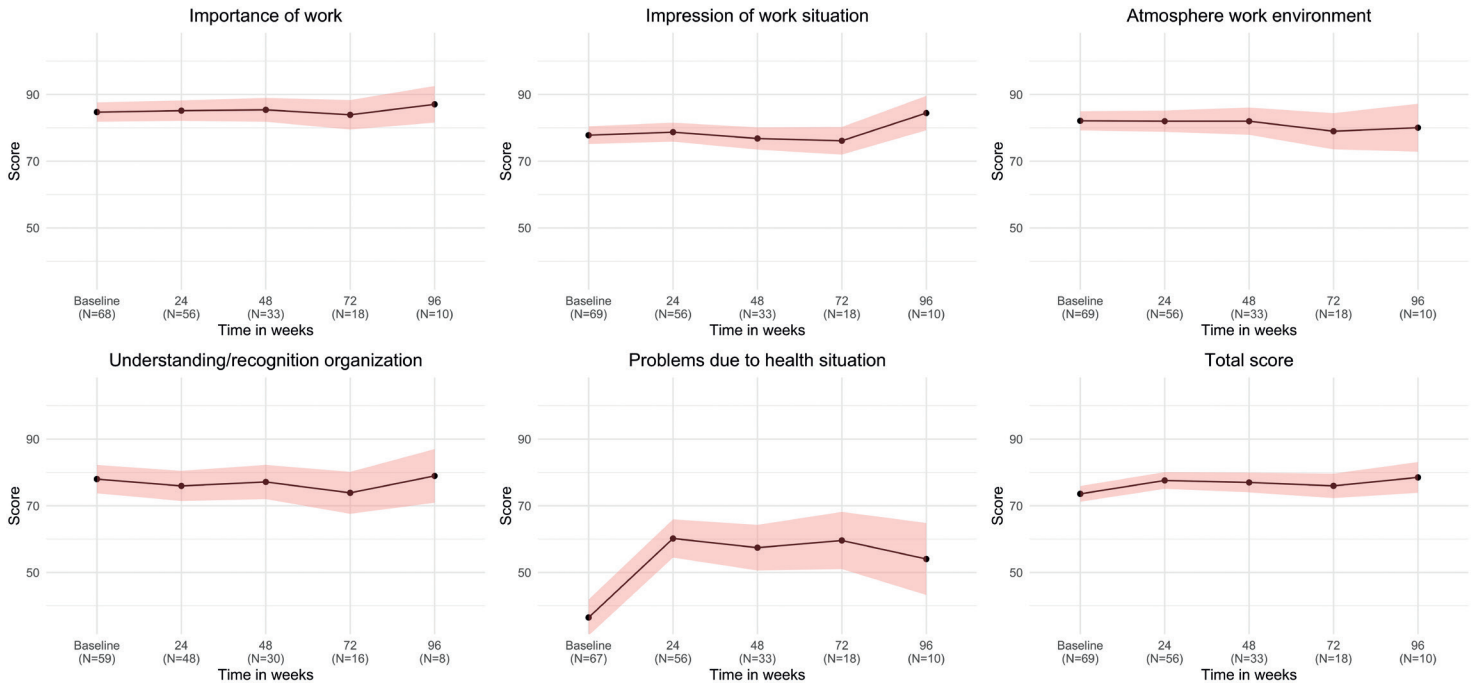

Figure 2. Quality of Working Life Questionnaire (QWLQ) mean (sub)scores over time from baseline to 96 weeks of follow-up

Results based on our linear mixed-effects models. Higher scores indicate better patient-reported quality of working life. The red area surrounding the black line represents the 95% confidence interval. To increase the legibility of this figure, data from the visits at 4 weeks of 3 patients were considered baseline data. Missing data: n=7, n=6, n=6, n=16, n=8, n=6 for subscale 1 to total score, respectively at baseline; n=10 for subscale 4, n=2 for the other scores at 24 weeks; n=7 for subscale 4, n=4 for the other scores at 48 weeks; n=2 for subscale 4 at 72 weeks and 96 weeks. As follow-up duration varied between patients, the number of patients per visit decreases over time.

Table 2. Characteristics significantly associated with change in Quality of Working Life Questionnaire (QWLQ) (sub)scores from baseline to 48 weeks of follow-up

(Sub)scale	Characteristics	Estimated difference in score ± SE	P-value
Meaning of work	Female	12.2 ± 4.5	0.018
	Days lost from usual activities	-16.5 ± 6.5	0.029
Perception of the work situation	Asian	-12.8 ± 3.1	<0.001
	Allergic rhinoconjunctivitis Atopic eye	9.3 ± 2.8	0.005
	disease	-12.6 ± 4.2	0.009
Atmosphere in the working environment	ISCED 2-4	36.3 ± 9.5	0.003
	Days lost from usual activities	-22.8 ± 6.1	0.004
	ISCED 5-6	29.1 ± 8.3	0.006
	Food allergy	-17.2 ± 5.9	0.016
	Female	12.0 ± 4.4	0.021
	Allergic rhinoconjunctivitis	12.8 ± 5.8	0.052*
	Asthma	10.8 ± 5.0	0.056*
Understanding and recognition in the organization	Asian	-29.5 ± 9.6	0.027
Problems due to the health situation	Patient-reported problems at work	24.7 ± 9.3	0.016
	Contact dermatitis	-33.5 ± 13.0	0.020
	ISCED 7-8	-41.7 ± 20.5	0.059*
Total score	Asian	-13.2 ± 4.8	0.022
	Female	9.7 ± 4.0	0.038
	Days lost from usual activities	-13.0 ± 6.0	0.060*

The reference standard was characteristic 'not present' or 'White' in case of 'Asian', 'Male' in case of 'Female', 'Unknown' in case of patch test/contact dermatitis and 'ISCED 0-1' in all ISCED variables. *, borderline significant. Results are based on our multivariate models.

QWLQ convergent validity

Spearman correlations for the total QWLQ are shown in Table 3, with corresponding scatter plots in Fig. S1A and S1B. For all PROMs no correlations were found ($p>0.05$) and correlation coefficients r did not exceed $|0.40|$. Only a borderline significant weak correlation was found for DLQI (r=-0.24, p=0.058).

Table 4 shows Spearman correlations of QWLQ subscale 5 'Problems due to the health situation' (scatter plots: Fig. S2A and S2B). We found a moderate positive correlation for EQ-5D-5L health state (r=0.43, $p<0.001$) and a strong negative correlation for DLQI (r=-0.65, $p<0.001$). In addition, weak negative correlations were found for VAS peak pain and mean sleep loss (r=-0.26, p=0.035 and r=-0.28, p=0.023, respectively).

Table 3. Spearman correlations coefficients for the Quality of Working Life Questionnaire (QWLQ) total score in relation with comparable constructs at baseline

Convergent Validity of the QWLQ total score: Spearman correlation coefficients		
Comparable construct	**Spearman correlation coefficient**	**P-value**
EQ-5D-5L health state	r = 0.17	0.186
POEM	r = 0.00	1.000
DLQI	r = -0.24	0.058
PGA	r = 0.04	0.764
NRS peak itch 0-10 past 24 hours	r = 0.05	0.674
NRS mean itch 0-10 past 7 days	r = -0.07	0.603
VAS peak pain 0-10 past 24 hours	r = -0.08	0.513
VAS mean sleep loss 0-10 past 3 days	r = -0.13	0.303

Table 4. Spearman correlations coefficients for the Quality of Working Life Questionnaire (QWLQ) subscale 5 'Problems due to the health situation' in relation with comparable constructs at baseline

Convergent Validity of QWLQ subscale 5: Spearman correlation coefficients		
Comparable construct	**Spearman correlation coefficient**	**P-value**
EQ-5D-5L health state	r = 0.43	**<0.001**
POEM	r = -0.20	0.111
DLQI	r = -0.65	**<0.00001**
PGA	r = 0.06	0.673
NRS peak itch 0-10 past 24 hours	r = -0.02	0.873
NRS mean itch 0-10 past 7 days	r = -0.03	0.813
VAS peak pain 0-10 past 24 hours	r = -0.26	**0.035**
VAS mean sleep loss 0-10 past 3 days	r = -0.28	**0.023**

Significant values are displayed in bold

Floor and ceiling effects

There were no patients in whom the lowest possible QWLQ total score (0) was observed. The highest possible QWLQ total score was found once in one patient (1 out of 201 observations). A ceiling effect was observed only for subscale 'Meaning of work' where in 41 out of 201 observations (20%) the highest score (100) was observed.

DISCUSSION

In this study we analyzed work-related patient characteristics of 93 AD patients treated with dupilumab in daily practice. We primarily aimed to describe the longitudinal work ability and QWL of this population. Our patients reported a decreased work ability and QWL at baseline, mainly due to health-related problems. Significant improvement of work ability and QWL was observed with treatment after 48 weeks. Furthermore, we assessed associations between patient characteristics and change in QWLQ and the convergent validity of the QWLQ.

The majority of working patients reported problems at work. In most cases a combination of problems was reported, including pruritus, fatigue, pain and psychological complaints. In earlier research, fatigue was found the main reason for work productivity loss in inflammatory bowel disease (IBD).[30] In half of the employed IBD population, disease activity and disease burden was found to cause work productivity loss, driving indirect costs.[30] It has been shown that the majority of moderate-to-severe AD patients miss at least 1 day of work per year.[31] We found that more than half of our working patients reported days lost from usual activities (3.5 median days per month), indicating potential work productivity loss. Another study in AD patients showed a mean of 9.6-19 hours per week work productivity loss.[32]

Regarding WAI, we found a decreased mean general work ability of 6.8 (0-10) and a mean physical and mental/emotional work ability of respectively 3.7 and 3.4 (1-5) at baseline, with significant improvement at 48 weeks. In other studies a mean general work ability of 5.1 was found in cancer survivors and of 5.4 in cancer patients at the time of diagnosis.[33, 34] In contrast, a mean general work ability ranging from 7.8 to 8.2 was found in nurses.[35] In other chronic diseases, common prognostic factors for work disability were health complaints, limitation in daily physical activities caused by the disease, heavy manual work and female gender.[36]

At baseline we observed a mean QWLQ total score of 74.0, together with a mean score of 37.4 for subscale 5 'Problems due to the health situation'. In cancer survivors a mean QWLQ total score of 75 and subscale 5 of 57 has been demonstrated, in contrast to a mean QWLQ total score of 79 and subscale 5 of 81 in employed people without cancer.[12] In IBD patients a mean QWLQ total score of 78 and subscale 5 of 54 were found.[37] The results for the other subscales were similar between our AD, and cancer survivor and IBD populations.[12, 37] The remarkably lower score for subscale 5 in our population show that patients with AD experience a relatively high QWL burden regarding their health situation. The overall decrease in QWL is shown to be mainly driven by this subscale. We found significant and clinically meaningful improvement of the scores at 48 weeks.[13] Greater improvement was observed in females compared to males.

Quality criteria have been defined for measurement properties of questionnaires, including convergent validity.[26] A positive rating for construct validity is given if at least 75% of results correspond to a priori hypotheses.[38] While our sample size was adequate (i.e. n=50-99),[38] we found no significant correlations between the QWLQ total score and the other PROMs. Thus, none of our hypotheses regarding moderate-to-strong correlations were confirmed. More suitable comparable constructs may be available (e.g. VAS overall QWL). Regardless, QWL seems not to be captured by broadly used validated PROMs in AD and therefore the QWLQ could be considered of added value. We found a strong negative correlation between DLQI and QWLQ subscale 5, implicating that perceived health problems are accompanied by a decrease of quality of life.

Limitations of this study include several factors resulting from the daily practice setting. Noncompliance and unintended dosing deviations are potential factors, as patients received their treatment at home. Bias may have been induced by the non-blinded observational nature. We did not focus on strict label use of dupilumab and patients that used comedication or continued treatment in an alternative dosing schedule due to ineffectiveness or side-effects were included in our analyses.

Implications for research and clinical practice

Further investigation of work ability and QWL using WAI and QWLQ in a larger population and comparing different treatments would be of interest. In the future QWLQ could be used on a group level as effect measurement of interventions in research, as well as on individual patient level to monitor different aspects of QWL and to intervene with supportive care if appropriate. The latter strategy may facilitate to identify patients that benefit from tailored interventions. A need exists for development of programs that can support this demand. Furthermore, investigating the impact on work productivity specifically can contribute to determining the cost-effectiveness of treatments.

Conclusion

The majority of AD patients starting with dupilumab, indicating moderate-to-severe disease, experiences days lost from work and other usual activities, demonstrating potential work productivity loss. Most working patients report problems at work, often a combination of pruritus, fatigue, pain and psychological complaints. Patients report a decreased work ability and experience a high burden regarding QWL, in particular due to health-related problems. There seems to be significant improvement of work ability and QWL with treatment over time.

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SUPPLEMENTARY MATERIALS

Table S1. Characteristics in the multivariate models for change in Quality of Working Life Questionnaire (QWLQ) (sub)scores from baseline to 48 weeks.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/w2s6p735d5.1

Figure S1A. Scatter plot with fit line for percentage QWLQ total score in relation to percentage EQ-5D-5L health state, POEM, DLQI and PGA at baseline.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/tftrgc7tty.1

Figure S1B. Scatter plot with fit line for percentage QWLQ total score in relation to percentage NRS peak pruritus 24 hours, NRS mean pruritus 7 days, VAS peak pain 24 hours and VAS mean sleep 3 days at baseline.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/6sxrt2x9c8.1

Figure S2A. Scatter plot with fit line for percentage QWLQ subscale 5 in relation to percentage EQ-5D-5L health state, POEM, DLQI and PGA at baseline.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/tp6y7x9fvw.1

Figure S2B. Scatter plot with fit line for percentage QWLQ subscale 5 in relation to percentage NRS peak pruritus 24 hours, NRS mean pruritus 7 days, VAS peak pain 24 hours and VAS mean sleep 3 days at baseline.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/9fty7tpx9j.1

Appendix S1. Work Ability Index (WAI): first three questions (WAI-1, WAI-2, WAI-3).

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/nw5k62hfyh.1

Appendix S2. Quality of Working Life Questionnaire (QWLQ).

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/j8zh7r35v6.1

APPENDIX

Conflicts of interest

MAM: consultancies for Sanofi and Pfizer; PS: consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), received a departmental independent research grant for TREAT NL registry from LeoPharma 2019, and Novartis in 2020 (and more companies agreed already to sponsor in order to have multisponsoring) for the TREAT NL registry, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and, is Chief Investigator (CI) of the systemic and phototherapy atopic eczema registry (TREAT NL) for adults and children and one of the main investigators of the SECURE-AD registry. All other authors declare that they have no conflicts of interest.

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THE CLINICAL RELEVANCE OF DUPILUMAB SERUM CONCENTRATION IN PATIENTS WITH ATOPIC DERMATITIS: A TWO-CENTER PROSPECTIVE COHORT STUDY

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ABSTRACT

Background

Dupilumab is prescribed in one dosage across adult atopic dermatitis patients. Differences in drug exposure may explain variation in treatment response.

Objective

Investigating the clinical relevance of dupilumab serum concentration in atopic dermatitis in real-world practice.

Methods

In two centres (Netherlands, UK), adults treated with dupilumab for atopic dermatitis were evaluated for effectiveness and safety pre-treatment and at 2, 12, 24 and 48 weeks; trough serum samples were analysed for dupilumab concentration at corresponding time points.

Results

In 149 patients, median dupilumab levels during follow-up ranged from 57.4-72.4μg/mL. Levels showed high inter-patient and low intra-patient variability. No correlation was found between levels and ΔEASI. At 2 weeks, levels of ≥64.1μg/mL predict EASI≤7 at 24 weeks (specificity:100%, sensitivity:60%; p=0.022). At 12 weeks, ≤32.7μg/mL predicts EASI>7 at 24 weeks (sensitivity:95%, specificity:26%; p=0.011). Inverse correlations were found between baseline EASI and levels at 2, 12 and 24 weeks (r=-0.25-0.36; p≤0.023). Low levels were particularly observed in patients with adverse events, treatment interval deviation and discontinuation.

Conclusion

At the on-label dosage, the measured range of dupilumab levels does not seem to yield differences in treatment effectiveness. However, disease activity does seem to influence dupilumab levels - higher baseline disease activity results in lower levels at follow-up.

INTRODUCTION

Dupilumab is a human monoclonal antibody against interleukin (IL)-4 receptor alpha that inhibits IL-4/IL-13 signalling.[1] In Europe dupilumab is approved for treatment of moderate-to-severe atopic dermatitis (AD) in patients aged ≥6 years. Dupilumab's product assessment report by the European Medicines Agency (EMA) mentions that a dose-response study was conducted comparing different dosing schedules. A dose-dependent Eczema Area and Severity Index (EASI) reduction was observed from baseline to week 16, with highest reductions in the 300mg fortnightly and weekly groups.[2] In studies comparing weekly and fortnightly dosing schedules no differences were found regarding efficacy and safety.[3,4] A fortnightly administration of 300mg was defined as the licensed posology. Consistent with phase III trial data,[5] we have shown that this dosage delivers a sustained improvement of patient- and investigator reported outcomes in real-world practice.[6-9]

Serum concentrations of therapeutics are determined by drug- and patient-related characteristics that affect absorption, distribution and elimination.[10,11] After a single subcutaneous injection of dupilumab, peak drug concentrations are achieved at approximately 7 days, followed by a slow decrease in concentration thereafter. Across clinical trials, steady-state concentrations resulting from fortnightly 300mg injections are achieved by week 16 with mean trough concentrations ranging from 60.3µg/mL to 80.2µg/mL.[12,13] After discontinuation, the median time to decrease below a non-detectable concentration is 10 weeks.[1,14] At the population level, the on-label adult dosage was determined to achieve sufficient drug exposure with concentrations at the plateau of the exposure–effect relationship.[15] At an individual level, patient characteristics may influence drug exposure and therefore treatment response (i.e. both effectiveness and safety).

Four and 8-week dosage intervals were described to be associated with lower serum concentrations and decreased effectiveness.[4] Clinical trial patients with lower trough levels at week 16 were found to have less clinical improvement, but no exposure-response relationship was identified for adverse events (AEs).[2] However, such data is limited, with published studies investigating the relationship between dupilumab levels and conjunctivitis as AE, and not on other aspects including effectiveness. Serum drug level data from the Phase 3 studies did suggest an inverse relationship whereby conjunctivitis incidence may decrease with higher week 16 trough concentrations of dupilumab.[16,17] Local under-treatment (inadequate drug exposure), due to a higher target burden or lower tissue distribution, were suggested as potential contributing factors.[16] However, this was not replicated in adolescents where the incidence of conjunctivitis showed no relationship with concentrations at 16 weeks.[18] Conjunctivitis

is a relevant adverse event in patients on dupilumab, but this diagnosis may capture a range of eye conditions including atopic eye disease and dupilumab-associated ocular surface disease, which likely differ in aetiology which complicates the study of potential contributory factors such as drug level.

Variation in treatment response to dupilumab exists.[16] Differences in drug exposure may explain this variation. Further investigating the relationship between dupilumab levels and treatment response would give insight into the potential of therapeutic drug monitoring. The utility of therapeutic drug monitoring has been proven in the use of TNF-antagonists for psoriasis.[19] As currently a one-size-fits-all approach is applied when prescribing dupilumab, we performed an exploratory study to investigate this standard dosing. The aim of this study was to investigate the clinical relevance (i.e. the influence on both effectiveness and safety) of serum concentrations of dupilumab in AD in real-world practice.

MATERIALS AND METHODS

Study design and population

A prospective cohort study was conducted. Patients with AD based on the U.K. working party's criteria,[20] receiving dupilumab treatment in the context of routine clinical care, were included from July 2018 to February 2021 at the Amsterdam University Medical Centers, The Netherlands (NL), and from July 2017 to November 2018 at the Guy's and St Thomas' NHS Foundation Trust, the United Kingdom (UK). All patients met the national reimbursement criteria for dupilumab, which stipulate a treatment episode with one or more conventional systemic therapies.[21,22] The majority of participants (n=103) were also participants of the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry.[23,24] In all patients additional informed consent was obtained for participation in this study. Ethical approval has been obtained from the appropriate local ethics committee. Treatment discontinuation resulted in discontinuation of study participation.

Study outcomes

Clinical outcomes included an investigator-assessed measure of effectiveness (EASI: 0-72[25]), patient-reported outcome measures (Numerical Rating Scale (NRS): 0-10, NRS peak pruritus past 24 hours (NL); mean pruritus past 7 days (UK)[26], Patient-Oriented Eczema Measure (POEM): 0-28[27] and Dermatology Life Quality Index (DLQI): 0-30[28]) and safety (AE definitions included in Table 3)[29], measured at baseline (NL+UK), 2 (UK), 12, 24 and 48 weeks (NL+UK).

Blood samples were collected at baseline (NL+UK), 2 (UK), 12 (NL+UK), 24 (NL) and 48 (NL) weeks. The time point of blood sampling was aspired to be at the trough level, just before a new dose administration. Samples were centrifuged, aliquoted into microtubes and frozen at -20°C (NL) and -80°C (UK). Serum levels were measured using an enzyme-linked immunosorbent assay (ELISA). Maxisorp microtiter plates were coated overnight at room temperature (RT) with 1 µg/mL monoclonal anti-dupilumab (clone 1G11). This is a chimeric antibody of rabbit origin, with a mouse IgG2b Fc, recombinantly expressed as described before.[30] After five times washing with PBS/0.02% Tween (PT), plates were incubated for 1h at RT with patient serum samples, diluted 100-fold and 2000-fold in high performance ELISA buffer (HPE, Sanquin). Subsequently, the plates were washed with PT and incubated for 1h with 0.5µg/mL mouse monoclonal antihuman IgG4 (clone MH164.4, Sanquin). After washing, the ELISA was developed with 1-step ultra TMB-ELISA Substrate Solution (thermoFischer) diluted with MQ (ratio 3:1). The reaction was stopped with 0.2M HCl. Delta of the absorption at 450 and 540nm was determined and compared to a titration curve of dupilumab in each plate. The lower limit of quantification is 0.3µg/mL; accuracy and precision ranged from 87% to 102% and 4.4% to 12.2% CV (coefficient of variation).

Statistical analyses

Patient characteristics and outcomes were summarized using descriptive statistics. Furthermore, we predefined the following analyses of interest.

To investigate the relationship between concentration and clinical response, concentration-effect curves were established. Patients were ordered categorically based on dupilumab level into groups of 10 with corresponding ΔEASI.[19,31] Sensitivity analysis included only patients with a moderate-to-severe baseline EASI (EASI≥6.0).[32] Both non-predictive (i.e. at individual time points) and predictive (i.e. levels predicting future response) analyses were performed. In addition, correlations between levels and (absolute) outcomes at each individual time point were explored using Spearman correlations, Chi-squared tests and Mann-Whitney tests, as appropriate. Predictive analyses were also undertaken by assessing the correlation between baseline EASI and dupilumab levels.

To further examine whether early drug exposure predicted clinical response, we used internationally agreed criteria for response and stratified patients into a group that did and did not reach EASI≤7 and ≥1 disease domain targets (EASI≤7, NRS≤4, POEM≤7, DLQI≤5) at 24 weeks, in accordance with the Treat-to-Target algorithm.[33] Subsequently, we investigated whether drug levels at 2, 12 and 24 weeks and baseline EASI predicted

outcomes at 24 weeks using Mann-Whitney tests and receiver-operator characteristics (ROC) curves.[19,31]

Statistical analysis of the data was performed using the software program SPSS (IBM SPSS Statistics 26). Missing data were excluded on a test-by-test basis. Results were considered statistically significant at $p<0.05$.

RESULTS

Patient characteristics

Of 178 consented to the study, 149 patients were included in the analyses. Twenty-nine patients were excluded based on a lack of serum sampling (n=24), refraining from starting dupilumab (n=3) or receiving dupilumab prior to participation (n=2). Baseline characteristics are shown in Table 1. The majority was male (63.1%), white (75.2%) and had skin type II (42.3%). The median age was 43 years and BMI was 24.7. Dupilumab was prescribed according to the licensed posology (600mg loading dose followed by 300mg fortnightly). However, one patient received 300mg at baseline due to a suspected adverse reaction to dupilumab. In 17 patients the dosing schedule was adjusted during follow-up (range: 10 days-5 weeks; see results section on treatment regimen deviations). Eighteen patients concomitantly used prednisone at baseline. Four patients continued prednisone treatment during follow-up and 14 (NL) patients used prednisone in a tapering schedule for a median of 24.5 days. The other 131 patients were treated with dupilumab monotherapy often in combination with oral antihistamines and topical treatments. The median follow-up duration was 48 weeks for the outcome measures (range: 0 to 58 weeks) and 24 weeks for the blood samples (range: -4 to 59 weeks). Median EASI, NRS, POEM and DLQI scores at baseline and during follow-up are described in Table 2.

Table 1. Patient characteristics at baseline

Patient characteristics at baseline (n=149)	
Sex – no. (%)	
Female	55 (36.9)
Male	94 (63.1)
Age in years – median (IQR)	43 (27.5-53.0)
Fitzpatrick skin type – no. (%)[1]	
I	16 (10.7)
II	63 (42.3)
III	38 (25.5)
IV	8 (5.4)
V	11 (7.4)
VI	6 (4.0)

Table 1. *(continued)*

Patient characteristics at baseline (n=149)	
Ethnicity – no. (%)[2]	
White	112 (75.2)
Black-African, Afro Caribbean	6 (4.0)
South Asian	9 (6.0)
Asian-Chinese	2 (1.3)
Asian-other	4 (2.7)
Mixed [a]	6 (4.0)
Other	1 (0.7)
BMI – median (IQR)[3]	24.7 (22.3-27.6)
Previous use of systemic therapies for AD – no. (%)	
Ciclosporin	124 (83.2)
Systemic corticosteroids	96 (64.4)
Methotrexate	90 (60.4)
Azathioprine	45 (30.2)
Mycophenolic acid/mycophenolate mofetil	44 (29.5)
Investigational medication	10 (6.7)
Upadacitinib/placebo (JAK inhibitor)	4 (2.7)
Baricitinib/placebo (JAK inhibitor)	3 (2.0)
Tralokinumab/placebo (mAb, IL-13)	2 (1.3)
Tralokinumab (mAb, IL-13)	1 (0.7)
Omalizumab	1 (0.7)
Other medication (including dupilumab)	0 (0)
Number of previously used systemic therapies per patient– no. (%)	
1	23 (15.4)
2	46 (30.9)
3	42 (28.2)
4	21 (14.1)
5	17 (11.4)
Concomitant systemic therapy at baseline – no. (%)	
None	51 (34.2)
Prednisone	18 (12.1)
Discontinued during study	14 (9.4)
Continued until study cut-off	4 (2.7)
Systemic antihistamines	89 (59.7)
Systemic antibiotics [b]	4 (2.7)
Systemic immunotherapy	0 (0.0)
EASI – median (IQR)[4]	16.8 (10.8-24.8)
NRS 24 hours pruritus – median (IQR)[1]	7.0 (6.0-8.0)
POEM – median (IQR)[1]	21.0 (16.0-25.0)
DLQI – median (IQR)[5]	15.0 (9.0-20.0)

AD, atopic dermatitis; BMI, body mass index; IQR, interquartile range; No., number; EASI, eczema area severity index; NRS, numeric rating scale (NRS peak pruritus past 24 hours (NL), NRS mean pruritus past 7 days (UK)); POEM, patient oriented eczema measure; DLQI, dermatology life quality index; [a] Black and Asian (n=2), Black and White (n=1), Asian and White (n=2); [b] minocycline 2dd 50 mg, flucloxacillin 3dd 500mg, flucloxacillin 4dd 500mg (2x); Missing data: [1] n=7, [2] n=9, [3] n=10, [4] n=4, [5] n=2.

Dupilumab trough drug levels

At baseline, 2, 12, 24, and 48 weeks, respectively, serum samples were obtained from 115, 41, 115, 71, and 53 patients. Dupilumab levels ranged from being undetectable at baseline to a level of 251.0µg/mL at 48 weeks. The minimum dupilumab concentration measured during follow-up was 22.2µg/mL. The median concentrations per time point are displayed in Table 2. Fig. 1A-B shows that dupilumab drug levels seem to reach a plateau by 12 weeks and to be stable over time, when assessing the ratios between time points (i.e. low intra-patient variability).

Table 2. Outcome measures and dupilumab serum concentrations at baseline and during follow-up

	EASI (0-72)		NRS (0-10)		POEM (0-28)		DLQI (0-30)		Serum concentration (µg/mL)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Baseline	16.8	10.8-24.8	7.0	6.0-8.0	21.0	16.0-25.0	15.0	9.0-20.0	0	0-0
2 weeks	12.5	7.1-19.8	3.5	2.3-5.0	23.5	8.0-18.0	7.0	4.0-10.0	57.4	45.9-67.8
12 weeks	6.1	2.8-11.2	3.0	1.0-5.0	8.0	4.0-13.0	4.0	1.0-8.0	69.5	44.6-94.1
24 weeks	5.5	3.1-9.3	2.0	1.0-6.0	9.0	4.0-15.0	3.5	1.3-7.0	72.4	47.8-101.0
48 weeks	4.4	2.1-8.4	3.0	1.5-5.0	9.0	5.0-14.0	3.0	1.0-8.0	72.0	48.4-101.7

IQR, interquartile range; EASI, eczema area severity index; NRS, numeric rating scale (NRS peak pruritus past 24 hours (NL), NRS mean pruritus past 7 days (UK)); POEM, patient oriented eczema measure; DLQI, dermatology life quality index. The range of concentrations was 1.9, 77.8, 224.0, 172.5 and 251.0 at respectively baseline, 2 weeks, 12 weeks, 24 weeks and 48 weeks.

Correlation between dupilumab levels and ΔEASI

There was no correlation between serum dupilumab at 12 and 24 weeks and change in EASI from baseline (ΔEASI) at respectively 12 and 24 weeks (Fig. 2A-B); this was also true for the subpopulation with moderate-to-severe baseline EASI (≥6.0) at 24 weeks and for the subpopulation on monotherapy dupilumab at 12 weeks (Supplementary fig. 1 and 2). All curves showed large inter-patient variability in dupilumab levels.

As for predictive analyses, Supplementary fig. 3 shows that serum levels at 12 weeks also do not seem to correlate with ΔEASI at 48 weeks. In additional curves we also found no correlation between serum levels at 2 and 12 weeks and ΔEASI at 24 weeks.

Early dupilumab levels, baseline severity and further prediction of response

At 24 weeks, 64.6% (n=73/113) patients reached EASI≤7 and 86.1% (n=105/122) patients reached ≥1 disease domain targets. We observed a higher dupilumab level at 2 and 12 weeks in patients that reached EASI≤7, compared to patients who did not (p=0.022 (median: 66.5 vs. 50.2µg/mL) and p=0.011 (76.0 vs. 57.62µg/mL), respectively).

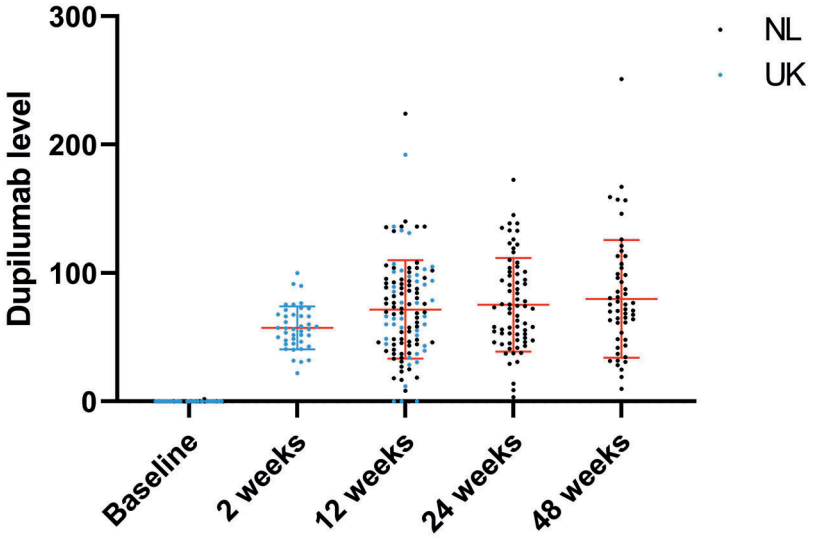

Figure 1A. Dupilumab serum levels over time. Dot plot of the dupilumab levels at different time points (with mean and SDs in red).

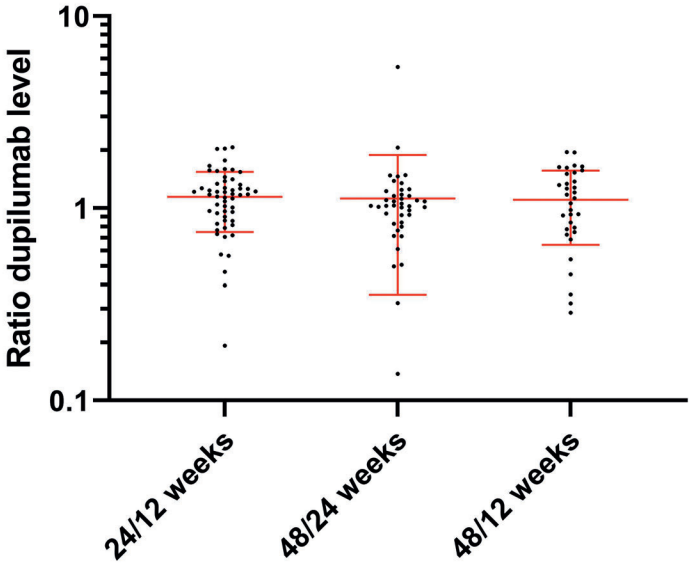

Figure 1B. Ratio of dupilumab serum levels. Dot plot of the ratios of the dupilumab levels at different time points (with mean and SDs in red), which approach 1 (i.e. the concentrations are similar over time).

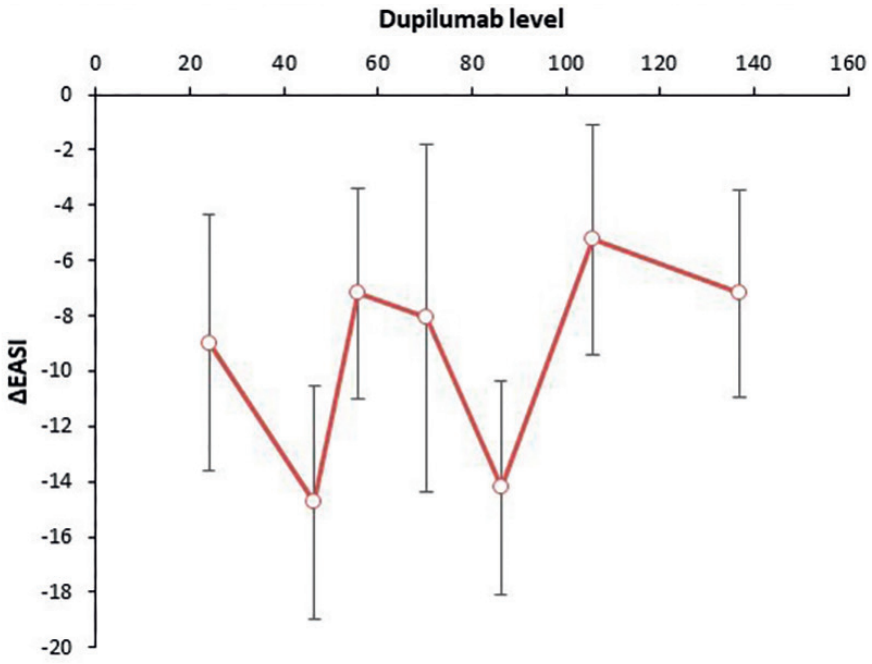

Figure 2A. Concentration-effect curve for dupilumab level and ΔEASI at 24 weeks.

Concentration-effect curve showing the dupilumab serum level in µg/mL at 24 weeks on the x-axis and correlating ΔEASI at 24 weeks (versus baseline) on the y-axis. All patients were sorted from low to high drug concentration, with each dot representing the mean concentration with SDs and correlating ΔEASI for 10 patients (last group 9 patients).

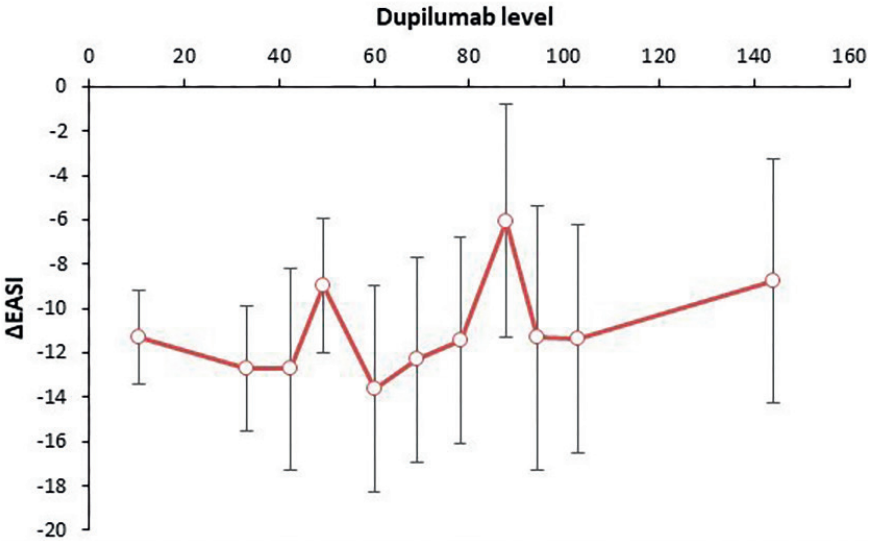

Figure 2B. Concentration-effect curve for dupilumab level and ΔEASI at 12 weeks.

Concentration-effect curve showing the dupilumab serum level in µg/mL at 12 weeks on the x-axis and correlating ΔEASI at 12 weeks (versus baseline) on the y-axis. All patients were sorted from low to high drug concentration, with each dot representing the mean concentration with SDs and correlating ΔEASI for 10 patients (last group 11 patients).

ROC curves in Fig. 3A-B show an area under the curve (AUC) of 0.760 (95% CI: 0.591-0.929, p=0.022) and 0.664 (95% CI: 0.552-0.777, p=0.011) for dupilumab levels at respectively 2 and 12 weeks. AUCs were significantly different from 0.5, indicating that dupilumab levels at 2 and 12 weeks have the ability to distinguish between the group that did and did not reach EASI≤7 at 24 weeks. At 2 weeks, a sensitivity of 60% and a specificity of 100% was found for 64.1µg/mL. At 12 weeks, a sensitivity of 95% and a specificity of 26% was found for a concentration of 32.7µg/mL. No difference was found for levels at 24 weeks (p=0.053, Fig. 3C); and for reaching ≥ 1 disease domain targets at 24 weeks and levels at any of the time points.

When investigating the predictive value of baseline severity, we found a lower baseline EASI score in patients reaching EASI≤7 at 24 weeks (p<0.001 (12.5 vs. 23.6)).

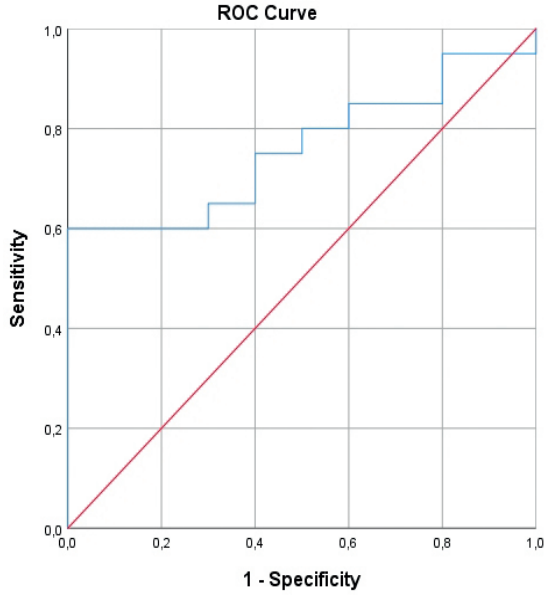

Figure 3A. ROC curve for patients reaching EASI≤7 at 24 weeks of treatment and dupilumab serum level at 2 weeks.

The AUC in the ROC curve is not significantly different from 0.5, indicating that dupilumab concentration does not have the ability to distinguish between the group that reached EASI≤7 (AUC 0.760, 95% CI: 0.591-0.929, p=0.022). At 64.1 µg/mL, a sensitivity of 60% and a specificity of 100% was found.

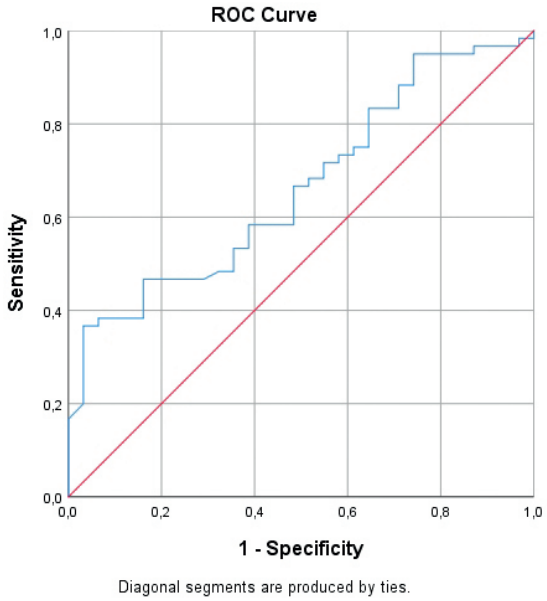

Figure 3B. ROC curve for patients reaching EASI≤7 at 24 weeks of treatment and dupilumab serum level at 12 weeks.

The AUC in the ROC curve is significantly different from 0.5, indicating that the dupilumab concentration has the ability to distinguish the group that reached EASI≤7 (AUC 0.664, 95% CI: 0.552-0.777, p=0.011). At 32.7µg/mL, a sensitivity of 95% and a specificity of 26% was found.

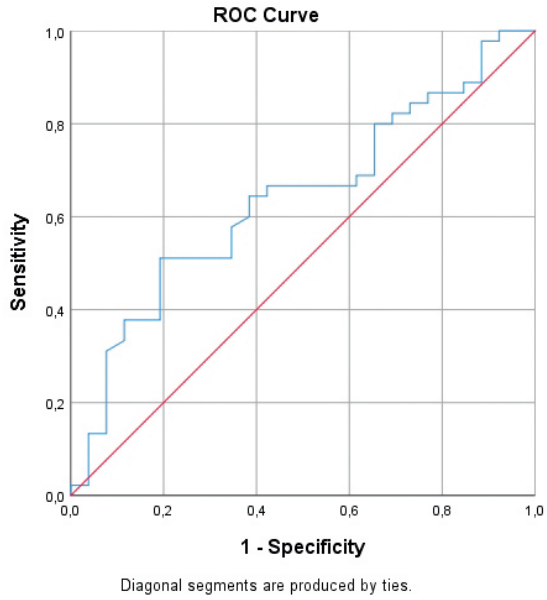

Figure 3C. ROC curve for patients reaching EASI≤7 at 24 weeks of treatment and dupilumab serum level at 24 weeks.

The AUC in the ROC curve is not significantly different from 0.5, indicating that dupilumab concentration does not have the ability to distinguish between the group that reached EASI≤7 (AUC 0.638, p=0.053, borderline significant). At 59.6µg/mL, a sensitivity of 67% and a specificity of 58% was found for EASI≤7.

Correlation between dupilumab levels and absolute outcomes

Analyzing data at the same time point, we found a weak negative correlation between dupilumab levels and absolute EASI at 24 (r=-0.31, p=0.009) and 12 weeks (r=-0.33, p<0.001). Correspondingly, when dividing patients into high and low level groups (based on the median dupilumab level), we found higher EASI scores at 2 and 12 weeks in patients with low serum levels at respectively 2 and 12 weeks (p=0.030 and p=0.015).

When analyzing predictive relationships between baseline EASI and dupilumab levels at follow-up, a correlation was found between baseline EASI and levels at 2, 12 and 24 weeks of follow-up (r=-0.25-0.36, p≤0.023).

Correlation between dupilumab levels and adverse events

In total, 126 AEs were registered in 72 patients (n=72/149, 48.3%; Table 3). The median number of days from start dupilumab until event presentation was 59 days. Eye disorders were most frequently reported (n=49), starting after a median of 70 days. Twelve serious AEs were reported, of which one (arthralgia) was considered possibly related to dupilumab.

At 24 weeks, 59% of patients with a low serum level (based on median) has experienced at least one AE, in contrast to 28% of patients with a high level (p=0.009). At 48 weeks, 68% of patients with low levels has experienced at least one AE, in contrast to 26% of patients with high levels (p=0.002). No associations were found for 2 and 12 weeks.

Correlation between dupilumab levels and treatment regimen deviations

In 17 patients (n=17/149, 11.4%) the dosing schedule was adjusted without resulting in treatment discontinuation, either by prolonging or shortening the injection interval. Eleven patients prolonged, all due to AEs. Five of these increased the interval to once every 3 weeks, one to once every 4 weeks and five to different intervals ranging from 2 to 5 weeks across the study. In six patients the interval was shortened to a 10-day interval due to ineffectiveness. One of these switched back to on-label use.

We found an association between low concentrations at 48 and 24 weeks and presence of treatment interval deviations during the study. At 48 weeks, 36.0% of patients with low levels has experienced interval deviations, in contrast to 7.4% of patients with high levels (p=0.012). Similar results were found for levels at 24 weeks (p=0.023). No association was found for 12 weeks.

Table 3. Adverse events

Number of patients with adverse events – no. (%)	72 (48.3)
Total number of adverse events – no.	126
Relatedness – no.[a]	
Not related	27
Doubtful	18
Possible	67
Probable	13
Very likely	0
Definite	0
Action on adverse event – no.[b]	
Treatment discontinuation	8
Adjustment of treatment schedule	8
No treatment adjustment	39
Course of adverse event – no.	
Recovered/resolved	42
Recovered/resolved with sequelae	23
Not recovered/resolved	49
Fatal	0
Unknown	12
Type of adverse event – no.	
Eye disorders	49
- (Kerato)conjunctivitis	25
- Combined diagnoses	13
- Other[c]	11
Infections and infestations	20
Skin and subcutaneous tissue disorders	12
- Eczema flare	4
- Facial redness	4
- Perioral dermatitis	1
- Panniculitis e.c.i.	1
- Molluscum contagiosum	1
- Basalcelcarcinoma	1
Gastrointestinal disorders	8
Cardiac disorders	6
Musculoskeletal and connective tissue disorders	4
Nervous system disorders	4
Respiratory, thoracic and mediastinal disorders	4
Renal and urinary disorders	4
General disorders and administration site conditions	4
Psychiatric disorders	2
Injury, poisoning and procedural complications	2
Endocrine disorders	2
Reproductive system and breast disorders	1
Blood and lymphatic systemic disorders	1
Investigations	1
Surgical and medical procedures	1
Ears and labyrinth disorders	1
Serious adverse events – no.	12
Median (IQR) number of days between start dupilumab and event	59 (14-125)

Table 3. *(continued)*
[a], missing data: n=1; [b], NL data only; missing data: n=71; [c], other: blepharitis (2x), vision loss, epiphora (2x), sicca complaints (3x), eyelid spasm, swelling eyelid, eye irritation
Definitions: In the Netherlands only severe AEs were registered. Severe AEs were defined as any undesirable experience occurring during dupilumab treatment resulting in referral to another specialist, prescription of medication (excluding antihistamines and indifferent treatments), treatment schedule adjustments or discontinuation, or causing considerable interference with usual activities, whether or not considered related to this treatment. Events that resulted in death, were life-threatening, required (prolonging of) hospitalization, resulted in persistent or significant disability, or congenital anomaly or birth defect, were also considered serious.[20] In the UK all AEs were registered, regardless of severity.
Further detail on the specific events are available from the corresponding author on reasonable request.

Correlation between dupilumab levels and treatment discontinuation

Seventeen patients (n=17/149, 11.4%) discontinued dupilumab. In five patients discontinuation occurred due to ineffectiveness, after 218 days on average. Two of these patients applied a 10-day interval prior to discontinuation. One patient discontinued due to combined ineffectiveness and AEs (eye complaints). Three patients discontinued resulting from non-adherence, one because of a child wish, one because of elective surgery and six due to AEs: eye complaints (n=4), facial redness (n=1) and panniculitis of unknown origin (n=1). The 17 patients who discontinued treatment with dupilumab, simultaneously stopped study participation (i.e. there are no patients that underwent serum sampling after discontinuation of dupilumab).

We found an association between low dupilumab levels at 48 weeks and treatment discontinuation during the study. Of patients with low levels at 48 weeks, 16.0% has discontinued treatment, in contrast to 0.0% of patients with high levels (p=0.031). No associations were found between discontinuation and levels at 2, 12 and 24 weeks.

DISCUSSION

This study gives an overview of dupilumab levels in real-world AD patients and how these levels affect treatment response. We found median levels consistent with published pharmacokinetics data from clinical trials.[12,13] In the available literature, treatment duration, gender and age have shown not to affect dupilumab levels and the impact of weight appears to be negligible.[10,13] No literature was available on the role of other potential factors, such as (baseline) disease activity. In accordance with other IgG antibodies, dupilumab has a low volume of distribution and slow rate of elimination.[11] Available pharmacokinetics data shows that a strong non-linear clearance is present, in particular with lower concentrations (below 10µg/ml).[10,11,15] This may have been reason for ascertaining a high dosage, as strategy to achieve maximum drug exposure. The lower bound of dupilumab concentration during follow-up in this study was 22.2µg/ml, which is high in comparison to other cytokine targeting biologics, such as ustekinumab or TNF-inhibitors.[19,34] Besides preventing a strong clearance rate, a high dosage could be

aspired to overrule immunogenicity. A therapeutic window for dupilumab concentration has not yet been defined.

In the context of effectiveness, drug levels did not seem to correlate with ΔEASI and therefore we are not able to define a therapeutic window. A large inter-patient variability in concentrations was observed, in which all measured concentrations seem to yield sufficient responses, as the group with the lowest dosages also reaches the minimal clinically important difference of 6.6 for EASI.[35] If patients are dosed much higher than required, high drug levels have the potential to impair the ability to determine relevant clinical differences based on these levels, as few if any patient will have suboptimal concentrations. However, we did observe a weak negative correlation between dupilumab levels and absolute EASI at 12 and 24 weeks. No correlations were found for the other outcome measures and time points, illustrating that higher drug levels do not necessarily correspond to lower EASI, NRS, POEM and DLQI. When dividing patients into high and low serum levels, we did find higher EASI in patients with low levels at 2 and 12 weeks.

How to interpret correlations between EASI and drug levels may be difficult. A concentration-response relationship may exist in either direction. An association between serum concentration and subsequently (Δ)EASI (as outcome) may be expected at optimal dosages within the therapeutic window and at the current dosage we did not find this association, potentially because dupilumab is highly dosed. This is in accordance with previous findings, where concentrations at the plateau of the exposure-effect relationship were observed.[15] However, a directional association between EASI and concentration (as outcome) could also be observed, corresponding with the results of this study.

Baseline EASI was shown to be subsequently negatively correlated with dupilumab levels, suggesting that disease activity has an influence on drug levels. As baseline EASI cannot be affected by exposure to dupilumab (i.e. at baseline patients were not exposed to dupilumab yet), the direction of this effect can only exist in one way (i.e. with drug level as the outcome and not the other way around). We hypothesize that higher disease activity leads to a higher clearance rate of dupilumab (e.g. because more target (IL4R) is available) and thereby lower drug levels of dupilumab (i.e. target-mediation disposition).

Interestingly, we found that dupilumab serum levels at 2 and 12 weeks have the ability to predict treatment response at 24 weeks. At 2 weeks, a serum level of ≥64.1μg/mL predicts a EASI≤7 at 24 weeks. At 12 weeks, a serum level of ≤32.7μg/mL predicts a EASI>7 at 24 weeks. However, these correlations may also be determined by the relation between drug levels and disease activity, as a correlation was also found between baseline EASI and EASI≤7 at 24 weeks.

As for safety and other treatment aspects, AEs were particularly observed in patients with low drug levels. This corresponds with trial data showing a trend for an inverse relationship between concentrations and conjunctivitis.[16,17] Given this is a real-world study, dosing intervals may have been amended to mitigate AEs like eye complaints, which makes this difficult to interpret (i.e. another example of a bidirectional correlation). We did not investigate the direction of this effect in this scoping study. Furthermore, we found more interval deviations and discontinuation in patients with low dupilumab serum levels.

Limitations

As a consequence of a real-world setting, no randomization or blinding was performed. No washout periods were applied, resulting in relatively low baseline severity scores, influencing ΔEASI analyses. All available measurements were included. Despite efforts to collect all data, protocol deviations were present. COVID-19 has resulted in missing data at random. In a small subset serum samples were not obtained at a trough level. Potentially, multiple testing could have increased the risk of false-positive results. Furthermore, dosing interval deviations, concomitant treatment, treatment non-adherence and anti-drug antibodies (ADA) may have influenced our findings. A more comprehensive assessment of total drug exposure would enable a more accurate evaluation of the relationship between dose, exposure and outcome. To do this accurately would require formal pharmacokinetic/pharmacodynamic (PK/PD) modeling, which is beyond the scope of this exploratory work. We did not evaluate ADA. In theory, ADA could decrease circulating functional drug levels. Based on trial data, ADA development to dupilumab can be considered low and not clinically relevant.[5] Lastly, few differences in data collection were present between the centers.

Implications for clinical practice and future research

Currently, therapeutic decision making is not influenced by dupilumab levels. We have found that there could be added value of measuring dupilumab levels in clinical practice. As dupilumab is administered in high dosages, it would be interesting to investigate whether dosage interval prolongation yields sufficient treatment responses. One study has already shown that effectiveness remains after increasing administration intervals.[36] Increasing dosage intervals and thereby lowering dosages could not only positively affect costs, but also safety aspects. Dose reduction on an individualized basis using proactive (based on levels predicting response) and reactive (based on current levels correlating with response) therapeutic drug monitoring should be subject of further investigation. A bidirectional relationship between serum levels and both effectiveness (including disease activity) and safety should be taken into consideration.

Conclusions

High inter-patient and low intra-patient variability of dupilumab levels was observed. No correlations were found between dupilumab serum levels and ΔEASI. Serum levels at 2 and 12 weeks were found to have the ability to predict EASI≤7 at 24 weeks. A correlation was found between baseline EASI and dupilumab drug levels at 2, 12 and 24 weeks. Low levels were particularly observed in patients with presence of AEs, treatment interval deviation and discontinuation. The interpretation of correlations with a bidirectional nature can be difficult.

All in all, at the current on-label dosage, the measured broad range of dupilumab levels does not seem to yield differences in treatment effectiveness. No relationship between serum drug concentration and effectiveness was identified. However, baseline disease activity influences dupilumab serum concentrations. Higher baseline disease activity results in lower dupilumab levels.

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SUPPLEMENTARY MATERIALS

Supplementary figure 1. Concentration-effect curve for dupilumab level and ΔEASI at 24 weeks in patients with a moderate-to-severe baseline EASI (≥6.0).

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/svn3h5n6y5.1

Supplementary figure 2. Concentration-effect curve for dupilumab level and ΔEASI at 12 weeks in patients on dupilumab monotherapy only.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/m765ggyfpx.1

Supplementary figure 3. Concentration-effect curve for dupilumab level at 12 weeks and ΔEASI at 48 weeks.

A digital version of this supplementary material can be found at:

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APPENDIX

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Conflicts of interest
RW: Principal or co-investigator in clinical trials – Abbvie, Amgen, Anaptys Bio, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, Janssen-Cilag, Kymab, Leo Pharma, Pfizer, Sanofi and UCB. Honoraria from and consultancy work for Abbvie, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Sandoz, Sanofi and UCB. Honoraria from NICE (clinical expert).

PS: receives departmental independent research grants for TREAT NL registry, for which she is Chief Investigator (CI), from pharma companies since December 2019, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital.

AB, CS and PS: Investigators on IMI-EU funded research consortium to identify biomarkers in atopic dermatitis; multiple industry partners including Sanofi (biomap-imi.eu). All financial compensation is paid to the department/hospital.

No other conflicts of interest were reported.

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Data availability statement
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

10

PATERNAL AND MATERNAL USE OF DUPILUMAB IN PATIENTS WITH ATOPIC DERMATITIS: A CASE SERIES

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ABSTRACT

Dupilumab is a relatively new treatment option for patients with moderate-to-severe atopic dermatitis. There is a lack of knowledge about treatment with dupilumab during conception in both males and females, as well as during pregnancy and lactation. We report four patients who expressed a wish to conceive during treatment with dupilumab in daily practice. Two male patients conceived during dupilumab treatment, and two female patients discontinued dupilumab because of anticipated pregnancy. Apart from disease flares in both patients that discontinued treatment, no complications were reported concerning the ability to conceive, the pregnancy and fetal outcomes. We present an overview of the current available literature on dupilumab during conception, pregnancy and lactation that can guide considerations for patients on dupilumab wishing to conceive a child. Preference is given to treatment with topical corticosteroids, phototherapy, systemic corticosteroids and ciclosporin, until more data is available.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, pruritic inflammatory skin disorder. Moderate-to-severe cases, requiring systemic immunomodulating therapy, include patients of reproductive age. A lack of knowledge exists on dupilumab treatment during conception in both males and females, as well as during pregnancy and lactation. In this case series, we present two males who conceived during treatment and two females that discontinued due to anticipated pregnancy.

REPORT

Patients were all diagnosed with AD based on the U.K. Working Party criteria and gave consent for participation in the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry, before starting on-label dupilumab in the context of routine clinical practice at the Amsterdam University Medical Centers.[1] All patients had moderate-to-severe disease (mean Eczema Area and Severity Index: 21.6) and were allowed to use concomitant systemic or topical treatments. Further patient characteristics are summarized in Table 1.

Data collection was performed using a predefined case record form, including paternal and maternal use (defined as the use of systemic therapy in anticipation of conception). After careful consideration by physicians and patients, a male received dupilumab while conceiving and two females discontinued in anticipation of pregnancy. Another male conceived unexpectedly. Both females were advised to use contraception for at least 3 months prior to conception, as the median time for dupilumab concentrations to fall below the lower limit of detection after discontinuation is 10-11 weeks.[2]

The first male expressed an active wish to father a child 12 weeks after starting dupilumab. Conception was successful at 33 weeks of treatment, resulting in their first pregnancy. The second male unexpectedly conceived at 69 weeks of treatment. Both patients continued dupilumab, resulting in sufficient disease control during conception. Both partners were healthy. Both pregnancies proceeded without complication, and the term neonates were healthy.

The first female patient discontinued dupilumab after 36 weeks of treatment, and conceived 34 weeks later. Between treatment discontinuation and pregnancy, she received narrow-band ultraviolet B phototherapy for 18 weeks. During pregnancy, her AD flared and was controlled with topical corticosteroids. After a full-term uncomplicated pregnancy, the patient delivered a healthy baby. She decided to breastfeed and her AD was well-controlled for a week, flaring thereafter. After stopping breastfeeding, the patient restarted dupilumab with a loading dose, 7 months after delivery.

Table 1. Patient characteristics

	Age of patient	Age of partner	Atopic comorbidities*	Obstetric history	Severity scores at baseline† (and restart dupilumab)	Concomitant systemic therapy at baseline† and during follow-up
Female 1	29	30	Asthma, allergic rhinoconjunctivitis, food allergies, allergic contact dermatitis	Uncomplicated	EASI: 7.1 (21.3) POEM: 24 (26) DLQI: 11 (18)	Baseline: none Follow-up: NB-UVB phototherapy for 18 weeks before pregnancy and during dupilumab discontinuation
Female 2	31	29	Asthma, allergic rhinoconjunctivitis, food allergies, allergic contact dermatitis	Uncomplicated	EASI: 32.2 (-) POEM: 27 (27) DLQI: 27 (11)	Baseline: prednisone (30mg/day) in a tapering schedule for 39 days Follow-up: ciclosporin (250-300mg/day) for 20 weeks and prednisone (5-30mg/day for 8 weeks) during pregnancy and during dupilumab discontinuation
Male 1	34	32	Allergic rhinoconjunctivitis	Uncomplicated	EASI: 34.6 POEM: 21 DLQI: 7	Baseline: none Follow-up: none
Male 2	26	27	None	Uncomplicated	EASI: 12.4 POEM: 28 DLQI: 27	Baseline: prednisone (5mg/day) for 1 day Follow-up: none

* Physician-assessed diagnosis of the following comorbidities: asthma, allergic rhinoconjunctivitis, atopic eye disease, eosinophilic esophagitis, food allergies and allergic contact dermatitis. † Baseline defined as at start of dupilumab treatment. EASI: Eczema Area and Severity Index (0-72); POEM: Patient-Oriented Eczema Measure (0-28); DLQI: Dermatology Life Quality Index (0-30); NB-UVB: narrow-band ultraviolet B.

The second female patient conceived a child 16 weeks after discontinuation of a 25-week dupilumab course. Thirty weeks after discontinuation she experienced a severe flare, for which she started treatment with bleach baths, emollients and potent topical steroids at our daycare unit. A week later (at 15 weeks of gestation) she started ciclosporin (250mg/day; 3.4mg/kg/day). Fourteen weeks thereafter, concomitant treatment with prednisolone (30mg/day) was deemed necessary. After consultation with her obstetrician, she was induced at 37 weeks, due to physical and mental distress resulting from AD. The patient delivered a healthy baby, without complication. She refrained from breastfeeding, to restart dupilumab. A loading dose of dupilumab was administered two days after delivery, resulting in complete relief of her complaints, within three weeks.

DISCUSSION

No published human clinical studies are available on dupilumab during pregnancy, breastfeeding or conception.[3] Pregnant or breastfeeding women, or those planning to conceive, were excluded from dupilumab trials.[2] Animal studies have shown no fetal abnormalities or impacts on fertility.[1] The European Medicines Agency reports that the spontaneous abortion rate in patients treated with dupilumab did not exceed the rate in the general population.[2]

In accordance with other atopic diseases, AD can worsen during pregnancy and impart a risk of serious infection.[3,4] Atopic diseases have shown to be associated with reduced fertility.[3] Both pregnancy and atopic diseases are characterized by Th2 upregulation.[3,5] Interestingly, considering the shift towards Th2 cell differentiation, targeting IL-4 with dupilumab has been suggested as potential treatment option for pregnant patients with Th2-dominant diseases, such as AD, to induce Th1:Th2 balance and disease improvement.[5] However, as this has never been investigated in pregnancy, this theory warrants further research, in particular on the risk of abortion.[5]

Two case reports have been published on dupilumab in pregnancy and lactation.[6,7] The first case concerned a patient who discontinued dupilumab at two weeks of gestation, followed by reintroduction at 20 weeks.[6] In the second case dupilumab was initiated at 24 weeks of gestation, in addition to treatment with prednisone.[7] At 40 and 37 weeks of pregnancy, respectively, both patients delivered a healthy baby, without complication. The first patient breastfed her infant while receiving dupilumab, during an uncomplicated observation period of 4 months.

It is unknown whether dupilumab is excreted in breast milk or whether systemic absorption occurs after ingestion. Because dupilumab is a large protein molecule, the amount in breast milk is expected to be low and absorption is unlikely because it is

probably destroyed in the infant's gastrointestinal tract.[8] However, the molecule size does not prevent placental transfer.[3,4,7]

The summary of product characteristics (SmPC) of dupilumab indicates that it is preferable to avoid dupilumab in pregnancy, unless a physician advises it and only if the potential benefit justifies potential risks.[1] In addition, a decision must be made whether to discontinue breastfeeding or dupilumab taking into account the benefits for mother and child.[1] The SmPC does not mention any restrictions for male patients who wish to father a child.[1]

The European Task force on Atopic Dermatitis advises avoiding dupilumab in pregnant or breastfeeding women until there is more experience. They report that there is no literature on male patients who wish to father a child, and that theoretically there could be a transfer of dupilumab to the seminal fluid.[9] For both sexes, preference is given to treatment with topical corticosteroids, phototherapy, systemic corticosteroids, ciclosporin and, only in select cases, azathioprine.[4,9] Due to the lack of evidence, guidelines recommend avoiding dupilumab during pregnancy and lactation.[10] Absolute contraindications exists for treatments such as methotrexate and mycophenolate mofetil.[4,9] Similarly to dupilumab, there is little human data available for emergent treatments such as JAK inhibitors and other biologics, resulting in negative recommendations for use during conception and pregnancy'.[4]

In practice, patients are reluctant to discontinue treatment. These concerns are justified, since we observed disease flares in two patients who discontinued and disease control in a further two patients who continued. It is important to take into consideration that absence of adequate treatment can also involve adverse effects for both mother, father and child.

We have reported pregnancies, without complication in two female patients that discontinued dupilumab prior to conception, and two female partner pregnancies of male patients treated with dupilumab during conception. More data is required from large prospective cohort studies to detect adverse events. At the moment, two registries are planned on dupilumab in pregnancy (R668-AD-1639, R668-AD-1760).[2] In addition, we will continue data collection in the TREAT NL registry.

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APPENDIX

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Conflicts of interest
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PART III

PHENOTYPES OF ATOPIC ECZEMA

11

CLASSIFYING ATOPIC DERMATITIS: A SYSTEMATIC REVIEW OF PHENOTYPES AND ASSOCIATED CHARACTERISTICS

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ABSTRACT

Atopic dermatitis is a heterogeneous disease, accompanied by a wide variation in disease presentation and the potential to identify many phenotypes that may be relevant for prognosis and treatment. We aimed to systematically review previously reported phenotypes of atopic dermatitis and any characteristics associated with them. Ovid EMBASE, Ovid MEDLINE and Web of Science were searched from inception till the 12th of February 2021 for studies attempting to classify atopic dermatitis. Primary outcomes are atopic dermatitis phenotypes and characteristics associated with them in subsequent analyses. A secondary outcome is the methodological approach used to derive them. In total, 8,511 records were found. By focusing only on certain clinical phenotypes, 186 studies were eligible for inclusion. The majority of studies were hospital-based (59%, 109/186) and cross-sectional (76%, 141/186). The number of included patients ranged from seven to 526,808. Data-driven approaches to identify phenotypes were only used in a minority of studies (7%, 13/186). Ninety-one studies (49%) investigated a phenotype based on disease severity. A phenotype based on disease trajectory, morphology and eczema herpeticum was investigated in 56 (30%), 22 (12%) and 11 (6%) studies, respectively. Thirty-six studies (19%) investigated morphological characteristics in other phenotypes. Investigated associated characteristics differed between studies. In conclusion, we present an overview of phenotype definitions used in literature for severity, trajectory, morphology and eczema herpeticum, including associated characteristics. There is a lack of uniform and consistent use of atopic dermatitis phenotypes across studies.

Systematic review registration number: CRD42018087500

INTRODUCTION

Atopic dermatitis (AD), also known as (atopic) eczema, is a common chronic inflammatory skin condition characterized by pruritus. It is a heterogeneous disease with a wide spectrum in clinical presentation, which may change over time. Besides a variety in clinical presentation (e.g., presence of the eczema in the flexures vs. non-flexural eczema), some have described distinct subtypes based on non-clinical features (e.g., presence of filaggrin (FLG) mutations or serum Immunoglobulin E (IgE)). AD is considered both an immunological and skin barrier disorder. The disease is influenced by endogenous factors, i.e. a genetic predisposition, as well as by exposure to environmental factors.[1]

In general, the term phenotype is a comprehensive concept and is used in numerous ways in the literature. There is a need for comparability between studies. A phenotype could be defined as a set of features of an individual resulting from the interplay between genetic and environmental factors. Due to its complexity in presentation and pathogenesis, various attempts have been made to classify AD into phenotypes.[2] Phenotypes within AD can be distinguished based on various features, which could include any static or dynamic feature such clinical presentation (i.e., morphology and course of disease), or non-clinical features (e.g., based on genetics or immunology).[3] The identification of clinically meaningful phenotypes could be a first step to enable stratification of patients in the context of personalised medicine.

The primary objective of this systematic review was to report AD phenotypes, focusing on certain clinical phenotypes, that have been published in the literature and how these were defined, as well as to investigate which patient characteristics were associated with these phenotypes in subsequent analyses. Our secondary objective was to summarize the methodological approaches used to derive the phenotypes. To this point in time, no studies have been undertaken to systematically review the literature and summarize previously defined phenotypes in the field of AD.

METHODS

Protocol and registration

The protocol for this systematic review has been published prior to the start of this study.[3] In addition, the protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42018087500).[4] The changes to the protocol are summarized in Supplementary material 1. The study is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[5]

Eligibility criteria

In the context of this systematic review, we have defined phenotype as any subtype or subgroup of AD patients in which associated characteristics were investigated.[3] Subgroups of AD patients could be defined based on any feature, including both clinical and non-clinical features. We have included published studies that have a main aim to describe at least one of the following five phenotypic groupings:

1) The AD phenotype is defined by disease severity (e.g., mild, moderate-to-severe, severe);
2) The AD phenotype is defined by disease trajectory (e.g., early-onset, late-onset);
3) The AD phenotype is defined by morphological features (i.e., based on findings at physical examination (e.g. flexural eczema)); and
4) The AD phenotype is defined by (history of) eczema herpeticum.

In these four phenotypic groupings the associated characteristics (e.g., FLG mutations) are subsequently investigated per phenotype. For papers that did not define the phenotype by morphological features (see under 3), but instead first determined the phenotype (e.g., based on FLG mutations) in order to describe morphological characteristics in these subgroups, we included as a fifth phenotype:

5) The study defines the AD phenotype based on a certain feature (e.g., FLG mutations) in order to investigate morphological characteristics in these phenotypes.

We have excluded studies of localised eczema such as hand eczema, if not mentioned specifically in patients with AD, and other types of eczema such as contact dermatitis and seborrheic dermatitis; literature reviews, case reports and case series; conference abstracts, books and book chapters; and studies on other phenotype categories than defined above (including subgroups based only on age, gender, ethnic populations, presence of triggers, comorbidities, immunology and genetics). Ichthyosis vulgaris (IV), prurigo nodularis and keratosis pilaris (KP) in AD patients were considered morphological features.

Search strategy and information sources

A comprehensive literature search strategy was developed in consultation with a clinical librarian. We have searched Ovid EMBASE, Ovid MEDLINE and Web of Science from inception till the 12th of February 2021. No language restrictions or filters were applied. The Ovid MEDLINE search strategy can be found in Supplementary material 2. In addition, the reference lists from three major review articles were hand searched for relevant studies.[1, 2, 6]

Study selection process

The results of the literature search were uploaded into Covidence online software. All titles and abstracts were screened independently by two reviewers, using a screening tool based on our eligibility criteria. Publications that both reviewers recorded as meeting the inclusion criteria were retrieved for full-text review and excluded when not meeting the criteria. Disagreements were discussed with a second reviewer if necessary. Persistent conflicts were resolved with a senior author. Thereafter, full-text publications were reviewed in duplicate by two separate reviewers. Disagreements were resolved after discussion between the reviewers and with a senior author if necessary.

Data extraction process

Data from each full-text publication was independently extracted by two reviewers (A.B., A.A., R.I., K.F., J.M.), using a data extraction form designed for this purpose. Discrepancies in data extraction were resolved by discussion if necessary.

Data items

We extracted the following data domains from the included publications using our predesigned data extraction form: study data, disease data and outcome data. The study data comprised the following items: year(s) conducted, study design, setting conducted in, country/countries conducted in, WHO region, and the number, age and gender of the participants with (atopic) eczema. The following disease data items were extracted: disease description, diagnostic criteria/codes, and disease severity definition. The following outcome data items were extracted: qualitative description of the phenotype(s), proportion of individuals in each phenotype (if relevant), qualitative description of the characteristic(s) (of a priori interest) potentially associated with the phenotype(s), result of the statistical analyses on the association, methodological approach for deriving phenotype(s) and/or investigating the association (including a data-driven approach using statistical techniques, rather than the predefinition of phenotypes, if applicable), and whether controls were included (including the number).

Synthesis of results

The results are reported descriptively. We anticipated that both the phenotype definitions and potentially associated characteristics that are investigated would vary between studies. Therefore, we expected heterogeneity in all outcomes. We have grouped studies into categories where possible and composed evidence tables per phenotype category. If more than one phenotype category was applicable to one study, the publication was grouped into all relevant categories.

Risk of bias assessment

Risk of bias was assessed per study using the critical appraisal checklists for analytical cross sectional studies, cohort studies and case control studies from the Joanna Briggs Institute (JBI), as appropriate.[7] In the forms we have treated the described phenotype as the outcome and the description of the potentially associated characteristics under investigation as the exposure. Traffic light tables were composed according to study design and phenotype category to visualize the qualitative results descriptively.

Quality of the evidence

We aimed to use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach for assessing the quality of evidence per phenotype category. As we anticipated that the phenotype definitions and potentially associated characteristics would vary between studies, an assessment was made whether the quality of evidence per phenotype category could be investigated.

RESULTS

Search results

We have screened 8,511 records and have assessed 675 full-text publications. In total, 186 studies, published between 1966 and 2021, fulfilled the inclusion criteria. Reference searching has yielded 6 additional publications. Fig. 1 gives an overview of the study selection process, including reasons for exclusion.

Study overview

Of the included articles, 59% (109/186) were hospital-based (medical specialist setting). Regarding study design, 76% (141/186) were cross-sectional studies. In 7% of studies (13/186) a data-driven approach was used to derive phenotypes, including two studies using existing data-driven phenotypes. The number of included AD patients ranged from seven to 526,808. Ninety-one (49%) publications investigated phenotypes based on disease severity (phenotype group 1). Phenotypes based on disease trajectory (phenotype group 2) were investigated in 56 (30%) studies. Thirty-six (19%) studies investigated morphological characteristics in other phenotypes (phenotype group 5). A morphology-based phenotype (phenotype group 3) and a phenotype of AD patients having eczema herpeticum (phenotype group 4) were investigated in 22 (12%) and 11 (6%) studies, respectively. There was overlap between phenotype categories in 26 studies, with two (n=22) to three (n=4) phenotype categories being investigated in one study. An overview of the study characteristics per study grouped per phenotype category can be found in Supplementary tables 1a-1e.

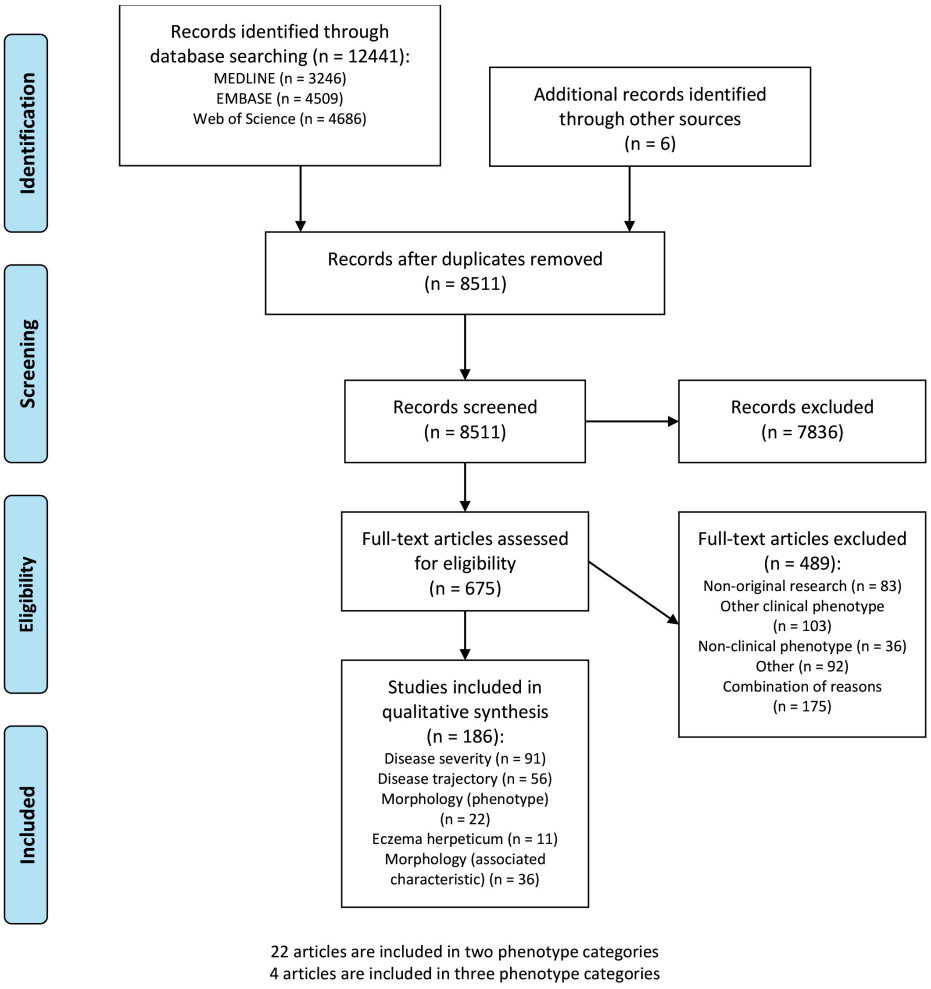

Figure 1. PRISMA flow diagram: results of the search strategy

Risk of bias

The risk of bias of studies is reported in Supplementary tables 2a-2e, demonstrating the qualitative results of the JBI critical appraisal checklists according to study design and phenotype category. We decided not give an overall estimation of the risk of bias per paper, but to descriptively report the checklist results per paper.

In various papers (30%, 27/91) within the disease severity category (phenotype group 1), no predefined scoring system or severity cut-offs were reported, resulting in the score unclear for outcome in the risk of bias assessment.[e.g.8-10] In many papers (27%, 15/56) on disease trajectories (phenotype group 2), age cut-offs were unclear or it was

unclear who assessed the age of onset (i.e., whether it concerned reports by patient, parent or physician).[e.g.11-13] A lack of detail was identified regarding phenotypes based on morphological features and the investigation of morphological characteristics in other phenotypes (phenotype group 3 and 5). Often (in 69%, 41/59) it was unclear who performed the assessment or no criteria or further specifications for the assessment of morphological characteristics were reported (i.e., when characteristics were considered present or not).[e.g.14, 15] Overall, in many cross-sectional studies (60%, 84/140) the subjects and setting were not described in sufficient detail.[e.g.16-18] In addition, the absence of inclusion of potentially confounding factors in the analyses of many studies (55%, 102/186) was noteworthy. A major source of bias across studies related to the two latter factors in the checklists.

Quality of the evidence

We found heterogeneity in the phenotypes and investigated characteristics that were reported in studies and the results of this review are descriptive. Therefore, following discussions with author M.L., an international leading GRADE researcher, assessing the quality of the evidence with GRADE was considered not relevant.

Study results

An overview of all studies in alphabetical order per phenotype category and details of the results are found in Supplementary tables 1a-1e. The results of the statistical analyses are summarized per phenotype category and per category of associated characteristics in Supplementary material 3. An overview of all phenotypic groupings and their investigated characteristics can be found in Fig. 2 (graphical abstract).

Phenotypes based on disease severity (phenotype group 1)

Within this phenotype category 86% (78/91) of studies were cross-sectional, 66% (60/91) were hospital-based only and in 2% (2/91) a data-driven approach was used. In the studies, the number of included AD patients ranged from seven to 526,808. Regarding WHO region, the majority of studies were conducted in the European Region (n=50, 55%), followed by the Western Pacific Region (n=21, 23%), the Region of the Americas (n=16, 18%), and the African Region and the Eastern Mediterranean Region (both n=1, 1%). Investigated characteristics included the following categories: skin barrier function (n=15)[19-33], serum blood cell types and markers (n=23)[9, 18, 23, 34-53], serum Ig levels and sensitization (n=15)[20, 22, 25, 51, 54-64], microbial colonization (n=10)[15, 65-73], DNA mutations (n=14)[10, 51, 74-85], skin parameters (n=8)[32, 86-92], personal and family history of allergy (n=4)[58, 93-95], comorbidities (n=7)[8, 51, 96-100], morphology (n=3)[51, 93, 101], and other characteristics (n=5)[51, 95, 102-104] (see Supplementary table 1a and Supplementary material 3).

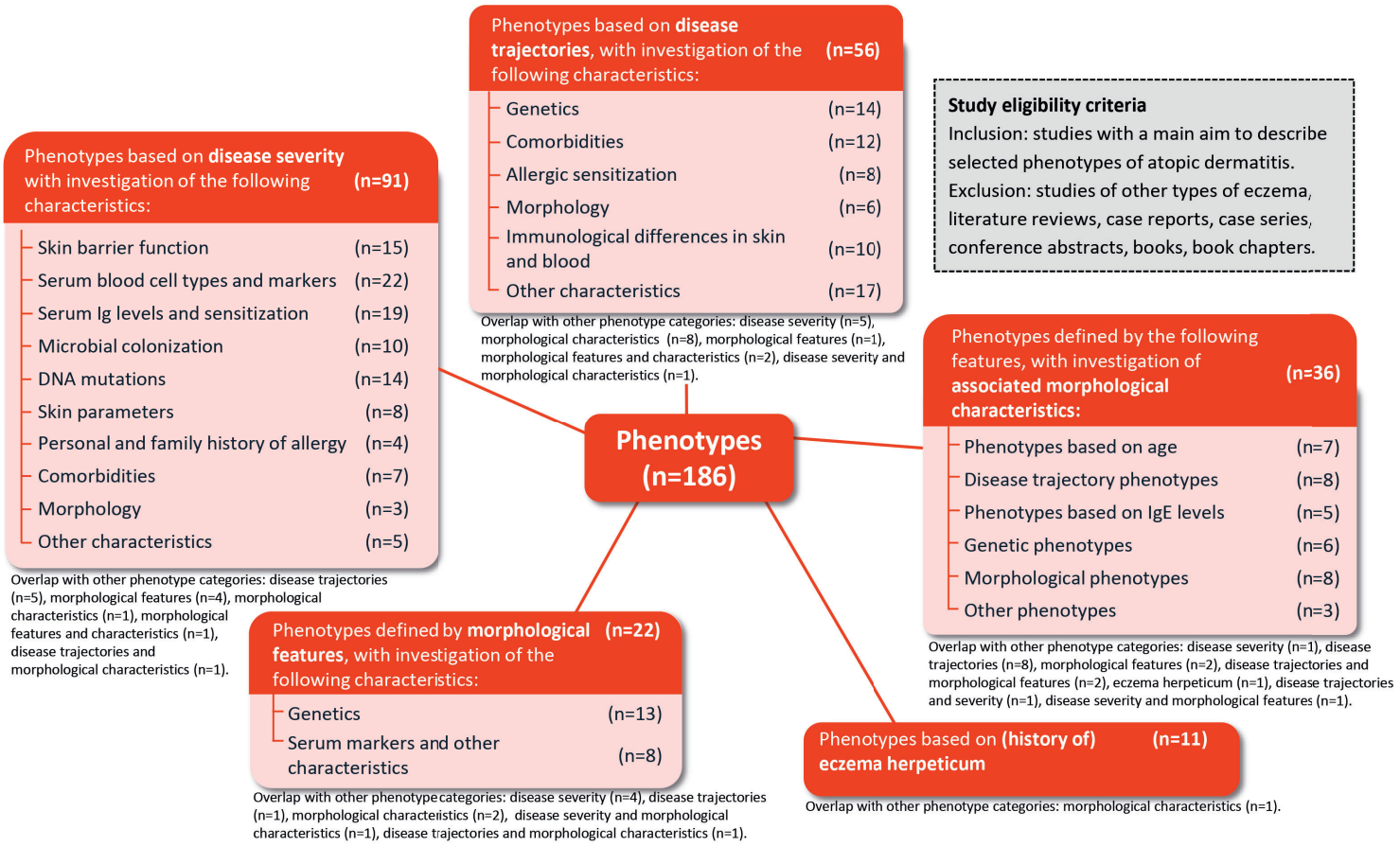

Figure 2. Graphical abstract

The use of different scoring systems for determining disease severity were identified among the included studies (e.g. SCoring Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI)). The SCORAD was most frequently used (in 39 out of 91 studies). Strikingly, we found that even when the same scoring system was used, cut-offs used to make a distinction between for example mild, moderate and severe AD differed between studies. For example, in studies mild AD has been defined as SCORAD ranging from <15 to <37 points.[22, 33, 34, 66] The threshold for severe AD ranged from >25 to >50 points.[25, 59, 79]. In addition, in many articles no further specification of the basis of the severity definition was given.[10, 15, 38, 42, 44, 68, 69, 89,52, 91]

Phenotypes based on disease trajectories (phenotype group 2)

Within this phenotype category 50% (28/56) of studies were cross-sectional, 57% (32/56) were hospital-based only and in 18% (10/56) a data-driven approach was used. In the studies, the number of included AD patients ranged from nine to 108,703. Most studies were conducted in the European Region (n=33/56, 59%). Thirteen studies (23%) were conducted in the Western Pacific Region, 9 (16%) in the Region of the Americas, and one (2%) in the South-East Asian Region. Investigated characteristics included genetics (n=14)[11, 17, 21, 51, 84, 105-113], comorbidities (n=12)[111, 112, 114-123], allergic sensitization (n=8)[12, 63, 112, 124-128], morphology (n=6)[13, 114, 121, 129-131], immunological differences in skin and blood (n=10)[16, 21, 86, 91, 132-137], and other characteristics (n=17)[111, 112, 114, 121, 124, 138-149] (see Supplementary table 1b and Supplementary material 3).

Many studies which investigated phenotypes based on disease trajectories (including age of onset) and their associated characteristics were cross-sectional studies (n=28/56, 50%; with predefined phenotypes based on age cut-offs), rather than longitudinal studies (n=28/56, 50%; using for example statistical data-driven approaches). Cross-sectional studies investigating phenotypes based on disease trajectory have the potential of recall bias and a lack of information on temporality. However, in comparison to the other phenotype categories longitudinal studies were predominantly seen within this category. Early-onset disease was the most reported phenotype (n=36/56, 64%). It predominantly concerned studies in adults retrospectively assessing self-reported early onset of disease. These findings should be interpreted with caution as a previous study has reported that using the question 'Have you had childhood eczema?' to determine age of onset of AD, leads to overestimation of the prevalence of childhood AD in adults.[195] The age cut-offs used diverged across studies. For example, early-onset disease was defined using an age cut-off that ranged from 3 months to 8 years. Therefore, use of the term early-onset currently has limited informative value. Besides using age cut-offs in the phenotype definition, inclusion of a maximum/minimum disease duration was added to the definition in five studies (e.g., early-onset disease as within 6 months of disease onset).[86, 91, 114, 132, 137]

Phenotypes defined by morphological features, with subsequent investigation of associated characteristics (phenotype group 3)

Within this phenotype category 95% (21/22) of studies were cross-sectional, 73% (16/22) were hospital-based only and a data-driven approach was used in none of the studies. In the studies, the number of included AD patients ranged from 21 to 2,205. Regarding WHO region, 59% (13/22) of studies were performed in the Western Pacific Region and 41% (9/22) in Region of the Americas and/or the European Region. Thirteen studies investigated genetic characteristics[105, 108, 150-160] and eight studies investigated serum markers and other characteristics[14, 15, 22, 45, 46, 101, 161, 162] (see Supplementary table 1c and Supplementary material 3).

Phenotypes based on history of eczema herpeticum (phenotype group 4)

Within this phenotype category 91% (10/11) of studies were cross-sectional, 36% (4/11) were hospital-based only (study setting was not reported in 6 studies). In addition, in none of the studies a data-driven approach was used. In the studies, the number of included AD patients ranged from 35 to 165,199. Nine (82%) of the studies were conducted in the Region of the Americas. One study (9%) was conducted in the European Region and one study (9%) in the Western Pacific Region. Various associated characteristics ware investigated [163-173] (see Supplementary table 1d and Supplementary material 3). Notably, in most studies the diagnosis of (history of) eczema herpeticum was confirmed by either anti-HSV antibody titer, PCR, Tzanck smear, immunofluorescence and/or culture test results. These are all objective assessments rather than a predefinition that could be subject to interpretation.

Phenotypes defined by any feature, with subsequent investigation of associated morphological characteristics (phenotype group 5)

Within this phenotype category 83% (30/36) of studies were cross-sectional, 72% (26/36) were hospital-based only and in none of the studies a data-driven approach was used. Regarding WHO region, 47% (17/36) of studies were performed in the European Region, 28% (10/36) in the Western Pacific Region, 14% (5/36) in Region of the Americas, 3% (1/36) in the South-East Asian Region and 3% (1/36) in the Eastern Mediterranean Region. In the studies, the number of included AD patients ranged from 31 to 6,208. Various phenotype categories were investigated, including phenotypes based on: age (n=7)[93, 174-179], disease trajectory (n=8) [12, 13, 114, 121, 129-131, 145], IgE levels (n=5)[126, 180-183], genetics (n=6)[184-189], morphology (n=8)[14, 101, 108, 131, 153, 163, 190, 191] and other phenotypes (n=3)[51, 192, 193] (see Supplementary table 1e and Supplementary material 3).

For phenotypes defined by morphological features and phenotypes defined by any feature with subsequent investigation of associated morphological characteristics, the

study region may be relevant. Potential differences in AD morphology by study region have been reported.[196] Therefore, the role of the region where the study took place should be considered. For studies investigating morphology including distribution of AD over the body surface it became clear that, apart from the reporting of affected body parts, often no further specification was given at all. The reproducibility of these studies is questionable, as specific criteria are unclear. Research shows that variability exists in how people distinguish body parts.[197] Further specification of how body parts are confined or when dermatitis was scored to be present (e.g. using size cut-offs) would have contributed to the quality of these studies.

DISCUSSION

Summary of evidence

We have undertaken a comprehensive analysis of the published literature on phenotype definitions used in literature and have described the characteristics associated with phenotypes. Phenotypes of patients with AD have been identified based on various features, including disease severity, disease trajectories, morphology and predisposition to eczema herpeticum. With this systematic review, we have gained insight on how these phenotype categories are reported in the literature, thereby contributing to developing a better understanding of AD. This systematic review highlights the heterogeneity that currently exists in the phenotyping of the AD population. In the literature many phenotypes based on many features are described. At the present time, no consensus exists on how these phenotypes of AD should be defined and the potential role of phenotypes in guiding both diagnostic and therapeutic management of patients is unknown.

Across the phenotype categories there were both differences and similarities in study characteristics. We identified mostly cross-sectional studies (n=141, 76%) in predominantly hospital-based settings (n=109, 59%). Hospital-based studies could be subject to selection bias due to referral criteria, potentially leading to the identification of other phenotypes than when a population-based approach was used. Therefore, hospital-based studies need to be interpreted cautiously.[194] Phenotypes based on disease severity were most frequently studied (n=91, 49%). The methodological approach for investigating phenotypes differed between studies. Besides the predefinition of a subgroup of patients based on certain features (e.g., cut-offs for age or severity), statistical data-driven approaches were also used to identify phenotypes in the minority of studies (n=13, 7%), for example by using latent class analysis or cluster analysis. Though these data-driven approaches are only used in a minority of studies aiming to investigate phenotypes, this can be considered a relatively unbiased way to identify phenotypes, in contrast to an approach using an investigator-imposed predefinition. The most frequently used data-driven approach is latent class analysis. Data-driven approaches have the potential to

identify patterns that are not obvious to clinical observation. Unfortunately, this only was performed in a small number of studies.

Strengths and limitations

No previous systematic reviews were undertaken to map the current evidence on AD phenotypes in the literature. A librarian was involved in composing a comprehensive and broad search strategy. The protocol of this systematic review was published and preregistered. Moreover, we adhered to PRISMA guidelines in the reporting of this study.

Limitations include that since both the phenotype definitions and the a priori defined characteristics of interest differed between studies, we were unable to pool results and did not use GRADE to assess the quality of evidence. Accordingly, no meta-analyses could be undertaken due to this heterogeneity in study outcomes and therefore we have reported on all studies separately in the evidence tables (Supplementary tables 1a-1e) and Supplementary material 3. Meta-bias resulting from publication bias or selective outcome reporting bias could not be assessed formally because of the qualitative nature of the study. However, both types of bias are deemed unlikely because of our rigorous search and descriptive nature of the studies. Studies were retrieved by our search when the term phenotype or synonyms of phenotype were specifically mentioned. In other words, studies that have used other terminologies (i.e., studies that describe phenotypes, but do not use the terminology phenotype or synonyms of phenotype) could have been missed. A bias for recent studies may have been introduced by the absence of these terminologies at inception of the used databases. Case reports and case series for example describing morphological phenotypes were excluded. Although we report associations between phenotypes and characteristics, these do not prove any causal relationship, and many are based on small sample sizes in hospital-based populations and hence should be interpreted with caution due to the possibility of referral and selection bias. In context of the scoping nature of this systematic review, we did not restrict to a specific study setting, size or confounder adjustment. Lastly, because the term phenotype is used in numerous ways in the literature, we had to define phenotype for consistency and in the context of this systematic review we have defined phenotype as a subtype or subgroup of patients with AD. In the context of precision medicine a semantic distinction with endo(pheno)types would be of interest. It was not feasible to include all potential phenotypic groupings in this study. Therefore, we were forced to make choices on which phenotypes to focus, which resulted in focusing only on the most clinically relevant phenotypes. Excluded phenotype categories include subgroups based only on age, gender, ethnic populations, presence of triggers, (allergic) comorbidities, immunology and genetics.

Implications and recommendations for future research

At the moment, the therapeutic management of AD is generally not based on phenotypes that could reflect potentially relevant differences in characteristics between patients, with the exception of severity. In theory, these differences in phenotypes could be associated with variations in treatment outcome. In the context of personalized medicine, stratification according to phenotype would be of interest to enable investigation of which patients are likely to respond best to certain therapies. In order to facilitate comparative or pooled analyses across studies in the future, phenotypes should be uniformly defined and consistently used. Ideally, researchers should use the same definitions for AD phenotypes in research, similarly to using the same core outcome set for outcome measurements in clinical trials and clinical practice (*homeforeczema.org*). This core outcome set already includes the recommendation of using the EASI to measure disease severity. A previous study has determined and recommended the following severity strata for EASI: 0: clear, 0.1-5.9: mild, 6.0-22.9: moderate, 23.0-72: severe.[198] We should preferably use the same outcome measurements and cut-offs to describe disease severity phenotypes. Regarding phenotypes based on disease trajectories, we ideally should use the same definitions for e.g. early-onset disease, by using uniform age cut-offs, when using non-data-driven approaches. However, first we should get a clearer picture of the predictive ability of such cut-offs. As for morphology, it would be desirable to develop (diagnostic) criteria for morphological phenotypes, as current diagnostic criteria for AD do not facilitate the identification of these or phenotypes in general.[199, 200] The current heterogeneity in phenotyping of AD has demonstrated a need for international harmonization. More research using unbiased data-driven approaches in well-defined, population-based settings should be considered to allow the identification of phenotypes that are not obvious to clinical observation. Selection of appropriate data-driven techniques should be guided by the nature of the dataset, e.g. whether it is cross-sectional or longitudinal, and by the types of input available (disease activity, severity, clinical presentation etc.). To date most cross-sectional data-driven techniques have been from the family of cluster analysis and longitudinal data techniques have been from the family of mixture models such as latent class analysis. Phenotypes identified by a wide range of cross-sectional data may be more richly characterized than phenotypes identified by a smaller range of fewer but longitudinally collected data, but their interpretation may be different. For example, cross-sectional phenotypes may describe clinical AD presentation well but may be less suitable to track the persistence or resolution characteristics that longitudinal phenotypes characterize, and vice versa. Whatever the method, the resulting phenotypes should be interpreted in context of the demographic characteristics (e.g. age, sex, ethnicity, geographic region) of the population represented by the sample used to derive them, i.e. not assumed to be applicable to populations not

included in the sample. Phenotype studies should also be replicated in independent populations to investigate the stability of the identified phenotypes. In addition, it would be of interest to investigate phenotypes based on allergic comorbidities, since we apprehend AD as part of a larger group of diseases with TH2 inflammation skewing. Lastly, the identification of clinically meaningful phenotypes in the context of treatment outcome should be pursued, by investigating therapeutic effectiveness and safety in patients stratified according to phenotype.

Conclusions

This systematic review has identified a lack in the uniform and consistent use of phenotypes of atopic dermatitis across studies. We have presented an overview of the phenotype definitions used in literature for disease severity, disease trajectory, morphology and eczema herpeticum. In addition, we describe characteristics reported to be associated with these phenotypes, and other phenotypes with subsequent investigation of associated morphological characteristics. Heterogeneity was observed in phenotype definitions used and in associated characteristics investigated within the same phenotypic grouping. Further research applying a consistent and uniform use of phenotype definitions and data-driven data approaches are recommended. The identification of clinically meaningful phenotypes and insights into underlying endotypes has the potential to improve therapeutic strategies, by working towards personalized medicine and ultimately leading to the improvement of care for this condition.

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SUPPLEMENTARY MATERIALS

Supplementary table 1a-1e. Evidence tables per predefined phenotype category.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/gzgzn6x65n.1

Supplementary table 2a-2e. Qualitative outcomes by the JBI Critical Appraisal Checklists.

A digital version of this supplementary material can be found at:

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Supplementary material 1. Changes to the original protocol.

A digital version of this supplementary material can be found at:

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Supplementary material 2. Ovid MEDLINE search strategy.

A digital version of this supplementary material can be found at:

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Supplementary material 3. Summary of main results per phenotype category and per category of associated characteristics.

A digital version of this supplementary material can be found at:

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APPENDIX

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Conflicts of interest
ALB, PIS, SML and MAMH are investigators on the European Union Horizon 2020-funded BIOMAP Consortium (*biomap-imi.eu*). KA received grants for investigator-initiated research to her institution from NIH, National Eczema Foundation, LEO Foundation, Pfizer and Cosmetique International and consulting fees from TARGET RWE. PIS has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), receives departmental independent research grants for TREAT NL registry, for which she is Chief Investigator (CI), from different pharma companies since December 2019, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital. SML received grants from Wellcome Trust and the Innovative Medicine Initiative Horizon 2020 (BIOMAP project) payed to her institution. AM received a grant from Wellcome Trust payed to her institution. No other disclosures were reported.

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Data availability statement
The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

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CHILDREN WITH ATOPIC ECZEMA EXPERIENCING INCREASED DISEASE SEVERITY IN THE POLLEN SEASON MORE OFTEN HAVE HAY FEVER AT YOUNG AGE AND A DARK SKIN TYPE

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ABSTRACT

Children with atopic eczema are known to experience seasonal variations in disease severity, with winter being the season in which severity generally increases. There is a lack of knowledge about the subgroup of children that experiences increased severity in spring and summer months. We aimed to investigate which phenotype characteristics best describe children flaring in the pollen season. A retrospective database analysis was conducted, including 110 children with difficult-to-treat atopic eczema aged 0 to 17 years. Relevant outcome parameters were extracted from medical records. In our population, 36% (n=40/110) of children reported flares of atopic eczema in the pollen season. These children were more often sensitized to ≥1 types of pollen (73% (n=29/40) vs. 28% (n=10/36), p<0.0001) and had more patient-reported hay fever (70% (n=28/40) vs. 19% (n=7/36), p<0.0001), compared to children that do not flare in the pollen season. Moreover, children flaring in the pollen season more often had a dark skin type (78% (n=31/40) vs. 44% (n=16/36), p=0.003). Based on stepwise multivariable analyses, children flaring in the pollen season were characterised by the combination of younger age, hay fever and dark skin type (C-statistic: 0.86). In conclusion, patient-reported flares in spring and summer are experienced by one third of children with difficult-to-treat atopic eczema. This phenotype can be characterised as young children having hay fever and a dark skin type and can be identified based on clinical parameters alone without the need to perform IgE blood testing or skin prick tests.

INTRODUCTION

Atopic eczema (AE) is one of the most common skin disorders, affecting up to 20% of the children in the general population.[1] The disorder is characterized by pruritic inflammation of the skin and can have a major impact on the quality of life of patients and their families. AE is considered both an immunological and skin barrier disorder.[2, 3] Children with AE often have allergic co-morbidities. Presence of eczema in the first two years of life is a risk factor for both allergic rhinoconjunctivitis and asthma.[4] Patients with AE are significantly more sensitized to aeroallergens than children without AE. Pollen prove to be one of the most common relevant aeroallergens in these patients.[5, 6]

In clinical practice, patients with AE experience seasonal variations in disease severity. Besnier described AE as a familial pruritic skin disease starting at young age, followed by a chronic fluctuating course with seasonal variations, that often occurs in combination with allergic rhinoconjunctivitis and asthma.[7] In general AE symptoms are worse in winter, due to potential dehydration of the skin by exposure to low humidity in the environment (e.g. cold weather and central heating).[8] However, a subgroup of patients experiences disease flares in spring and summer months.

We hypothesize that there are two possible subtypes of AE - one that is worsened in spring and summer and the other is worsened in winter. The objective of this study was to characterize the phenotype of AE children that experience flares during spring and summer months. First, we investigated whether sensitisation to pollen and/or hay fever are associated with flaring in spring and summer (the pollen season). Next, we investigated what other phenotype characteristics, in particular having asthma and the patient's skin type, are distinguishing for this subgroup.

METHODS

Study design

A retrospective database analysis was performed at the specialized day care treatment unit of the department of Dermatology of the Amsterdam UMC in the Netherlands. Predetermined outcome parameters were extracted from a standardized intake-questionnaire, including the demographic characteristics gender, date of birth and Fitzpatrick skin type. During the intake, children and their caregivers were asked about seasonal variations in AE symptoms, by inquiring about an increase of their symptoms in the pollen season. The parameters hay fever and asthma were defined as patient-reported current or history of hay fever and asthma. Results from total Immunoglobulin E (IgE) levels and from radioallergosorbent-tests and skin prick tests were collected to detect allergen-specific IgE levels against grass, tree and herb pollen. Sensitisation was

considered present in case of a positive prick skin test or >3,50 kU/L allergen-specific IgE antibodies against pollen in serum. In case no information on either skin prick testing or IgE levels was present, this data was considered missing. Light skin types were defined as skin types 1, 2 and 3, and skin types 4, 5 and 6 as dark skin types. Obtaining ethical approval was not necessary according to the Medical Ethics Committee of the Amsterdam UMC (W20_308 # 20.343). The study was carried out in accordance with the provisions of the Declaration of Helsinki.

Patient population

The cohort consisted of children with difficult-to-treat AE (aged till 17 years) referred to our specialized day care treatment unit for AE because of unresponsiveness to conventional outpatient treatments such as topical and/or systemic therapy from January 2011 till October 2015. All of the included children were considered to have physician-assessed AE, diagnosed by a dermatologist.

Statistical analyses

Descriptive differences between patient characteristics were compared using the Chi-square test, Mann-Whitney test or unpaired t-test where appropriate.

In addition, to find the combination of variables to describe children with AE flaring in the pollen season, we performed stepwise logistic regression analyses, by Akaike information criterion (AIC), using 500 bootstrap samples in five imputed datasets.[9] We considered the following variables to be selected in our model: age, gender, dark vs light skin type, asthma, allergic rhinoconjunctivitis, grass pollen sensitisation, tree pollen sensitisation and herb pollen sensitisation. Missing values were imputed using an expectation-maximization with bootstrapping approach.[10] We developed one clinical model where the variables based on pollen sensitisation were excluded, as blood or skin prick tests are not always performed in daily practice, especially not in younger children. To investigate the additional value of the variables based on pollen sensitisation, we included these variables in an extended model as a sensitivity analysis.

Statistical analysis of the data was performed using the software program SPSS (IBM SPSS Statistics 23) and R: Language and Environment for Statistical Computing, version 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Results were considered statistically significant at $p<0.05$ for all analyses.

RESULTS

This study included 110 children, 58 boys and 52 girls, with a mean age of 7.7 (± 5.1 standard deviation (SD)) years (Table 1). The majority of children had a dark skin type (65%, n=71). Flaring of AE in the pollen season was experienced in 36% (n=40) of the children, and 33% (n=36) did not experience pollen season-related flares. For 17% (n=19) the relation between the pollen season and AE was unclear or unknown, and 14% (n=15) of the children experienced their first flare of AE.

Table 1. Patient characteristics

Patient characteristics (n = 110)	
Gender – no. (%)	
Male	58 (53%)
Female	52 (47%)
Age – mean ± SD (range)	7.7 ± 5.1 years (0-17)
Skin type – no. (%)	
I	1 (1%)
II	12 (11%)
III	24 (22%)
IV	29 (26%)
V	23 (21%)
VI	19 (17%)
unknown	2 (2%)
Skin type - median	4
Pollen season-related flares	
Yes	40 (36%)
No	36 (33%)
Unknown	19 (17%)
First exacerbation	15 (14%)
Total IgE level – median (IQR)[1]	1513.00 kU/L (415.00-4500.00)

No., number; SD, standard deviation; [1], n = 51.

Children with pollen season-related flares were found to be more sensitized to ≥1 types of pollen compared to children that do not flare in the pollen season (73% (n=29/40) vs. 28% (n=10/36), p<0.0001). This association was also seen separately for sensitisation to tree pollen (50% (n=20/40) vs. 22% (n=8/36), p=0.004) and grass pollen (60% (n=24/40) vs. 28% (n=10/36), p=0.003), but not herb pollen (Table 2). We also found that children with pollen season-related flares had more patient-reported hay fever (70% (n=28/40) vs. 19% (n=7/36), p<0.0001), compared to children without pollen season-related flares. There was a trend observed for an increased prevalence of asthma in the group experiencing pollen season-related flares (48% (n=19/40) vs. 25% (n=9/36), p=0.05). Although higher median total IgE values were found in patients flaring in the pollen season, no statistical difference was found (2087.0 vs 1404.5, p=0.26).

Table 2. Patient characteristics regarding pollen season-related flares

Patient characteristics regarding pollen season-related flares (n = 76)			
	Patients with pollen season-related flares (n = 40)	**Patients without pollen season-related flares (n = 36)**	**p-value**
Gender (% of total, no.: male vs. female)	50% vs. 50% (20 vs. 20)	47% vs. 53% (17 vs. 19)	0.81
Age (mean, ± SD, range)	9.0 ± 4.6 years (2-17 years)	9.0 ± 4.8 years (2-17 years)	0.96
Skin type (% of total, no.)	Light: 23% (9) Dark: 78% (31)	Light: 56% (20) Dark: 44% (16)	**0.003**
Sensitisation (% of total, no.)[1]	Tree pollen: 50% (20) Grass pollen: 60% (24) Herb pollen: 15% (6) Combined (≥1 types of pollen)[2]: 73% (29)	Tree pollen: 22% (8) Grass pollen: 28% (10) Herb pollen: 8% (3) Combined (≥1 types of pollen)[2]: 28% (10)	**0.004** **0.003** 0.52 **<0.0001**
Hay fever[3] (% of total, no.)	70% (28)	19% (7)	**<0.0001**
Asthma[4] (% of total, no.)	48% (19)	25% (9)	0.05
Total IgE level[5] (median (IQR))	2087.0 (556.5-5320.0) kU/L	1404.5 (362.8-3265.3) kU/L	0.26

No., number; SD, standard deviation; significant results are presented in bold face; [1], missing data for tree pollen: n = 23, for grass pollen: n = 19, for herb pollen: n = 27, for combined pollen: n = 21; [2], sensitisation to one or more types of pollen, [3], missing data: n = 8; [4], missing data: n = 3; [5], missing data: n = 39.

Interestingly, children with a dark skin type more often experienced pollen season-related flares of AE (78% (n=31/40)), while in the group without pollen season-related flares only 44% (n=16/36) of the children had a dark skin type (p=0.003). When we stratified our population based on skin type (Table 3), sensitisation to ≥1 types of pollen was more prevalent in dark skin types in comparison to light skin types (52% (n=37/71) vs. 46% (n=17/37), p=0.04). There were no significant differences found for sensitisation to tree, grass and herb pollen separately (p=0.85, p=0.34, p=0.69, respectively). Children with dark skin types more often had hay fever compared to children with light skin types (41% (n=29/71) vs 30% (n=11/37)), although we did not find a significant difference (p=0.15). No statistical difference was found for median total IgE values between patients with light and dark skin types (1513.0 vs 1765.0, p=0.27).

Table 3. Patient characteristics regarding skin type

Patient characteristics regarding skin type (n = 108)			
	Light skin type[1] (n = 37)	**Dark skin type[2] (n = 71)**	**p-value**
Gender (% of total, no.: male vs. female)	65% vs. 35% (24 vs. 13)	47% vs. 54% (33 vs. 38)	0.08
Age (mean, ± SD, range)	7.9 ± 5.2 (0-17 years)	7.8 ± 5.1 (0-17 years)	0.97
Sensitisation[3] (% of total, no.)	Tree: 43% (16) Grass: 43% (16) Herb: 16% (6) Combined (≥1 types of pollen)[4]: 46% (17)	Tree: 35% (25) Grass: 42% (30) Herb: 14% (10) Combined (≥1 types of pollen)[3]: 52% (37)	0.85 0.34 0.69 **0.04**
Pollen season-related flares (% of total, no.)			**0.003**
Yes	24% (9) Skin type 1: - Skin type 2: 8% (3) Skin type 3: 16% (6)	44% (31) Skin type 4: 16% (11) Skin type 5: 14% (10) Skin type 6: 14% (10)	
No	54.0% (20) Skin type 1: - Skin type 2: 16% (6) Skin type 3: 38% (14)	22.5% (16) Skin type 4: 11% (8) Skin type 5: 7% (5) Skin type 6: 4% (3)	
Hay fever[5] (% of total, no.)	30% (11)	41% (29)	0.15
Asthma[6] (% of total, no.)	32% (12)	31% (22)	0.76
Total IgE level[7] (median (IQR))	1513.0 (386.0-2372.0) kU/L	1765.0 (444.8-5798.8) kU/L	0.27

No., number; SD, standard deviation; significant results are presented in bold face; [1], light skin types were defined as skin type 1, 2 and 3; [2], dark skin types were defined as skin type 4, 5 and 6; [3], missing data for tree pollen: n = 33, for grass pollen: n = 29, for herb pollen: n = 41, for combined pollen: n = 33; [4], sensitisation to one or more types of pollen; [5], missing data: n = 18; [6], missing data: n = 12; [7], missing data: n = 57.

Multivariable stepwise regression analysis (Figure 1) showed a combination of hay fever (odds ratio (OR) 42.07; 95% confidence interval (CI) 5.75-307.55, p<0.001), dark skin type (OR 5.13; 95% CI 1.35-19.48, p=0.02) and age (OR 0.80; 95% CI 0.66-0.96, p=0.02) to be the most important characteristics associated with pollen season-related flares. Asthma was also seen more often in children with pollen season-related flares (OR 2.25; 95% CI 0.57-8.95, p=0.25). Bootstrapped optimism corrected C-statistic of the model without the variables based on pollen sensitisation was 0.86, and 0.88 for the model including these variables (Figure S1). Both models were able to identify children with pollen season-related flares, showing that the addition of information on pollen sensitisation did not significantly improve the model (p=0.93).

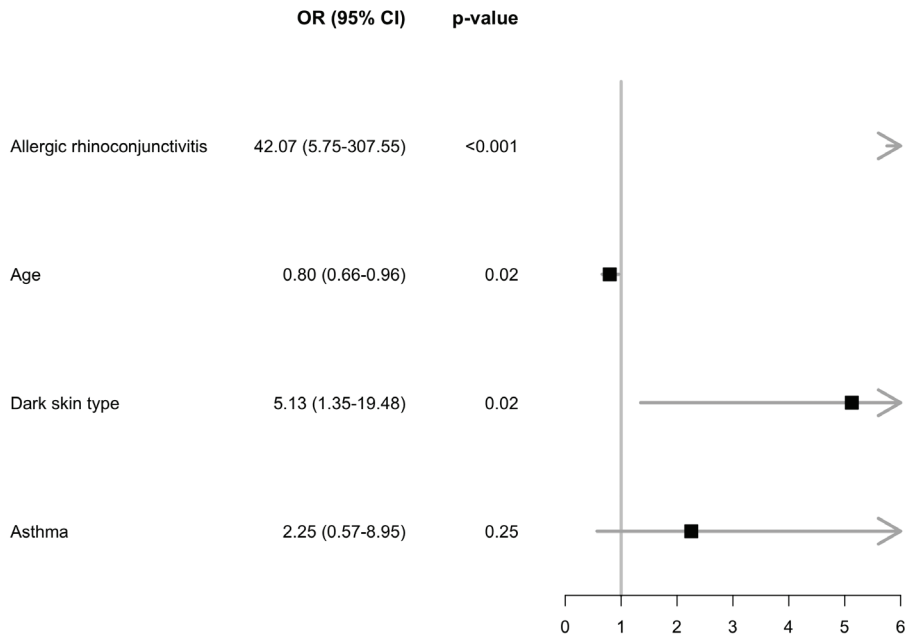

Figure 1. Forest plot main analysis
This figure displays the selection of the most important characteristics based on our stepwise logistic regression model. The following variables were included: age, gender, dark vs light skin type, asthma, allergic rhinoconjunctivitis.

DISCUSSION

We showed that a subgroup (36%) of children with difficult-to-treat AE experiences pollen season-related flares. Patients flaring in the pollen season more often have sensitisation to pollen, hay fever and a dark skin type. In general, ≥60% of inhalant allergen sensitisations are thought to be clinically relevant, with the highest clinical relevance seen for sensitisation to grass pollen.[11] In our population the most common sensitisation was against grass pollen, and children with pollen season-related flares of AE more often seemed to have hay fever as a clinically relevant manifestation of immunological sensitisation.

Seasonal flares of AE have been described in literature, but research on its associated phenotype characteristics is sparse. A study performed in Japan investigated 682 AE patients, of which 66% reported seasonal worsening of their symptoms. The proportion of patients with flares in spring and summer was 25% and 19% respectively, with 11% and 36% experiencing flares during autumn and winter.[12] A German study identified two patterns of seasonal flares among children with AE, with 54% of their subjects experiencing symptoms mainly in winter and the remaining 46% mainly in summer.

In the latter group symptoms were worse with high pollen exposure, in particular in patients sensitized to pollen.[13] A study measuring skin symptoms in Korean children with AE demonstrates worse symptoms in spring, autumn and winter relative to summer, with April as the worst month.[14]

We found that the best combination of characteristics associated with flaring in the pollen season are younger age, hay fever and dark skin type, indicating that younger children having hay fever and a dark skin type are at increased risk for pollen season-related flares. Children with dark skin that already have developed hay fever at a young age probably represent an immunologically different subgroup within the AE population. Our model showed that asthma may also be an important characteristic, but larger studies are needed to confirm this association.

Out of all variables, hay fever was the most important with an OR of 42.07 in our main analysis. Our model selected the combination of the least variables that best describes the outcome. Our sensitivity analysis showed that adding pollen sensitisation to the model did not increase the accuracy of predicting flaring in the pollen season. Based on this we can conclude that in clinical practice, children flaring in the pollen season can be identified based solely on clinical characteristics and therefore performing blood or skin prick tests is not necessary for this specific aim.

Our results showed that children with dark skin types more often experience flares of AE in the pollen season. We also found that children with dark skin types are more often sensitized to pollen and we believe this could be the explanation for flaring in the pollen season. In literature it has been demonstrated that AE is more prevalent in black and mixed race populations, with genetics as possible cause.[15,16] An increased prevalence of sensitisation among dark skin types has also been demonstrated in other studies.[17,18] In addition to a potential genetic predisposition, racial disparities in sensitisation and allergies may represent exposure to environmental factors, such as location of residence, socioeconomic status and/or education.[18,19] We should be aware of the possibility that children with dark skin are more likely to flare during spring and summer months.

Being a retrospective study, our findings depended on pre-existing and occasionally incomplete documentation in medical records, despite all efforts to record all data. Moreover, we based our findings on self-reported increases of disease severity, rather than clinically observed flares measured with severity scores. The term pollen season is subject to some extent of interpretation by children and their caregivers. In addition, the pollen season is indirectly accompanied by exposure to other external factors that have the ability to influence the course of AE. For example, sweating and heat can cause

pruritus,[20, 21] An abnormal sweating response is observed in patients with AE.[20, 22] Also, patients can have allergies for sunscreen ingredients.[23]

As for the therapeutic management of flares of AE in the pollen season, it is important to make these patients aware of their risk for flaring in the pollen season. Patients may benefit from avoiding pollen exposure, treatment with antihistamines and treatment targeting improvement of the skin barrier function.[24] Allergen-specific immunotherapy is also suggested, but has not been demonstrated valuable yet.[25] Treatment adherence impacts the utility of this option.[26]

Conclusion

Our findings indicate that patient-reported pollen season-related flares of AE are present in approximately one third of children with difficult-to-treat AE. Sensitisation to one or multiple types of pollen and a current or history of hay fever occurs significantly more frequent in this subgroup. Furthermore, children with dark skin types more often experience flaring in the pollen season than children with light skin types. Sensitisation to ≥1 types of pollen is more prevalent in dark skin types in comparison to light skin types. The phenotype of children with AE flares in the pollen season is best characterised by having hay fever, being of young age and having a dark skin type.

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SUPPLEMENTARY MATERIALS

Figure S1. Forest plot sensitivity analysis.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/nwsgv6sndx.1

APPENDIX

Conflicts of interest

None declared.

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COMPARISON OF REAL-WORLD TREATMENT OUTCOMES OF SYSTEMIC IMMUNOMODULATING THERAPY IN ATOPIC DERMATITIS PATIENTS WITH DARK AND LIGHT SKIN TYPES

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ABSTRACT

Background

Few data exist on differences in treatment effectiveness and safety in atopic dermatitis patients of different skin types.

Objective

To investigate treatment outcomes of dupilumab, methotrexate, and ciclosporin, and morphological phenotypes in atopic dermatitis patients, stratified by Fitzpatrick skin type.

Methods

In an observational prospective cohort study, pooling data from the Dutch TREAT NL and UK-Irish A-STAR registries, data on morphological phenotypes and treatment outcomes were investigated.

Results

235 patients were included (light skin types (LST): Fitzpatrick skin type 1-3: n=156 (Ethnicity: White: 94.2%), dark skin types (DST): skin type 4-6: n=68 (Black African/ Afro-Caribbean: 25%, South-Asian: 26.5%, Hispanics: 0%)). DST were younger (19.5 vs. 29.0 years; $p<0.001$), more often had follicular eczema (22.1% vs. 2.6%; $p<0.001$), higher baseline EASI scores (20.1 vs. 14.9; $p=0.009$), less allergic contact dermatitis (30.9% vs. 47.4%; $p=0.03$) and less previous phototherapy use (39.7% vs. 59.0%; $p=0.008$). When comparing DST and LST corrected for covariates including baseline EASI, DST showed greater mean EASI reduction between baseline and 6 months with only dupilumab (16.7 vs. 9.7; adjusted $p=0.032$). No differences were found for adverse events for any treatments ($p>0.05$).

Limitations

Unblinded, non-randomized.

Conclusion

Atopic dermatitis differs in several characteristics between LST and DST. Skin type may influence treatment effectiveness of dupilumab.

INTRODUCTION

Atopic dermatitis (AD), also known as atopic eczema, is a chronic pruritic inflammatory skin disorder which is among the most common dermatological conditions. AD is more prevalent in black and mixed race populations and differences seem to exist between AD in darkly pigmented and light skin, including variations in genetics and immunology.[1-6] Dark skin has been shown to have inherent structural properties that may trigger pruritus, such as higher transepidermal water loss and an increased size of mast cells.[7,8] Higher natural moisturizing factor levels and down-regulated keratinocyte differentiation have been shown in dark skin compared to light skin, suggesting differences in pathophysiological mechanisms.[9-11] This may imply a potential biological basis for differences in treatment response between light and dark skin. Clinically, AD can also present differently in dark skin.[4,5,6] Follicular eczema is an example of a morphological phenotype that is more frequently seen in African-American, Hispanic, and Asian patients.[12] A systematic review confirmed differences in morphological AD characteristics by study region.[13] Nevertheless, studies investigating the effectiveness and safety of systemic therapy in AD patients of different skin types are lacking, and only a few studies focus on this topic.[14-20] Studies investigating treatments in AD patients are predominantly conducted in white patients.[14]

In this study we aimed to investigate the effectiveness and safety of dupilumab, ciclosporin and methotrexate in AD patients with different skin types. In addition, we wanted to investigate the association between morphological phenotypes and skin types. We hypothesized that AD patients with dark skin types (DST) have different treatment outcomes and morphological phenotypes compared to patients with light skin types (LST). We specifically focused on skin type instead of ethnicity or race, as skin type could be determined more objectively. Ethnicity or race are complex terminologies that, in addition to skin colour may also cover country of origin, physical features, cultural traditions and the concept of mixed ethnicity. We hypothesized skin type to be a proxy for genetic differences between patients, underlying potential differences in pathophysiology, and subsequently, morphology and treatment response.

METHODS

Study design

We conducted a registry-embedded observational prospective cohort study, using real-world data from the Dutch TREAT (TREatment of ATopic eczema) NL (*treatregister.nl*) and UK-Irish A-STAR (Atopic eczema Systemic TherApy Register; *astar-register.org*) registries.

Setting

Patients were included at two centers in the Netherlands (November 2017 to June 2020), and 13 centers in the United Kingdom (October 2018 to April 2021). Study visits were at baseline, 4 weeks, and then approximately every 3 months, alongside routine clinic appointments.

Participants

Eligible patients were all children and adults with AD according to the U.K. working party's diagnostic criteria, starting treatment with dupilumab, ciclosporin and/or methotrexate in the context of routine clinical care. All dupilumab patients met the national criteria for dupilumab treatment, which stipulate prior treatment of at least 4 months with 1 or more conventional systemic therapies. Patients were allowed to use other systemic immunomodulating treatments and topical treatments concomitantly. The study size resulted from the inclusion of eligible patients in the abovementioned timeframes.

Variables

Data collection was based on the TREAT Registry Taskforce core dataset.[21,22] Data on Fitzpatrick skin type and morphological phenotype based on standardized proforma (e.g. (non-)flexural eczema, palmar hyperlinearity, pompholyx, discoid eczema, nodular prurigo, follicular eczema, keratosis pilaris, erythroderma, ichthyosis vulgaris; definitions included in Supplementary material 1) were collected. LST were defined as Fitzpatrick skin types 1-3, and DST as Fitzpatrick skin types 4-6. Effectiveness was analyzed using the Eczema Area and Severity Index (EASI),[23] Numerical Rating Scale (NRS) peak pruritus past 24 hours,[24] Patient-Oriented Eczema Measure (POEM)[25] and Dermatology Life Quality Index (DLQI), Children's DLQI (CDLQI) or Infants' Dermatitis Quality of Life Index (IDQLI).[26] Safety was assessed through the reporting of adverse events at each visit (AEs; definitions are included in Supplementary table 1a).

Definition of treatment endpoint

In previous studies, comparison of the effectiveness of methotrexate and ciclosporin at the same predefined treatment endpoint was considered a disadvantage due to differences in speed of action.[27,28] Therefore, we defined appropriate treatment endpoints per treatment. Methotrexate has a relatively slow onset of action, and we therefore chose 6 months as treatment endpoint. To allow direct comparisons, we chose the same endpoint for dupilumab, even though the drug has a faster onset of action. In our dataset, ciclosporin was often terminated before 6 months of treatment, for instance because of side effects or ineffectiveness. As ciclosporin has a fast onset of action, we therefore analyzed the data at 3 months instead.

Statistical analyses

Patient characteristics, safety and treatment discontinuation data were summarized using descriptive statistics and assessed during the entire follow-up period of this study. For univariate comparisons, Mann-Whitney tests and chi-squared tests were used as appropriate.

Baseline scores were compared to treatment endpoint scores using paired t-tests. To investigate differences between treatment groups in delta scores and the course of scores over time, we used linear mixed-effects models with an interaction between time and treatment. We modeled the change in scores over time, using Natural Cubic Splines with the optimal degrees of freedom based on the minimal Bayesian Information Criterion. To test if there is a difference between skin types in scores during treatment, an ANOVA test was conducted to assess the difference between the model with skin type and a model where this interaction term was removed. We included a random intercept for each patient and, in addition to skin type, included variables for which we found a significant difference between DST and LST in the models as potential confounders (including age, baseline severity score, follicular eczema, allergic contact dermatitis and previous phototherapy use). Missing values for the covariates were included as unknown.

Effects were considered statistically significant if $p<0.05$. Analyses were performed using SPSS 24.0 (IBM, Armonk, NY, U.S.A.) and R version 3.4.1 (Foundation For Statistical Computing, Vienna, Austria).

We have included a RECORD/STROBE checklist as Supplementary material 2.

RESULTS

Baseline patient characteristics

In total, 235 patients were included (Table 1). The majority of patients were male (59.1%), 67.7% were white, 156 patients (66.4%) had LST and 68 patients (28.9%) DST. Skin types of 11 patients were missing and excluded from analyses comparing skin types.

DST were on average younger when entering the registries compared to LST (median age 19.5 vs. 29.0 years; $p<0.001$). Higher baseline EASI scores were recorded in DST (20.1 vs. 14.9; $p=0.009$). Allergic contact dermatitis and previous use of phototherapy were more prevalent in LST (47.4% vs. 30.9%; $p=0.026$ and 59.0% vs. 39.7%; $p=0.008$, respectively). We also found a correlation between ethnicity and skin type ($p<0.001$).

Table 1. Baseline patient characteristics

	Study cohort (n=235)[a]	**Light skin type (n=156, 66.4%)**	**Dark skin type (n=68, 28.9%)**	**p-value**
Sex – no. (%): Male/Female	139 (59.1)/96 (40.9)	93 (59.6)/63 (40.4)	40 (58.8)/28 (41.2)	0.91
Age, median (IQR) – years	26.0 (14.0-45.0)	29.0 (17.3-48.0)	19.5 (13.0-32.3)	**<0.001**
Age of onset AD, median (IQR) – years[1]	0 (0-3)	0 (0-3)	0 (0-4)	0.92
EASI, median (IQR)[2]	17.0 (9.175-27.325)	14.9 (7.6-25.8)	20.1 (10.8-30.6)	**0.009**
NRS pruritus past 24h, median (IQR)[3]	7 (6-8)	7 (6-8)	7 (4-9)	0.38
POEM, median (IQR)[4]	21 (16-24)	21 (16-24)	20 (13-24)	0.67
DLQI, mean ± SD[5]	14.1 ± 7.0	13.8 ± 6.9	14.8 ± 7.2	0.32
Patients per treatment group – no. (%)				
Dupilumab	168 (71.5)	121 (77.6)	42 (61.8)	
Methotrexate	65 (27.7)	37 (23.7)	22 (32.4)	
Ciclosporin	26 (11.1)	19 (12.2)	7 (10.3)	
BMI – median (IQR)[b]	24.7 (22.6-27.8)	24.7 (22.6-27.3)	24.8 (21.8-30.1)	0.63
Educational status[c, 6]				0.28
ISCED 0-2: Early childhood, primary and lower secondary education	57 (24.3)	38 (24.4)	14 (20.6)	
ISCED 3-5: Upper secondary to short cycle tertiary education	103 (43.8)	73 (46.8)	27 (39.7)	
ISCED 6-8: Bachelor's, Master's, Doctoral or equivalent level	64 (27.2)	40 (25.6)	21 (30.8)	
Ethnicity – no. (%)[7]				**<0.001**
White (Europe, Russia, Middle East, North Africa, USA, Canada, Australia)	159 (67.7)	147 (94.2)	4 (5.9)	
Black African, Afro-Caribbean	18 (7.7)	0 (0)	17 (25.0)	
Asian-Chinese	5 (2.1)	0 (0)	5 (7.4)	
South-Asian (India, Pakistan, Sri Lanka, Nepal, Bhutan, Bangladesh)	23 (9.8)	4 (2.6)	18 (26.5)	
Asian-other (Korea, China north of Huai River)	8 (3.4)	0 (0)	7 (10.3)	
Hispanic or Latino	1 (0.4)	1 (0.6)	0 (0)	
Mixed	19 (8.1)	4 (2.6)[d]	15 (22.0)[e]	
Other	1 (0.4)	0 (0)	1 (1.5)	

Table 1. *(continued)*

	Study cohort (n=235)[a]	Light skin type (n=156, 66.4%)	Dark skin type (n=68, 28.9%)	p-value
Fitzpatrick skin type – no. (%)[6]				**<0.001**
I/II	17 (7.2)/87 (37.0)	17 (10.9)/87 (55.8)	0 (0)/0 (0)	
III/IV	52 (22.1)/29 (12.3)	52 (33.3)/0 (0)	0 (0)/29 (42.6)	
V/VI	29 (12.3)/10 (4.3)	0 (0)/0 (0)	29 (42.6)/10 (14.7)	
Fitzpatrick skin type – median (IQR)	3 (2-4)	2 (2-3)	5 (4-5)	**<0.001**
Morphological phenotypes – no. (%)				
Flexural eczema[8]	169 (71.9)	113 (72.4)	49 (72.0)	0.96
Non-flexural eczema[8]	173 (73.6)	116 (74.4)	51 (75.0)	0.31
Palmar hyperlinearity[9]	64 (27.2)	45 (28.8)	18 (26.5)	0.29
Pompholyx[10]	13 (5.5)	10 (6.4)	3 (4.4)	0.84
Discoïd (syn. nummular) eczema[11]	7 (3.0)	4 (2.6)	3 (4.4)	0.41
Prurigo nodularis[12]	14 (6.0)	6 (3.8)	7 (10.3)	0.13
Follicular eczema[13]	19 (8.0)	4 (2.6)	15 (22.1)	**<0.001**
Keratosis pilaris[14]	12 (5.1)	5 (3.2)	7 (10.3)	0.09
Erythroderma[15]	14 (6.0)	9 (5.8)	3 (4.4)	0.58
Ichthyosis vulgaris[16]	11 (4.7)	6 (3.8)	5 (7.4)	0.34
Infraorbital Dennie-Morgan skin folds[17]	13 (9.8)	10 (10.5)	3 (7.9)	0.53
Infra-auricular fissure(s)[18]	14 (10.5)	11 (11.6)	3 (7.9)	0.29
Skin infection[19]	17 (7.2)	11 (7.1)	4 (5.9)	0.95
Allergic co-morbidities – no. (%)				
Asthma[f,7]	128 (54.5)	87 (55.8)	41 (60.3)	0.68
Allergic rhinoconjunctivitis[f,7]	129 (54.9)	92 (59.0)	37 (54.4)	0.69
Atopic eye disease[f,20]	18 (7.7)	13 (8.3)	5 (7.4)	0.53
Eosinophilic oesophagitis[f,20]	2 (0.8)	1 (0.6)	1 (1.5)	0.86
Allergic contact dermatitis[g]	97 (41.3)	74 (47.4)	21 (30.9)	**0.026**
Food allergy	118 (50.2)[h] / 93 (39.6)[i]	76 (48.7)[h] / 63 (40.4)[i]	42 (61.8)[h] / 30 (44.1)[i]	0.18 / 0.14
Family history of AD and allergic diseases[j,21]- no. (%)	140 (59.6)	98 (62.8)	42 (61.8)	0.84

Table 1. *(continued)*

	Study cohort (n=235)[a]	Light skin type (n=156, 66.4%)	Dark skin type (n=68, 28.9%)	p-value
Previous use of systemic therapies for AD – no. (%)[5]	190 (80.9)	134 (85.9)	50 (73.5)	0.052
Ciclosporin	127 (54.0)	89 (57.1)	35 (51.5)	0.57
Azathioprine	38 (16.2)	29 (18.6)	6 (8.8)	0.14
Methotrexate	96 (40.9)	64 (41.0)	28 (41.2)	0.80
Mycophenolic acid/mycophenolate mofetil	30 (12.8)	19 (12.2)	10 (4.7)	0.71
Systemic corticosteroids	99 (42.1)	76 (48.7)	23 (33.8)	0.09
Dupilumab[k]	2 (0.9)	0 (0)	1 (1.5)	0.26
Other medication[l]	2 (0.9)	2 (1.3)	0 (0)	0.52
Investigational medication	14 (6.0)	11 (7.1)	3 (4.4)	0.60
Previous use of phototherapy – no. (%)	122 (51.9)	92 (59.0)	27 (39.7)	**0.008**
Concomitant immunomodulating therapy – no. (%)	37 (15.7)	24 (15.4)	13 (19.1)	0.49
Systemic corticosteroids[m]/Other[n]	30 (12.8)/7 (3.0)	20 (12.8)/4 (2.6)	10 (14.7)/3 (4.4)	0.70/0.47

AD, atopic dermatitis; BMI, body mass index; IQR, interquartile range; SD, standard deviation; No., number; ISCED, International Standard Classification of Education; EASI, Eczema Area Severity Index; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index. Significant p-values displayed in bold. Missing data: [1]n=15, [2]n=5, [3]n=33, [4]n=14, [5]n=16, [6]n=11, [7]n=1, [8]n=51-57, [9]n=25, [10]n=59, [11]n=62,[12]n=59, [13]n=64, [14]n=22, [15]n=20, [16]n=58, [17]n=53, analysis of NL data, [18]n=56, analysis of NL data, [19]n=16, [20]n=2, [21]n=10. [a] AD based on the U.K. working party's diagnostic criteria: n=133 (NL), n=102 (UK), [b] Excluding patients <18 years, [c] <18 years: ISCED of parents, [f] physician-diagnosed, [g] positive patch test; never tested (n=24), tested negative (n=15), unknown (n=12) or missing (n=87), [h] patient-reported, [i] patient-reported food allergy was confirmed by a physician diagnosis; patient-reported food allergy (n=131), [j] first degree family member with at least one of the following allergic diseases: AD, asthma, allergic rhinoconjunctivitis, atopic eye disease or other, [k] open-label extension study, [l] dimethyl fumarate (n=1), rituximab (n=1), [m] predniso(lo)ne, [n] ciclosporin (n=3), long-term clarithromycin (n=1), methotrexate (n=1), mycophenolate mofetil (n=1), ciclosporin and dupilumab concomitantly (n=1).

Effectiveness according to skin type

In total, 168 patients were treated with dupilumab (LST: n=121 (72.0%), DST: n=42 (25.0%)), 65 patients with methotrexate (LST: n=37 (56.9%), DST: n=22 (33.8%)) and 26 patients with ciclosporin (LST: n=19 (73.1%), DST: n=7 (26.9%)).

For dupilumab and methotrexate, an ANOVA test revealed a significant p-value for skin type as interaction term for EASI ($p<0.001$ and $p=0.04$, respectively), indicating that the course of EASI over time differs between DST and LST. Results of the linear mixed-effects models displaying the course of the scores over time according to skin type are shown for EASI only (Figure 1). Both skin type groups show improvement over time. Other scores are shown in Supplementary figure 1-3.

To get insight into how DST and LST are different, we compared baseline scores to treatment endpoint scores (Table 2). Significant improvement over time was observed for all outcome measures in both skin type groups when treated with dupilumab (e.g. ΔEASI for DST: 16.7; $p<0.001$, ΔEASI for LST: 9.7; $p<0.001$). LST also showed significant improvement in all outcome measures for methotrexate (e.g. ΔEASI: 11.0; $p=0.019$) and ciclosporin (e.g. ΔEASI: 13.1; $p<0.001$). In DST treated with methotrexate and ciclosporin, EASI showed significant improvement for methotrexate (Δ5.7; $p=0.048$) and borderline significant improvements were found for DLQI (Δ4.9; $p=0.051$) for methotrexate and EASI for ciclosporin (Δ12.9; $p=0.054$). Both groups reached the minimal clinically important difference (MCID)[29-31] for all outcomes with dupilumab. For methotrexate, patients with DST did not reach the MCID for EASI, POEM and NRS pruritus. For ciclosporin, DST did not reach the MCID for NRS pruritus. When comparing DST and LST, DST showed a significantly greater improvement in EASI when treated with dupilumab, even after adjustment for age, baseline severity, follicular eczema, allergic contact dermatitis and previous phototherapy use (Δ16.7 vs. Δ9.7; $p=0.032$; Table 2). We found no difference in EASI improvement between DST and LST for methotrexate and ciclosporin, as well as no difference in any of the other scores for all treatments.

Concomitant therapy during follow-up

In total, 31 (18%), 13 (20%) and 7 (27%) patients used conventional systemic therapy concomitantly with dupilumab, methotrexate and ciclosporin, respectively (Supplementary table 2a-c). No differences were found for usage of concomitant systemic therapy or mean usage duration between DST and LST ($p>0.05$).

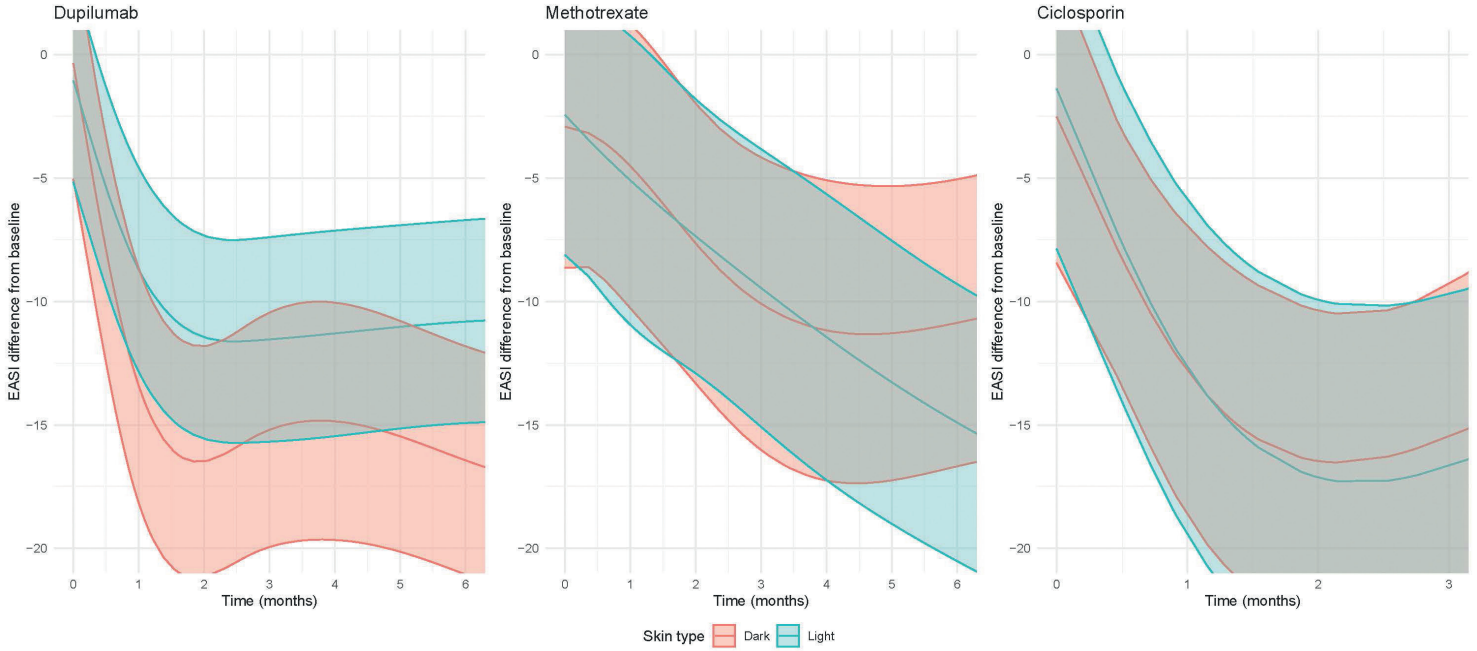

Figure 1. Difference in Eczema Area and Severity Index (EASI) from baseline (delta EASI) over time for each treatment group

Estimated mean differences in EASI scores from baseline (including 95% confidence interval) for our linear mixed-effects models, with continuous values for time and time displayed in weeks and corrected for age, baseline EASI scores, follicular eczema, allergic contact dermatitis and previous use of phototherapy, in patients with atopic dermatitis. Higher delta scores indicate greater improvement of disease activity and/or burden. The median follow-up duration for the outcome measurements varied from 38 to 46 weeks (IQR: 14-74 weeks) for dupilumab, from 17 to 19 weeks (IQR: 1-47 weeks) for methotrexate and from 15 to 17 weeks (IQR: 0-32 weeks) for ciclosporin. Dupilumab: n=168 at baseline (light skin types (LST): n=121; dark skin types (DST): n=42), n=125 at 6 months (LST: n=90; DST: n=35). Methotrexate: n=65 at baseline (LST: n=37; DST: n=22), n=25 at 6 months (LST: n=15; DST: n=10). Ciclosporin: n=26 at baseline (LST: n=19; DST: n=7), n=15 at 3 months (LST: n=11; DST: n=4).

Table 2. Effectiveness of dupilumab, methotrexate and ciclosporin according to skin type

			Baseline score	Follow-up score	p-value†	.Δ score
Dupilumab	**EASI**	**Mean score dark skin type (SD)**	24.2 (13.0)	7.5 (7.1)	**<0.001**	16.7 (13.0)
		Mean score light skin type (SD)	18.0 (13.0)	8.3 (7.5)	**<0.001**	9.7 (11.0)
		p-value Δ difference‡				**0.032**
	POEM	**Mean score dark skin type (SD)**	20.2 (6.0)	10.1 (6.0)	**<0.001**	10.1 (6.4)
		Mean score light skin type (SD)	19.9 (5.7)	10.5 (6.8)	**<0.001**	9.4 (6.8)
		p-value Δ difference‡				0.33
	DLQI	**Mean score dark skin type (SD)**	15.6 (6.8)	6.2 (7.6)	**<0.001**	9.4 (8.5)
		Mean score light skin type (SD)	14.1 (6.7)	5.7 (5.7)	**<0.001**	8.4 (7.3)
		p-value Δ difference‡				0.54
	NRS	**Mean score dark skin type (SD)**	6.9 (1.8)	3.5 (2.2)	**<0.001**	3.4 (2.3)
		Mean score light skin type (SD)	7.2 (2.3)	3.4 (2.7)	**<0.001**	3.7 (3.0)
		p-value Δ difference‡				0.99
Methotrexate	**EASI**	**Mean score dark skin type (SD)**	12.9 (9.2)	7.2 (3.9)	**0.048**	5.7 (7.4)
		Mean score light skin type (SD)	19.0 (13.2)	7.9 (5.8)	**0.019**	11.0 (14.7)
		p-value Δ difference‡				0.52
	POEM	**Mean score dark skin type (SD)**	13.8 (9.5)	10.5 (7.8)	0.32	3.2 (8.5)
		Mean score light skin type (SD)	18.5 (9.6)	10.9 (6.8)	**0.007**	7.5 (8.4)
		p-value Δ difference‡				0.19
	DLQI	**Mean score dark skin type (SD)**	9.9 (6.9)	5.0 (3.5)	0.051*	4.9 (5.9)
		Mean score light skin type (SD)	12.6 (8.3)	7.0 (7.5)	**0.011**	5.6 (6.0)
		p-value Δ difference‡				0.26
	NRS	**Mean score dark skin type (SD)**	5.2 (3.1)	3.8 (2.3)	0.17	1.3 (2.1)
		Mean score light skin type (SD)	5.9 (2.9)	3.2 (2.2)	**0.037**	2.7 (3.2)
		p-value Δ difference‡				0.74
Ciclosporin	**EASI**	**Mean score dark skin type (SD)**	23.2 (14.7)	10.3 (14.4)	0.054*	12.9 (8.3)
		Mean score light skin type (SD)	21.3 (8.5)	8.2 (11.4)	**<0.001**	13.1 (6.9)
		p-value Δ difference‡				0.98
	POEM	**Mean score dark skin type (SD)**	19.8 (9.3)	13.5 (8.4)	0.29	6.2 (9.7)
		Mean score light skin type (SD)	19.6 (6.4)	8.0 (9.3)	**0.008**	11.6 (9.9)
		p-value Δ difference‡				0.39
	DLQI	**Mean score dark skin type (SD)**	16.2 (9.0)	6.8 (7.3)	0.12	9.5 (8.7)
		Mean score light skin type (SD)	13.8 (5.7)	3.1 (2.4)	**<0.001**	10.7 (5.9)
		p-value Δ difference‡				0.36
	NRS	**Mean score dark skin type (SD)**	7.2 (2.2)	5.0 (2.9)	0.25	2.2 (3.2)
		Mean score light skin type (SD)	7.1 (2.2)	2.4 (2.5)	**0.005**	4.7 (3.7)
		p-value Δ difference‡				0.63

Table 2. *(continued)*
Mean scores (SD) for dark and light skin type at baseline and follow-up (6 months dupilumab, 6 months methotrexate, 3 months ciclosporin), and the corresponding differences for each skin type. Δ-score: reduction in score between baseline and follow-up. The p-value Δ difference‡ between the Δ-scores for light and dark skin type was assessed according to a multivariable linear model, corrected for age, baseline score, follicular eczema, allergic contact dermatitis and previous use of phototherapy. †Paired t-tests for comparison between baseline and follow-up. Number of patients per treatment group: dupilumab: dark: n=35, light: n=90; methotrexate: dark: n=10, light: n=15; ciclosporin: dark: n=4, light: n=11. EASI, Eczema Area and Severity Index (0-72); POEM, Patient-Oriented Eczema Measure (0-28); DLQI, Dermatology Life Quality Index (0-30); NRS, Numerical Rating Scale (0-10). Significant p-values displayed in bold. *, borderline significant. The minimal clinically important difference for improvement is a decrease of 6.6 points for EASI, 3.4 points for POEM, 3.3 points for DLQI, and 2.7 points for NRS pruritus.

Safety

In total, 79 potentially related adverse events were reported during the study (Supplementary table 1a-c). No serious adverse events were reported. In none of the treatment groups differences were found in the total number of adverse events, when comparing DST and LST (p>0.05).

Treatment discontinuation

A significant difference in treatment discontinuation was found between treatments, with most discontinuation for ciclosporin (n=12/26, 46.2%), followed by methotrexate (n=20/65, 30.8%) and dupilumab (n=23/168, 13.7%) (p<0.001). The most frequent reasons for discontinuation were side-effects and/or treatment ineffectiveness (Supplementary table 3). However, no differences in treatment discontinuation were found between DST and LST (p>0.05).

Differences in morphological phenotypes

We found a higher prevalence of follicular eczema in DST (22.1% vs. 2.6%; p<0.001) (Table 1). No differences were found between skin types for the other morphological features ((non-)flexural eczema, palmar hyperlinearity, pompholyx, discoid eczema, nodular prurigo, keratosis pilaris, erythroderma, ichthyosis vulgaris, infraorbital Dennie-Morgan skin folds and infra-auricular fissure(s)). No analyses could be performed to investigate if the morphological phenotypes respond differently to treatment due to low numbers.

DISCUSSION

In this study we investigated treatment outcomes and morphological phenotypes in AD patients with DST vs. LST receiving treatment with dupilumab, methotrexate and ciclosporin in a daily practice setting. Patients with DST had significantly more severe disease at baseline, indicated by higher EASI. We found that EASI scores improved in both DST and LST when treated with dupilumab, methotrexate and ciclosporin, although this change did not reach statistical significance in DST ciclosporin patients, probably related to the small sample size. When comparing treatment effectiveness between DST

and LST, DST patients showed a significantly greater EASI improvement in comparison to LST when treated with dupilumab after correction for baseline differences, but not with methotrexate or ciclosporin. No differences were found between DST and LST for total number of adverse events. Taken together, skin type may potentially influence treatment effectiveness of dupilumab, but does not seem to affect safety. Concerning morphological phenotypes, follicular eczema was significantly more common in DST.

DST patients had significantly higher baseline EASI scores, indicating more severe disease at the time of inclusion. DST were also significantly younger. Higher disease severity in DST has been reported previously,[1-4] and a retrospective study showed that children with treatment resistant AD more often had DST.[32] Patients with skin type IV were also found to have higher scores of EASI, DLQI and Investigator Global Assessment, compared to patients with Fitzpatrick skin type II.[33] Nonetheless, our registries contain more patients with LST than DST. This may result from the geographical location of the including centers, or it may reflect a potential disparity in receiving systemic therapies amongst the subgroups. Other studies showed racial and ethnic disparities in receiving therapies in AD and other diseases.[34,35] Black psoriasis patients are reported to be less likely to receive biologics than white patients due to potential financial and racial barriers in the US.[36] More research on disparities in receiving systemic AD therapies and potential causal factors of differences in severity amongst subgroups would be of interest.[37-39]

We found that allergic contact dermatitis was more prevalent in LST vs. DST. Dark skin has been shown to be less permeable compared to light skin,[40,41] and this could be a possible explanation. Another explanation could be that allergic contact dermatitis is more difficult to diagnose in DST. However, it may also be possible that LST are more commonly investigated for contact allergy, e.g. because they have better access to healthcare. The higher numbers of previous phototherapy in LST could be explained by a higher age in this subgroup. No statistically significant differences were found between DST vs. LST for other characteristics, such as age of onset, BMI, educational status, family AD history and allergic diseases and concomitant therapy use.

Regarding morphology, we found significantly more follicular eczema in DST. Others have described follicular eczema in Hispanic and Asian populations,[12,42-44] rather than directly comparing populations or focusing on skin type as was done in this study. Follicular eczema is characterized by follicular prominence clinically and follicular spongiosis histopathologically.[12] Remarkably, the investigated morphological characteristics (e.g. pompholyx, discoid eczema, nodular prurigo, keratosis pilaris, erythroderma and ichthyosis vulgaris) were only present in a small minority of patients. Due to limited numbers, we were not able to investigate treatment effects within morphological phenotypes.

In our registries, dupilumab was most frequently prescribed (71%), followed by methotrexate (28%) and ciclosporin (11%). Interestingly, prescription of methotrexate was more common than ciclosporin, despite the latter being an on-label treatment option for adults. For all treatments, side-effects were the main reason for discontinuation of treatment, followed by ineffectiveness.

Several limitations result from the daily practice setting. Due to the absence of randomization for treatment allocation, differences may arise in treatment groups because of selection bias. Dupilumab treatment requires previous use of conventional systemics. Also, bias may have been induced by the non-blinded observational nature of the study, including for severity assessments, with erythema being particularly difficult to assess in DST. We also had relatively low numbers of DST, especially in the methotrexate and ciclosporin groups. We did not stratify patients based on treatment dosage and included patients on combined systemic therapies. Only severe AEs were registered in the Netherlands as part of the TREAT core dataset.[22]

In summary, we found significant differences between AD patients with DST and LST, such as more severe disease at baseline and more follicular eczema in DST. Importantly, skin type may also influence treatment effectiveness of dupilumab in AD, as DST showed significantly greater EASI improvement than LST. Larger studies are needed to confirm these results, and skin type should therefore be considered a confounder in future AD intervention studies. Moreover, further research investigating whether morphological phenotypes respond differently to treatments is needed.

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SUPPLEMENTARY MATERIALS

Supplementary material 1. Criteria were defined for the assessment of morphological characteristics. Presence of dermatitis was assessed based on the location on the skin surface using size cut-offs for the lesions.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/s9y7fh7nbx.1

Supplementary material 2. The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/6zrg834255.1

Supplementary figure 1. Difference in Patient-Oriented Eczema Measure (POEM) from baseline (delta POEM) over time for each treatment group.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/4khfjgm2n7.1

Supplementary figure 2. Difference in Dermatology Life Quality Index (DLQI) from baseline (delta DLQI) over time for each treatment group.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/hscd3ysgvd.1

Supplementary figure 3. Difference in Numerical Rating Scale (NRS) peak pruritus past 24 hours from baseline (delta NRS) over time for each treatment group.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/dcxtdbg86k.1

Supplementary table 1(a-c). Overview of potentially related adverse events during treatment, including action, course and type.

A digital version of this supplementary material can be found at:

https://doi.org/10.17632/gfygbsw82y.1

Supplementary table 2(a-c). Concomitant immunomodulating therapy during treatment.

A digital version of this supplementary material can be found at:

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Supplementary table 3. Overview of treatment discontinuation.

A digital version of this supplementary material can be found at:

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APPENDIX

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Conflicts of interest

A.L. Bosma, S.J. Brown, P.I. Spuls, C. Flohr and M.A. Middelkamp-Hup are investigators on the European Union Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/). M.R. Ardern-Jones has undertaken consultancy or received sponsorship or his department has received funding from from Abbvie, Almirall, Ducentis, Janssen, Leo, Lilly Pfizer, Sanofi Genzyme. S.J. Brown holds a Wellcome Trust Senior Research Fellowship (220875/Z/20/Z) and has received research funding but no personal payments from Pfizer, Abbvie, Janssen, Sosie-Heptares and the European Lead Factory. J.R. Ingram receives a stipend as Editor-in-Chief of the British Journal of Dermatology and an authorship honorarium from UpToDate. He is a consultant for Boehringer Ingelheim, ChemoCentryx, Novartis and UCB Pharma and has served on advisory boards for Insmed, Kymera Therapeutics and Viela Bio, all in the field of hidradenitis suppurativa (HS). He is co-copyright holder of HiSQOL, Investigator Global Assessment and Patient Global Assessment instruments for HS. His department receives income from copyright of the Dermatology Life Quality Instrument (DLQI) and related instruments. A.D. Irvine: received consulting fees from Arena, Amirall, Pfizer, Regenron, Sanofi, Novarti, Abbvie, Benevolent Ai, and Lilly; Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Leo, Abbvie, Lilly, and Sanofi; Participation on a Data Safety Monitoring Board or Advisory Board for Novartis (paid); Leadership or fiduciary role in other board, society, committee or advocacy group at International

Eczema Council (unpaid) and Irish Hospital Consultants Association (unpaid). G. Ogg is funded by the Medical Research Council, and NIHR Oxford Biomedical Research Centre and has received research awards or undertaken advisory roles for Sanofi, Leo Pharma, Eli Lilly, UCB, Novartis, Janssen and BMS. N.J. Reynolds has performed consultancy work/ lectures for Almirall UK LTD, Abbvie, LEO Pharma, Lilly UK, Novartis UK Sanofi Genzyme though Newcastle University. Income to Newcastle University, no personal income (over last 5 years). R.B. Warren has received research grants from AbbVie, Almirall, Amgen, Celgene, Janssen, Lilly, Leo, Medac, Novartis, Pfizer & UCB, and consulting fees from AbbVie, Almirall, Amgen, Arena, Astellas, Avillion, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, DiCE, GSK, Janssen, Lilly, Leo, Medac, Novartis, Pfizer, Sanofi, Sun Pharma, UCB & UNION. R.T. Woolf: principal or co-investigator in clinical trials – Abbvie, Amgen, Anaptys Bio, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, Janssen-Cilag, Kymab, Leo Pharma, Pfizer, Sanofi and UCB. Honoraria from and consultancy work for Abbvie, Eli Lilly, Janssen-Cilag, Leo Pharma, Novartis, Sandoz, Sanofi and UCB. Honoraria from NICE (clinical expert). P.I. Spuls has done consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), received a departmental independent research grants for TREAT NL registry from Pharma since December 2019, is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis, for which financial compensation is paid to the department/hospital and, is Chief Investigator (CI) of the systemic and phototherapy atopic eczema registry (TREAT NL) for adults and children. C. Flohr is Chief Investigator of the UK National Institute for Health Research-funded TREAT (ISRCTN15837754) and SOFTER (Clinicaltrials.gov: NCT03270566) trials as well as the UK-Irish Atopic eczema Systemic Therapy Register (A-STAR; ISRCTN11210918) and a Principle Investigator in the European Union (EU) Horizon 2020-funded BIOMAP Consortium (http://www.biomap-imi.eu/). He also leads the EU Trans-Foods consortium. His department has received funding from Sanofi-Genzyme for skin microbiome work. M.A. Middelkamp-Hup has done consultancies for Sanofi, Pfizer and Leo Pharma and one of the main investigators of the TREAT NL registry. No other disclosures were reported.

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DISCUSSION

DISCUSSION

In this thesis, increasing international standardization and cooperation to investigate treatments for atopic eczema using the TREAT Registry Taskforce and the TREAT NL registry (**Part I**), real-world experience with dupilumab in atopic eczema (**Part II**) and phenotypes of atopic eczema (**Part III**) are subject of thorough discussion and investigation. As a result, this thesis contributes to the understanding of treatment response in real-world patients with atopic eczema. A discussion of the findings including the main conclusions of the studies are set out in this chapter.

The TREAT Registry Taskforce and the TREAT NL registry

The TREAT Registry Taskforce aims to collect data from available photo- and systemic therapies from patients in routine clinical practice. Data is collected in a harmonized and standardized fashion across TREAT registries. The TREAT core dataset is aligned with HOME (Harmonizing Outcome Measures for Eczema) recommendations (*homeforeczema.org*). The HOME initiative has developed a consensus-based core outcome set for clinical trials and is developing one for clinical practice.[1] Data collected in TREAT can be used for the purpose of conducting a long-term safety study. A study protocol for this is presented in **Chapter 2**. The main objective of this study is to characterize the long-term safety profile of dupilumab compared to other systemic immunomodulating therapies for the treatment of adult and pediatric patients with atopic eczema in a real-world setting. This study is currently ongoing. Moreover, this protocol can be used as a framework for similar studies investigating other (novel) therapies and relies on a standardized approach across the established registries. In general, publishing a study protocol can improve the quality of research, reduce publication bias, increase the study reproducibility, prevent unnecessary duplication of efforts and provide an opportunity for collaboration.

Within large international initiatives collaboration is key. To proceed, the desire to pool data should be supported by a technical ability, enabled by the availability of patient data and an overlap in data collection. **Chapter 3** provides insight into the current established registries within the TREAT Registry Taskforce. We have identified that a total of 4,702 participants have been recruited in the 8 registries within the TREAT Registry Taskforce as of the 1st of May 2022. The results of a mapping exercise, that identified the overlap in data collection between registries, will facilitate future comparative or joint analyses. Pooled analyses across all TREAT registries can be performed on multiple important domain items, covering the main aims of analyzing data on the (cost-)effectiveness and safety of therapies. This includes the intended analyses described in Chapter 2. Within a network for psoriasis registries, heterogeneity in data and a lack of compatibility of different datasets have been identified as difficult

factors.[2] These foreseen challenges have led to choosing a different strategy for atopic eczema, by developing a core dataset prior to data collection. However, remaining challenges also came to light. Undertaking large studies in daily practice is difficult, especially when limited time is available. Feasibility was identified as the main reason for not including all core dataset items in the individual registry datasets and seems to be a recurrent point of discussion within the field of routine data collection.

To facilitate data collection in a daily practice setting, we have learned that feasibility is important. Implementing principles like 'Registration at the source' ('Registratie aan de bron') can ideally help to facilitate generating data, by enabling the re-use of data collected in the context of routine clinical care for research purposes. However, speaking from personal experience, implementing this can turn out to be difficult due to regulations imposed by institutions. Besides, at least a part of the data can be collected by patients themselves at home or in the waiting room, thereby further reducing the registration burden for healthcare providers. Selecting a web-based application for this purpose is described in **Chapter 4**. The described selection process resulted from our experience of undergoing this process for the TREAT NL registry. An overview of potentially relevant requirements is discussed, as well as the required steps and accompanying template to select a suitable application. With this, researchers are provided with guidance for selecting the maximally appropriate web-based application (app) for the collection of patient-reported outcomes for research purposes. Over the past years, the use of apps have become increasingly popular. Several years ago the European Commission has started a stakeholder consultation to help the uptake of mobile health in the EU.[3] It also has been shown that self-management apps have the potential to improve outcomes in chronic conditions.[4]

Real-world experience with dupilumab in atopic eczema

Due to a simultaneous introduction of dupilumab as the first biological for atopic eczema and initiation of the TREAT NL registry, we have had the opportunity to further investigate this new treatment modality, which was previously only investigated in RCTs, in daily practice. The first analyses with data from the TREAT NL registry involved two studies in patients treated with dupilumab (**Chapter 5** and **Chapter 6**). In these studies, we saw a profound and sustained improvement in both investigator- and patient-reported outcome measures for effectiveness, both in the short and long term. This is in agreement with trials where a relatively healthier population is being investigated. As for safety, eye complaints were the most common adverse events in both studies, but did not result in treatment discontinuation. A reporting bias may have been introduced by specifically asking for eye complaints, after this turned out to be an important side-effect in trials. We have seen that a small proportion of patients discontinues treatment due to ineffectiveness and/or other side-effects. Dupilumab does not work equally

well for every single patient and therefore it is important that more therapies become available. We also have seen that concomitant systemic medication is common. Slightly less than half of the included patients were on another systemic therapy at the time of initiating dupilumab. Collecting data in daily practice means that no wash-out periods are applied. Therefore, relatively lower severity scores were observed in comparison to clinical trials. In psoriasis, higher disease severity, measured by investigator-reported skin scores, has shown to be associated with higher relative reduction of severity scores.[5] **Chapter 7** elaborates on several methodological aspects of these studies and daily practice studies in general. Methods applied in RCTs do not necessarily lend themselves well for daily practice research. We refrained from performing EASI-50/75 analyses because of the lower baseline EASI scores, which would distort EASI-50/75 analyses without enabling any meaningful comparison with RCTs. The results from these daily practice studies supplement results from several clinical trials demonstrating the efficacy and safety of dupilumab.[6] Overall, dupilumab treatment in daily practice with a duration of up to 84 weeks, in combination with topical treatment, can be considered an effective and generally well-tolerated treatment for atopic eczema.

As is shown in **Chapter 8**, patients with moderate-to-severe atopic eczema starting treatment with dupilumab report a decreased work ability and quality of working life, mainly due to health-related problems. We have found a relatively large impact on problems due to the health situation in our population of patients with atopic eczema, compared to cancer survivor and inflammatory bowel disease populations.[7,8] A positive correlation has been found between work impairment and disease severity in another study.[9] In our study, significant improvement of work ability and quality of working life was observed with dupilumab treatment. Quality of working life seems not to be captured by broadly used validated PROMs in atopic eczema and therefore implementing the QWLQ (Quality of Working Life Questionnaire) could be considered of added value. By using the QWLQ, patients could be identified that may benefit from tailored interventions. At the moment, an example of such an initiative is 'Emma at Work', that is aimed towards people with a chronic condition. This program for young people enables training and coaching sessions and the introduction to a network of potential employers.[10] Patients in general indicate that they need support for work-related concerns from their medical specialists and/or other professionals.[11] The prevalence of atopic eczema in combination with a high disease burden, accompanied by direct costs (i.e. hospital visits and prescription of medication) and indirect costs (i.e. work productivity loss), make atopic eczema an expensive disease.[12,13]

Biologicals, such as dupilumab, are relatively expensive treatments. When adhering to the on-label usage of a two-weekly dosing schedule, the costs for dupilumab are more than € 16.000,- per year. Currently, a one-size-fits-all approach is applied when

prescribing dupilumab. Differences in drug exposure (serum concentration) may explain variations in treatment response. Therapeutic drug monitoring comprises the measuring of the concentration of a specific drug in patients' blood in order to individually adjust the dosage. In **Chapter 9** we did not find a correlation between dupilumab serum concentration levels and ΔEASI, suggesting that the currently applied dosage does not fall within the optimal therapeutic window. The main reason for this seems to be that dupilumab is highly dosed. All measured concentrations seem to yield sufficient responses. If patients are dosed much higher than required, the high levels have the potential to impair the ability to determine relevant clinical differences based on these levels. How to interpret correlations between EASI and drug levels may be difficult. A concentration-response relationship may exist in either direction. An association between serum concentration and subsequently (Δ)EASI (as outcome) may be expected at optimal dosages within the therapeutic range. However, a directional association between EASI and concentration (as outcome) could also be observed, corresponding with the results of this chapter. Baseline EASI was shown to be correlated with dupilumab levels, suggesting that disease activity has an influence on drug levels. The interpretation of correlations with a bidirectional relationship between serum levels and both effectiveness (including disease activity) and safety can be difficult.

In **Chapter 10** we present four cases of two male patients who conceived during dupilumab treatment and two female patients that discontinued dupilumab because of anticipated pregnancy. Apart from disease flares in both patients that discontinued treatment, no complications were reported concerning the ability to conceive, the pregnancy and fetal outcomes. At the moment, based on the available literature, preference is given to treatment with topical corticosteroids, phototherapy, systemic corticosteroids and ciclosporin, instead of dupilumab, until more data is available. Interestingly, considering the shift towards Th2 cell differentiation in pregnancy, targeting IL-4 has been suggested as potential treatment option for pregnant patients with Th2-dominant diseases, to induce Th1:Th2 balance and disease improvement.[14] In a cohort study investigating 298 pregnancies in patients with psoriasis receiving or eligible to receive biologics and/or conventional systemic therapies, similar birth outcomes were found as in the general population.[15] Since the publication of our case series, several case reports have been published on the uncomplicated treatment with dupilumab during pregnancy.[16-19] These reports may impact recommendations in future guidelines and consensus papers.

Phenotypes of atopic eczema

In **Chapter 11** an overview of phenotype definitions used in literature for disease severity, disease trajectory, morphology and eczema herpeticum, including their associated characteristics, is given, thereby contributing to developing a better

understanding of the disease. A lack of uniform and consistent use of atopic eczema phenotypes across studies was identified. Heterogeneity was observed in the phenotype definitions used and also in the associated characteristics investigated within the same phenotypic grouping. At the present time, no consensus exists on how phenotypes of atopic eczema should be defined and the potential role of phenotypes in guiding both diagnostic and therapeutic management of patients is currently unknown. However, phenotypes should reflect relevant differences in patient characteristics, leading to variations in treatment response. At the moment, the therapeutic management of atopic eczema is not based on phenotypes reflecting potentially relevant differences in patient characteristics, with the exception of disease severity, as patients with moderate-to-severe disease often receive systemic immunomodulating therapies. Within the population of patients with atopic eczema, many subgroups (phenotypes) can be identified based on many features, also including seasonality of symptoms and skin type. Chapter 12 and 13 elaborate further of these two phenotypes of interest.

Seasonal flares of atopic eczema have been described in literature, but research on its associated phenotypic characteristics is limited. In general, symptoms of atopic eczema are thought to be worse in winter, due to further dehydration of the skin by exposure to low humidity in the environment (e.g. cold weather and central heating).[20] However, a subgroup of patients experiences disease flares in spring and summer months. In **Chapter 12** we have concluded that patient-reported flares in spring and summer are experienced by one third of children with difficult-to-treat atopic eczema. Sensitisation to ≥1 of pollen and a current or history of hay fever is more common in this subgroup of patients. Furthermore, children with dark skin types more often experience flaring in the pollen season and have more sensitisation to ≥1 types of pollen, than children with light skin types. The phenotype of patients with patient-reported flares in spring and summer can be characterized as young children having hay fever and a dark skin type. This phenotype can be identified based on clinical parameters alone without the need to perform IgE blood testing or skin prick tests. An increased prevalence of sensitisation among dark skin types has also been demonstrated in other studies.[21,22]

Phenotypes based on skin type are further discussed in Chapter 13. At the moment, there is a lack of studies specifically investigating the effectiveness and safety of systemic therapies in different skin types and morphological phenotypes. As a first step, we performed the study described in **Chapter 13**. In this study we primarily aimed to investigate the effectiveness and safety of treatment with dupilumab, ciclosporin and methotrexate in atopic eczema patients with different skin types in daily practice, by stratifying patients as such in our analyses. We found a higher baseline disease severity in dark skin types in this study. This is interesting, as a study comparing disease severity in Black and white children, reported that Black children show a non-

significantly lower risk of severe disease, while a highly significantly increased risk was found after adjusting for erythema score (i.e. after exclusion of erythema scores).[23] Erythema acts like a confounder, being associated with the exposure (skin colour) as well as the outcome (severity).[23] This indicates that erythema could be a misleading indicator of severity in dark patients. The EASI score, that was used in all clinical studies reported in this thesis, includes the scoring of erythema and therefore inherently can be considered a limitation when used to study patients of colour. However, the EASI partially overcomes this by upgrading erythema scores in dark skin to avoid underestimation. In Chapter 13 we found that skin type may influence treatment effectiveness of dupilumab. Dupilumab showed a greater effectiveness in patients with dark skin types. One may argue that with this we do not prove a causal effect of skin type. However, an observational study can be considered the most appropriate study type to investigate skin type, as one cannot perform a RCT with randomization for skin type to correct for all potential confounders. A directional effect of skin type is further suggested by the fact that skin type, unlike treatment effect, is static. As for our second aim in this chapter of investigating the association between morphological phenotypes and skin types, we found a higher presence of follicular eczema in dark skin types in comparison to light skin types. The presence of follicular eczema in minority populations has previously only been described in reports of these populations.[24-26] No comparative analyses between populations and focusing specifically on skin type have been undertaken before. Some may consider Fitzpatrick skin type an artificial way of separating groups within populations. However, skin type is feasible to register in clinical practice and we have shown that these skin types are actually helpful to identify clinically meaningful differences.

General advantages and limitations of real-world research

Data from registries have great external validity due to the observational nature of data collection in contrast to RCTs. Patients selected for RCTs differ from real-world patients due to strict in- and exclusion criteria. A registry population can be considered a better representation of the population of interest. Also, the feasibility of RCTs is limited. In daily practice it may even be a challenge to perform a pragmatic RCT, for example one that involves randomization for treatment allocation. Nowadays patients are well informed, know that they qualify for certain treatments and are not willing to risk the possibility of receiving what they consider to be an inferior drug. An advantage of real-world research is that its observational nature makes that patients are generally very willing to participate. However, this type of research also has its drawbacks. There are limitations to an observational study design, due to the occurrence of different forms of bias: information bias (e.g. absence of blinding), selection bias (e.g. based on eligibility criteria for treatment) and confounding (e.g. absence of randomization).

For this reason, registry data have a limited ability to provide evidence on the internal validity of treatments. Other factors include the lack of wash-out, the use of co-medication, potential noncompliance and unintended dosing deviations. Individuals commencing novel systemic treatments have often received and failed on multiple systemic therapies in the past. Less strict requirements are also applied with regard to follow-up visit schedules. Statistical analyses should take into account that patients were not seen strictly at the same points in time, for example by using statistical models. It is important to be aware of these limitations and to take this into account when interpreting the results.

Future perspectives

There is still much to learn within the field of atopic eczema. Registries can provide a platform for research to answer these needs. When pooling data across countries, differences in registry datasets, prescribing practices, reimbursement restrictions, in- and exclusion criteria, modalities for data collection and languages should be taken into consideration. Harmonization of data collection, both on a national and international level, is important to investigate large numbers of patients. Large registry-embedded head-to-head studies of good quality are required to further investigate systemic therapies.[27-29] In the TREAT NL registry, long-term data is collected from patients with atopic eczema in daily practice to investigate the (cost-)effectiveness and safety of the available systemic therapies and phototherapies. Many studies further investigating this will follow.

Future studies within TREAT NL registry and the TREAT Registry taskforce will include the further investigation of safety and studies comparing dupilumab with other systemic therapies (as described in Chapter 2). In order to perform meaningful analyses, we aim for a standardized data collection of at least 5 years and as long as possible follow-up for each participant. In general, still few studies have been conducted directly comparing treatments. Besides, we have entered a new therapeutic era with the introduction of many novel treatments, which are not yet investigated in daily practice at all. More novel therapies such as biologics (-mabs) and JAK inhibitors (-nibs) will become available in the future. When these treatments become available, long-term real-world data can be collected in registries. Research on novel alternative treatment options is of great importance for patients in whom current available treatments are not ideal due to ineffectiveness and/or side effects. Patients are willing to accept limitations of treatments when there are no alternatives. Importantly, novel therapies will need to be used responsibly in clinical practice, also in view of the high costs. When we look at the place of conventional treatments in psoriasis in the Netherlands, these treatments have remained available as a first option in patients who require systemic therapies, despite the availability of many biologics for this indication.

It is also for that reason that it would be lucrative to perform comparisons between novel and conventional systemic therapies, as the latter are cheaper. If many novel expensive treatments are introduced, it is all the more important to investigate and compare treatments in order to guarantee an optional cost-effectiveness of care. Further strategies to control cost could include the implementation of therapeutic drug monitoring. Dose reduction of dupilumab should be subject of further investigation. It would be interesting to investigate whether dosage interval prolongation yields sufficient treatment responses. In accordance with studies performed in psoriasis,[30] a therapeutic window for dupilumab could then be defined to implement therapeutic drug monitoring. Microsampling techniques have been proposed as alternative for serum sampling to facilitate sampling in daily practice.[31] A bidirectional relationship between serum levels and both effectiveness (including disease activity) and safety should always be taken into consideration in the interpretation of future studies. Another strategy to reduce costs in the future, would be to investigate the impact on work as a measure for the cost-effectiveness of treatments.

Diverse research is important to ensure the inclusion of patients representative of the population of interest. Diversity is an increasingly important topic in medical research. As described before, study participants in RCTs are usually white, middle-aged men.[32] Patients from minority populations are often underrepresented in clinical studies. As these studies are the cornerstone of treatment development, this hampers our ability to work towards personalized medicine strategies for all patients. Current clinical decision making does not take a patient's skin color into account. A discrepancy exists regarding the proportion of white to other patient populations included in studies and these proportions in the real-world population, with an overrepresentation of white populations in studies.[33] Five factors are thought to contribute to this: low income, investigator bias, mistrust in medical research and professionals, limited health and research literacy, and lack of access to transportation.[33] In a post hoc analysis from three phase 3 trials assessing the efficacy and safety of dupilumab versus placebo by racial subgroup, only 6.2% of patients were classified as Black/African American,[32] despite patients with dark skin type having a higher disease prevalence.[34-36] If treatments are not carefully investigated within the entire target population, this could lead to disappointing real-world results. There is a need for studies with a greater inclusion of minority subgroups to enable the development of targeted treatments for a disease that affects a multi-ethnic population.[37]

Working towards personalized medicine will eventually guide in determining what is the best treatment for which patient, with regard to both effectiveness and safety, and both on the short and long term. The BIOMAP initiative has been established to shed light on biomarkers as predictors for disease course and treatment response (*biomap-*

imi.eu). In future studies, patient stratification according to phenotype would be of interest to enable investigation of which patients are likely to respond best to certain therapies. However, the current lack of phenotype definitions can be challenging. In order to facilitate comparative or pooled analyses across studies in the future, clinical relevant phenotypes should first be identified, and then these should be consistently used. More research using unbiased data-driven approaches should be performed to allow the identification of phenotypes that are clinically relevant, but may not be obvious to clinical observation. The identification of clinically meaningful phenotypes in the context of treatment outcome should be pursued, by investigating therapeutic effectiveness and safety in patients stratified according to phenotype. By working towards personalized medicine, therapeutic strategies can ultimately be developed to improve the care for this condition.

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15A

SUMMARY

SUMMARY – UNDERSTANDING TREATMENT RESPONSE IN REAL-WORLD PATIENTS WITH ATOPIC ECZEMA

Atopic eczema is a common and chronic inflammatory skin disorder that is characterized by the presence of pruritic lesions on the skin. It concerns a heterogeneous disease, in which many subgroups of patients (i.e. phenotypes) can be identified. It may present as a mild to a severe disease. A subset of patients with moderate-to-severe atopic eczema requires systemic therapy, such as for example treatment with ciclosporin, methotrexate or dupilumab, in order to achieve sufficient disease control.

There is a lack of evidence regarding many aspects of the systemic therapies that are available for atopic eczema. In particular, good comparative research, research on different subgroups of patients and the long-term (cost-)effectiveness and safety of therapies is lacking. It is not feasible to perform long-term randomized controlled trials (RCTs) to investigate all potential comparisons between treatments and subgroups. In registries, data are collected from patients in daily practice to answer questions in relation to various aspects of treatments, including questions that cannot be properly investigated by means of RCTs (**Chapter 1**).

In this thesis increasing international standardization and cooperation to investigate treatments for atopic eczema using the TREAT Registry Taskforce and the TREAT NL registry (***Part I***), real-world experience with dupilumab in atopic eczema (***Part II***) and phenotypes of atopic eczema (***Part III***) are discussed and investigated, to contribute to a better understanding of treatment response in patients with atopic eczema in daily practice.

Part I: The TREAT Registry Taskforce and the TREAT NL registry

In the TREAT NL registry, long-term data is collected from patients with atopic eczema in daily practice to investigate the effectiveness, cost-effectiveness and safety of the available systemic therapies and phototherapies. The registry is part of the international TREAT Registry Taskforce with the pursuit of a harmonized data collection across the registries to enable this.

In **Chapter 2** we have established a study protocol for a long-term safety study on dupilumab in comparison to other systemic therapies within the TREAT Registry Taskforce to assess the long-term safety risk of these therapies in a routine clinical care setting. Adult and paediatric patients who start treatment with dupilumab or another systemic immunomodulating agent for their atopic eczema will be included. The primary endpoint of this study is the incidence of malignancies compared between the treatment groups. Secondary endpoints include other serious adverse events and adverse events of special interest, such as eye disorders and eosinophilia. With this protocol we have

provided a framework that can be used for similar studies investigating other (novel) therapies and relies on a standardized approach across the established registries.

In **Chapter 3** an overview is given of the status of the current established registries within the TREAT Registry Taskforce. We have identified that more than 4,700 participants have been recruited in eight registries within the taskforce as of 1st of May 2022. In order to harmonize data collection, the TREAT Registry Taskforce has previously developed a core dataset. A mapping exercise was performed to assess the degree of overlap and the pooling ability between the registry datasets. Pooled analyses across all TREAT registries were deemed possible on multiple important dataset domain items, covering the main aims of analyzing data on (cost-)effectiveness and safety. The results of the mapping exercise will facilitate comparative and joint analyses across countries in the future.

Chapter 4 reports on the process of selecting a web-based application for the collection of patient-reported outcomes. This selection process resulted from our experience of finding a suitable application to measure patient-reported outcomes for the TREAT NL registry. An overview of potentially relevant requirements is discussed, including investigator, legal, security, patient, feedback, and interoperability requirements, as well as the required steps and an accompanying template to select a suitable application. With this, researchers are provided with guidance for selecting the maximally appropriate web-based application for the collection of patient-reported outcomes for research purposes.

Part II: Real-world experience with dupilumab in atopic eczema

The first analyses with data from the TREAT NL registry involved two prospective cohort studies in patients treated with dupilumab in routine clinical care at the Amsterdam UMC and Erasmus MC, which are demonstrated in **Chapter 5** and **Chapter 6**. Summarizing, we observed a sustained improvement of both investigator- and patient-reported outcome measures over time. Many patients used concomitant systemic therapy at baseline. Eye complaints were the most common adverse events in both studies, but did not result in treatment discontinuation. A small proportion of patients discontinued treatment due to ineffectiveness and/or side-effects. All in all, dupilumab treatment of up to 84 weeks, in combination with topical treatment and initial concomitant systemic treatment, can be considered an effective and generally well-tolerated treatment.

Chapter 7 concerns a commentary in which we elaborate on several methodological aspects of the study presented in Chapter 6 and daily practice studies in general. Not all methods applied in RCTs necessarily lend themselves well for daily practice research. We refrained from performing analyses on EASI-50/75 (i.e. 50 or 75% improvement of disease severity from baseline as measured by Eczema Area and Severity Index

(EASI)) because of lower baseline EASI scores, resulting from the observational nature of the study, which would distort these analyses without even enabling any meaningful comparison with RCTs.

In **Chapter 8** we aimed to investigate how patients with atopic eczema starting treatment with dupilumab, indicating moderate-to-severe disease, perceive their work ability and quality of working life, and how this is affected by treatment, by performing a daily practice prospective observational cohort study. The majority of patients experienced days lost from work and other usual activities, demonstrating potential work productivity loss. Most working patients reported problems at work, often a combination of pruritus, fatigue, pain, and psychological complaints. We have found a decreased work ability and quality of working life in our population, mainly due to health-related problems. Significant improvement of work ability and quality of working life is observed with dupilumab treatment.

The clinical relevance of dupilumab serum levels is investigated in the two-center prospective cohort study of **Chapter 9**. Dupilumab is currently prescribed in one dosage across atopic eczema patients. Based on this dosage, no correlations were found between dupilumab serum levels and disease severity as measured by a difference in EASI score, potentially due to the fact that drug levels are high. A correlation was found between baseline EASI and dupilumab drug levels at 2, 12 and 24 weeks. In addition, low serum levels were particularly observed in patients with adverse events, treatment interval deviation and discontinuation. All in all, with the current standardized dosing scheme, the current range of dupilumab levels does not seem to influence treatment effectiveness. However, disease activity does seem to influence drug levels. Higher baseline disease activity results in lower dupilumab levels at follow-up. In this manuscript the difficulty of the interpretation of bidirectional correlations is discussed.

Chapter 10 reports on a case series of 4 patients: two male patients who conceived during dupilumab treatment and two female patients that discontinued dupilumab because of anticipated pregnancy. Apart from disease flares in both patients that discontinued treatment, no complications were reported concerning the ability to conceive, the pregnancy and fetal outcomes. In this article an overview is given of the available evidence in literature on dupilumab during conception, pregnancy and lactation that can guide considerations for patients on dupilumab wishing to conceive a child. Based on the available literature, preference was given to treatment with topical corticosteroids, phototherapy, systemic corticosteroids and ciclosporin in pregnancy, instead of dupilumab, until more data is available.

Part III: Phenotypes of atopic eczema

By performing a systematic review we aimed to give an overview of how atopic eczema phenotypes have been previously reported in literature and which characteristics associated with these phenotypes have been described (**Chapter 11**). Phenotypes are important as they could reflect relevant differences in characteristics between patients, for example leading to variations in treatment response. Identified studies were mostly cross-sectional studies in hospital-based settings, investigating predefined phenotypes and their associated characteristics. Data-driven approaches to identify phenotypes were only used in a minority of studies. In this chapter, we present an overview of phenotype definitions used in literature for severity, trajectory, morphology and eczema herpeticum. A lack of clinically relevant phenotypes and the uniform and consistent use of phenotypes across studies was identified.

In the retrospective study of **Chapter 12** we have concluded that patient-reported flares in spring and summer are experienced by one third of children with difficult-to-treat atopic eczema. Sensitisation to ≥1 of types of pollen and a current or history of hay fever has shown to be more common in this subgroup of patients. Furthermore, we found that children with dark skin types more often experienced flaring in the pollen season and had more sensitisation to ≥1 types of pollen, than children with light skin types. The phenotype of patients with patient-reported flares in spring and summer can be characterized as young children having hay fever and a dark skin type. This phenotype can be identified based on clinical parameters alone without the need to perform IgE blood testing or skin prick tests.

Skin type is further subject of investigation in **Chapter 13.** In this chapter we have investigated the effectiveness and safety of systemic therapy with dupilumab, methotrexate and ciclosporin, by stratifying patients according to having a light skin type versus a dark skin type in our analyses. In addition, we have investigated the association between morphological phenotypes and skin types in this population. Prospective cohort data from the Dutch TREAT NL and UK-Irish A-STAR registries was used. Our main findings were that atopic eczema differs in several characteristics between light and dark skin types. In comparison to patients with light skin types, patients with dark skin types were younger, more often had follicular eczema, higher baseline EASI scores, less allergic contact dermatitis and less previous phototherapy use. In addition, dark skin types showed greater mean EASI reduction between baseline and 6 months with dupilumab. Therefore, we concluded that skin type may influence treatment effectiveness of dupilumab.

A discussion of the findings of this thesis including the main conclusions of the individual studies are set out in **Chapter 14**. Next to a general discussion, the

advantages and limitations of real-world research are discussed, as well as future perspectives. Advantages include external validity, representation of the population of interest, feasibility and willingness of patients to participate. Limitations include the occurrence of different forms of bias, lack of wash-out, use of co-medication, potential noncompliance, unintended dosing deviations and less strict visit schedules. In the future, large and good-quality studies comparing different treatments are of interest. In this respect harmonization of data collection is important. Investigating treatments in specific phenotypes will be the first step in working towards personalized medicine. It is expected that the coming years more new expensive treatments will become available. It will be important to collect data and generate evidence in order to guarantee a (cost-) effective and safe healthcare for patients with atopic eczema. After all, the ultimate goal is to improve the care for this condition.

15A

15B

SAMENVATTING

SAMENVATTING – HET BEGRIJPEN VAN BEHANDELRESPONS BIJ ATOPISCH ECZEEM IN DE DAGELIJKSE PRAKTIJK

Atopisch eczeem is een veelvoorkomende en chronische inflammatoire huidziekte die wordt gekarakteriseerd door de aanwezigheid van jeukende plekken op de huid. Het betreft een heterogene ziekte, waarbij vele subgroepen patiënten (fenotypes) kunnen worden geïdentificeerd. Het kan zich presenteren als een milde tot ernstige ziekte. Een deel van de patiënten met matig-tot-ernstig atopisch eczeem vereist systemische therapie, zoals bijvoorbeeld behandeling met ciclosporine, methotrexaat of dupilumab, om voldoende ziektecontrole te bereiken.

Er is een gebrek aan kennis met betrekking tot vele aspecten van de beschikbare behandelingen bij atopisch eczeem. In het bijzonder, goed vergelijkend onderzoek, onderzoek naar diverse subgroepen patiënten en de lange termijn (kosten)effectiviteit en veiligheid van systemische therapie en lichttherapie ontbreekt. Het zal niet haalbaar zijn om (langetermijn-) RCTs uit te voeren om alle mogelijke vergelijkingen tussen de behandelingen en subgroepen te onderzoeken. In registers worden gegevens verzameld van patiënten in de dagelijkse praktijk om vragen te beantwoorden ten aanzien van verscheidene aspecten van behandelingen, ook vragen die middels RCTs niet goed te onderzoeken zijn (**Hoofdstuk 1**).

In dit proefschrift wordt het vergroten van internationale standaardisatie en samenwerking om behandelingen voor atopisch eczeem te onderzoeken met hulp van de TREAT Registry Taskforce en het TREAT NL register (***Deel I***), praktijkervaring met dupilumab bij atopisch eczeem (***Deel II***) en fenotypes van atopisch eczeem (***Deel III***) beschreven en onderzocht, om bij te dragen aan het beter begrijpen van de behandelrespons bij patiënten met atopisch eczeem in de dagelijkse praktijk.

Deel I: De TREAT Registry Taskforce en het TREAT NL register

In het TREAT NL register worden langetermijn gegevens verzameld van patiënten met atopisch eczeem in de dagelijkse praktijk om de effectiviteit, kosteneffectiviteit en veiligheid van de beschikbare systemische therapieën en lichttherapieën te onderzoeken. Het TREAT NL register is onderdeel van het internationale samenwerkingsverband de TREAT Registry Taskforce met het streven om een geharmoniseerde gegevensverzameling in alle betrokken registers te realiseren om dit mogelijk te maken.

In **Hoofdstuk 2** wordt een studieprotocol voor een langetermijn veiligheidsstudie naar dupilumab in vergelijking met andere systemische therapieën binnen de TREAT Registry Taskforce beschreven om het veiligheidsrisico op de lange termijn van deze therapieën

in de dagelijkse praktijk te onderzoeken. Volwassenen en kinderen, die starten met behandeling met dupilumab of een ander systemisch geneesmiddel voor hun atopisch eczeem, zullen worden geïncludeerd. Het primaire eindpunt van deze studie is de incidentie van maligniteiten vergeleken tussen de behandelgroepen. Secundaire eindpunten zijn onder meer andere ernstige bijwerkingen en specifieke bijwerkingen, zoals oogaandoeningen en eosinofilie. Met dit protocol bieden we een raamwerk dat kan worden gebruikt voor soortgelijke onderzoeken naar andere (nieuwe) therapieën en is gebaseerd op een gestandaardiseerde aanpak binnen de gevestigde registers.

In **Hoofdstuk 3** wordt een overzicht gegeven van de status van de huidige opgerichte registers binnen de TREAT Registry Taskforce. In totaal werden er per 1 mei 2022 meer dan 4700 deelnemers geïncludeerd in de acht registers. Om data harmonisatie mogelijk te maken heeft de TREAT Registry Taskforce eerder een core dataset ontwikkeld. Een mapping exercise werd uitgevoerd om de mate van overlap en de poolbaarheid van de datasets van de registers te beoordelen. Gepoolde analyses binnen alle TREAT registers werden mogelijk geacht voor meerdere belangrijke dataset domein items, die de belangrijkste doelstellingen van het onderzoeken van de (kosten)effectiviteit en veiligheid bleken te dekken. De resultaten van de mapping exercise zullen internationale vergelijkende en gezamenlijke analyses faciliteren in de toekomst.

Hoofdstuk 4 beschrijft het proces van het selecteren van een web-based applicatie voor de verzameling van patiënt-gerapporteerde uitkomstmaten. Dit selectieproces is voortgekomen uit onze ervaring van het zoeken naar een geschikte applicatie om patiënt-gerapporteerde uitkomsten te meten voor het TREAT NL register. Een overzicht van mogelijk relevante vereisten komt aan bod, inclusief vereisten met betrekking tot onderzoekers, juridische zaken, beveiliging, patiënten, feedback en interoperabiliteit, evenals de vereiste stappen en een begeleidende template om een geschikte applicatie te selecteren. Hiermee bieden wij andere onderzoekers handvatten om de meest geschikte web-based applicatie voor het verzamelen van patiënt-gerapporteerde uitkomstmaten voor onderzoeksdoeleinden te selecteren.

Deel II: Praktijkervaring met dupilumab bij atopisch eczeem

De eerste analyses met gegevens vanuit het TREAT NL register betroffen twee prospectieve cohort studies naar patiënten die behandeld werden met dupilumab in de dagelijkse praktijk in het Amsterdam UMC en Erasmus MC, welke worden gepresenteerd in **Hoofdstuk 5** en **Hoofdstuk 6**. Samenvattend zagen we een over de tijd een aanhoudende verbetering van zowel onderzoeker- als patiënt-gerapporteerde uitkomstmaten. Veel patiënten gebruikten bijkomende systemische therapie ten tijde van baseline. In beide studies waren oogklachten de meest voorkomende bijwerkingen, maar deze klachten resulteerden niet in het stoppen van de behandeling. Een klein deel

van de patiënten stopte met de behandeling vanwege ineffectiviteit en/of bijwerkingen. Al met al, tot 84 weken behandeling met dupilumab, in combinatie met lokale en initiële bijkomende systemische behandeling, kan worden beschouwd als een effectieve behandeling, die over het algemeen goed wordt verdragen.

Hoofdstuk 7 betreft een commentaarstuk waarin we ingaan op verscheidene methodologische aspecten van de studie die gepresenteerd wordt in Hoofdstuk 6 en dagelijkse praktijk studies in het algemeen. Niet alle methoden die in RCTs worden toegepast lenen zich even goed voor onderzoek in de dagelijkse praktijk. Wij hebben afgezien van het verrichten van EASI-50/75 analyses (i.e. 50 of 75% verbetering van ziekte-ernst vanaf baseline zoals gemeten met Eczema Area and Severity Index (EASI)) vanwege de lagere baseline EASI scores, als gevolg van het observationele karakter van de studie, die deze analyses zouden vertekenen zonder zelfs een zinvolle vergelijking met RCTs mogelijk te maken.

In **Hoofdstuk 8** streefden wij ernaar om te onderzoeken hoe patiënten met atopisch eczeem die behandeling met dupilumab starten, wijzend op een matige-tot-ernstige ziekte, hun werkvermogen en kwaliteit van leven met betrekking tot werk inschatten, en hoe dit wordt beïnvloedt door behandeling, door middel van een prospectieve observationele cohort studie in de dagelijkse praktijk. De meerderheid patiënten misten dagen van werk en andere gebruikelijke activiteiten, wat een potentieel verlies van werkproductiviteit betekent. De meeste werkende patiënten rapporteerden problemen op het werk, vaak een combinatie van jeuk, vermoeidheid, pijn en psychologische klachten. We vonden een verminderd werkvermogen en kwaliteit van leven met betrekking tot werk in onze populatie, voornamelijk vanwege gezondheidsproblemen. Met dupilumab behandeling werd significante verbetering hiervan aangetoond.

De klinische relevantie van dupilumab serum spiegels werd onderzocht in de prospectieve cohortstudie van **Hoofdstuk 9.** Dupilumab wordt momenteel in één standaarddosering voorschreven aan patiënten met atopisch eczeem. Op basis van deze dosering zien we geen correlatie tussen dupilumab serum spiegels en ziekte-ernst gemeten met een verschil in EASI score, mogelijk omdat de dupilumab spiegels hoog zijn. Een correlatie werd gevonden tussen baseline EASI en dupilumab spiegels bij 2, 12 en 24 weken. Verder werden lagere serum spiegels voornamelijk gezien in patiënten met bijwerkingen, met behandelinterval-aanpassingen en die behandeling staakten. Al met al, lijkt met het huidige doseerschema, de huidige range aan dupilumab spiegels de effectiviteit van behandeling niet te beïnvloeden. Echter, ziekteactiviteit lijkt wel een invloed te hebben op de spiegels. Een hogere baseline ziekteactiviteit resulteert in een lagere dupilumab spiegels bij follow-up. In dit hoofdstuk wordt de lastige interpretatie van bidirectionele correlaties besproken.

Hoofdstuk 10 betreft een case serie bestaande uit 4 patiënten: twee mannelijke patiënten die een kind hebben verwekt tijdens behandeling met dupilumab en twee vrouwelijke patiënten die behandeling met dupilumab staakten vanwege een zwangerschapswens. Afgezien van opvlammingen van de ziekte-ernst in de twee patiënten die behandeling staakten, werden er geen complicaties gerapporteerd betreffende het vermogen om zwanger te worden of te maken, de zwangerschap en foetale uitkomsten. In dit artikel wordt een overzicht gegeven van het beschikbare bewijs in de literatuur over dupilumab tijdens conceptie, zwangerschap en borstvoeding, welke als leidraad zou kunnen worden gebruikt voor patiënten die dupilumab gebruiken en een kinderwens hebben. Op basis van de beschikbare literatuur ging de voorkeur uit naar behandeling met lokale corticosteroïden, lichttherapie, systemische corticosteroïden en ciclosporine in de zwangerschap, als alternatief voor dupilumab, totdat er meer data beschikbaar is.

Deel III: Fenotypes van atopisch eczeem

Middels een systematische review hebben wij een overzicht gegeven van hoe fenotypes van atopisch eczeem voorheen zijn gerapporteerd in de literatuur en welke karakteristieken geassocieerd met deze fenotypes zijn beschreven (**Hoofdstuk 11**). Fenotypes zijn belangrijk, omdat ze relevante verschillen in karakteristieken tussen patiënten kunnen weergeven, die bijvoorbeeld kunnen leiden tot variaties in behandelrespons. De geïdentificeerde studies waren voornamelijk cross-sectionele studies welke werden uitgevoerd in ziekenhuizen, die vooraf gedefinieerde fenotypes en hun geassocieerde karakteristieken onderzochten. Data gestuurde methoden om fenotypes te identificeren werden slechts in een minderheid van de studies gebruikt. In dit hoofdstuk presenteren we een overzicht van de fenotype definities die worden gebruikt in de literatuur voor ziekte-ernst, ziektebeloop, morfologie en eczema herpeticum. Er is sprake van een gebrek aan klinisch relevante fenotypes en het uniform en consistent gebruik van fenotypes in de literatuur.

In de retrospectieve studie van **Hoofdstuk 12** hebben we geconcludeerd dat patiënt-gerapporteerde exacerbaties worden ervaren door één derde van de kinderen met moeilijk te behandelen atopisch eczeem. Sensibilisatie voor ≥1 soort pollen en (een voorgeschiedenis van) hooikoorts bleek vaker voor te komen bij deze subgroep patiënten. Verder vonden we dat kinderen met donkere huidtypen vaker last hadden van exacerbatie in het pollenseizoen en meer sensibilisatie hadden voor ≥1 soort pollen, dan kinderen met lichte huidtypen. Het fenotype met patiënt-gerapporteerde exacerbaties in het voorjaar en de zomer kan worden gekarakteriseerd als jonge kinderen met hooikoorts en een donker huidtype. Dit fenotype kan worden geïdentificeerd op basis van klinische parameters zonder de noodzaak om IgE-bloedtesten of huidpriktests uit te voeren.

Huidtype wordt verder onderzocht in **Hoofdstuk 13**. In dit hoofdstuk hebben we de effectiviteit en veiligheid van systemische behandeling met dupilumab, methotrexaat en ciclosporine onderzocht, door patiënten op basis van een licht huidtype versus een donker huidtype te verdelen in onze analyses. Daarnaast hebben we het verband tussen morfologische fenotypes en huidtypen onderzocht in deze populatie. Prospectieve cohort gegevens van het Nederlandse TREAT NL en het Verenigd Koninkrijk-Ierse A-STAR register werden hiervoor gebruikt. Onze belangrijkste bevindingen waren dat er verschillen bestaan in karakteristieken tussen lichte en donkere patiënten met atopisch eczeem. In vergelijking met patiënten met lichte huidtypen, waren patiënten met donkere huidtypen jonger, hadden zij vaker folliculair eczeem, hogere baseline EASI scores, minder contactallergieën en minder voorgaand gebruik van lichttherapie. Bovendien toonden patiënten met donkere huidtypen een grotere verbetering van EASI score na 6 maanden behandeling met dupilumab. Wij concludeerden dat skin type de effectiviteit van behandeling met dupilumab kan beïnvloeden.

Een discussie van de bevindingen in dit proefschrift inclusief de belangrijkste conclusies van de individuele studies zijn uiteengezet in **Hoofdstuk 14**. Naast een algehele discussie, worden de voordelen en beperkingen van dagelijkse praktijk onderzoek uitgelegd, evenals toekomstperspectieven benoemd. Voordelen bestaan uit externe validiteit, representatie van de relevante populatie, de haalbaarheid en bereidheid van patiënten om deel te nemen. Beperkingen betreffen onder meer het optreden van verschillende vormen van bias, het gebrek aan wash-out, gebruik van comedicatie, mogelijke medicatie-ontrouw, onbedoelde doseringsafwijkingen en minder strikte bezoekschema's. In de toekomst dienen grote en kwalitatief goede onderzoeken waarin verschillende behandelingen worden vergeleken te worden uitgevoerd. Harmonisatie van gegevensverzameling is daarbij erg belangrijk. Het onderzoeken van behandelingen in specifieke fenotypes zal de eerste stap zijn richting 'personalized medicine'. Zeker met oog op nieuwe dure behandelingen die op de markt zullen komen voor atopisch eczeem in de toekomst, is het belangrijk om data te verzamelen en bewijs te genereren om een (kosten-)effectieve en veilige gezondheidszorg voor patiënten met atopisch eczeem te garanderen. Het uiteindelijke doel is immers om de zorg voor deze aandoening te verbeteren.

15B

APPENDICES

LIST OF ABBREVIATIONS

AD	Atopic Dermatitis
ADCT	Atopic Dermatitis Control Test
AE	Atopic Eczema or Adverse Event
AIC	Akaike Information Criterion
AMC	Academic Medical Center, Amsterdam
Amsterdam UMC	Amsterdam University Medical Centers
A-STAR	Atopic eczema Systemic TherApy Register
AZA	Azathioprine
BMI	Body Mass Index
CDLQI	Children's Dermatology Life Quality Index
CI	Confidence Interval
CRF	Case Record Form
CsA	Cyclosporine A
CV	Coefficient of Variation
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DST(s)	Dark Skin Type(s)
EASI	Eczema Area and Severity Index
e.g.	exempli gratia (for example)
EH	Eczema Herpeticum
EHR	Electronic Health Record
ELISA	Enzyme-Linked ImmunoSorbent Assay
EMA	European Medicines Agency
EMC	Erasmus MC University Medical Center
ENCEPP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ETFAD	European Taskforce For Atopic Dermatitis
FDA	Food and Drug Administration
FIRST	French atopIc deRmatitiS cohorT
FLG	Filaggrin
GDPR	General Data Protection Regulation
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HDM	House Dust Mite
HR	Hazard Ratio
HSV	Herpes Simplex Virus
HOME	Harmonising Outcome Measures for Eczema
IBD	Inflammatory Bowel Disease

IDQoL	Infants' Dermatitis Quality of Life index
i.e.	id est (that is)
IGA	Investigator Global Assessment
IgA	Immunoglobulin A
IgE	Immunoglobulin E
IL	Interleukin
IQR	Interquartile range (25th-75th percentile)
ISCED	International Standard Classification of Education
ISO	International Organization of Standardization
JBI	Joanna Briggs Institute
IV	Ichthyosis Vulgaris
KP	Keratosis Pilaris
LME	Linear Mixed-Effects
LST(s)	Light Skin Type(s)
MCID	Minimal Clinically Important Difference
MedDRA	Medical Dictionary for Regulatory Activities
MMF	Mycophenolate mofetil
MPA	Mycophenolic acid
MTX	Methotrexate
NMF	Natural Moisturizing Factor
NMS	Non-Melanoma Skin Cancer
NRS	Numerical Rating Scale
NVDV	Nederlandse Vereniging voor Dermatologie en Venereologie (Dutch Society of Dermatology and Venereology)
OLE	Open-Label Extension
OR	Odds Ratio
PBMC	Peripheral Blood Mononuclear Cel
PGA	Patient Global Assessment
PH	Palmar Hyperlinearity
PI	Principal Investigator
PN	Prurigo Nodularis
POEM	Patient-Oriented Eczema Measure
PT	PBS/ 0.02% Tween
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
PROM(s)	Patient-Reported Outcome Measure(s)
PROSPERO	Prospective Register of Systematic Reviews
QWL(Q)	Quality of Working Life (Questionnaire)
R2	R-squared
RCT(s)	Randomized Controlled Trial(s)

RECAP	Recap of Atopic Eczema
ROC	Receiver-Operator Characteristics
RR	Relative Risk
RT	Room temperature
SC	Steering Committee
SCORAD	SCORing Atopic Dermatitis
SCRATCH	Severe and ChRonic Atopic dermatitis Treatment CoHort
SD	Standard Deviation
SE	Standard Error
SmPC	Summary of Product Characteristics
SNP	Single Nucleotide Polymorphism
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TARC	Thymus and Activation-Regulated Chemokine
TCS	Topical corticosteroids
TCI	Topical calcineurin inhibitors
TEWL	Trans Epidermal Water Loss
TREAT (NL)	TREatment of ATopic eczema (the Netherlands)
VAS	Visual Analogue Scale
WAI	Work Ability Index
WHO	World Health Organization

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Children with atopic eczema experiencing increased disease severity in the pollen season more often have hay fever at a young age and a dark skin type

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Comparison of real-world treatment outcomes of systemic immunomodulating therapy in atopic dermatitis patients with dark and light skin types

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PHD PORTFOLIO

PhD candidate: Angela Leigh-Ann Bosma
PhD period: July 2017 – September 2023
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
Practical biostatistics	2016	1.1
Basic Course Regulations and Organization for Clinical Investigators (eBROK)	2018	1.5
EndNote	2018	0.1
Project Management	2018	0.6
Searching for a Systematic Review	2019	0.1
Research Data Management	2019	0.7
Clinical Epidemiology: Systematic Reviews	2019	0.7
Clinical Epidemiology: Observational Epidemiology	2019	0.6
	Total	**5.4**

Presentations	Year	ECTS
Clinical scientific meeting, Department of Dermatology, Academic Medical Center, Amsterdam, the Netherlands *Oral presentation:* 'Bath therapy as part of the treatment strategy in patients with atopic dermatitis'	2013	0.3
Clinical scientific meeting, Department of Dermatology, Academic Medical Center, Amsterdam, the Netherlands *Oral presentation:* 'Pollen-gerelateerde seizoensgebonden toename van ziekteactiviteit bij atopisch eczeem'	2016	0.3
Clinical scientific meeting, Department of Dermatology, Academic Medical Center, Amsterdam, the Netherlands *Oral presentation:* 'TREAT NL register'	2019	0.3
TREatment of Atopic eczema (TREAT) Registry Taskforce meeting, Milan, Italy *Oral presentations:* 'Safety study protocol and Feasibility of current 'What, How and When to measure''	2019	0.3
LACUNE dag Nederlandse Vereniging voor Dermatologie en Venereologie, Utrecht, the Netherlands *Oral presentation:* 'TREAT NL register'	2019	0.3
Wetenschappelijke vergadering Nederlandse Vereniging voor Dermatologie en Venereologie, Amsterdam, The Netherlands *Oral presentation:* 'Bewijs uit registratiestudies voor atopisch eczeem'	2020	0.6
11th Georg Rajka International Symposium on Atopic Dermatitis (ISAD), Seoul, South Korea (virtual meeting) *Poster presentation:* 'Work ability and quality of working life in patients with moderate-to-severe atopic dermatitis'	2021	0.3

11th Georg Rajka International Symposium on Atopic Dermatitis (ISAD), Seoul, South Korea (virtual meeting) *Poster presentation:* 'Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: Results of the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry'	2021	0.3
11th Georg Rajka International Symposium on Atopic Dermatitis (ISAD), Seoul, South Korea (virtual meeting) *Poster presentation:* 'Children with atopic eczema experiencing increased disease severity in the pollen season more often have hay fever at young age and a dark skin type'	2021	0.3
7th congress of the Skin Inflammation and Psoriasis International Network (SPIN), Paris, France *Oral presentation:* 'Classifying atopic dermatitis: a systematic review of phenotypes and associated characteristics'	2022	0.6
	Total	**3.6**

(Inter)national conferences	**Year**	**ECTS**
European Dermato-Epidemiology Network (EDEN) Forum, Berlin, Germany	2018	0.5
10th Georg Rajka International Symposium on Atopic Dermatitis (ISAD), Utrecht, the Netherlands	2018	0.7
27th European Academy of Dermatology and Venereology (EADV) Congress, Paris, France	2018	1.0
24th World Congress of Dermatology (WCD), Milan, Italy	2019	0.5
28th European Academy of Dermatology and Venereology (EADV) Congress, Madrid, Spain	2019	1.0
11th Georg Rajka International Symposium on Atopic Dermatitis (ISAD), Seoul, South Korea (virtual meeting)	2021	0.5
7th congress of the Skin Inflammation and Psoriasis International Network (SPIN), Paris, France	2022	0.5
	Total	**4.7**

Other	**Year**	**ECTS**
Weekly clinical scientific meetings, Department of Dermatology, Academic Medical Center	2017-2022	3.5
Harmonising Outcome Measures for Eczema (HOME) scientific meeting, Utrecht, the Netherlands	2018	0.1
Biomarkers in Atopic Dermatitis and Psoriasis (BIOMAP) scientific meeting, Copenhagen, Denmark	2018	0.5
TREatment of Atopic eczema (TREAT) Registry Taskforce scientific meeting, Paris, France (organization and participation)	2018	0.3
Biomarkers in Atopic Dermatitis and Psoriasis (BIOMAP) scientific meeting, London, the United Kingdom	2019	0.5
TREatment of Atopic eczema (TREAT) Registry Taskforce scientific meeting, Milan, Italy (organization and participation)	2019	0.3
	Total	**5.2**

2. **Teaching**

Supervising	**Year**	**ECTS**
Supervising students for bachelor thesis: - Rowdy de Groot - Fiona Rigutto	2018, 2020	4.6
Supervising students for master thesis: - Rowdy de Groot - Beau van Nieuwenhuizen - Merve Günal - Manja Bloem - Madeline Heidema - Hajar El Khattabi	2019-2021	14.9
	Total	**19.5**

Lecturing	**Year**	**ECTS**
Lecture on 'Wanneer nog prednison voor atopisch eczeem?' during education for Residents Dermatology, Department of Dermatology, Academic Medical Center, Amsterdam, the Netherlands	2019	0.3
Teacher of practicum Medische Consultvoering Klinisch Redeneren 'De Eerste Indruk' for medical students of the VUmc, Amsterdam, the Netherlands	2020	0.3
Lecture on drug-induced SCLE during education for Residents Dermatology, Department of Dermatology, Academic Medical Center, Amsterdam, the Netherlands	2020	0.3
Lecture on CAT 'De klinische relevantie van dupilumab serum spiegels' during education for Residents Dermatology, Department of Dermatology, Academic Medical Center, Amsterdam, the Netherlands	2022	0.3
	Total	**1.2**

3. **Other activities**

	Year	**ECTS**
Reviewer for British Journal of Dermatology (2) and Journal of Investigative Dermatology (2)	2018 – 2020	0.7
	Total	**0.7**

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