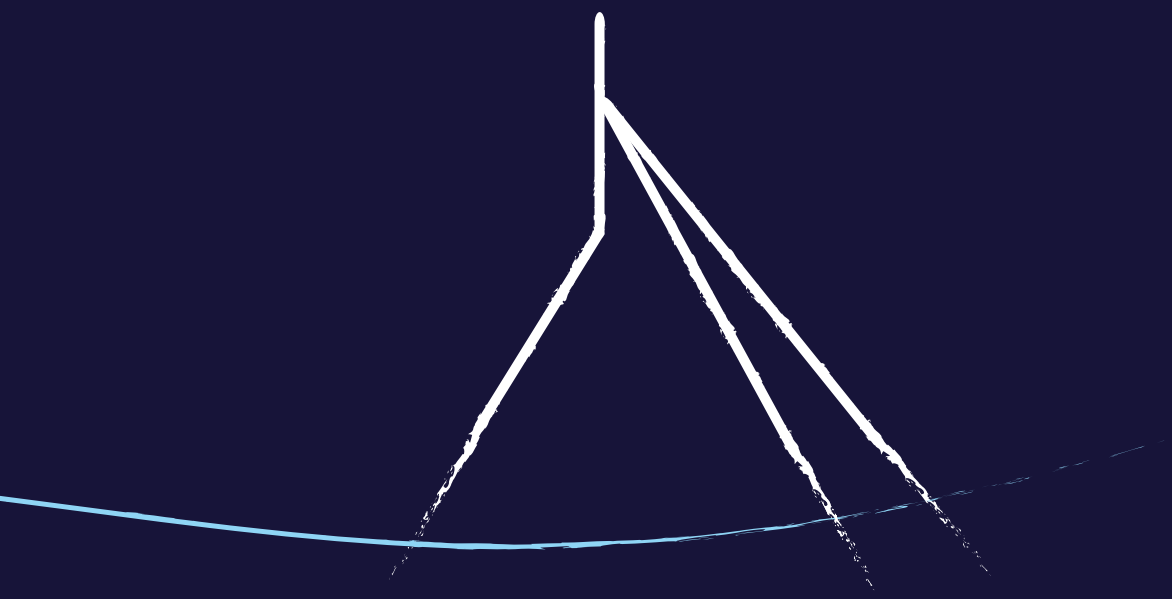
Linde E.M. de Wijs

First Experiences with Dupilumab for Atopic Dermatitis Patients in Daily Practice

Filling the unmet needs?



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Eerste ervaringen met dupilumab voor atopisch eczeem in de dagelijkse praktijk

Het vervullen van onvervulde behoeften?

Proefschrift

ter verkrijging van de graad van doctor aan de
Erasmus Universiteit Rotterdam
op gezag van de rector magnificus

Prof. dr. A.L. Bredenoord

en volgens besluit van het College voor Promoties.

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Promotor	Prof. dr. T. Nijsten
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Copromotor	Dr. D.J. Hijnen

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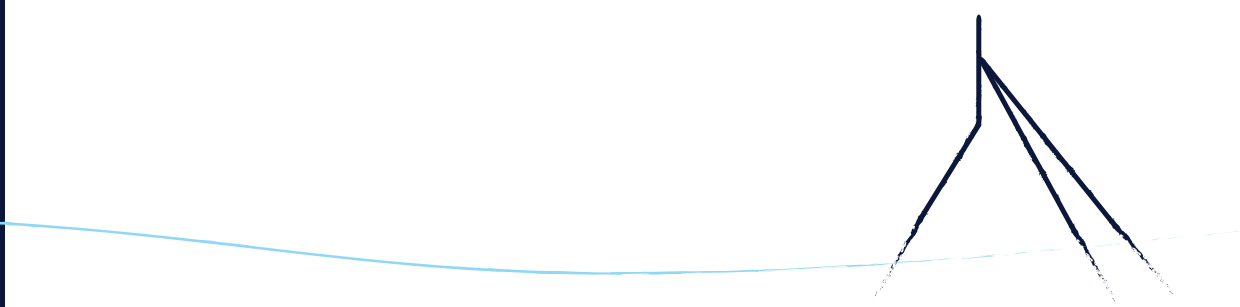
General introduction



GENERAL BACKGROUND

Intense pruritus, recurrent eczematous lesions, sleep deprivation, shame, and detrimental effects on emotional and social life. These are all hallmarks of atopic dermatitis (AD), a very heterogeneous chronic inflammatory skin disease which affects 15-20% of children and up to 10% of adults worldwide.[1-6] Approximately 10-20% of these patients are suffering from severe disease.[7] The most prominent hallmarks of AD are pruritus, which generally corresponds with disease severity, xerosis, onset in early childhood, and a personal or family history of associated diseases.[1] Diseases that frequently co-occur with AD mainly include atopic manifestations (i.e. asthma, allergic rhinitis, keratoconjunctivitis, and food allergy) or IgE-mediated sensitization to specific allergens, but also mental health disorders and other systemic immune-mediated inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel diseases, alopecia areata, and vitiligo).[1, 8] AD is associated with the highest disease burden among all skin disorders.[1, 4, 9] Many patients with severe AD suffer from social stigmatization, depression, diminished self-esteem and loss of work productivity (possibly due to absenteeism). This often results in additional health and economic burdens for patients and relatives.[10-13]

CLINICAL CHARACTERISTICS

AD is associated with heterogeneous lesions characterized by papules, papulovesicles, xerosis, edema, crusting, scaling, and post-inflammatory hyper- or hypopigmentation which are present in a chronic fluctuating course.[1, 5, 8] In a further disease stage, lichenification and fissuring manifest. Xerosis usually occurs during active periods of the disease, but also when the disease is quiescent. The onset of the disease usually occurs in early childhood, although it can manifest at any point in life. Most frequently affected sites change during childhood and adolescence. In general, patients with AD often show typical associated clinical signs such as the Hertoghe's sign (i.e. rarefaction of lateral eyebrows), Dennie-Morgan infraorbital folds (i.e. fold in the skin below the eyelid), and hyperlinear palms or soles (i.e. increased density and depth of palmar creases).

Apart from the general heterogeneity of AD, typical ethnic- or geography-dependent clinical and immunological heterogeneity has been described.[14, 15] AD in Asians was described as a blended phenotype with clinical features of both AD and psoriasis.[16] Asian studies reported relatively high numbers of (sharply demarcated) truncal lesions, erythroderma, auricular involvement, excoriated papules,

indurated nodules, and lichenification.[15] Orbital darkening and papular lichenoid lesions were more frequently present in African patients.[15] Besides, erythema tends to be more violaceous in black patients.[1] Although it is unknown whether these differences are particular to regions or ethnicity, these differences might reflect differences in genetics, allergens, culture-specific behavior, lifestyle, and environmental factors such as climate.[15]

DIAGNOSIS AND DISEASE SEVERITY

AD is diagnosed based on a physician's assessment considering clinical features (both signs and symptoms), a characteristic medical history, and possible coexisting associated diseases.[1] Most of these features are described in diagnostic criteria such as the Hanifin and Rajka criteria and U.K. diagnostic Criteria for Atopic Dermatitis, which are still used for proper diagnoses of AD nowadays.[17, 18]

Disease severity can be determined using patient- and physician-reported outcome measures. The global multi-stakeholder Harmonising Outcome Measures for Eczema (HOME) initiative developed a consensus-based Core Outcome Set (COS) to standardize outcome measures for clinical trials and clinical practice.[19] In clinical trials, the minimum outcome set that should be measured and reported includes physician-reported signs (Eczema Area and Severity Index, EASI), patient-reported symptoms (Patient-Oriented Eczema Measure, POEM; Numeric Rating Scale itch, NRS itch), quality of life (Dermatology Life Quality Index, DLQI) and long-term disease control (Atopic Dermatitis Control Tool, ADCT; Recap of atopic eczema, RECAP). [20, 21] At this moment, the process of agreement for a COS which is suitable for use in daily practice is still ongoing.[22] In addition to improvements in the use and reporting of clinical outcome measures, objective serological measures for disease severity would be of great value.[23] These biomarkers are not subject to inter-and intra-observer variability, in contrast to clinical outcome measures. Although the use of biomarkers is increasing in studies assessing disease severity and treatment effect, the use of biomarkers in daily practice is uncommon in the Western world until now. However, in Japan serum thymus and activation-regulated chemokine (TARC/CCL17) levels have been used widely as a biomarker for disease severity and as a tool for "tight (disease) control" since 2008, especially during topical treatment in daily practice.[24]

PATHOPHYSIOLOGY

AD has a complex multifactorial pathogenesis, characterized by interaction of dysfunctional cell-mediated immunity, genetic susceptibility associated with abnormalities in the skin barrier, changes in the skin microbiome, and environmental and lifestyle factors.

Dysfunctional cell-mediated immunity

In AD patients, an altered T helper (Th) cell activation with mainly dysregulation of Th2 cells results in inflammation apparent as eczematous lesions.[5] Th2 cells are activated through epidermal inflammatory dendritic and innate lymphoid cells. Activated T cells subsequently release cytokines, with interleukin(IL)-4, IL-13, and IL-31 being the most important cytokines. These cytokines then activate downstream Janus kinase (JAK)- signal transducer and activator of transcription (STAT) pathways. As a result, inflammation and pruritus are caused by the change in the immunoglobulin class produced by B cells (i.e. IgE class switching) and antigen-specific IgE production through activation of B cells and plasma cells. Immunohistological changes in skin biopsies can be characterized by mainly spongiosis and T-cell infiltrations, more prominent in lesional skin, but also present in non-lesional skin.[5]

While acute AD is characterized by a Th2 dominant inflammatory response with a central role for interleukins(IL)-4 and IL-13, chronic lesions show progressive immune activation of Th1, Th2, Th17, and Th22-subsets.[25] Differences in immunoendotypes are also hypothesized to be ethnical- or geography-dependent.[16, 26] Although increased activation of Th2 pathways is found in all ethnicities, Asian AD patients were found to have increased activation of Th1 and Th17 compared to black patients and patients of European ancestry.

Pruritus, which is the clinical hallmark of AD, is caused by signaling between pruritogens and the small sensory nerve fibers in the skin.[27] While pruritogens are mainly released by inflammation, scratching can result in skin barrier damage, activation of alarmins, and subsequent release of pruritogens through hypersensitization of nerve fibers as part of the itch-scratch cycle.

Genetic susceptibility (and abnormalities in the skin barrier)

A family history of atopic diseases, and AD in particular, is the strongest risk factor for developing AD.[28] Although we know that genetic factors play an important role in the development of AD, less than 20% of AD heritability has been identified in genome-wide association studies.[29] One of the genes that has been identified,

is the gene encoding the skin barrier protein filaggrin (*FLG*).[30] Filaggrin is a major structural protein in the epidermis which is important for an adequate skin barrier. Loss-of-function mutations in *FLG* lead to a dysfunctional skin barrier through reduced filaggrin expression, resulting in natural moisturizing factor deficiency. Natural moisturizing factor is needed for keeping keratinocytes together. Consequently, patients with a FLG mutation have an increased transepidermal water loss, leading to dry skin, and an increased microbial dysbiosis. In patients who carry this loss-of-function mutation, there is a 3-5 times higher risk of developing AD compared to patients without this mutation.[31] Besides *FLG* mutations, impairment of the epidermal barrier function is caused by physical damage due to scratching and microbial dysbiosis. Additionally, the predominantly type-2-skewed immune dysregulation further exacerbates downregulation of epidermal structural proteins and epidermal lipids, which favours epidermal barrier disruption.[8] On the other hand, epithelial barrier disruption promotes the initiation of Th2 cell-mediated responses resulting in a vicious cycle of inflammation and barrier disruption.

Dysbiosis in the skin microbiome

AD is associated with microbial dysbiosis at both affected and unaffected skin.[32] There is a loss of community diversity (especially preceding flares) and predominant colonization with the pathogenic *Staphylococcus aureus,* and *Malassezia* yeasts to a lesser extent. *S. aureus* causes barrier disruption and shows direct proinflammatory effects such as type 2 immune activation.[33] *Malassezia* and other cutaneous yeasts could contribute to inflammation as well. Some patients show specific IgE reactivities to *Malassezia* antigens, but definite underlying principles remain poorly understood.[34]

Environmental and lifestyle factors

In the past 30 years, there has been an increase in the prevalence of AD. Environmental factors might play a role in this increase. This is supported by observations such as the urban-rural gradient with a higher risk for AD in urban compared with rural areas, and increasing cleanliness due to increased socio-economic wealth.[35, 36] Furthermore, climate conditions, exposure to ultraviolet radiation, diets high in sugars and polyunsaturated fatty acids, and air pollution are among the factors that are considered important as well.[37, 38] However, robust evidence supporting these factors and hypotheses is sparse.[5]

TREATMENT OF ATOPIC DERMATITIS

Currently, there is no cure for AD. The main goals of treatment are therefore improving signs and symptoms, establishing continuous disease control, and consequently improving productivity in daily life and quality of life. Since AD is a multifactorial disease, its treatment requires a multilevel approach including avoidance of relevant triggers, improvement of the impaired skin barrier, and reducing inflammation.

First, attention for triggering factors is needed. These are environmental factors that can trigger AD, e.g. irritants, psychological stress, contact allergens, and environmental or food allergens.[1] These factors should be avoided if possible, although strict avoidance recommendations should only be provided in case of proven evidence of relevant allergen sensitization.[39] Second, skin barrier impairment should be improved by the usage of moisturizers.[40] Daily usage of moisturizers does not only improve the skin barrier but has also been shown to reduce AD severity leading to a reduced need for (topical) anti-inflammatory agents.[5] Avoidance of triggers and application of moisturizers are advised in eczema-free intervals as well. Third, inflammation should be reduced using anti-inflammatory treatment. Anti-inflammatory treatment follows a step-up (or step-down) approach.[1] The indicated therapy is selected according to disease severity, comorbidities, comedication, age, impairment in daily life, and individual patient goals. Topical therapy is widely endorsed as the first step in AD treatment. When appropriate topical therapy is ineffective or infeasible, phototherapy, systemic immunosuppressive therapy, or systemic immunomodulatory therapy is indicated. The role of therapies aiming to normalize the microbial dysbiosis is still debated. Although treatment guidelines and standards of care are mostly consistent in Europa and the United States, a worldwide divergence in disease management and therapeutic approaches of AD exists.[41, 42]

Until recently, treatment of patients with moderate-to-severe AD was limited to conventional systemic immunosuppressants, which remained unchanged for years (**Figure 1**). However, the development of targeted monoclonal antibodies and small molecule antagonists has increased rapidly in the last few years.[43] At the same time, there has been a strong push towards patient-centered medicine in the past decades.[44, 45] Attention for self-management combined with (psycho)social support, adequate coping, and patient (or caregiver) education of AD has been shown to improve disease severity and quality of life.[46, 47] In general, treatment should be tailored to the needs of every individual patient.

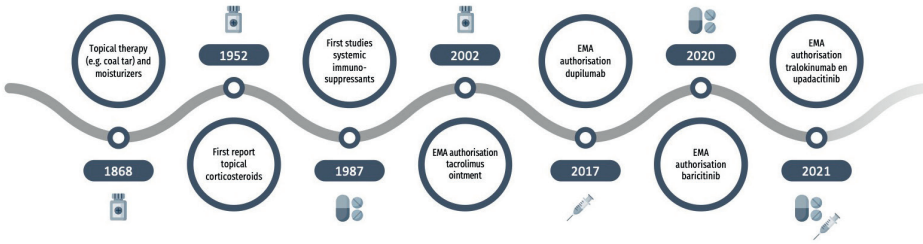


Figure 1. Timeline of therapeutic options for the treatment of atopic dermatitis

Topical anti-inflammatory agents

Topical corticosteroids

Treatment with topical corticosteroids (TCS) is considered as the first-line anti-inflammatory therapy.[48] TCSs are classified into four potency classes in Europe, and seven classes in the United States. Choice of classes is based on disease activity, age, and anatomical location. TCS should be used intermittently or according to a tapering schedule to minimize (local) side effects, which include e.g. skin atrophy, purpura, striae, dyspigmentation, and facial acneiform changes. When used intermittently, this therapy bears little risk. Systemic side effects are rare when used appropriately, but can include hypothalamic-pituitary-adrenal suppression or growth retardation.

Topical calcineurin inhibitors

Topical calcineurin inhibitors (TCI), which include tacrolimus ointment and pimecrolimus cream, are steroid-sparing topical anti-inflammatory agents.[48] Compared to TCS, TCI have reduced clinical effectiveness, are more expensive and some patients experience burning or pruritus in the first week of use. On the other hand, the use of TCI is not associated with atrophy which makes TCI application at susceptible sites or as maintenance therapy useful.

Ultraviolet phototherapy

If disease control could not be established with topical therapy, phototherapy might be considered. Usually, narrow-band ultraviolet B radiation or light and medium-dose ultraviolet A1 radiation is administered, for a short period of 6-12 weeks.[48] Possible disadvantages of UV therapy include photodamage, skin carcinogenesis, cataract formation, and frequent time-consuming visits.

Systemic therapy

Systemic immunosuppressive therapy

Conventional systemic immunosuppressive therapy comprises agents which do not target specific points of immune dysregulation. The most commonly used immunosuppressants for AD are cyclosporin A (CsA), methotrexate, mycophenolate mofetil, mycophenolic acid, and azathioprine. Systemic glucocorticoids (i.e. oral or intramuscular) should only be used for short-term flare treatment or as bridging therapy to (conventional) systemic immunosuppressants or immunomodulators. Robust evidence on the effectiveness of many of these drugs is largely missing. Although the effectiveness of CsA has been demonstrated in multiple studies, its use is limited by potential end-organ toxicity.[49] Therefore, CsA is recommended for short-term use in patients with moderate-to-severe AD, up to continuous use of 1-2 years maximum.

Biologics and small molecule antagonists

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.[50] Dupilumab has been approved for biweekly subcutaneous administration in AD patients in 2017.[51] Although countries apply their own criteria for indication, dupilumab is generally endorsed for use in patients with moderate-to-severe AD who are not adequately controlled with topical prescription therapies or when those therapies are not advisable. AD patients in the Netherlands are eligible for dupilumab treatment after failure of at least 1 systemic immunosuppressant which is used for at least 4 months in an adequate dose (unless contra-indicated). These criteria are set by a multidisciplinary team of physicians, insurers, and patient representatives. These guidelines are not receptive to the interpretations of patients and physicians, and might therefore be restrictive for use in AD care. Dupilumab showed improvement of disease severity, itch, sleep disturbance, anxiety, depression, and quality of life with dupilumab as monotherapy or in combination with TCS in phase III trials.[50, 52] Thirty-eight percent of the patients who used dupilumab reached Investigator Global Assessment (IGA) 0/1 (i.e. clear/almost clear)0/1 in these trials, which was statistically significant better than patients treated with placebo. The most frequently observed side effects were conjunctivitis, herpes infections, and injection-site reactions. Dupilumab is approved for treatment of children with AD and adults with asthma and nasal polyposis as well.

As shown in **figure 1**, baricitinib has recently been registered as the first Janus kinase (JAK) inhibitor for treatment of AD.[53] Baricitinib is selective for JAK 1/2, which are involved in the signal transduction of cytokine receptors. The criteria that are applicable for indication of dupilumab treatment, are applied for baricitinib treatment as well. In clinical trials, baricitinib showed an overall significant improvement of itch within a few days. However, only 14-17% of the patients reached the primary endpoint of IGA 0/1.[54] Recently, tralokinumab and upadacitinib were authorized for AD treatment as well.[55, 56] Tralokinumab is an antibody which blocks binding of IL-13 to both IL-13Rα1 and IL-13α2 by targeting IL-13.[57] In clinical trials, 38.9% of the patients reached IGA 0/1. Upadacitinib is a selective JAK1 inhibitor which showed an early reduction in pruritus.[58] In clinical trials, 62% of the patients treated with upadacitinib 30mg daily achieved IGA 0/1 at 16 weeks of treatment. Overall, it can be speculated that biologic therapies are more adapted for long-term control and have a relatively slow mode of action, while the JAK inhibitors provide a rapid effect on pruritus and inflammation but might have a more questionable benefit-risk ratio.[43]

THE AD PIPELINE

Recently, translational research has fostered the development of more than 70 new topical, oral or injection compounds which are candidates to become novel therapeutic options for AD.[43] These consist of mainly targeted small molecule antagonists and biologic therapies with targets such as OX40(L) (adaptive immune response), IL-31 (itch), and JAK1 (Janus kinases). However, drug candidates developed to modulate the microbiome (e.g. TLR5 and TNFR activation) or targeting the innate immune response (e.g. IL-33) are under investigation as well. This revolution with many new potential drugs being developed calls for evaluation of long-term effectiveness and pharmacovigilance in routine care in order to get insight into the risk-benefit ratio of drugs and to be able to perform analyses in subgroups of patients. In addition, comparative studies between agents would be of added value. Ultimately, precision medicine with selection of patients for certain therapies based on phenotypes or endotypes would be highly valuable since the 'one-size-fits-all' approach is definitely not applicable in such a heterogeneous disease.

AIMS AND OUTLINE OF THIS THESIS

In the past few years, insights from molecular and clinical research have been translated into new AD clinical trials and the approval of new therapies. Dupilumab, the first biologic approved for treatment of AD, was licensed in 2017 after being proven successful in large clinical trials. However, there might be considerable differences in patient characteristics and treatment responses between clinical trials and daily practice (i.e. efficacy versus effectiveness). Observational studies in a real-world setting are therefore essential to document the benefits and harms of a therapy in a wider patient population. In this thesis, we used a clinical approach to evaluate AD treatment, and dupilumab treatment in particular, in daily practice.

To optimally tailor AD care to patients' needs, especially considering the many emerging therapeutic options, insight into patients' needs and preferences regarding AD care is needed. Therefore, the aim of **Chapter 2** was to explore patients' needs and preferences regarding AD care in order to provide a complete overview concerning all aspects of today's AD care.

Dupilumab is the first biologic that has been approved for treatment of moderate-to-severe AD and is proven efficacious in clinical trials. In **Chapter 3**, the effectiveness of dupilumab in daily practice was evaluated. In **Chapter 3.1**, the clinical effectiveness up to 16 weeks of treatment was assessed. Effectiveness and safety during long-term dupilumab treatment were evaluated in **Chapter 3.2**.

Phase-III clinical trials investigating dupilumab treatment have shown clinically relevant improvement of AD which was equal among all racial subgroups. However, a direct comparison of the effectiveness of dupilumab in daily practice in Asian and Caucasian AD patients was lacking. Yet, differences in immunoendotypes and coping strategies between races are known. Therefore, the aim of **Chapter 4** was to investigate the effectiveness of dupilumab in AD patients in the Netherlands versus Japan up to 80 weeks of treatment.

Phase II and III trials showed trends for better effectiveness of dupilumab treatment for atopic dermatitis in a weekly or biweekly dosing interval, compared to longer dosing intervals. However, literature about adjusted dose regimens during treatment in daily practice is lacking. Therefore, the aim of **Chapter 5** was to determine the effect of adjusted dose regimens of dupilumab on AD disease severity in time in daily practice.

Throughout the world, there was a need for guidance on the transition from systemic immunosuppressants to dupilumab in AD patients. We emphasize the importance of preventing patients from having unnecessary AD relapses or rebound flares due to (abrupt) discontinuation of systemic immunosuppressants before the start of dupilumab treatment. For that reason, the aim of **Chapter 6** was to propose an approach for the transition from systemic immunosuppressants to dupilumab in AD patients.

In clinical trials conjunctivitis, herpes infections, and injection-site reactions were found to be the most frequently observed side effects. During dupilumab treatment in daily practice, new possible side effects of dupilumab treatment became noticeable. The aim of **Chapter 7** was to gain better insights into the nature and diagnostics of one of these possible side effects of dupilumab treatment. In **Chapter 7.1** we aimed to evaluate the sharply demarcated paradoxical erythema in a head and neck distribution, differing from their usual AD lesions. Distinction of allergic contact dermatitis from other causes of this erythema in dupilumab treated AD patients and patients with a general sub-optimal response to dupilumab treatment might be of great clinical interest. However, literature about the impact of dupilumab on patch testing was sparse and controversial. Therefore, the aim of **Chapter 7.2** was to report on the reliability of patch testing in dupilumab treated AD patients.

In our cohort of dupilumab treated AD patients, joint complaints were increasingly observed. Therefore, the aim of **Chapter 8** was to investigate the proportion and nature of this possible side effect of dupilumab treatment.

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Chapter 2

Needs and preferences of patients regarding atopic dermatitis care in the era of new therapeutic options: a qualitative study

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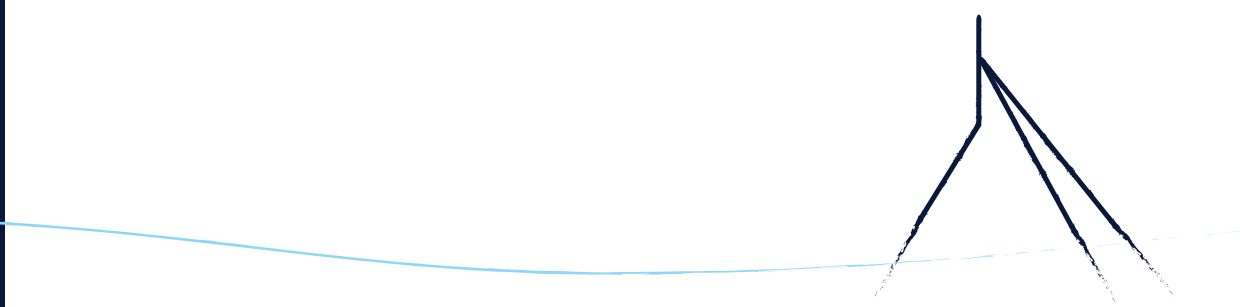

ABSTRACT

Background To optimally tailor atopic dermatitis (AD) care to patients' needs, especially considering the many emerging therapeutic options, insight into patients' needs and preferences regarding AD care is needed.

Objectives To explore patients' needs and preferences regarding AD care.

Methods A qualitative study consisting of three focus groups with a total of 20 adult AD patients was conducted. All sessions were transcribed verbatim and inductively analysed using several phases of coding to create an overview of patients' needs and preferences.

Results AD patients emphasized the need for a patient-tailored approach in all identified aspects of AD care. With regard to consultations, patients stressed the need for a personal approach and increased recognition of the disease impact. The impact level should mainly be determined by patients themselves. With regard to the organisation of AD care, the need for psychosocial and medical supportive care as well as quick access to healthcare providers during disease flares were emphasized. Within the decision making process, patients indicated that the provided information, the role of the patient and physician, whether or not treatment goals should be set, and decisive factors for indication and feasibility of novel therapies should be patient-dependent.

Conclusions AD care should be patient-tailored with increased attention for the psychosocial burden, as well as better access to healthcare during disease flares. In order to provide patient-tailored care, the personal situation, needs, and preferences of the patient should be taken into account in the therapeutic decision making process, with respect for the autonomy of the patient.

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disease, characterized by a relapsing and remitting disease course. AD related symptoms including itch, pain, and insomnia are known to have a large impact on quality of life.[1-4] Better acceptance and recognition of the emotional and psychological burden associated with AD are among the most important wishes of AD patients.[3]

AD treatment is mainly focused on medicinal therapy, usually starting with topical treatment including emollients, topical corticosteroids, and calcineurin inhibitors.[5] Until recently, treatment of patients with moderate-to-severe AD was limited to phototherapy or conventional systemic immunosuppressants. However, the number of therapeutic options has increased rapidly in the last few years.[6] At the same time, patients' preferences, standards, and expectations are changing and play an increasing role in therapeutic decision making.[7, 8]

Experiences, needs, and preferences regarding specific topics (e.g. autonomy, influence of (social) media, influence on family life or financial impact) have been assessed, mainly among adolescents or parents of paediatric AD patients.[1-3, 9-11] However, a complete overview concerning all aspects of today's AD care is needed to adequately provide patient-tailored AD care, especially in times of many emerging therapies. Therefore, the aim of this study was to explore patients' needs and preferences regarding AD care.

METHODS

A qualitative study consisting of three focus groups was conducted to obtain an in-depth understanding of patients' views on AD care. Qualitative research is particularly suitable as it primarily focuses on interpretations, rather than quantification of patients' beliefs, emotions, behaviors, and interactions in daily life.[12] Additionally, the interactive and dynamic process of focus groups attributes to identification and clarification of patients' views, leading to richer and more diverse information in comparison to individual interviews.[13, 14] This focus group study was designed and is reported in accordance with the Standards for Reporting Qualitative Research (SRQR) recommendations.[15]

Study setting and participants

This study was conducted at the Erasmus MC University Medical Center (University Hospital). Purposive sampling was used to obtain a variable sample of AD patients in terms of age, sex, and therapeutic experiences.[14, 16, 17] Eligible patients were recruited at the outpatient clinic of the Erasmus MC and Maasstad Hospital (general hospital) and received a study information leaflet. Patients could sign up by contacting the researchers. They were offered a voucher of €40 for participating. After analysis of three focus groups with a total of 20 participants (6-8 participants per focus group), we concluded that data saturation was reached and selection of participants ended.

Data collection

Prior to the start of the focus groups, patients provided written informed consent and completed a patient characteristics questionnaire. After we made sure that all participants felt able to share their views and experiences, the focus groups started, structured by a topic guide which was based on researchers' experiences, literature, and therapy guidelines.[18, 19] Discussions were moderated by an experienced moderator of focus groups (ML or SE) and a physician with extensive experience in treating AD patients, but not involved in direct patient care of the participants (LW). All focus groups were audiotaped and transcribed verbatim.

Data analysis

The transcripts were analysed by using Nvivo version 12 plus. An inductive approach to data analysis was applied using several phases of coding (guided by a codebook) combined with the constant comparison technique (i.e. comparing emerged concepts with new data and across groups). [20] First, the transcripts were thoroughly read and roughly summarized by one researcher (LW) to get a holistic understanding of the focus groups. Subsequently, the first two transcripts were openly coded (i.e. inductively and line-by-line) [20] by one researcher (LW) and independently checked by another (ML). This resulted in a list of unstructured codes. More abstract and structured concepts of relevance were obtained through axial coding. [20] Using this structured coding scheme, the transcript of the third focus group was coded (LW) and independently checked (SE). No new concepts emerged during coding of the third focus group and data saturation was reached. The identified concepts and their subcategories were discussed during several multidisciplinary (psychologist, dermatologist, and PhD-student) research team meetings. This resulted in an overview of core needs and preferences within three central aspects of AD care.

RESULTS

Patient characteristics

Table 1 provides sample characteristics and demographics.

Table 1. Participants' characteristics.

	FG 1	FG 2	FG 3	Total
Setting	Erasmus MC	Maasstad Hosp.	Erasmus MC	
Participants – n	8	6	6	20
Age (years)				
median (IQR)	34 (20-48)	28 (27-57)	33 (31-40)	31 (24-48)
min, max	19, 63	21, 62	20, 63	19, 63
Female – n (%)	5 (64)[a]	4 (67)	2 (33)	11 (55)
Current treatment – n (%)				
Topical	1 (13)	2 (33)	1 (17)	4 (20)
Systemic immunosuppressant	5 (63)	4 (67)	2 (33)	11 (55)
Biologic	2 (25)	0 (0)	3 (50)	5 (25)
Self-reported impact of disease – n (%)				
Very low	1 (13)	0 (0)	2 (33)	3 (15)
Low	2 (25)	0 (0)	0 (0)	2 (10)
Neutral	1 (13)	2 (33)	0 (0)	3 (15)
High	2 (25)	1 (17)	1 (17)	4 (20)
Very high	2 (25)	3 (50)	3 (50)	8 (40)

FG, focus group; IQR, interquartile range; [a] n=1 transgender man

Patients' needs and experiences in AD care: a patient-tailored approach

Several needs and preferences were identified within three main aspects of AD care (Figure 1): consultations with physicians, organisation of AD care, and the therapeutic decision making process. These needs and preferences are described in detail below. The need for a patient-tailored approach emerged as an overarching theme in all aspects of AD care. Patients stressed the need to better take patients' characteristics and personal needs and preferences into account throughout AD care.

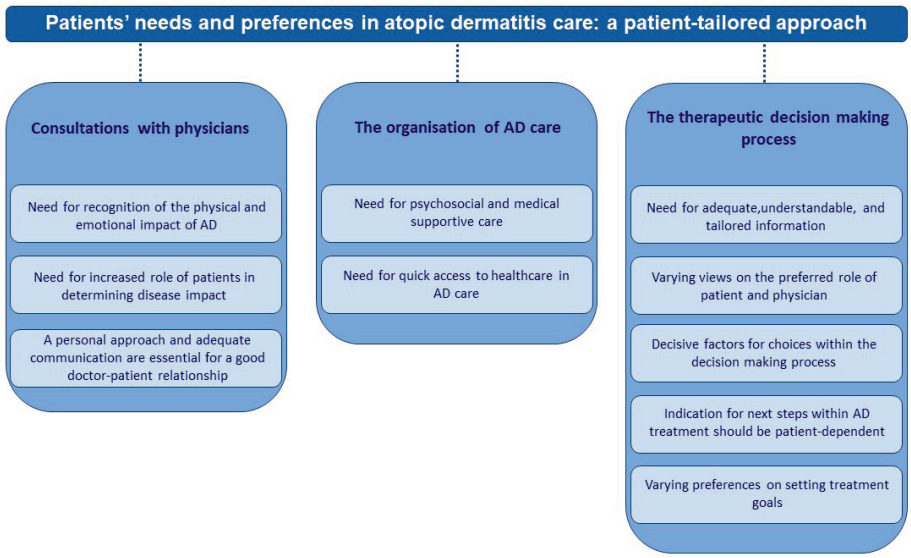

Figure 1. Overview of needs and preferences of patients in atopic dermatitis (AD) care

The consultations with physicians

Need for recognition of the physical and emotional impact of AD

Patients reported that the major impact on both physical and emotional well-being of AD is sometimes underestimated by physicians. Patients emphasized the need for an increased recognition of the total burden and chronic pattern of their disease. Receiving empathy and being taken seriously were reported to be crucial in AD care.

> *'The moment you tell your physician that this is a real issue in your life, that it really is all-consuming, and your physician responds with 'oh well, it is not that bad'. It feels like a slap in the face.'* – focus group (FG) 1

Patients identified a need for physicians to pay particular attention to certain feelings (e.g. shame, loneliness, stress, and fear) and behaviors (e.g. social avoidance and poor sleeping behavior) associated with AD. Patients prefer their physician to take the initiative in talking about the impact of the disease, as they often feel uncomfortable to do so themselves (e.g. because of the busy schedules of physicians).

Need for increased role of patients in determining disease impact

Patients mentioned that physicians should take into account that the consultation is only a snapshot of the disease course, which complicates the assessment of a relapsing disease. Patients highlighted the need to be able to show the eczema at its worst, for which patients use tools including writing down symptoms or photographing lesions during exacerbations. However, when discussing the severity of their disease in times of remission, they often feel unheard.

> *'AD does not only feel like a struggle against your own body, but it is also a struggle to be taken seriously and to prove that you are eligible for certain therapies instead of being sent home with another ointment.' – FG 3*

Patients expressed the need for an increased role of patients in determining the level of disease impact. Most patients agreed that the treating physician is responsible for the evaluation of the medical situation (e.g. giving instructions, discussing treatment options, and performing laboratory tests). However, AD does not stop when the patients leave the clinic and patients indicated that they themselves are responsible for evaluating the disease impact in daily life. As such, patients highlighted that a physician's respect for their autonomy in assessing the impact on their daily life would be appreciated.

A personal approach and adequate communication are essential for a good doctor-patient relationship

Patients indicated that the relationship between patient and physician plays an important role in their perceived quality of AD care. Patients prefer a personal approach and want their physician to be familiar with their situation, without making them feel like one of many. Although patients prefer repeated consultations with the same physician, they believe a switch in physicians does not negatively influence the quality of care as long as there is a good collaboration and communication between physicians. In terms of communication, patients stressed the importance of physicians who truly listen to their story and make them feel at ease.

> *'It feels so good that my physician makes time for me, because my experiences with previous physicians were like 'here are your ointments, good luck'.' – FG 2*

According to patients, simple signs including eye contact, physicians introducing themselves properly at the first consultation, and asking for patients' preferences can facilitate in building an adequate relationship. Furthermore, patients indicated

that it is very important that physicians adapt to the (communicative) level of the patient by for instance speaking in layman's terms, taking time to explain, and literally asking if they have any questions.

The organisation of AD care

Need for psychosocial and medical supportive care

Patients indicated a need for low-threshold (psycho)social and medical supportive care. Patients understand that a physician's time is limited and accept that this additional care is provided by other healthcare workers. Patients mentioned that initial supportive care by means of extra attention and time for questions could be provided by specialized nurses.

> *'A physician has limited time during a consultation, I do understand that, but sometimes you are feeling so bad and so itchy, and everything that goes with that. It is a real problem and feels like a handicap. In situations like this, an additional appointment with a nurse who has time to listen to your story, who is in close contact with your physician, and could potentially discuss any important considerations, would be much appreciated.' – FG2*

However, the need for more profound psychosocial support provided by a psychologist or therapist varied between patients. Patients indicated that this need should be identified during their consultations and that support should be easily available when needed. Patients experienced that getting an appointment with a psychologist often takes time and effort from their side. Therefore, a direct referral to a psychologist or therapist, in particular one with experience in skin diseases, would be highly appreciated. Furthermore, patients often reported positive experiences with support from patient associations and peer contact. As such, they felt it would be useful to provide more information about these associations in hospitals and other healthcare institutions since many patients might not be aware of the existence of these groups.

Need for quick access to healthcare in AD care

As reported by patients, AD care is not always easy accessible during disease flares. Patients experienced that timing of standard consultations is not always appropriate due to the fluctuation in severity over time. As such, they expressed the need for quick access to care when their disease flares, in order to optimize treatment and induce remission as soon as possible. They did not report a preference for a

dermatologist or e.g. specialized nurse in particular. However, patients mentioned several complicating factors in this process; it is difficult to get in touch with their physician, and the non-medical staff (e.g. administrative staff taking phone calls) is not able to understand or adequately assess the severity of their flare.

> *'My doctor tells me 'do call us if it gets worse'. And when I do, the clinic tells me my doctor is not available, but that I can be scheduled for a consultation by phone. Well, that easily takes three days and by the time I can speak to my doctor my symptoms have reduced.' – FG 1*

According to patients, clear instructions at the first consultation on what to do in case of exacerbations and an appropriate and personal doctor-patient relationship facilitates the quick access to care.

The therapeutic decision making process

Need for adequate, understandable, and tailored information

Patients indicated that being provided with adequate and understandable information is crucial in AD care. This information should be patient-tailored since some patients prefer comprehensive information, while others prefer a more concise overview.

Patients highlighted several aspects in the content of this information that were crucial for them. First, patients mentioned that they are more motivated to adhere to therapy when they are aware of the underlying principles. Therefore, patients require improved disease-related information. Second, patients would like to be informed about different treatment options, their mechanism of action, and possible side effects. This should preferably be tailored to the individual patient's situation and preferences. Additionally, patients preferred to be informed about potential next steps in the treatment process. They stated that knowing which other options are available will put them at ease. Third, information about possible external influences on their disease and non-medical advice including the influence of nutrition, climate, and allergies as well as practical recommendations (e.g. daily care skin products) would be highly appreciated. On the other hand, patients indicated that repeating of basic advices (e.g. advice for limited water exposure) is very bothersome since they feel that they already passed that stage, which emphasizes the need for continuous patient-tailored information.

'I hear the same advice all the time: 'you should not shower too often, not too warm and not too long, don't use soap'. It is so annoying to hear this for the eighth time…' – FG 2

Patients indicated that they believe that underexposure of specific topics (e.g. nutritional influences) in evidence-based guidelines used by physicians, might be related to a lack of evidence. Even though patients understand that information about these topics on the internet might lack of scientific evidence, patients would appreciate physicians to understand their search for additional information. In this context, an online forum monitored by physicians would be of added value. Meetings organised by patient associations were also often considered very informative. In addition, patients considered having the possibility to access their digital medical file a positive development.

Varying views on the preferred role of patient and physician

Patients vary in their views regarding the preferred role of the physician and patient in the decision making process. Some patients prefer to have a more leading role and want to be informed on different treatment options by their physician, resulting in an interactive decision making process. According to these patients, getting enough time to read and consider the provided information is essential. This autonomy would enhance shared decision making and reduce the trial and error feeling experienced by some patients.

'I prefer it to be an interaction between me and my physician, in which I also have a say. I know myself best and I read up on specific therapies.' – FG1

Other patients prefer their physicians to have the leading role since these patients feel that their physicians have better overview on their situation and treatment options.

'I often feel like 'oh well, you are the professional, so tell me what would be best'.' – FG2

Generally, patients stated that physicians should get insight into each individual patient's preference regarding their preferred role, resulting in an appropriate decision making process for each patient.

Decisive factors for choices within the decision making process

Patients mentioned that several factors play an important role in their therapeutic choices. With regard to side effects, most patients are willing to accept side effects as long as they are reversible and if the therapy shows sufficient effectiveness on their skin disease and quality of life. However, other patients feel resistance for creating new problems, by treating the initial problem.

> *'I always weigh the options: it is either one thing or the other. If I want to get rid of my eczema, I need to accept certain side effects.' – FG1*

Patients reported that the method and frequency of administration are important in terms of feasibility, and that this should be considered by physicians as well. Additionally, patients indicated that treatment choices are also dependent on previous therapeutic experiences. A physician's recommendations and expectations regarding specific treatment options are considered important factors as well.

Importantly, patients indicated that practical aspects including travel time and travel costs do not determine their therapeutic choices, as long as they receive high quality care.

Indication for next steps within AD treatment should be patient-dependent

Patients stated that a next step in their treatment is indicated when their current therapy is insufficiently effective (i.e. the disease negatively interferes with daily life) or inappropriate (e.g. due to side effects). Determining whether a certain, new treatment is indicated should be patient-dependent, as the impact of the disease in daily life and contributing factors differ between patients.

Most patients reported to know that therapeutic history is an important factor in their indication for new therapies (e.g. patients must have used at least one systemic immunosuppressant for 4 months to be eligible for dupilumab treatment [21]). Although patients have high expectations of novel therapies, they generally agree with the recommended stepwise approach when taking into account the high costs. However, they feel that physicians should be able to make some exceptions for very severe cases with a high impact on quality of life, although patients agreed that making these distinctions can be difficult.

> *'If people are really suffering and they cannot even leave their bed and are not able to participate in normal life due to their eczema, then the physician should be able to skip a few steps in the treatment process.' – FG 2*

Additionally, patients voiced that when a patient has been treated with a systemic immunosuppressant without sufficient effectiveness, they should be able to step up more quickly to the novel therapies. They stressed that this could prevent a high burden for these patients.

Varying preferences on setting treatment goals

Most patients reported to have abstract treatment goals (e.g. increased quality of life), which are generally not discussed with their physician. Patients often feel uncertain about the effectiveness of the initiated therapy based on negative experiences with previous therapies. Consequently, they protect themselves from disappointment by not setting and discussing individual treatment goals.

> *'The physician can also not guarantee that my eczema will disappear completely. So setting big goals is an illusion for me because I find it difficult to know whether I am able to achieve that goal.' – FG2*

Other patients mentioned that they experience more guidance and motivation when setting and evaluating individual goals. Patients agreed that when realistic goals are discussed together with the patient, subsequent evaluation of these goals during consultations is essential.

DISCUSSION

This qualitative in-depth focus group study revealed the needs and preferences of patients regarding AD care in the era of new therapeutic options. A variety of needs and preferences were identified concerning consultations with physicians, AD care organisation, and the therapeutic decision making process. The need for a more patient-tailored approach was an overarching theme in all aspects of AD care.

With regard to consultations, patients stressed the need for autonomy in determining the impact of AD in daily life and increased recognition of the burden of disease by physicians.[5] To address these needs, supportive tools for patients to indicate the impact and disease control over a longer time period such as the Atopic Dermatitis Control Tool, validated health-related quality of life measures, or the use of personal health records (PHR) could be of added value.[21-24] Patients also indicated a need for psychosocial and medical supportive care. Studies assessing the implementation of supportive care for children with AD and their families have

revealed positive results. Although applied interventions require further development, this could guide a more general implementation of supportive care.[25-28]

Consistent with previous research [29, 30], our study showed that a trustful relationship with a personal approach, a physician who is truly listening to you, and the feeling of being taken seriously are essential for patients in AD care. Ha et al. stated that many doctors overestimate their ability in communication and therefore implementation of improved formal training in communication skills in the medical curriculum could be useful.[29, 31] A strong doctor-patient relationship might also contribute to an increased accessibility in AD care during disease flares as physicians can often intuitively determine the urgency, by knowing the patient personally. However, patients reported a struggle in contacting healthcare providers when needed. Several solutions to enable quick access to healthcare, including virtual care which has rapidly been adopted because of the COVID-19 pandemic[32], have been described. Quick accessible care showed positive outcomes and optimized resource utilization in other chronic inflammatory conditions.[33, 34] Additionally, tools for self-management including PHR[24], flare self-assessment[35] and written eczema action plans with individualized guidance on e.g. treatment use have been shown to help in AD and other allergic diseases.[36-40]

In order to create a (therapeutic) 'patient journey' that suits the patient best, the decision making process should be patient-tailored and optimized through e.g consideration of the patient's personal situation regarding eligibility and feasibility of therapies, and the patient's right to self-determination. Patients emphasized the importance of physicians being able to make patient-dependent exceptions on applied guidelines, which are based on relatively homogeneous populations. These exemptions are particularly needed when the disease highly interferes with patients' daily life. Previous studies showed that therapeutic decisions should indeed be patient-centered, fair, and cost-effective in the ideal situation.[41] However, this remains a practical challenge partly because of the lack of insight into cost-effectiveness of the recently introduced therapies in daily practice.[42] A shift towards more patient-centered indication criteria incorporating the disease impact in daily life in addition to current criteria concerning therapeutic history, would be highly appreciated by patients. This would facilitate in making fair choices, in particular for expensive therapies.[8, 41] Agencies such as the FDA and the NHS also promote patient-centered care and improved patient access to better affordable drugs.[43-45] In addition to patient-centered care (i.e. care that is respectful of, and responsive to, individual patient preferences, needs and values) [46], personalized medicine (i.e. tailoring care based on patients' genetic information or other biomarkers)[47] is also

considered important in order to achieve individualized care.[48] Although their sources are different and it remains unclear whether and how these two could be combined on a practical level, personalized medicine might as well contribute to individual flexibility and variability in treatment decisions, and moving away from one-size-fits-all solutions.[47]

In this study, we investigated a contemporary topic using data obtained from a variable sample of patients, originating from a general and an University hospital. Our qualitative data were analysed using multiple phases of coding alternating with consensus discussions within our multidisciplinary team, enhancing the robustness of our results. [20, 49] However, the design of this study does not allow us to draw conclusions on potential differences between patients from different medical settings. In addition to this study focusing on patients' views, future studies investigating views of healthcare providers on different aspects of AD care might be of added value in order to further optimize AD care.

This study demonstrated that AD patients have a variety of needs and preferences regarding care. AD care in general should be patient-tailored, with increased attention for the psychosocial burden, as well as better access to healthcare during disease flares. In order to provide patient-tailored care, therapeutic decisions should be patient-dependent and the interference of the disease in daily life should be incorporated when considering indication for novel therapies. Additional needs and preferences of patients concerning, for instance, the provided information or feasibility of therapies should be taken into account in the therapeutic decision making process, with respect for the patient's autonomy.

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Chapter 3.1

Effectiveness of dupilumab treatment in 95 patients with atopic dermatitis: daily practice data

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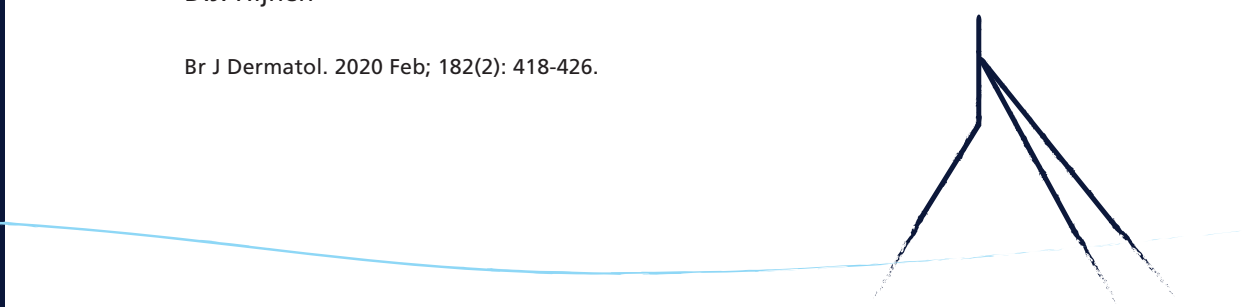


ABSTRACT

Background Dupilumab is the first biologic registered for the treatment of moderate-to-severe atopic dermatitis (AD) and efficacy was shown in phase 3 clinical trials (investigator global assessment 0/1 at week 16: 38%). Currently, there are limited daily practice data available for dupilumab, especially when it is combined with systemic immunosuppressants.

Objectives To evaluate dupilumab treatment in daily practice in patients with AD up to 16 weeks of treatment.

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

Results Ninety-five patients were included. Of these, 62 patients were using systemic immunosuppressants at baseline; the use of systemic immunosuppressants was 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% confidence interval (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 (nonocular) 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 outcome measures 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 moisturizers, AD is mostly treated with topical corticosteroids (TCS) and topical 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 cyclosporin 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 unfavourable 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 3 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 one 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) (online supplementary material).[15] Patients visited the outpatient clinic at baseline, week 4, and between 12 and 16 weeks of treatment. In Amsterdam, 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 immunosuppressants 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 one MCID-unit, 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 side effects 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 changes of PROMs (NRS peak pruritus, POEM and DLQI) over time in the first 16 weeks of treatment were analysed. These estimated mean scores were based on our linear mixed-effects (LME) models.

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 linear mixed-effects (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 models 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 analysed 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 normalise the residuals and improve the model fit was confirmed by evaluation of histograms and Akaike Information Criterion (AIC) (online supplementary material). 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 the Akaike Information Criterion (online supplementary ma-

terial).[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

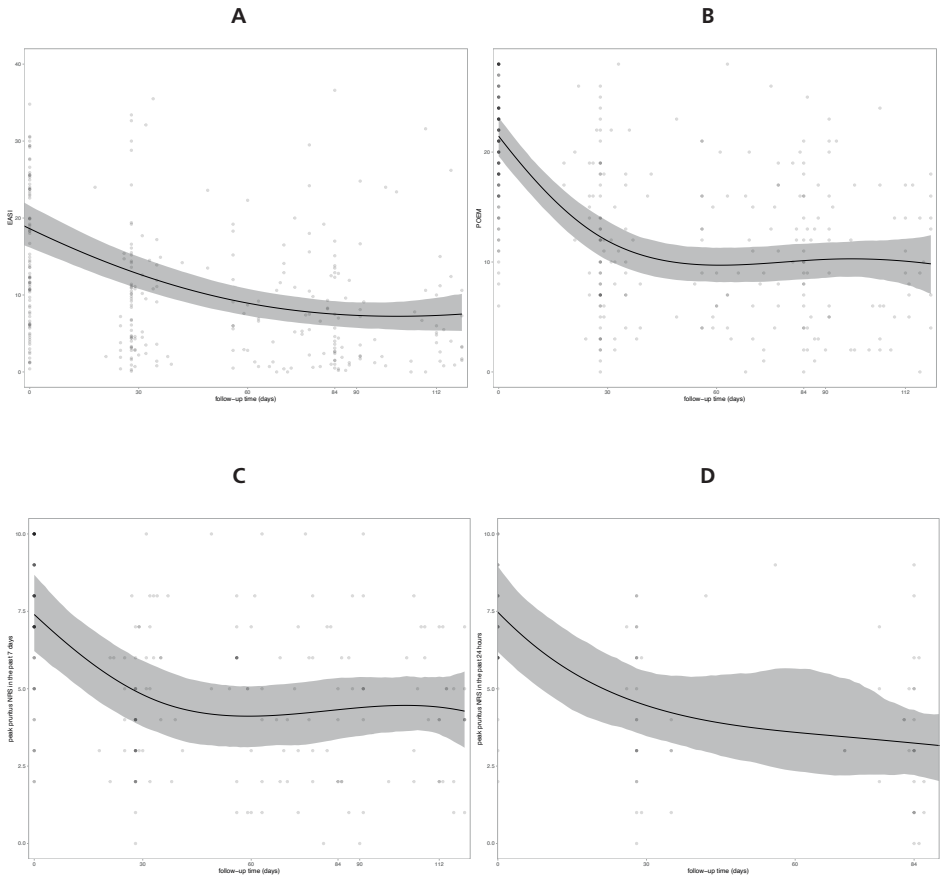
Figures 1a-d show the changes in the outcome measures over time, until 12 weeks (NRS pruritus 24h) and 16 weeks (EASI, POEM, NRS pruritus 7d) of treatment. The

Table 1. Demographic and dlinical dharacteristics of the patients at baseline (n=95)

Characteristic	n=95[a]
Age at start of dupilumab, years - median (IQR)	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	
Years – median (IQR)	0 (0.0 – 2.0)[1]
0 - <2 years – no. (%)	68 (72)
2 - <6 years – no. (%)	11 (12)
6 - <18 years – no. (%)	8 (8)
≥18 years– no. (%)	7 (8)
Disease duration until start of dupilumab, years – mean (SD)	35.5 (16.5)[1]
Previous conventional systemic immunosuppressants – no. (%)[c,d]	
Cyclosporin A	84 (88)
Methotrexate	55 (58)
Azathioprine	29 (31)
Mycophenolic acid/mycophenolate mofetil	36 (38)
Number of previous 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)conjunctivitis[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 the past 7 days and 24 hours, respectively) in patients with atopic dermatitis from start until 16 weeks of dupilumab treatment (n=95)



Linear mixed-effects models were 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 since the outcome measure was recorded in Amsterdam UMC at week 12 only.

IGA score measured at baseline and follow-up, and change in estimated mean DLQI score are shown in Figure S1 and Figure S2. Furthermore, the estimated mean EASI score and PROMs at start and 16 weeks of treatment, which were based on our LME models, 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 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 16 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 models, 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 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, and NRS pruritus 7d and 24h was reached in 66%, 86%, 65%, 65%, and 70% of the patients, respectively.[27,28]

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 and discontinued in 34 (34/43=79%) patients within the first 16 weeks of treatment. In five patients with flares or insufficient response during dupilumab treatment, systemic glucocorticosteroids were started for periods of 2-8 weeks. Three patients were treated with systemic antibiotics.

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

Discontinued systemic immunosuppressive treatment prior to or at start of treatment – no. (%)	**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

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

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

Side effects

In our cohort, 59 patients (59/95=62%) reported eye symptoms, including redness, itching, stinging, burning, tearing, scaling, crusting, or 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 eight (8/95= 8%) patients, with recurrent infections during follow-up in three 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.

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 of dupilumab treatment. 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 topical therapy and conventional systemic immunosuppressants. Dupilumab treatment resulted in a rapid decrease of EASI, IGA, POEM, DLQI, and NRS pruritus scores in the first 16 weeks of treatment (Figure 1a-d, S1, S2; Table 2). 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, although this 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 the limitedly available daily practice literature were different, we tried to compare our results (online supplementary material).[11,33-37] Overall, patients in the current study had lower baseline EASI scores compared to patients in previous dupilumab studies and trials.[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 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 clinical trials (online supplementary material).[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 with 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. 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 two different conventional systemic immunosuppressants, in contrast to a minority (26-28%) which used at least one 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 in clinical trials and daily practice studies after at least 12 weeks of treatment (Table 2). However, 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 of 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 signicantly 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 two University 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. Workings Party's Diagnostic Criteria for Atopic Dermatitis), we were able to analyse the data using LME models. 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 standardised data is important to evaluate the effectiveness and safety of dupilumab treatment in daily practice on the long term. The TREAT Registry Taskforce (https://treat-registry-taskforce.org/) is an international network of national registries which 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 were 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 re-

port 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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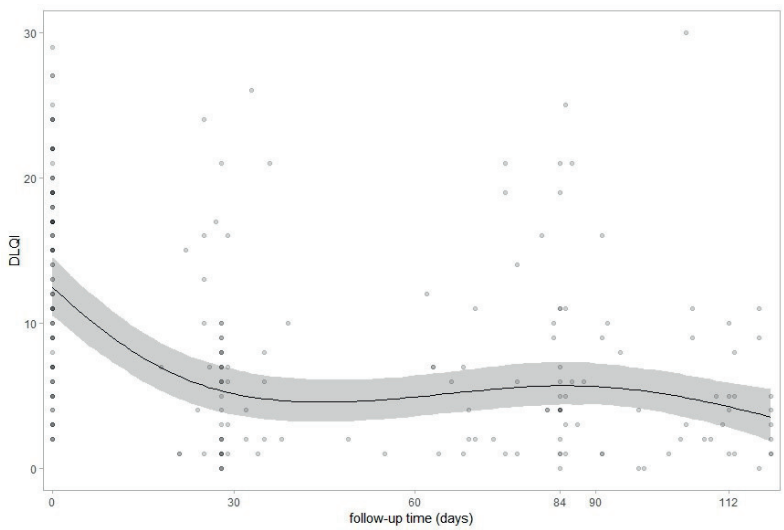
Table S1. Patient-reported side effects

Side effects	Number of patients (%)
Side effects leading to treatment discontinuation – no. (%)	
Monoarthritis	1 (1)
Other side effects[a] – no. (%)	
Injection-site reaction	2 (2)
Headache	7 (7)
(Allergic)(kerato)conjunctivitis/blepharitis/sicca[b]	59 (62)
Patient-reported associated symptoms	46 (48)
Ophthalmologist-diagnosed disease[c]	13 (14)
Fatigue	4 (4)
Dry mouth/lips	2 (2)
Influenza	5 (5)
Nausea	2 (2)
Other gastro-intestinal complaints	2 (2)
Orofacial (non-ocular) Herpes simplex infection	8 (8)

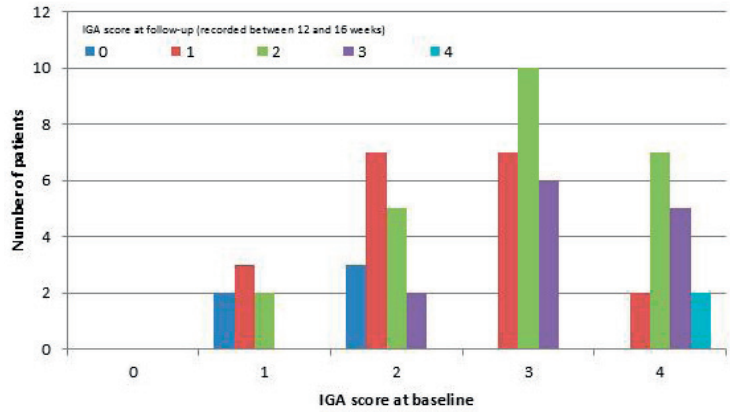
[a] Non-severe side effects occurring in <2 patients were not included in "other side effects".[b]Eye symptoms were registered every visit; subjects with missing data: n=4. [c]Sixteen patients consulted an ophthalmologist.

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)



A linear mixed-effects model was used to model the changes over time. Higher scores indicate a worsened state. The grey area represents the 95% confidence interval. We included measurements from baseline until 16 (+7 days) weeks of dupilumab treatment. Estimated mean DLQI score (0-30) decreased from 12.5 (95%CI 10.5-14.5) at baseline to 4.3 (95%CI 2.8-5.9) at 16 weeks of dupilumab treatment. The Minimal Clinically Important Difference (4) is reached after 12 days.

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



Horizontal axis represents IGA at baseline (missing data: n=15); vertical axis represents number of patients reaching the IGA represented by the different coloured columns (missing data: n=24) at follow-up (between 12 and 16 weeks).

Chapter 3.2

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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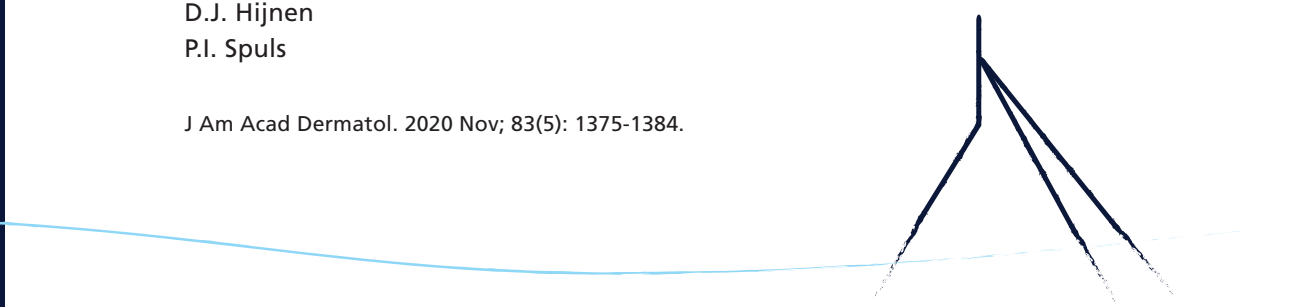


ABSTRACT

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

Objectives 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 AD patients starting dupilumab in routine clinical care.

Results Of the 221 included patients, 103 used systemic immunosuppressants at baseline. At 84 weeks of treatment, we found an absolute change of -15.2 (Standard Error (SE) 1.7) for Eczema Area and Severity Index score, -16.9 (SE 1.4) for Patient-Oriented Eczema Measure score, and -17.2 (SE 1.6) for Dermatology Life Quality Index score. As for Investigator Global Assessment and Numeric Rating Scale 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).

Conclusions 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 AD 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 disease 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. However, a subgroup of around 15% of patients suffers from moderate-to-severe AD and phototherapy and systemic 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 who 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 IMID 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 one 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 immunosuppressants 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 analysed 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 pruritus (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 analysing 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 summarised using descriptive statistics. We analysed 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 analyse EASI, POEM, and DLQI, and ordinal logistic mixed-effects models to analyse 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.

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 two and the median age at start of dupilumab was 41 years (IQR 27-52). Unless contraindicated, all patients were previously treated with other systemic 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 cyclosporin A (n=37/103, 35.9%) or systemic corticosteroids (n=36/103, 35.0%). Eighty-three patients discontinued this concomitant therapy after a median of 50 days (Table S1). 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	n=221
Sex – no. (%)	
Male	127 (57.5)
Female	94 (42.5)
Age at start dupilumab, years - median (IQR)	41 (27-52)
Age of onset AD, years	
Median age (IQR)	0 (0-4)[1]
<2 years – no. (%)	153 (69.2)
≥2-<6 years – no. (%)	19 (8.6)
≥6-<12 years – no. (%)	11 (5.0)
≥12-<18 years – no. (%)	9 (4.1)
≥18 years – no. (%)	28 (12.7)
Ethnicity – no. (%)	
White	178 (80.5)
Black	19 (8.6)
Asian	22 (10.0)
Other	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 [a]	143 (64.7)
Allergic (rhino)conjunctivitis and/or atopic (kerato)conjunctivitis [a]	179 (81.0)
Food allergies [a]	30 (40.0)
Allergic contact dermatitis	113 (51.1)[3]
Family history of atopic diseases[b] – no. (%)	160 (72.4)[4]
Previous use of systemic therapies for AD – no. (%)	
Cyclosporin A	197 (89.1)
Azathioprine	46 (20.8)
Methotrexate	103 (46.6)
Mycophenolic acid/mycophenolate mofetil	75 (33.9)
Systemic corticosteroids	136 (61.5)[5]
Other medication[c]	24 (10.9)
Investigational medication[d]	9 (4.1)

Table 1. Patient characteristics at baseline (*continued*)

Patient characteristics	n=221
Number of previous used systemic immunomodulating therapies[e] – no. (%)	
0	3 (1.4)[f]
1	68 (30.8)
2	90 (40.7)
3	42 (19.0)
≥ 4	18 (8.1)
Previous use of phototherapy – no. (%)	
Yes	166 (75.1)
No	33 (14.9)
Unknown	22 (10.0)
Immunomodulating therapy at start dupilumab – no. (%)	
None	118 (53.4)
Cyclosporin A	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[g]	1 (0.5)
Investigational medication	0 (0.0)
Treatment at outpatient daycare treatment unit in the past year[h] – no. (%)	13 (17.3)
Hospitalization for AD in the past year[h] – 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=1 (0.5%), [4] n=16 (7.2%), [5] n = 49 (22.2%)
[a] patient-reported in EMC and physician-diagnosed in Amsterdam UMC; [b] first degree family member with at least one of the following atopic diseases: AD, asthma or allergic (rhino)conjunctivitis; [c] 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); [d] 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); [e] not including the use of systemic corticosteroids; [f] present 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); [h] other: alitretinoin; [g] data only available for Amsterdam UMC patients (n=75)

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 a concomitant systemic therapy for AD, 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

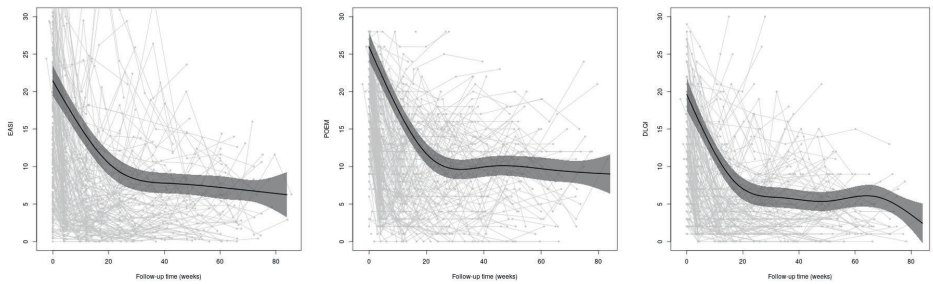
Outcomes / Time	EASI (0-72)				POEM (0-28)				DLQI (0-30)			
	Est. score	SE	Est. change score from baseline	SE	Est. score	SE	Est. change score from baseline	SE	Est. score	SE	Est. change score from baseline	SE
Baseline	21.4	1.0			25.9	1.0			19.6	1.1		
4 weeks	18.0	0.9	-3.4 (-15.9%)	0.3	21.4	0.8	-4.6 (-17.8%)	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

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

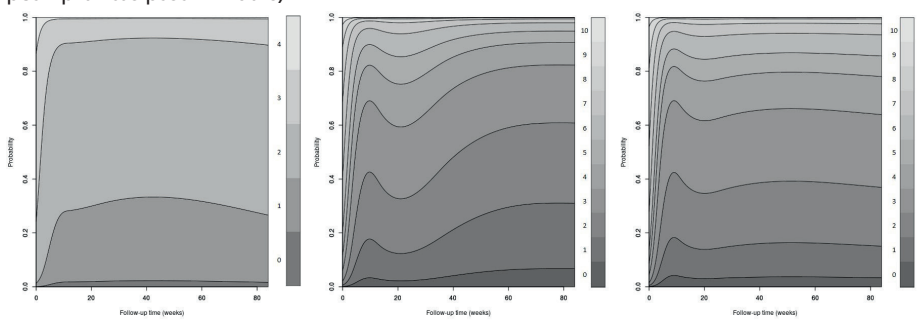
The course until 84 weeks of treatment for all six outcome measurements is shown in Figure 1 and Figure 2. An improvement of all outcome measurements is observed, in particular in the first 12 weeks of treatment. The estimated change in

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))



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.

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 score 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.

score from baseline until 84 weeks was: -15.2 (SE 1.7) for EASI, -16.9 (SE 1.4) for POEM, and -17.2 (SE 1.6) for DLQI (table 2). As for IGA and NRS pruritus, we found a trend for improvement of the scores. The daily practice setting resulted in different follow-up durations for each outcome measure (online supplementary material). 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).

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 with 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 with skin type II (n=126). In addition, the use of concomitant systemic immunosuppressants 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 (online supplementary material).

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 one 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 seven 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	46
Eye complaints	24
(Kerato)conjunctivitis	4
Sicca complaints	2
Blepharitis	1
Epiphora	15
Combined diagnoses[b]	8
Musculoskeletal and connective tissue disorders	
Joint/muscle strain complaints	6
Arthritis	2
Cardiac disorders	
Angina pectoris	3
Acute coronary syndrome	1
Injury, poisoning and procedural complications	
Bone fracture (not spontaneous)	2
Endocrine disorders	
Adrenal insufficiency[c]	2

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

Total number of severe adverse events – no.	79
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]	2
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] combination of eye complaints above, possibly combined with ectropion/epiphora; [c] due to discontinuation of long-term treatment with systemic corticosteroids; [d] 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 two patients to once every 4 weeks. Eight out of these nine patients prolonged due to severe adverse events: eye complaints in six patients and depressed mood in two 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 two 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, four were shortened to a 10-day and eight to a weekly interval. One of these patients eventually discontinued treatment due to persisting ineffectiveness. In six 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 seven patients treatment was discontinued due to ineffectiveness after 66, 111, 123, 126, 166, 204, or 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 which developed a few days after the first dupilumab injection[14], paradoxical facial erythema[15], and panniculitis. These complaints resolved after discontinuation. Three patients discontinued because of anticipated pregnancy.

DISCUSSION

We analysed patient characteristics, treatment aspects, and the effectiveness and safety of dupilumab treatment in 221 AD patients in daily practice up to 84 weeks of treatment, in combination with topical and/or 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 (Figure 1, Figure 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 of treatment.[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 in clinical trials.[18-23] A likely explanation is that in these trials washout periods were applied and/or concomitant therapy was not allowed. Interestingly, our baseline scores for POEM and DLQI were comparable or higher compared to clinical trials. After 12-24 weeks of treatment, we found similar scores of both investigator- and 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 who 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 patients using concomitant systemic AD 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 a reporting bias. In both hospitals there was a low threshold for referral to an ophthalmologist in case of (worsening of) eye complaints. Eye complaints did not result in treatment discontinuation in our patients. This might be explained by absence of alternative adequate therapeutic options for AD, possibly resulting in a higher degree of acceptance of side effects.

Several limitations result from the daily practice setting. While there were no reasons to suspect treatment non-compliance during treatment, this could not completely be ruled out since 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 were registered as part of the TREAT core dataset.[7] In the EMC AEs were registered by inquiring about side effects.

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 aiming to collect these data, while ensuring uniformity in data collection (treat-registry-taskforce.org).[28] In addition, research on alternative treatment op-

tions for AD is of great importance for the patients for whom dupilumab is not an ideal treatment option due to ineffectiveness or side effects.

CONCLUSION

Long-term dupilumab treatment in a routine clinical setting can be considered an effective therapy 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 of treatment. Dupilumab is initially often prescribed in combination with other systemic immunomodulating therapies and is well-tolerated in most patients. Eye complaints were the most frequently reported severe AEs, but did not result in treatment discontinuation.

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Table S1. Concomitant immunomodulating therapy

Concomitant immunomodulating therapy	no. (%)	Median days of continuation after starting dupilumab treatment (IQR)
Patients discontinuing systemic immunomodulating therapy after starting dupilumab	**83 (37.6)**	**50 (28.0-112.0)**
Cyclosporin A	31 (14.0)	84 (50.0-153.0)
Azathioprine	6 (2.7)	41 (28.0-50.8)
Methotrexate	6 (2.7)	119 (58.0-169.8)
Mycophenolic acid/mycophenolate mofetil	8 (3.6)	112 (43.3-158.5)
Systemic corticosteroids	31 (14.0)	28 (13.0-42.0)
Alitretinoin	1 (0.5)	131

IQR, interquartile range; No., number; SD, standard deviation; In total, 103 patients used systemic immunomodulating therapy after starting dupilumab. Eighteen of these patients were using systemic immunomodulating therapy from start dupilumab till study cut-off point: cyclosporine A (n=6), azathioprine (n=2), methotrexate (n=4), mycophenolic acid/mycophenolate mofetil (n=3), systemic corticosteroids (n=3). Two patients stopped for respectively 14 and 33 days with systemic corticosteroids treatment and then restarted with systemic corticosteroids which they were still using at the end of study. This table displays the 83 patients that discontinued systemic concomitant immunomodulating therapy during the study.

Chapter 4

Dupilumab treatment in patients with atopic dermatitis: a comparative cohort study between the Netherlands and Japan shows a discrepancy in patient-reported outcome measures

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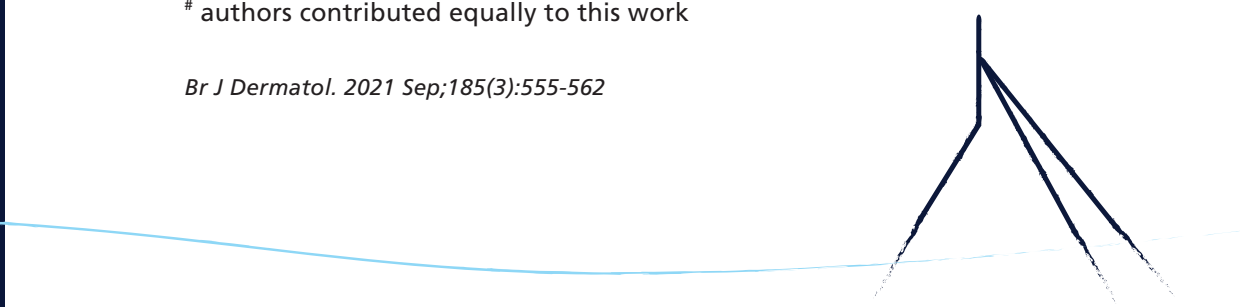


ABSTRACT

Background Dupilumab was equally effective among all racial subgroups in clinical trials, but a direct comparison in daily practice is lacking.

Objective To investigate the effectiveness of dupilumab in patients with atopic dermatitis (AD) in the Netherlands and Japan over 80 weeks of treatment.

Methods A longitudinal comparative cohort study was conducted in patients with AD who were treated with dupilumab in daily practice. We used linear mixed-effects models to determine changes over time.

Results We found statistically significant differences in sex, disease onset, body mass index, and therapeutic history between Dutch (n=208) and Japanese (n=153) patients. The baseline Eczema Area and Severity Index (EASI) score was higher in Japanese patients (23.8 vs. 14.8), while baseline Patient-Reported Outcome Measures (PROMs) were higher in Dutch patients. EASI scores decreased quickly to a level indicating 'mild disease' (EASI < 7), and remained low in both countries. However, PROMs showed different trajectories with better scores in Japan.

Conclusions Dupilumab showed significant, comparable, and sustained improvement of EASI scores in Japanese and Dutch patients. However, we found striking differences in the effect on PROMs between the countries, with a better outcome in Japanese patients.

INTRODUCTION

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease. The prevalence of AD in diverse ethnic groups shows wide ranges (1–25%), with a higher prevalence reported in Asians compared with Europeans.[1,2] Although individuals with any ethnicity and skin type can be affected, phenotypical and immunological differences due to environmental factors, pigmentation, distinct T-helper (Th) cell profiles, epidermal structure, and presence of FLG mutations have been described.[2–5] Recently, Koga et al.[6] found a stronger Th17/Th22 polarization and a more blended phenotype with features of both AD and psoriasis in Asian patients with AD compared with Europeans.[4,6] Until now, literature about the racial differences in coping mechanisms and the perception of disease in AD is lacking.

In most countries, topical corticosteroids (TCS), topical calcineurin inhibitors and emollients represent the first step in the treatment of AD. In Japan (JP), serum thymus and activation-regulated chemokine (TARC/CCL17) levels have been used widely as a biomarker for disease severity and as a tool for 'tight (disease) control' since 2008, especially during topical treatment in daily practice. TARC is a chemokine that plays a role in attracting inflammatory cells to the skin. After expression on the vascular endothelium, TARC is released in blood, resulting in measurable levels reflecting disease severity.[7] In about 15% of patients with AD, topical treatment is insufficiently effective and systemic treatments including cyclosporin A (CsA), methotrexate (MTX), azathioprine, mycophenolic acid (MPA), mycophenolate mofetil (MMF) and dupilumab are indicated.[8] In the Netherlands (NL), dupilumab treatment is reimbursed (100%) when a patient has been treated with at least one systemic immunosuppressant for four months.[9] In Japan, dupilumab treatment is indicated (70% reimbursed) for patients with moderate-to-severe AD who are not controlled despite adequate topical treatment for at least six consecutive months, not necessarily limited by prior systemic therapies. Systemic immunosuppressants are less frequently prescribed in Japan. Prescription of MTX, MPA and MMF for AD is not allowed, but short courses of CsA (maximum of 12 weeks) or oral corticosteroids are used.[1] In clinical trials, dupilumab was found to be equally effective among all racial subgroups.[1,10] However, a direct comparison of the effectiveness of dupilumab in daily practice in patients with AD in Japan and the Netherlands is currently lacking.[3]

In both Osaka and Rotterdam, treatment effect and disease severity in daily practice are assessed using physicians' and patients' observations and experiences supported by clinical scores including Eczema Area and Severity Index (EASI),

Patient-Oriented Eczema Measure (POEM), Numeric Rating Scale (NRS) pruritus, and Dermatology Life Quality Index (DLQI). In addition, serum TARC levels were measured in Japanese patients.

Here, we aim to investigate the effectiveness of dupilumab treatment in patients with AD in the Netherlands compared with Japan.

METHODS

We conducted a longitudinal comparative cohort study, using data that was prospectively collected in daily practice at the Erasmus MC University Medical Center (Rotterdam, the Netherlands (NL)) and the Osaka Habikino Medical Center (Habikino, Osaka, Japan (JP)) from October 2017 until June 2020.

All patients with AD (aged ≥ 13 years in NL, ≥ 15 years in JP) who started dupilumab treatment were informed about the collection of data and patients who gave consent to publish pseudonymized information relating to them were consecutively included. In the Erasmus MC, data were collected as part of the Immune-Mediated Inflammatory Disorders (IMID) Registry. Dupilumab was used according to the product label and dose adjustments and use of concomitant systemic immunosuppressants were recorded.[11] Additionally, patients were encouraged to continue the use of topical treatment.

Data were collected at the start of dupilumab treatment, after 4 weeks (NL), after 3–4 months of treatment, and every 3–4 months thereafter. Patient characteristics, therapeutic history, and current AD treatment were recorded at baseline. Disease severity, symptoms, and the impact on quality of life were assessed at every visit using EASI (0–72), POEM (0–28), DLQI (0–30) and NRS pruritus (0–10). The peak pruritus score of the past 7 days was recorded in Japan, whereas the peak pruritus score of the past 24 hours was recorded in the Netherlands. Blood samples were collected from all Japanese patients at all visits in order to measure serum biomarker levels (i.e. TARC). Side effects were not recorded in a standardized manner in Japan and therefore this is beyond the scope of this study.

Data analysis

Because data were collected in daily practice, follow-up schemes show a variance in timing of visits. We used linear mixed-effects (LME) models to evaluate the effectiveness of dupilumab and to describe and present the change of the repeatedly

measured, continuous score of interest in time (days since start of treatment). We analysed measurements recorded at visits from the start up to 80 weeks of treatment. We used natural cubic splines in both the fixed and random-effects models to capture the nonlinear evolution over time. Sex, age, and country were included as covariates in our model, including an interaction of time and country. Please see the online supplementary material for additional information.

Ethical approval

Our study was exempted from evaluation by the local Medical Research Ethics Committees (NL: MEC-2017-1123,W18_097#18.123; JP: OHMC-MEC-1067). The study was conducted in accordance with STROBE recommendations.

RESULTS

In total, 361 patients with AD (NL, n=208; JP, n=153) were consecutively included. As shown in Table 1, the majority of the patients were male with a statistically significant difference in proportion between NL (53%) and JP (85%) ($p<0.001$). The median age at the time of initiation of dupilumab was 33 (NL, interquartile range (IQR) 24–51) and 34 (JP, IQR 21–45) years, with a younger onset of AD in NL compared with JP ($p<0.001$). Atopic comorbidities were more frequently reported in NL (65–77%) than in JP (41–65%), and a statistically significant lower body mass index (BMI) (24.9 vs. 22.9) was found in JP. About 90% of the Dutch patients had used CsA compared with less than 50% of the Japanese patients. These differences between countries were also found for MTX and MPA/MMF. Additionally, we found a difference in the use of concomitant systemic immunosuppressants in the transition to dupilumab treatment between the countries (NL: 124 of 208; JP: 58 of 153) (Table 1). Immunosuppressants were tapered and discontinued in 111 of 124 Dutch and 53 of 58 Japanese patients, after a median of 85 (NL, IQR 42–167) and 56 (JP, IQR 28–133) days of treatment. The remaining patients (NL, n=13; JP, n=5) were still using immunosuppressants at the time of analysis. A subset of the Japanese patients (n=7) was treated intensively with TCS during a clinical admission in the hospital just before starting dupilumab treatment.

Table 1. Demographics and clinical characteristics at baseline

Characteristic	the Netherlands (n=208)	Japan (n=153)	P-value
Male sex – no. (%)	111 (53)	130 (85)	<0.001*
Age of onset AD[1]			<0.001*
0 - <2 years – no. (%)	116 (56)	65 (43)	
2 - <6 years – no. (%)	21 (10)	29 (19)	
6 - <18 years – no. (%)	21 (10)	35 (23)	
≥18 years– no. (%)	34 (16)	23 (15)	
Age at start of dupilumab, years - median (IQR)	33 (24-51)	34 (21-45)	0.016*
Number of adolescents (<18 yrs) – no. (%)	4 (2)	24 (16)	<0.001*
Race – no. (%)[2]			<0.001 [b]*
White	163 (78)	-	
Black	14 (7)	-	
Asian	11 (5)	153 (100)	
Other	2 (1)[a]	-	
Fitzpatrick skin type – no. (%)			<0.001 [c]*
I	4 (2)	-	
II	144 (69)	-	
III	22 (11)	71 (46)	
IV	16 (8)	81 (53)	
V	18 (9)	1 (1)	
VI	4 (2)	-	
Atopic/allergic conditions – no. (%)[d]			
Asthma[3]	135 (65)	63 (41)	<0.001*
Allergic (rhino)conjunctivitis[3]	161 (77)	100 (65)	0.009*
Allergic contact dermatitis[4]	98 (47)	1 (1)	<0.001*
BMI - median (IQR)[5]	24.9 (22.2-27.9)	22.9 (20.3-26.5)	<0.001*
Family history of atopic diseases – no. (%)[6]	150 (72)	101 (66)	0.381
Previous use of phototherapy – no. (%)[7]	126 (61)	35 (23)	<0.001*
Number of previous used conventional systemic immunosuppressants – no. (%)			<0.001 [c]*
0	7 (3)	83 (54)	
1	64 (31)	70 (46)	
2	98 (47)	-	
≥3	39 (19)	-	
Previously used conventional systemic immunosuppressants – no. (%)			
Cyclosporin A[8]	187 (90)	70 (46)	<0.001*
Methotrexate[9]	77 (37)	-	<0.001*
Azathioprine	39 (19)	3 (2)	<0.001*

Table 1. Demographics and clinical characteristics at baseline (*continued*)

Characteristic	The Netherlands (n=208)	Japan (n=153)	P-value
Mycophenolic acid/mycophenolate mofetil	78 (38)	-	<0.001*
Therapy until start of dupilumab / continued after start of dupilumab – no. (%)[10]			
Cyclosporin A	62 (30) / 60 (97)	57 (37) / 57 (100)	<0.001* / <0.001*
Methotrexate	23 (11) / 11 (48)	-	<0.001* / NA
Azathioprine	12 (6) / 9 (75)	1 (1) / 1 (100)	0.009* / 1.0
Mycophenolic acid/mycophenolate mofetil	18 (9) / 17 (94)	-	<0.001* / NA
Other[e]	29 (14) / 28 (97)	1 (1) / -	<0.001* / <0.001*
None	64 (31) / NA	93 (61) / NA	-

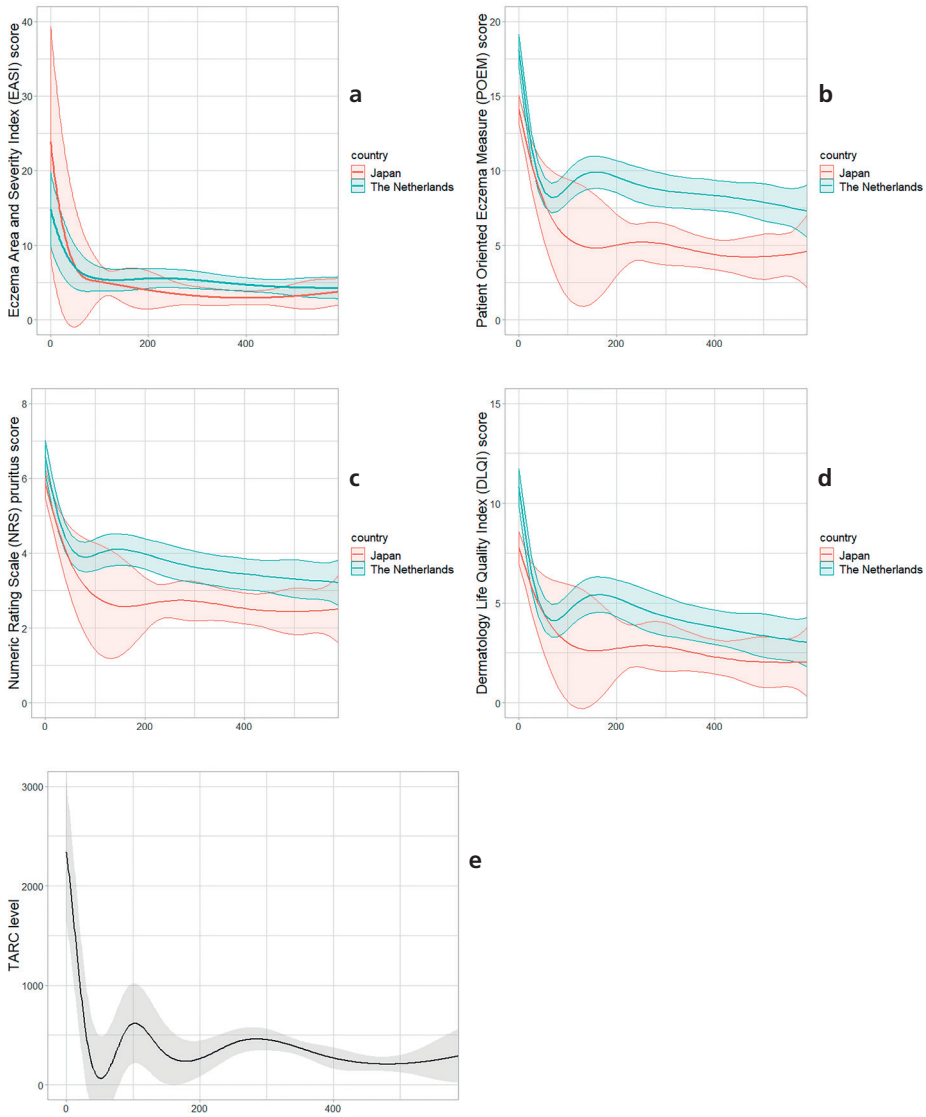
Missing values: [1] The Netherlands (NL) n=16, Japan (JP) n=1 [2]NL n=18 [3]NL n=1 [4]NL n=51 [5]NL n=31 [6]NL n=15, JP n=13 [7]NL n=52 [8]JP n=2 [9]JP n=1 [10]NL n=1

[a]Indian: n=2, [b]categories combined into white and other, in order to be able to conduct statistic tests, [c]categories combined into 1+2 vs 3-6 (skintype) and 0 vs ≥1 (previous therapies), in order to be able to conduct statistic tests (more than two categories and several cells with <5 counts, fisher exact only possible as 2x2) [d]patient-reported or physician diagnosed, [e]oral corticosteroids: n=27 NL, n=1 JP; alitretinoin n=2 NL. Statistical tests: proportions: Chi-squared test (E<5: Fisher's exact); distributions across JP/NL: Mann-Whitney U test.
* p<0.05, statistical significance

In our cohort, 61% of the patients (NL, n=122; JP, n=98) were treated with dupilumab according to the product label [once every 2 weeks (Q2W)] during total follow-up. Eight percent of the patients (NL, n=29; JP, n=0) were (temporarily) treated in a shortened interval (<2 weeks) and 25% of the patients were treated in an extended interval (NL, n=35; JP, n=55). Thirty-three (NL, n=20; JP, n=13) patients discontinued dupilumab treatment due to insufficient effectiveness (NL, n=10; JP, n=1), side effects (NL, n=4), a combination of insufficient effectiveness and side effects (NL, n=4), financial considerations (JP, n=11), changed diagnosis (JP, n=1), or anticipated pregnancy (NL, n=2).

The disease course from baseline until 80 weeks (=560 days) of treatment is shown in Figure 1a–e. The number of unique patients with recorded EASI scores at specific time points ranged from 194 (NL) and 145 (JP) at the start of dupilumab treatment, to 103 (NL) and 85 (JP) at 1 year, and subsequently 44 (NL) and 38 (JP) at 1.5 years of treatment (online supplementary material).

Figure 1a-e. Effectiveness of dupilumab in patients with atopic dermatitis: outcome measures over time during dupilumab treatment



All outcome measures have shown clinically relevant improvement with at least one unit of minimal clinically important difference. (a) The EASI score shows a rapid decrease with comparable trajectories in both countries, while Patient-Reported Outcome Measures (PROMs) [(b) Patient-Oriented Eczema Measure and (c) Numeric Rating Scale (NRS)-Pruritus] showed different trajectories with relatively high scores and a clinically relevant, better outcome for PROMs in JP patients. (c) NRS-Pruritus shows peak pruritus past 24 h (NL) and mean pruritus past 7 days (JP). (d) DLQI score in time during dupilumab treatment. (e) TARC levels after starting dupilumab treatment (in JP patients). Bands show 95% confidence interval.

The estimated severity scores (Table 2) indicate moderate-to-severe AD at baseline. Interestingly, although the physician-reported severity scores were higher in Japanese patients (i.e. EASI 23.8 vs. 14.8 in NL) at baseline, all patient-reported outcome measures (PROMs) indicated worse disease in NL at start of treatment. A statistically significant difference in estimated baseline scores between JP and NL was found for POEM (P =<0.001), DLQI (P =<0.001) and NRS pruritus (P = 0.022), while a minimal clinically important difference (MCID) between both populations at baseline was observed for EASI (actual difference 9.0; MCID 6.6) and POEM (actual difference 4.0; MCID 3.4). The baseline TARC level, which was measured only

Table 2. Effectiveness of dupilumab: Estimated (clinical) severity scores over time

	the Netherlands		Japan	
	Eczema Area and Severity Index (EASI) score			
	Est. score (95%CI)	**-% from baseline**	**Est. score (95%CI)**	**-% from baseline**
Baseline	14.8 (9.9-19.7)	-	23.8 (8.6-39.0)	-
4 wks	9.4 (5.8-13.0)	-36.5%	11.6 (0.6-22.6)	-51.3%
12 wks	5.7 (3.9-7.5)	-61.5%	5.3 (1.4-9.2)	-77.7%
52 wks	4.9 (4.0-5.8)	-66.9%	3.0 (2.0-4.0)	-87.4%
80 wks	4.3 (2.9-5.7)	-70.9%	3.6 (1.8-5.4)	-84.9%
	Patient Oriented Eczema Measure (POEM)			
	Est. score (95%CI)	**-% from baseline**	**Est. score (95%CI)**	**-% from baseline**
Baseline	18.1 (17.0-19.2)	-	14.1 (13.2-15.0)	-
4 wks	11.3 (10.3-12.3)	-37.6%	10.2 (8.7-11.7)	-27.7%
12 wks	8.4 (7.4-9.4)	-53.6%	6.0 (2.6-9.4)	-57.4%
52 wks	8.4 (7.4-9.4)	-53.6%	4.6 (3.4-5.8)	-67.4%
80 wks	7.5 (6.3-8.7)	-58.6%	4.4 (2.9-5.9)	-68.8%
	Dermatology Life Quality Index (DLQI) score			
	Est. score (95%CI)	**-% from baseline**	**Est. score (95%CI)**	**-% from baseline**
Baseline	10.8 (9.9-11.7)	-	7.8 (7.0-8.6)	-
4 wks	6.3 (5.5-7.1)	-41.7%	5.7 (4.5-6.9)	-26.9%
12 wks	4.2 (3.4-5.0)	-61.1%	3.3 (0.8-5.8)	-57.7%
52 wks	4.0 (3.1-4.9)	-63.0%	2.5 (1.5-3.5)	-67.9%
80 wks	3.1 (2.0-4.2)	-71.3%	2.0 (0.8-3.2)	-74.4%
	Numeric Rating Scale (NRS) pruritus			
	Est. score (95%CI)	**-% from baseline**	**Est. score (95%CI)**	-% from **baseline**
Baseline	6.6 (6.2-7.0)	-	5.9 (5.5-6.3)	-
4 wks	4.9 (4.5-5.3)	-25.8%	4.5 (3.9-5.1)	-23.7%
12 wks	3.9 (3.5-4.3)	-40.9%	3.0 (1.8-4.2)	-49.2%
52 wks	3.5 (3.1-3.9)	-47.0%	2.6 (2.1-3.1)	-55.9%
80 wks	3.2 (2.7-3.7)	-51.5%	2.5 (1.9-3.1)	-57.6%

Table 2. Effectiveness of dupilumab: Estimated (clinical) severity scores over time (*continued*)

	the Netherlands		Japan	
	Dermatology Life Quality Index (DLQI) score			
	Est. score (95%CI)	**-% from baseline**	**Est. score (95%CI)**	**-% from baseline**
Baseline	10.8 (9.9-11.7)	-	7.8 (7.0-8.6)	-
4 wks	6.3 (5.5-7.1)	-41.7%	5.7 (4.5-6.9)	-26.9%
12 wks	4.2 (3.4-5.0)	-61.1%	3.3 (0.8-5.8)	-57.7%
52 wks	4.0 (3.1-4.9)	-63.0%	2.5 (1.5-3.5)	-67.9%
80 wks	3.1 (2.0-4.2)	-71.3%	2.0 (0.8-3.2)	-74.4%
	TARC levels			
	Est. score (95%CI)	**-% from baseline**	**Est. score (95%CI)**	**-% from baseline**
Baseline	-	-	2339 (350)	-
4 wks	-	-	578 (254)	-75.3%
12 wks	-	-	483 (202)	-79.4%
52 wks	-	-	339 (41)	-85.5%
80 wks	-	-	255 (105)	-89.1%

in JP, was estimated to be 2239 pg/mL (95% CI 1553–2925) (maximum reference value 450 pg/mL).

After 12 weeks of treatment, we observed an estimated mean EASI of 5.7 and an absolute change from baseline (Δ) of –9.1 (–61.5%) in NL and 5.3 (Δ –18.5; –77.7%) in JP; a mean POEM of 8.4 (Δ –9.7, –53.6%) in NL and 6.0 (Δ –8.1, –57.4%) in JP; a mean DLQI of 4.2 (Δ –6.6, –61 . 1%) in NL and 3.3 (Δ –4.5, –57.7%) in JP; and a mean NRS-pruritus of 3.9 (Δ –2.7, –40.9%) in NL and 3.0 (Δ –2.9, –49.2%) in JP (Table 2). All outcome measures have shown improvement with at least one MCID unit. As shown in Figure 1 (b-d), all PROMs in Dutch patients showed an increase after 12–16 weeks of treatment, which was not reflected by the EASI score (Figure 1a). A continued improvement of PROMs from about 21 weeks (approx. 150 days) until approximately 70–80 weeks (about 490–560 days) is observed in both countries. We found statistically significant differences in POEM scores from about 145 days of treatment until the end of follow-up between patients in JP and NL; DLQI scores from about 200 to 230 days of treatment; and NRS pruritus scores from about 175 to 275 days, and 330 to 465 days of treatment (Figure 1a–d). After 80 weeks (560 days) of treatment, we found a difference between the countries in all outcome measures, with better outcomes in JP compared with NL, as shown in Table 2, respectively: EASI Δ0.7, POEM Δ3.1, DLQI Δ1.1, NRS Δ0.7.

DISCUSSION

In this longitudinal comparative cohort study, we evaluated the effectiveness of dupilumab in Dutch and Japanese patients with AD in daily practice. Dupilumab showed significant improvement on all outcome measures in both Japanese and Dutch patients in time. Although the mean estimated baseline EASI score was higher in Japanese patients, baseline PROMs were significantly higher in Dutch patients. The mean estimated EASI scores of patients in Japan and the Netherlands decreased quickly to a score indicating 'mild disease', with a comparable trajectory from 12 weeks until the end of follow-up. Strikingly, PROMs showed different trajectories with relatively high levels and clinically relevant, better outcomes for PROMs in patients in Japan.

Interestingly, we found large differences in demographics and clinical characteristics of Japanese compared with Dutch patients at baseline. We found a higher number of male patients in JP (85%, $p<0.001$), a later onset of disease in Japanese patients ($p<0.001$) and lower BMI ($p<0.001$) compared with Dutch patients. This is partly in line with data from an observational registry of adult Japanese patients with AD, and phase III trial data.[1,12] In this studies, 56–80% of the included patients were male, with a median onset of AD at 3–4 years of age. However, a study conducted by the Japanese Dermatological Association including all disease severity categories concluded that there is no sex difference in the incidence of AD in Japan.[13] This might suggest a higher risk for developing severe AD in male patients; however, literature on this topic is lacking. Kato et al. found significant negative correlations between BMI and EASI reduction on the long term, suggesting that dupilumab might be less effective in obese patients.[14] However, the addition of BMI as a covariate in our analyses did not result in clinically relevant changes of the outcome. Additionally, we found higher incidences of atopic comorbidities in Dutch patients, which might be explained by the fact that in the Japanese cohort only physician-diagnosed atopic comorbidities were registered, while in the Dutch cohort patient-reported conditions were also included. Differences in previous and concomitant use of systemic immunosuppressants can be explained by differences in prescription behavior and regulations between countries, as discussed earlier. However, we have recently shown that the use of concomitant systemic immunosuppressants does not affect long-term treatment effectiveness.[15]

Analysis of our outcome measures showed large confidence intervals for the Japanese patients, as shown in Figure 1a–d. This can be explained by the overrepresentation of males in the Japanese cohort. Additional sensitivity analyses ruled

out the influence of this overrepresentation on the differences found between the countries. Factors that may explain these differences include racial disease-specific differences, differences in healthcare organisation and cultural practices, and racial differences in coping and disease experiences. In our study, we found differences in POEM and NRS between the countries. However, differences in DLQI were less evident. This may be because the DLQI is not disease-specific and includes only questions regarding general physical disabilities. The minor differences in EASI and DLQI scores between countries suggest that cultural differences, e.g. differences in coping, may explain the discrepancy which was found between PROMs in JP and NL. It is known that cultural characteristics determine the perception of health and illness. Japan is known to have a relatively low absenteeism (i.e. sickness absence) and high presenteeism (i.e. sickness presence) rate compared with other countries, which might reflect a different culture-related coping strategy as well.[16] However, there have been no publications on this topic for AD in particular.[17] Additionally, various dimensions of disease or illness perception have been associated with different aspects of the outcome.[18] Secondly, the discrepancy might also be the result of the difference in AD healthcare organisation. In Japan, focus on concomitant TCS use is expected to be higher compared with NL, possibly resulting in improvement of their disease. This focus on concomitant topical treatment is mainly due to the experience-based knowledge of accurate remission levels with concomitant TCS based on serum TARC levels.

The rebound effect that was found in the Dutch cohort from approximately 12 weeks of treatment might be the result of a response shift due to (temporal) recalibration.[19] This shift might be the result of changing expectations of the patients during (effective) treatment (i.e. patients become more critical during effective therapy).[19] It could be speculated that Japanese patients are less susceptible to this response shift, partly because of the gratitude that could possibly be higher due to the personal financial investment that is required during dupilumab treatment in Japan (approximately ¥40000/€317 per month).[20] Notably, this rebound phenomenon was reflected by increasing TARC levels in Japanese patients, although levels remained within the reference value that is used in daily practice (< 600 pg/mL) (Figure 1e). Overall, PROMs showed relatively high levels during follow-up with a POEM up to 10.0 in NL and 6.0 in JP, which is in line with the available literature.[21,22] This might suggest that consideration of PROMs in addition to disease severity measures including EASI is of added value in the evaluation of treatment effectiveness in studies and daily practice.

The declining ratio between actual and expected measurements, possibly considered a limitation, could be explained by the extended intervals between follow-up visits in patients with effective treatment (online supplementary material). Furthermore, there were minor differences in outcome measures and visit schedules between the countries, but these did not complicate our analyses using the LME models. In addition, side effects were not analysed in this study due to the absence of standardized records of side effects in daily practice.

This is the first study that directly compared dupilumab treatment in adult AD patients in Japan and the Netherlands. Dupilumab showed significant improvement of AD in Japanese and Dutch patients. Although the effect on was similar, we found differences in the effect on PROMs. These differences might be the result of cultural- or healthcare system-related differences. Therefore, we believe that in addition to racial disease-specific differences, healthcare system- or culture related characteristics should be considered when interpreting patient-reported outcome measures in clinical trials. Additionally, more objective outcome measures such as biomarkers which are not subjected to behavior would be highly valuable.

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Chapter 5

Adjusted dose regimens in dupilumab treatment for atopic dermatitis: daily practice experiences

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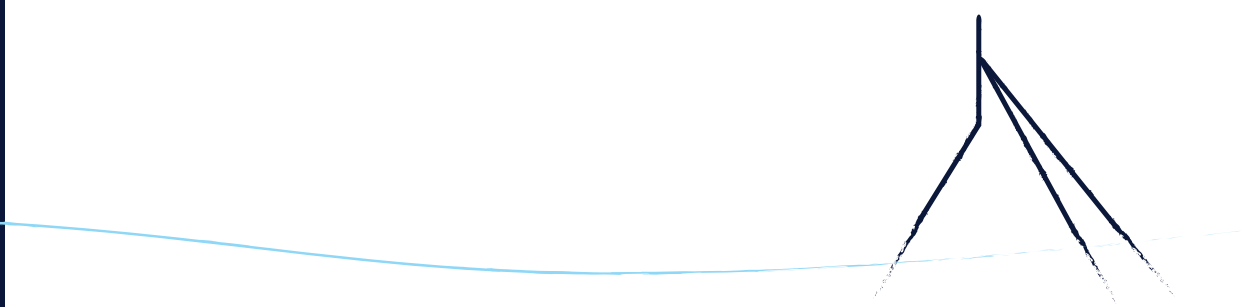
Manuscript in preparation



ABSTRACT

Background Clinical trials investigating dupilumab treatment in atopic dermatitis patients showed a trend towards better effectiveness with a weekly or biweekly dosing interval, compared with extended dosing intervals. However, literature about adjusted dose regimens in daily practice is lacking.

Objectives To evaluate adjusted dose regimens of dupilumab treatment for atopic dermatitis in daily practice.

Methods An observational, longitudinal cohort study was conducted in AD patients who started dupilumab treatment in daily practice. Dose regimens were adjusted upon shared decision making between physicians and patients in daily practice, without strict criteria. Disease courses of patients with shortened or extended intervals were illustrated using spaghetti plots. In addition, data of patients who were treated in a standard or extended interval were analysed using linear mixed effect models in order to determine the estimated effectiveness of extended dose regimens.

Results In total, 180 AD patients were consecutively included in our study. Patients with an extended interval (n=28) had relatively low Eczema Area and Severity Index (EASI) scores at the time of adjustment (range: 0-7) and the majority of patients showed continuous effectiveness after adjustment. In patients with a shortened interval (n=26), the scores at the time of adjustment were more widespread (range: 0-34) and follow-up showed variable disease courses. Based on the LME model, we found an overall continuous improvement of EASI scores in time, in either patients with a normal or extended interval.

Conclusions Patients who were treated in an extended interval in daily practice showed sustained effectiveness, similar to patients with a standard interval. The effect of shortened intervals on disease severity could not be adequately analysed due to methodological limitations in this retrospective study.

INTRODUCTION

Atopic dermatitis (AD) is a common, inflammatory skin disease which can have a large impact on quality of life. It is characterized by invalidating clinical manifestations including recurrent eczematous lesions, itch, and sleep loss.[1, 2]

Dupilumab was the first biologic that was approved for AD treatment and inhibits interleukin (IL) 4 and IL-13 signaling by targeting the interleukin (IL) 4 receptor subunit α.[3] The 16-week and 1-year efficacy and safety of weekly and biweekly dosing intervals for 300mg dupilumab in comparison to placebo were confirmed in phase II and III clinical trials.[4-6] No statistically significant or clinically relevant differences were found between both dose regimens. A dose-finding study showed that dupilumab 300 mg every week or every other week had better outcomes compared with 300 mg dupilumab every 4 weeks, although it is arguable whether the differences are clinically relevant.[7] However, EMA and FDA approved dupilumab treatment in a regimen of 300mg every 2 weeks for treatment of moderate-to-severe AD.[8, 9]

In daily practice, long-term treatment with dupilumab, without adjustments of dose regimens is therefore considered common practice. However, several reasons in favour of extended dosing intervals exist. First, an increasing number of side effects including allergic conjunctivitis, facial redness, alopecia, and joint complaints are reported in literature.[10-15] In some patients, a longer dosing interval (Q3W, Q4W) resulted in reduction of side effects.[16]

Second, the relatively high costs of dupilumab treatment in daily practice (approximately €17 000/year excl. additional healthcare costs in the Netherlands), might advocate for attempting to extend dosing intervals. On the other hand, several patients in our out-patient clinic reported to experience disease flares in the second week of their 2-week interval which might promote shortened intervals.

Until now, literature on shortened or extended dupilumab dose intervals in daily practice is lacking. Therefore, we aimed to evaluate adjusted dose regimens of dupilumab treatment for atopic dermatitis in daily practice.

METHODS

We conducted an observational, longitudinal cohort study using data that was prospectively collected in daily practice at the Department of Dermatology at the

Erasmus MC University Medical Center (Rotterdam, The Netherlands) in the context of the Erasmus MC Immune-Mediated Inflammatory Disorders (IMID) Registry, from October 2017 until October 2020. All adolescent and adult AD patients who started dupilumab treatment were informed about the collection of data. Data of patients who were treated for at least 12 weeks at the time of data-analysis and who gave consent to publish pseudonymized information relating to them were consecutively included. Also, patients who were treated in an adjusted dose regimen should have been treated in this interval for 12 weeks to be eligible for inclusion in this study.

Dupilumab 300 mg treatment was started biweekly (Q2W) in all patients, according to the product label. Dupilumab dose regimens were adjusted in daily practice through shared decision making between patient and physician, without uniform dose adjustment criteria. Reasons for extending the interval could be presence of side effects or sustained disease control. Reasons for shortening the interval included insufficient effectiveness or increased disease activity (e.g. itch) in the days prior to dupilumab injections in the Q2W interval. Adjustments in dupilumab dose regimens and use of concomitant systemic immunosuppressants were recorded. The use of topical therapy including moisturizers, topical corticosteroids and calcineurin inhibitors was encouraged.

Data collected at every visit until a second adjusted dupilumab dose regimen, or end of study (October 15, 2020), whichever occurred earlier, were included in our analyses. Data collected after a second dose adjustment were censored. At baseline, patient characteristics, therapeutic history, and current AD treatment were recorded. We collected Eczema Area and Severity Index (EASI: 0-72) scores at every visit to assess disease severity in time. As EASI scores can only be collected during a live consultation and not all dose regimens were adjusted during live consultations due to the corona pandemic, this resulted in missing of EASI scores at the time of dose adjustment. In patients with missing EASI scores at dose adjustment, the last EASI score before adjustment was used.

Data analysis

To compare characteristics between patients treated with different dose regimens, we used a chi-squared test (E<5: Fisher's exact) for comparison of proportions and Mann-Whitney U or Kruskal-Wallis tests for comparison of distributions across different dose regimens. Disease severity in time was plotted for every individual patient using spaghetti plots. Because data was collected in daily practice, follow-up schemes show variation in the timing of visits. We used linear mixed effects

(LME) models to evaluate the effectiveness of extended and normal dupilumab dose regimens. The dependent variable were the repeatedly measured EASI scores, and the independent variables were group (extended or normal regimen), time since start of dupilumab treatment, gender, age at start of treatment (in years) and BMI. In addition, an interaction effect between group (using normal as reference category) and the time since change in interval was included in the model to describe the direct effect of a change interval on subsequently measured EASI scores. This analysis thus accounts for an effect of a change of interval on subsequent EASI scores that builds up linearly over time. The effect of the time since start of dupilumab treatment was modeled using natural cubic splines, to account for non-linear association between scores and time since start of treatment. The number of degrees of freedom of the splines (which determines the complexity/smoothness of the non-linear association) was chosen using the Akaike Information Criterion (AIC). To account for the within-patient correlations of the repeatedly measured EASI scores, a random intercept and a random slope of time since start of treatment were included in the model. The variables age and BMI were omitted from the final analysis due to non-significance. The results of the linear mixed models for the predicted EASI scores were shown graphically, as a function of the treatment group, time since start of treatment and time since change in interval. 95% confidence intervals for the predicted values were determined. 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) (R packages: splines and lme4).

Due to the retrospective design of this study, details on the timing of EASI scoring within the dupilumab interval were lacking. Timing of EASI scoring within the 2 weeks between injections might be of particular relevance for patients whose intervals were shortened due to flaring at the end of the second week. For this reason, data of patients treated in a shortened dose regimen were only used for showing individual disease courses, but were not included in the analysis of the estimated effectiveness using LME models.

Ethical approval

Our study was exempted from evaluation by the local Medical Research Ethics Committees (NL: MEC-2017-1123; W18_097#18.123). The study conduct was in accordance with the STROBE recommendations.

RESULTS

In total, 180 AD patients were consecutively included in our study (Table 1). Patients were treated in the standard Q2W interval (n=126), a shortened QW interval (n=26), or an extended interval (n=28). In general, gender was equally distributed in all groups, and the age at start of dupilumab was not significantly different between groups (p=0.362). The majority of patients were Caucasian, while the proportions of races within the different groups were not statistically different. Although BMI was highest in the shortened interval group and lowest in the extended interval group, differences in BMI were not statistically significant. As discussed in the methods section, some patients lacked an EASI score determined at the exact time of date adjustment (shortened n=17/26; extended n=17/28).

Sustained disease control was the reason for extending the interval in twenty patients (n=20/28) (Table 1). In eight patients the interval was extended due to side effects, resulting in less side effects in three patients. Insufficient effectiveness and/or increased disease severity in the second week after injection were the reasons for shortening the dosing interval in all 26 patients. Patients were treated

Table 1. Patient characteristics

	Normal interval (q2w) (n=126)	Shortened interval (n=26)	Extended interval (n=28)	Sign.[#]
Female sex – no. (%)	57 (45)	11 (42)	15 (54)	0.665[A]
Age, years – median (IQR)	36 (26-51)	27 (22-48)	35 (28-58)	0.362[B]
Race – no. (%)				0.123 [A]
Caucasian	104 (83)	20 (77)	25 (89)	
Black	7 (6)	5 (20)	1 (3)	
Asian	10 (8)	1 (4)	1 (3)	
Other	2 (2)	0 (-)	1 (3)	
Missing	3 (2)	0 (-)	0 (-)	
BMI – median (IQR)	24.6 (22.0 – 27.4)[1]	26.0 (23.0 – 28.9) [2]	24.0 (21.8 – 25.9) [3]	0.208[B]
Age at onset AD	0 (0-10)[4]	0 (0-7)	0 (0-16)	0.768[B]
Atopic/allergic conditions – no. (%)				0.992 [A]
Asthma	85 (68)	17 (68)	19 (66)	
Allergic (rhino)conjunctivitis	101 (80)	20 (77)	23 (82)	
Allergic contact dermatitis	55 (44)[5]	13 (50) [6]	13 (46)	
Therapeutic history AD – no. (%)				0.582[A]
Cyclosporin A	109 (87)	25 (100)	28 (97)	
Methotrexate	44 (35)	12 (48)	15 (52)	

Table 1. Patient characteristics (*continued*)

	Normal interval (q2w) (n=126)	Shortened interval (n=26)	Extended interval (n=28)	Sign.[#]
Azathioprine	22 (18)	2 (8)	9 (31)	
Mycophenolic acid	46 (37)	8 (32)	10 (35)	
Weeks of treatment at interval adjustment– median, (IQR)	-	39 (27-65)	62 (47-83)	0.014[C]
Reason for interval switch – no. (%)	-			0.000[D]
Sustained disease control		0 (-)	20 (71)	
Side effects		0 (-)	8 (29)	
Insufficient effectiveness, flares		26 (100)	0 (-)	
Patients with a second dose adjustment	-			
Number of patients – no. (%)		8 (31)	8 (29)	0.860[A]
Number of weeks after first adjustment – median (IQR)		30 (18-43)	18 (13-26)	0.619[C]
Reasons for second dose adjustment – no. (%)	-			0.077[D]
Insufficient disease control		4 (50)	8 (100)	
Side effects		2 (25)	0 (-)	
Sustained disease control		2(25)	0 (-)	

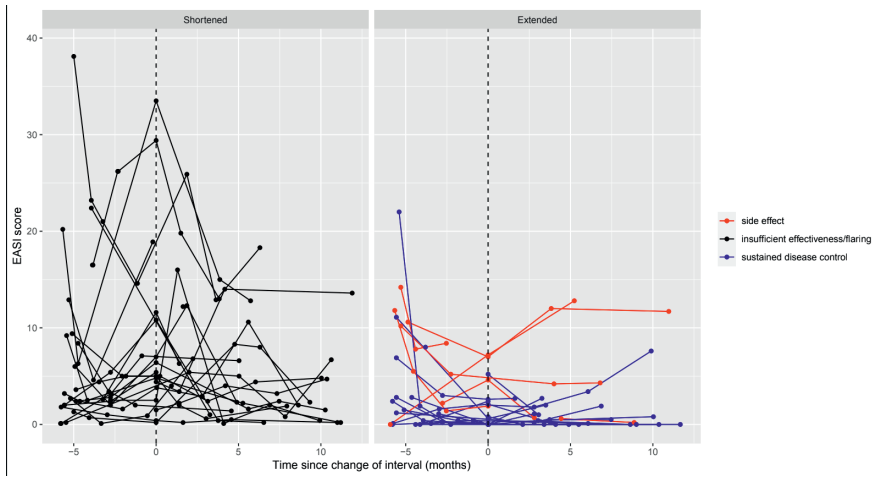
Missing values: [1]n=3, [2]n=16, [3]n=5, [4]n=6, [5]n=29, [6]n=7
[A]chi-square, [B]Kruskal-Wallis Test, [C]Mann Whitney U test, [D]Fisher's exact

for a median of 39 weeks (IQR 27-65) when the interval was shortened, and 62 weeks (IQR 47-83) at the time of interval extension. Twenty of the patients with an extended interval persisted until end of study, while eight patients switched again to the Q2W interval before the end of study due insufficient disease control with extended intervals. A second interval switch was applied in eight of the patients treated in a shortened interval (8/26). This was due to insufficient disease control (n=4), side effects (n=2), or sustained disease control (n=2).

Individual disease courses of patients treated with different dose regimens are shown in figure 1. Patients with an extended interval had relatively low EASI scores at the time of adjustment (range: 0-7) and the majority of patients showed continuous effectiveness after adjustment. Patients with extended intervals due to side effects (red lines), showed worse EASI scores after interval extension compared to patients with extended intervals due to sustained disease control (blue lines). In patients with shortened intervals, the severity scores at the time of adjustment were more widespread ranging from 0-34, and follow-up showed a more variable disease course compared to patients with an extended interval. This might be the result of variance in timing of EASI scoring within the 2-week treatment interval.

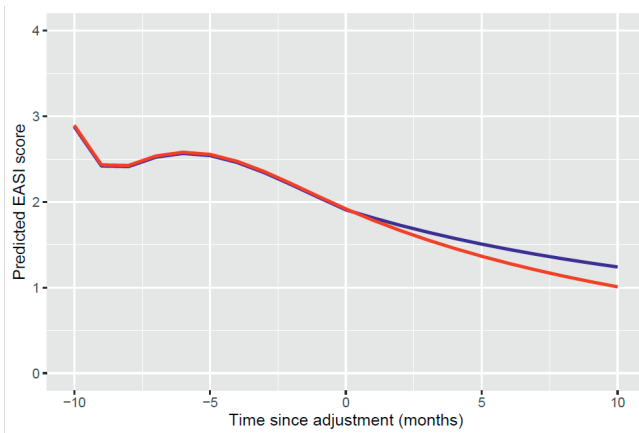
Based on the LME model, we found an overall continuous improvement of EASI scores in time, regardless of the applied dose interval (Table S1). Our analyses showed a minor, non-significant negative effect on disease severity (i.e. worse disease) in patients with an extended interval. However, patients still improved according to EASI scores due to the overall improvement in time, resulting in sustained disease control (figure 2).

Figure 1. Disease severity of individual patients treated in adjusted dupilumab dose regimens in time



Individual disease courses of patients with a shortened interval (black), and extended interval due to sustained disease control (blue) or experienced side effects (red) were illustrated using spaghetti plots. Disease severity scores (Eczema Area and Severity Index) were shown in time, expressed as time since adjusted dose regimen.

Figure 2. Disease severity of patients treated in a standard or extended dupilumab dose regimen



The estimated severity scores of patients treated in a standard (Q2W) interval (red) or an extended interval (blue) are shown, illustrated as cubic splines. Scores are based on our LME models.

DISCUSSION

To our knowledge this is the first study investigating the effect of adjusted dose regimens on disease severity in AD patients treated with dupilumab in daily practice. In this study, dose regimens were adjusted through shared decision making between physician and patients due to reasons such as sustained effectiveness, side effects, insufficient effectiveness, or disease flares in the second week of the standard interval. Our analyses showed that patients who were treated in an extended interval showed sustained effectiveness, similar to patients with a standard interval. The effect of shortened intervals on disease severity could not be adequately analysed due to methodological limitations resulting from the retrospective design of this study.

Differences in effectiveness of several dose regimens were investigated in phase II and III trials, but results remained debatable.[4-7] Phase 2b dose-ranging trials showed that 300mg QW and 300mg Q2W dose regimens had better outcomes, but this study was not powered to directly compare different dose regimens[7]. In the LIBERTY AD SOLO-CONTINUE trial (phase III), high-responding patients who were treated with dupilumab in the (LIBERTY AD) SOLO 1 and 2 clinical trials, were rerandomized.[17] Patients were rerandomized (2:1:1:1) to continue in their original regimen of 300mg dupilumab every 1 or 2 weeks, or to cross-over to a longer dosing interval of 4, or 8 weeks for a total duration of 36 weeks. This study revealed a maintained response over time which was approximately similar in the weekly and biweekly interval. This response was numerically, but overall not statistically significant, better than the longer dosing intervals. As a result, the approved regimen of dupilumab 300mg every 2 weeks was recommended for long-term treatment.[17] In this study, an extended interval of dupilumab administration every three weeks was not investigated.

However, possibilities for any dose tapering in case of sustained disease control would be of great relevance due to the high costs associated with innovative therapies (e.g. drug costs dupilumab Q2W are approximately €15.000 per patient per year in the Netherlands). Most of the current evidence on biologic tapering results from studies evaluating the effect of adjusted dose regimens in other diseases including psoriasis vulgaris (PSO). Tapering of biologics in patients with PSO who showed stable and low disease activity or clinical remission seemed to be safe and effective, although the optimal dose tapering strategy still needs to be determined and implemented in daily practice[18-24].

At present, there are several research gaps that need further exploration in order to adequately taper drugs in inflammatory diseases such as PSO and AD. This includes the evaluation of the long-term impact of tapering on disease activity, quality of life, and safety. This might require the use of (clinical) criteria for dose tapering. However, determining strict criteria for dose tapering might be complicated in a highly heterogeneous and multifactorial disease such as AD. To take this heterogeneity of the population and disease into account, criteria should at least include several specific outcome domains (e.g. EASI, Patient-Oriented Eczema Measure), which is comparable to the treat-to-target approach as recently published. In patients in this study, dupilumab was tapered based on a shared decision making process between the healthcare provider and patient. In case of agreement on achievement of sustained disease control, the dosing interval could be extended. Shortened intervals were applied in case of insufficient disease control or a patient experiencing disease flares in the second week of their 2-week dosing interval. Supportive tools which indicate disease control, such as the Atopic Dermatitis Control Tool (ADCT) could be used. Because of the highly fluctuating nature of AD and subjectiveness of the currently used measures in AD, (biologic) predictors for successful dose-adjustment would be highly valuable. Currently, there are no data available on predictors for successful dose tapering during dupilumab treatment. In studies investigating predictors for successful dose tapering in PSO, it was found that lower body mass index (BMI) and early treatment effect turned out to be possible predictors for successful dose tapering.[25] In our study, patients who were switched to an extended interval showed a lower BMI compared with patients in the standard or shortened interval, although this was not statistically significant. However, the non-randomized design of this study does not allow for analysing predictive factors of the effect of random adjustment of the dose regimen. Still, we found that when patient and physician agreed on achieving disease control, dose adjustment was successful in the majority of patients, resulting in sustained disease control (figure 2).

There are several limitations in this study arising from the retrospective and observational design. These include the lack of standardised dose-adjustment strategies and limited observation period. Due to the observational nature of the data, it is difficult to disentangle the direct causal effect of the dose regime (e.g. a shortening of the interval would be hypothesized to lead to lower subsequent EASI scores) from the reverse causal effect that patients with more severe disease severity and thus higher EASI scores are usually not assigned extended dupilumab intervals. To account for this issue, we used LME models incorporating both fixed and random effects. The independent variable group (e.g. gender, time since start treatment,

dose regimen adjustment) served to model the statistical association due to the aforementioned reverse causal effect of EASI scores on treatment interval. Another limitation due to the retrospective design of this study was the inability to model the effect of a shortened interval in time. Since information about the timing within the treatment interval at the time of EASI scoring was lacking, this could have limited the validity in illustrating the estimated effect on EASI scores in time from the moment of dose adjustment.

In conclusion, our study demonstrated that extended dupilumab dose intervals, based on a shared decision making process between patients and physicians, seems to be effective in daily practice. Unfortunately, the effect of shortened intervals could not be determined due to methodological limitations of this study. Future studies in daily practice are warranted to determine the optimal dose-adjustment eligibility criteria, dose regimens, and definitions of successful dose adjustment.

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Table S1. Statistical parameter Linear Mixed-Effects Model

	Estimate	Conf. low	Conf. high	p-value
Intercept	1.939	1.689	2.189	5.209e-39
Adjustments_simple Extended	-0.005123	-0.3675	0.3573	9.779e- 1
ns(Time_since_start_treatment, 4)1	-1.164	-1.420	-0.9081	2.456e-18
ns(Time_since_start_treatment, 4)2	-1.605	-2.050	-1.160	4.345e-12
ns(Time_since_start_treatment, 4)3	-3.966	-4.677	-3.255	2.580e-22
ns(Time_since_start_treatment, 4)4	-2.331	-3.591	-1.071	3.496e- 4
Gender - male	0.3768	0.1139	0.6397	5.538e- 3
Adjustments_simple_time_dependent extended	0.01947	-0.04827	0.08720	5.738e- 1

lmer(log_EASI_score ~ Adjustements_simple + Adjustments_simple_time_dependent:Time_months_since_adjustment + ns(Time_since_start_treatment,4) + Gender + (Time_since_start_treatment| Rnumber) , data=data, REML = TRUE, control = lmerControl(optimizer ='optimx', optCtrl=list(method='nlminb')))

Chapter 6

An approach for the transition from systemic immunosuppressants to dupilumab

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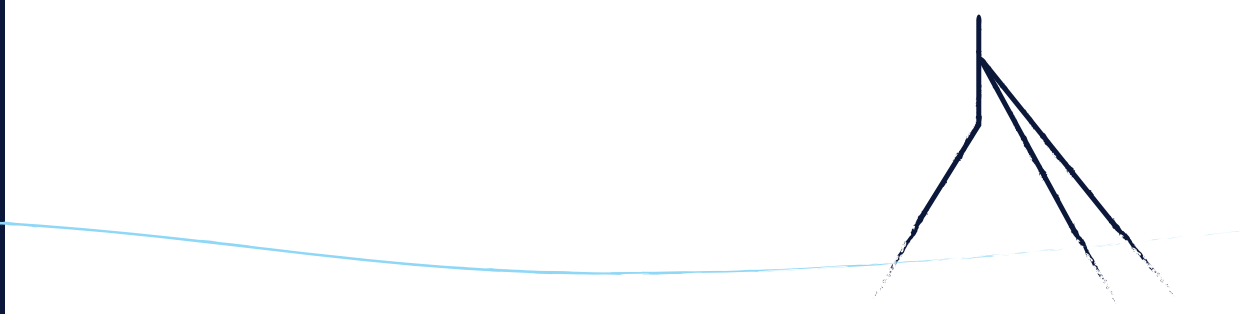


Dear Editor,

Atopic dermatitis (AD) is a complex and heterogeneous chronic inflammatory skin disease. A subset of patients require systemic immunosuppressants including cyclosporin A (CsA), azathioprine (AZA), mycophenolate mofetil (MMF), mycophenolic acid (MPA), and methotrexate (MTX).[1] Dupilumab is the first biologic for treatment of AD, mostly started in patients with insufficient effectiveness or side effects of systemic immunosuppressants. In daily practice, approximately 65% of patients are still using systemic immunosuppressants when starting dupilumab.[2] Although a significant reduction in itch can be present by week 2, clinically relevant AD improvement continues until at least 8-12 weeks of dupilumab treatment.[2, 3] Additionally, abrupt discontinuation of systemic immunosuppressants is unpreferable due to a possible rebound phenomenon.[1, 3-6] We found that tapering the immunosuppressants after start of dupilumab results in a seamless transition between therapies. In our patients (n=88), we did not find side effects resulting from this combination treatment.[2, 5]

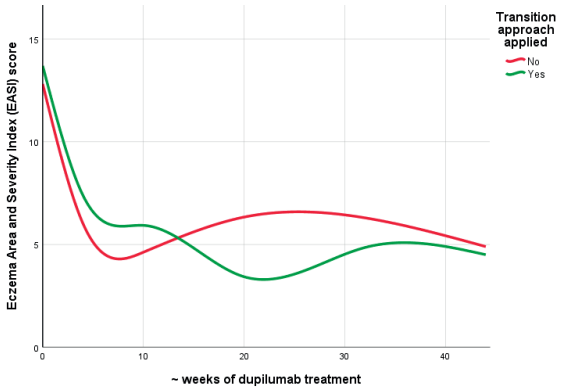
Based on clinical experience in 44 patients, we propose an approach for the transition from conventional systemic immunosuppressants (excluding oral corticosteroids) to dupilumab (Table 1, Fig. 1). This approach is only applicable in absence of serious side effects. The timing of consultations (live/telemedicine) can be adjusted to local protocols. We recommend to assess disease control at every visit using Atopic Dermatitis Control Tool (ADCT) or Recap of atopic eczema (RECAP).[7, 8] However, it should not replace shared decision making between physician and patient. Note that this is a clinical guideline based on expert opinion and that decisions can be affected by many factors, e.g. current symptoms, season, patient's mental state, relative patient burden of signs and symptoms, and experiences with tapering the immunosuppressant. We therefore only aim to provide guidance, but no strict cut-off levels for achieving disease control. Additionally, a prospective study on the utility of this approach would be of added value for validating this transition approach.

Table 1. Approach for transition from conventional immunosuppressants to dupilumab monotherapy.

		✔ Disease control ✔	✘ No disease control ✘
	Week 0-8	**Week 8 - …**	
CsA	Maintain dose *(eg: 2dd100mg)*	**Every 2 weeks** (wk 10, 12, 14, 16, 18) 25% dose reduction (of dose at start) *Earliest discontinuation: 14 weeks of dupilumab treatment* *(e.g.: 2dd75mg (wk 8-10) – 2dd50mg (wk10-12) – 2dd25mg (wk 12-14) – discontinue (wk 14))*	Current dose used for (≈) <8 weeks: Continue immunosuppressant at same dose for another 4 weeks. Current dose used for (≈) > 8 weeks: Consider continuation of concomitant immunosuppressant at the lowest possible, effective dose on the long term. *and/or* Consider discontinuation of dupilumab treatment.
MTX **AZA** **MPA** **MMF**	Maintain dose *(eg: MTX 15mg weekly)*	**Every 4 weeks** (wk 12, 16, 20, 24, 28) 50% dose reduction (of dose at start) *Earliest discontinuation: 12 weeks of dupilumab treatment* *(e.g.: 7.5mg weekly (wk 8-12) – discontinue (wk 12))*	

All steps are guided by the assessed disease control and physicians' and patients' shared decision making. Atopic Dermatitis Control Tool (ADCT) or Recap of atopic eczema (RECAP) can be used to determine disease control. Note that this is a general approach for several systemic immunosuppressants used in the treatment of moderate to severe AD, including: CsA, MTX, AZA, MPA, and MMF. Some formulations will not allow e.g. 50% of the original dose, or doses may not be effective. We suggest to make a rational treatment decision based on experience with the specific immunosuppressant.

Figure 1. Disease severity of patients with and without the use of the proposed transition approach



Green line: Eczema Area and Severity Index (EASI) scores for AD patients (n=44) with concomitant systemic immunosuppressants that were slowly tapered and discontinued after at least 12–14 weeks of dupilumab treatment, according to the transition approach described in the current article. *Red line*: EASI scores for AD patients (n = 61) that discontinued immunosuppressants at the start or in the first 12–14 weeks of dupilumab treatment. EASI scores were measured at baseline, after approximately 4 weeks, 8–12 weeks, 16–24 weeks, 28–36 weeks and 40–48 weeks of treatment.

For all systemic immunosuppressants, we recommend to maintain the dose that was used at start of dupilumab for the first 8 weeks. After 8 weeks, the dose of the immunosuppressant can be reduced in case of disease control. From that moment, the approach differs for patients using CsA and other immunosuppressants in order to prevent a rebound phenomenon in CsA treated patients. In patients treated with MTX/AZA/MMF/MPA, the dose can be reduced to ~50% until the next visit (at approximately 12 weeks). In good responders, we suggest to discontinue the immunosuppressant after 12 weeks of dupilumab treatment (applicable in ~40% of our patients). Due to the high risk of a rebound phenomenon, we propose tapering more gradually in CsA treated patients. In case of disease control after 8 weeks, the dose can be reduced to ~75% of the dose at start of dupilumab treatment. In good responders, the CsA dose will be reduced to ~50% after 10 weeks of treatment, and subsequently ~25% after 12 weeks of treatment. CsA can be discontinued in good responders after approximately 14 weeks of treatment (applicable in ~60% of our patients).

In case of insufficient disease control at a visit, immunosuppressants will be continued at the same dose until the next visit. Additionally, topical treatment using moisturizers, topical corticosteroids and calcineurin inhibitors should be optimized. Dupilumab discontinuation or continuation of the systemic immunosuppressants on the long term at the lowest possible dose should be considered when: (1)

disease control is not reached after two subsequent visits with a similar dose, (2) patients are treated with dupilumab for at least 12 weeks, and (3) topical treatment is optimal. With many new drugs being developed, this might be also the point where a switch to a different drug can be considered.

In conclusion, we propose a practical treatment approach for the transition from systemic immunosuppressants to dupilumab based on shared decision making.

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Chapter 7.1

Clinical and histopathological characterization of paradoxical head and neck erythema in patients with atopic dermatitis treated with dupilumab: a case series

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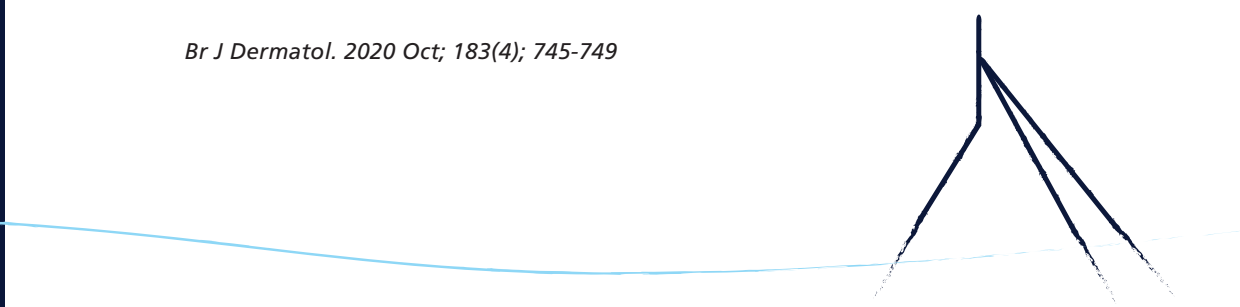


ABSTRACT

Dupilumab is the first biologic registered for the treatment of atopic dermatitis (AD). We report on seven AD patients presenting with a paradoxical head-neck erythema which appeared 10 to 39 weeks after start of dupilumab treatment. Patients presented with a relatively sharply demarcated, patchy erythema in the head and neck area that showed no or less scaling compared to their usual eczema. Only one patient experienced symptoms of itch and burning, although this was notably different from his pre-existent facial AD. Except for a notable "red face", eczema on other body parts had greatly improved in six out of seven patients with a mean NRS treatment satisfaction of 9/10 at time of biopsy. Treatment of the erythema with topical and systemic drugs was unsuccessful. Despite the presence of this erythema, none of our patients discontinued dupilumab treatment.

Lesional skin biopsies showed an increased number of ectatic capillaries, and a perivascular lymphohistiocytic infiltration in all patients. In addition, epidermal hyperplasia with elongation of the rete ridges was observed in four patients, resembling a psoriasiform dermatitis. Additional immunohistochemical stainings revealed increased numbers of plasma cells, histiocytes and T-lymphocytes. Interestingly, spongiosis was largely absent in all biopsies. We report on AD patients treated with dupilumab developing a paradoxical erythema in a head-neck distribution. Both clinically and histopathologically we found a heterogeneous response, which was most suggestive of a drug-induced skin reaction.

Dupilumab is the first biologic registered for treatment of moderate-to-severe atopic dermatitis (AD). By binding to the IL-4 receptor alpha chain, dupilumab blocks IL-4 and IL-13 signaling, thereby modulating the T-helper (Th)2-mediated inflammation in AD.[1] In clinical trials, conjunctivitis, herpes infections, and injection-site reactions were found to be the most frequently observed side effects.[1] Currently, only one case of paradoxical, refractory erythema in a head-neck distribution that developed during dupilumab treatment is reported.[2]

Here, we describe a series of seven AD patients who were treated with dupilumab and developed a paradoxical erythema in a head-neck distribution, differing from their usual AD lesions. Until now, we did not systematically check for this erythema in our dupilumab treated AD patients (n>150). However, we increasingly seem to observe this phenomenon. We recorded medical history, patient- and physician reported outcome measures, clinical symptoms and obtained lesional skin biopsies for histological examination.

The patient characteristics are summarised in Table 1. The erythema appeared after at least 10 weeks of dupilumab treatment and patients were treated with dupilumab for 12-71 weeks at time of biopsy. Concomitant treatment included topical corticosteroids (TCS) and topical calcineurin inhibitors (TCI) but no systemic immunosuppressants. There were no relevant (non-atopic, dermatologic) comorbidities and patients did not use any other systemic drugs. Prior to dupilumab treatment, six out of seven patients suffered from erythematosquamous lesions in the head and neck area, associated with symptoms of itching and burning in five of these patients. Patients noted that the signs and symptoms of the paradoxical erythema were different from their regular eczema. Strikingly, 6/7 patients did not report any symptoms of itch and burning in the head and neck area during dupilumab treatment.

During dupilumab treatment, patients presented with a sharply demarcated, patchy erythema in the head and neck area that showed less or no scaling compared to their usual eczema (Figure 1a-b). Follicular accentuation was absent. Only one patient who presented with scaling lesions experienced symptoms of itch and burning, although notably different from the pre-existent symptoms. Treatment of the erythema with topical and systemic drugs, including potent TCS, TCI, emollients, antifungal medication, antibiotics, antihistamines, and oral corticosteroids was unsuccessful (Table 1). Although the lesions did not respond to treatment, all patients continued dupilumab treatment.

Table 1. Patient and clinical characteristics (n=7)

	Patient						
	1	2	3	4	5	6	7
Patient characteristics							
Sex	M	F	M	M	M	M	M
Age, years	28	29	26	19	58	35	46
Disease duration, years	16	29	26	19	52	35	46
Fitzpatrick skin type	2	3	2	2	3	2	2
Asthma/Allergic rhinoconjunctivitis	+ / +	+ / +	– / +	+ / +	– / +	+/+	+/+
Allergic contact dermatitis[a]	+	–	–	+	N.A.	N.A.	–
Occupation, hobbies	Office job	Office job	Biologic crop control, soccer	Student	Warehouse worker	PE teacher, tenniscoach	Salesman
Previous systemic immunosuppressants	CsA, MMF, AZA, MTX, APR, UST, prednisone	CsA, prednisone	CsA, prednisone	CsA, AZA, prednisone	CsA, MTX, prednisone	CsA, MTX, prednisone	CsA, MTX, prednisone
Clinical characteristics							
Onset of erythema, weeks of dupilumab treatment	39	28	16-29	16-28	10-22	20	11
Treatment duration at time of biopsy, weeks	49	53	42	51	22	71	12
Signs & symptoms before dupilumab *(+/-)*							
Erythema	+	+	+	+	-	+	+
Scaling	+	+	+	+	-	+	+
Itch	+	-	+	+	-	+	+
Burning sensation	+	-	+	+	-	+	+

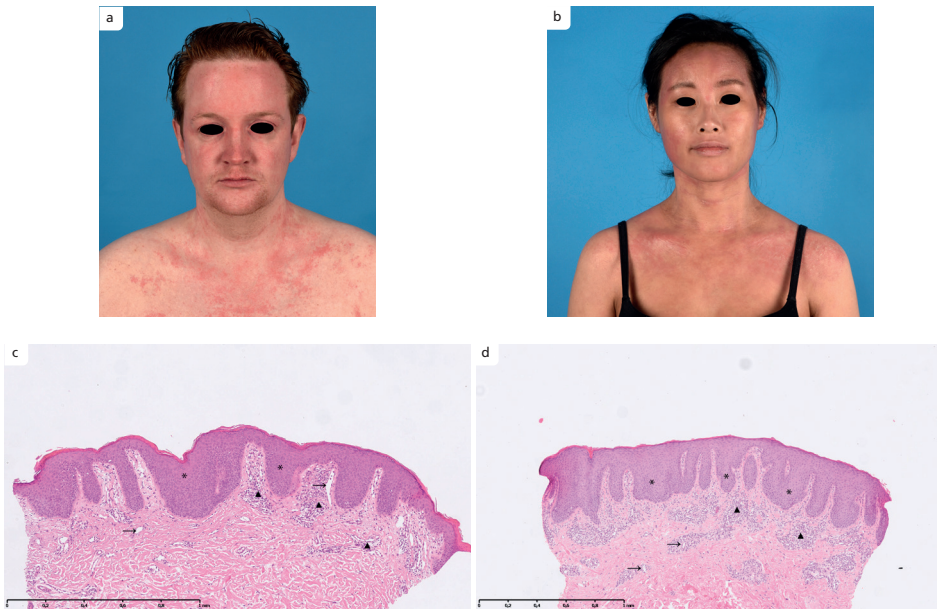
Table 1. Patient and clinical characteristics (n=7) (*continued*)

	Patient						
Signs & symptoms of paradoxical erythema *(+/-)*							
Erythema	+	+	+	+	+	+	+
Scaling	+	+/-	-	-	-	-	-
Itch	+ [b]	-	-	-	-	-	-
Burning sensation	+ [b]	+/-	-	-	-	-	-
Worsening influcence of.,. nfluence of *(+/-)*							
UV	-	-	+	-	-	-	-
Alcohol	-	N.A.	-	-	-	-	-
Smoking	-	N.A.	N.A.	N.A.	N.A.	-	-
Re-testing allergic contact dermatitis [c]	N.A.	-	-	N.A.	N.A.	+	N.A.
Topical prescriptions [d,e]	Class 3-4 TCS, TCI, emollients, ivermectine	Class 3-4 TCS, emollients	Class 3-4 TCS, emollients, fusidic acid	Class 3-4 TCS, emollients	Class 3-4 TCS, emollients	Class 3 TCS, TCI, emollients	Class 5 TCS
Systemic prescriptions [d]	prednisone	prednisone	antifungals antibiotics antihistamine	antihistamine	none	none	none

CsA, cyclosporin A; MMF, mycophenolate mofetil; AZA, azathioprine; MTX, methotrexate; APR, apremilast; UST, ustekinumab; TCS, topical corticosteroids; TCI, topical calcineurin inhibitors; N.A., not applicable

[a]Epicutaneous patch-proven allergic contact dermatitis, tested prior to dupilumab treatment; [b]symptoms were notably different from pre-existing situation; [c]Epicutaneous patch-proven allergic contact dermatitis, (re)tested after onset of erythema; [d]Prescribed for head-neck erythema; [e]WHO classification for topical corticosteroids.

Figure 1a-d. Clinical pictures (a,b) of paradoxical erythema in a head-neck distribution with corresponding histological H&E staining (c, d) of lesional biopsies



(a) Patient 1: 28 year old male patient showing a relatively sharply demarcated, minimally scaling, patchy erythema of the face and neck (scalp not affected) which was associated with burning and itching, but notably different from his usual eczema. (b) Patient 2: 29 year old female patient showing a minimally scaling, patchy erythema of the face and neck (scalp not affected) which was asymptomatic. (c,d) Histological examination of lesional skin biopsies of subjects 1 (c) and 2 (d), both obtained from the neck, revealed psoriasiform epidermal hyperplasia with bulbous elongated rete ridges (*), increased numbers of ectatic capillaries in the papillary dermis (→) and a moderate perivascular lymphocytic infiltrate (▲). Interestingly, spongiosis was largely absent in all biopsies.

All patients experienced an initial clinically relevant reduction of the total Eczema Area and Severity Index (EASI) score (Table S1). However, in all seven patients, disease severity scores increased again after 10-39 weeks of treatment. In the same period, all patients gradually developed an erythema specifically in the head and neck region which was reflected by a disproportional increase of the head-neck EASI subscore (Table S1). Despite the development of this erythema, the mean NRS treatment satisfaction rated by patients at time of biopsy was still 9 on a 10-point scale.

Histopathologic examination of lesional skin biopsies (n=7) included H&E (Hematoxylin & Eosin) (Figure 1c-d) and immunohistochemical stainings for CD3, CD20, CD68, CD138 and CD117 (Table S2). Histopathology showed epidermal hyperplasia with bulbous elongated rete ridges, increased numbers of ectatic capillaries in

the papillary dermis and a moderate perivascular lymphocytic inflammation reminiscent of a psoriasiform dermatitis in four patients (Figure 1c-d). Biopsies from the other three patients also showed increased ectatic capillaries and perivascular lymphocytic exocytosis, but no epidermal hyperplasia. Overall, a small number of eosinophils was found, and neutrophils and melanophages were largely absent. We found normal numbers of mast cells (CD117), T-cells (CD3) and histiocytes (CD68). There were variable numbers of plasma cells (CD138), but B-cells (CD20) were largely absent (Table S2). Surprisingly, spongiosis was largely absent in all biopsies.

DISCUSSION

We describe a paradoxical erythema in a head-neck distribution that developed in AD patients during dupilumab treatment. Histopathology showed a psoriasiform hyperplasia in four out of seven patients, with ectactic capillaries in six out of seven patients. Interestingly, spongiosis was absent in five out of seven patients. Although, the histological findings could represent an atypical manifestation of chronic AD, the clinical manifestation with a sharply demarcated, patchy erythema, and absence of itch was not typical for AD.[3] Although these patients were very satisfied with their overall treatment result, it has been shown that involvement of the face or neck are associated with higher patient-perceived importance of almost or complete skin clearance.[4]

The histopathology of acute AD lesions is characterized by spongiosis and perivascular lymphocytic and eosinophilic infiltrates.[3] Subacute and chronic lesions show acanthosis, sometimes in a psoriasiform pattern, hyper- and parakeratosis, fibrosis, spongiosis, dense infiltrates of mononuclear cells, eosinophils and increased mast cells.[3] Interestingly, we found that most of these histopathological hallmarks of AD were missing in the biopsies. Spongiosis as well as mononuclear, mast cell and eosinophilic infiltrates were mostly absent, confirming our clinical observation that these are not typical AD lesions.

AD has been hypothesized to be a biphasic T-cell driven disease, with a predominance of Th2 cytokines in the acute phase and increased expression of Th1/Th17/Th22 cytokines in the chronic phase.[5] As dupilumab targets IL-4RA, it blocks the key signaling pathways for Th2 T-cell differentiation.[1] Blocking the Th2 pathway could hypothetically result in a shift towards a more Th1/Th17/Th22 dominated response, resulting in the psoriasiform reaction pattern that we observed.[6] Fowler et al.

(2019), recently reported the development of psoriatic lesions during dupilumab treatment in two patients,[7] but in contrast to our findings, they describe typical psoriasis lesions that were not located in the head-neck region.

Because we only found this paradoxical erythema in a typical head and neck distribution, we also considered allergic contact dermatitis (ACD), *Malassezia furfur* associated head and neck dermatitis, *Demodex* associated rosacea like dermatosis, and a drug-induced photosensitivity reaction. Patch testing for allergic contact dermatitis (ACD) was performed in three patients during dupilumab treatment but only one patient showed postive patch tests to lanolin and cocamidopropyl betaine. However, avoidance of the allergens did not improve this erythema and the histopathological findings were not suggestive of ACD.[8] It has been suggested that (co)sensitization to human and/or fungal (including *Malassezia* spp.) enzyme superoxide dismutase might play an important role in the pathogenesis of atopic dermatitis and associated head and neck dermatitis.[9,10] In murine models it was recently shown that *Malassezia* induces Th17 driven inflammation.[11] In AD patients treated with dupilumab, IL-4R blockade might facilitate a Th17 dominated response. However, in these mouse models, *Malassezia* also triggered massive infiltration of neutrophils and monocytes in the skin, which we did not find in the biopsies of our patients. Increased Th17 cytokine expression could also be in favour of *Demodex* colonization, which is associated with rosacea.[12] However, the clinical presentation in our patients was not typical for rosacea. In addition, histological features of rosacea were absent.[13] The distribution of the lesions in our patients was also suggestive of a drug induced photosensitivity reaction, but none of our patients was using a known photosensitive drug and remarked influence of UV-radiation on the erythema was denied.[14] Furthermore, the most common histological pattern found in drug induced photosensitivity reactions is a vacuolar interface dermatitis,[15] which was not present in our patients.

We speculate that this paradoxical head-neck erythema is a dupilumab-induced skin reaction. From personal communication with other AD experts we know that others have also observed this phenomenon. This emphasizes the importance of daily practice registries to gain better insights in the incidences of this phenomenon. Also, further research is needed to elucidate the underlying pathophysiological process.

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Table S1. Disease severity (sub)scores at baseline and during dupilumab treatment

Patient	EASI score at t=0		EASI score at t=1		EASI score at t=2		Proportion of head and neck region in total change EASI [a]
	EASI	Head and neck subscore	EASI	Head and neck subscore	EASI	Head and neck subscore	
1	10.4	2.0	0.1 ↓↓	0.1 ↓↓	7.1 ↑ ↑ ↑	5.4 ↑↑↑	76%
2	34.8	2.4	3.2 ↓↓	0.8 ↓↓	7.6 ↑↑↑	2.4 ↑↑↑	36%
3	19.9	5.4	5.5 ↓↓	2.1 ↓↓	12.0 ↑↑↑	4.0 ↑↑	29%
4	12.3	1.2	9.3 ↓	0.3 ↓↓	11.5 ↑	2.0 ↑↑↑	77%
5	25.2	1.2	N.A.	N.A.	4.7 (N.A.)	1.5 (N.A.)	N.A.
6	18.3	1.5	5.1 ↓↓	0.9 ↓	10.2 ↑↑	2.8 ↑↑↑	37%
7	27.8	3.2	4.5 ↓↓	0.9 ↓↓	3.2 ↓	1.8 ↑↑	N.A.

EASI, Eczema Area and Severity Index; N.A., not available
↕: increase/decrease of <50% *(compared to last measurement)*
↕↕: increase/decrease of 50-100% *(compared to last measurement)*
↕↕↕: increase/decrease of >100% *(compared to last measurement)*
t=0: baseline, before start of dupilumab treatment
t=1: the last clinical assessment before onset of the paradoxical head-neck erythema
t=2: the first clinical assessment after onset of the paradoxical head-neck erythema
[a] The head and neck area accounts for 20% of the total EASI score. This means that if the total eczema would have worsened proportionally, the proportion of the EASI score in the total change would have been 20%.

Table S2. Histopathological findings in lesional skin biopsies (n=7)

	Patient						
	1	2	3	4	5	6	7
Histopathological findings							
Epidermal							
Psoriasiform hyperplasia	yes	yes	yes	no	no	no	yes
Serum	yes	no	yes	no	no	no	no
Spongiosis	yes (minimal)	no	yes	no	no	no	no
Parakeratosis	yes	no	yes	no	no	no	no
Basal vacuolisation	no	no	yes	no	no	no	yes
Lymphocytic exocytosis	scant	scant	scant	scant	scant	scant	scant
Apoptosis	no	no	no	no	no	no	no
Dermal							
Total infiltrate	moderate	moderate	moderate	moderate	scant	moderate	moderate
Level	superficial	mid-ret	deep	superficial	superficial	superficial	superficial
Perivascular	yes	yes	yes	yes	yes	yes	yes
Interstitial	no	no	no	no	no	no	no
Perifollicular	no	no	yes	yes	yes	yes	no
T-lymphocytes (CD3)	moderate	moderate	moderate	moderate	moderate	moderate	moderate
B-lymphocytes (CD20)	absent	scant	scant	absent	absent	absent	scant
Histiocytes (CD68)	moderate	moderate	moderate	moderate	moderate	moderate	moderate
Plasmacells (CD138)	scant	scant	moderate (and deep)	absent	absent	moderate	moderate
Eosinophils	scant	scant	absent	scant	scant	scant	scant
Neutrophils	scant	moderate	absent	scant	absent	absent	absent
Mast cells (CD117)	normal	normal	normal	normal	normal	normal	normal
Melanophages	absent	absent	absent	scant	scant	scant	scant
Vessels							
Number	increased	increased	increased	normal	increased	normal	increased
Ectatic	yes	yes	yes	yes	yes	no	yes
Other		pustule in follicle					

Chapter 7.2

Effects of dupilumab treatment on patch test reactions: a retrospective evaluation

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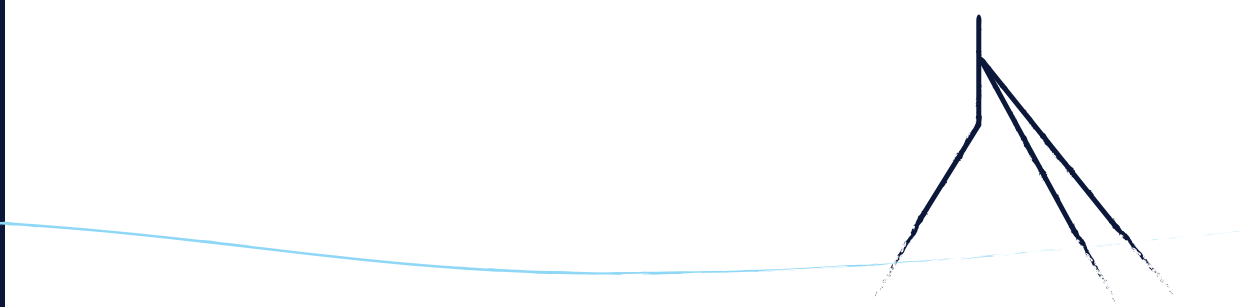

ABSTRACT

Background Literature about the impact of dupilumab on patch testing is sparse and controversial.

Objectives To evaluate the reliability of patch testing in dupilumab treated patients with atopic dermatitis (AD).

Methods We conducted a cohort study from August 2017 until May 2019 in Rotterdam, The Netherlands and in Chicago, IL USA. AD patients treated with dupilumab who had a positive reaction in a patch test conducted prior to dupilumab treatment and who were re-tested during dupilumab treatment (both tests according to ICDRG criteria) were included. We reported on the reproducibility of positive reactions in the first patch test, elicited by allergens that were re-tested during dupilumab treatment.

Results Twenty patients were repeatedly patch tested. In the first patch test, 37 allergens elicited 56 positive reactions. Thirty-seven of these 56 positive reactions, were negative at re-testing. Additionally, we found three indeterminate (?+) reactions at re-testing. None of the patients had stronger patch test reactions during dupilumab treatment.

Conclusions Only 29% of the positive patch test reactions in the patch tests conducted prior to dupilumab treatment, could be confirmed during dupilumab treatment. Therefore, this study suggests that patch test reactions in dupilumab treated AD patients might be suppressed, possibly leading to false-negative reactions.

INTRODUCTION

Atopic dermatitis (AD) and allergic contact dermatitis (ACD) are complex immunological conditions affecting up to 10% and 20% of the general population, respectively.[1, 2] ACD is a type IV (delayed-type) T cell-mediated hypersensitivity reaction that is caused by repeated or prolonged exposure of contact allergens to the skin and typically presents with erythematous and pruritic patches in an exposure-dependent distribution.[3] Epicutaneous patch testing is the gold standard for diagnosing ACD by indicating the causative allergens.[4] Although reproducibility rates of positive patch test reactions vary according to literature (56-96%), it is thought that allergy patch testing is reasonably reproducible as long as inconsistencies in methodology are minimized.[5-8] The primary management of ACD is avoidance of the allergen(s).[9] Limited data shows efficacy of topical corticosteroids or topical calcineurin inhibitors in ACD, but evidence regarding the effectiveness of systemic immunosuppressive or -modulating agents or phototherapy assessed in ACD is currently lacking.[10]

The relation between AD and ACD is complex, not completely understood, and multifactorial.[11] It has been suggested that ACD is at least as common in patients with AD as in the general population.[12-15] The potentially shared immunological pathways may aggravate and increase the probability of contact sensitization in patients with AD. It is hypothesized that some allergens evoke immunological pathways that more closely overlap with AD than others.[16] Additional factors that might play a role in the association between AD and ACD are the downstream effects of Th2 cytokines (including IL-4, IL-5, IL-13, and IL-31) that may contribute to a skin barrier disruption which facilitates allergen penetration.[3, 17, 18] Additionally, frequent application of creams and ointments containing contact sensitizers might also play a role.[19]

Recently, dupilumab, the first biologic for the treatment of AD which inhibits the effects of IL-4 and IL-13, has been approved. It has been suggested in previous case reports that dupilumab might also be an effective and safe treatment for (comorbid) ACD.[18] However, literature about the impact of dupilumab on patch testing and the effect on patients with AD and comorbid ACD is sparse and controversial.[20] In addition, development of erythema that is strictly located at the head and neck area is reported as a phenomenon that becomes notable during dupilumab treatment.[21] There are reports of experts debating on ACD as the major reason for this facial erythema.[22] However, several other hypotheses, including dupilumab-induced skin reactions, *Malassezia furfur* associated head and neck dermatitis

or *Demodex* associated rosacea-like dermatosis were suggested.[21, 23] Distinction of ACD from other causes of the erythema in these patients and patients with a general suboptimal response to dupilumab treatment might be of great clinical interest. However, the reliability of patch testing in dupilumab treated patients remains unclear.

Here, we report our data and experiences on the reliability of patch testing in dupilumab treated AD patients who had a positive reaction in an epicutaneous patch test (PT) conducted prior to dupilumab treatment.

METHODS

Study design and patients

We conducted a retrospective cohort study from August 2017 until May 2019 in the Erasmus MC University Medical Center, Rotterdam, The Netherlands and Northwestern Medicine, Chicago, IL USA. This study was not subject to evaluation by the local Medical Research Ethics Committees because all data was collected as part of standard of care. Patients were eligible to participate in this study if they were aged ≥18 years, having AD in accordance to the Hanifin and Rajka diagnostic criteria, and had at least 1 positive reaction in a previous PT conducted before the start of dupilumab treatment, elicited by an allergen that was re-tested during dupilumab treatment (after at least 12 weeks of treatment). Detailed results regarding these PTs including strength of reactions (according to ICDRG criteria: +++;++;+;?+;-) had to be available. Dupilumab was administered subcutaneously (300mg) every other week, after an initial loading dose of 600mg. Patients were excluded if they used systemic glucocorticosteroids dosed >10 mg per day within 2 weeks prior to testing, had sun(bed) exposure 2 weeks prior to patch testing, used topical corticosteroids/calcineurin inhibitors/emollients on the intended place of patch testing 48 hours prior to testing, or when having eczema on the intended PT area. The use of any other relevant concomitant drugs was recorded. Patients who met the inclusion criteria and gave consent to publish information relating to them were consecutively included.

Study procedure

Results of PTs conducted prior to dupilumab treatment (referred to as first PT), were obtained (intra- and extramural) after written approval of the included patients. During the first PT, the Allergeaze European Baseline Series (Rotterdam) and Allergeaze American Core Series (Chicago), with possible expanded series were ap-

plied. All PTs during dupilumab treatment, after this referred to as second PT, were conducted in our clinics. PTs were conducted using van der Bend® Patch Test Chambers (Van der Bend BV, Brielle, The Netherlands) with allergens from allergEAZE allergens® (Brial Allergen gmbH, Greven, Germany). Possible reactions were read on day 2 and day 3, in accordance with the recommendations of the ICDRG criteria.[24] All tests were performed in our clinics and were assessed and interpreted by the same medical team, consisting of an ACD-experienced dermatologist assisted by specialized dermatology nurses. Patches were either applied on the upper back or the forearm, depending on the number of patches and were covered with hypoallergenic tape (Medipore™, 3M). On day 2, the patches were removed and readings were performed by a specialized dermatology nurse. Patients with patches on their arm could optionally be instructed to remove the patches themselves. They were asked to mark the patch sites and to make standardised photographs directly after removing the patches. These photographs were e-mailed to our medical team and possible reactions were determined. On day 3, all patients consulted our dermatologist and present reactions were determined. Test results defined as ?+ were considered indeterminate and neither classified as positive nor negative. Patients were informed of the possibility of a delayed reaction and were instructed to make an appointment for day 7 or to (let someone) check the tested sites on day 5–7 and visit our dermatologist the same day in case of (doubtful) signs or symptoms (e.g., itch/burning sensations/erythema/papules/vesicles). Additionally, patients were instructed to continue allergen avoidance during dupilumab treatment similar to the situation before they started dupilumab treatment, even if all reactions turned negative in the second PT.

RESULTS

In total, 20 patients were patch tested prior to, and during dupilumab treatment (Rotterdam: n=16; Chicago: n=4). Table 1 shows that the majority of patients were female (14/20=70%) with a mean age of 51 years (SD=16). Patients had a history of AD for at least 4 years, most frequently with an onset of AD in their first year of life (11/20=55%). Most patients reported a medical history of asthma (12/20=60%), allergic rhinoconjunctivitis (16/20=80%), and food allergy (10/20=50%).

Table 1. Patient characteristics

Characteristic	Cohort (n=20)
Age, years - mean (SD)	51 (16)
Female sex – n (%)	14 (70)
BMI - mean (SD)[1]	26.4 (6)
Race – n (%)	
White	16 (80)
Asian	4 (20)
Age of onset AD	
Years – median (IQR)	0 (0-12)
0 - <2 years – n (%)	11 (55)
2 - <6 years – n (%)	2 (10)
6 - <18 years – n (%)	3 (15)
≥18 years – n (%)	4 (20)
Atopic/allergic conditions – n (%)	
Asthma	12 (60)
Allergic (rhino)conjunctivitis	16 (80)
Food allergy	10 (50)
Family history – n (%)	
Atopic dermatitis[2]	9 (45)
Asthma[2]	8 (40)
Allergic (rhino)conjunctivitis[3]	11 (55)
Time between patch tests, years – median (IQR)	5.5 (2-8)
Duration of dupilumab treatment at time of second patch test, weeks – mean (SD)	36 (15)
Clinic (second patch test)	
Erasmus MC University Medical Center, Rotterdam	16 (80)
Northwestern Medicine, Chicago	4 (20)
Distribution of recalcitrant dermatitis prior to dupilumab – n (%)[a]	
Generalized	4 (20)
Hand	9 (45)
Head-neck	10 (50)
Feet	4 (20)
Distribution of recalcitrant dermatitis during dupilumab – n (%)[a]	
Generalized	1 (5)
Hand	2 (10)
Head-neck	7 (35)
Feet	2 (10)
No recalcitrant dermatitis	9 (45)

SD, standard deviation; BMI, body mass index; AD, atopic dermatitis; IQR, interquartile range.
Missing data: [1]n=6 (6%), [2]n=2 (13%), [3]n=3
[a] Multiple recalcitrant locations in one patient possible (prior to dupilumab: 2 locations: n=5; 3 locations: n=1 / during dupilumab: 2 locations: n=1)

In the first PT, a median number of 2.5 positive patch test reactions per patient was found (IQR 1-4; range 1-8). A total of 37 different allergens elicited a + or stronger reaction, resulting in 56 positive reactions (Table 2, Table 3). At the time of the

Table 2. Results of epicutaneous patch tests conducted prior to (PT1) and during dupilumab treatment (PT2) – stratified by tested allergens

	Subject number	1	2	3	4	5	6	7	8
	Patch test (PT) 1 / 2	1 / 2	1 / 2	1 / 2	1 / 2	1 / 2	1 / 2	1 / 2	1 / 2
	Time between PTs (years)	3	2	2	17	13	7	3	7
	Systemic therapy	- / dupi	AZA / dupi	- / dupi	- / dupi +myf	- / dupi	- / dupi	csa / mtx+dupi	- / dupi
Metals	nickel sulfate hexahydrate						+ / -	++ / -	+ / -
	cobalt (II) chloride hexahydrate								+ / -
Fragrances	fragrance mix				+ / -	++ / -			
	fragrance mix II	+ / -							
	balsam of Peru				+ / -	++ / -			
	isoeugenol					++ / -			
Preservatives	idopropynyl butylcarbamate							+ / -	
	imidazolidinyl urea					++ / -			
	methyldibromo glutaronitrile			++ / +					
	paraben mix				+ / -				
	thimerosal					+ / -			
Rubber accelerator	carbamix			++ / +					
Woolalcohols	lanolin alcohol	++ / -						+ / -	
	wolalcohol undefined							+ / -	
Food ingredients	clove					+ / -			
	curry					+ / -			
Hair products	p-phenylenediamine					+ / -			
Adhesives	colophony			++ / +				+ / + [a]	
UV filter	benzophenone-4		+ / ?+						
Total number of positive reactions (PT1/PT2)		2 / 0	1 / 0	3 / 3	3 / 0	8 / 0	1 / 0	5 / 1	2 / 0

Table 2. Results of epicutaneous patch tests conducted prior to (PT1) and during dupilumab treatment (PT2) – stratified by tested allergens (continued)

	Subject number	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
	Patch test (PT) 1 / 2	1 / 2	1 / 2	1 / 2	1 / 2	1 / 2	1 / 2	1 / 2	1 / 2
	Time between PTs (years)	6	5	2	7	2	8	2	10
	Systemic therapy	- / dupi	- / dupi	- / dupi	-/dupi	-/dupi	-/dupi	-/dupi +csa	- / dupi
Metals	nickel sulfate hexahydrate	+ / -			+ / ?+				
	potassium dichromate			+ / +					
Fragrances	fragrance mix		+ / +				+ / -		
	fragrance mix II					+ / +			
	balsam of Peru					++ / +			
Preservatives	methylisothiazolinone							+ / +	
Rubber accelerator	carbamix						+ / -		
	2-mercaptobenzothiazole			+++ / ++					
	mercapto mix			+++ / ++					
Fabric dyes	textile dye mix			+ / ?+					
Woolalcohols	amerchol L 101					++ / -			
Adhesives	bisphenol A epoxy resin						++ / -		
Topical medications	budesonide		++ / -						
	hydrocortisone-17-butyrate								+ / -
	neomycin sulfate		+ / -						
Compositae	sesquiterpenelactone mix							+ / +	
Undefined	bicycle handlebar						+ / -		
Total number of positive reactions (PT1/PT2)		1 / 0	3 / 1	4 / 3	1 / 0	3 / 2	4 / 0	2 / 2	1 / 0

Table 2. Results of epicutaneous patch tests conducted prior to (PT1) and during dupilumab treatment (PT2) – stratified by tested allergens (continued)

	Subject number	17	18	19	20
	Patch test (PT) 1 / 2	1 / 2	1 / 2	1 / 2	1 / 2
	Time between patch tests (years)	6	10	4	5
	Systemic therapy	- / dupi	- / dupi	- / dupi	- / dupi
Metals	nickel sulfate hexahydrate gold sodium thiosulfate	++ / ++			++ / + + / -
Fragrances	balsam of Peru fragrance Mix cinnamic aldehyde	++ / - ++ / -	+ / -		
Preservatives	methylchloroisothiazolinone	++ / -			
Rubber accelerator	carba mix 1,3-diphenylguanidine			++ / + + / -	
Woolalcohols	amerchol L 101		+ / -		
Topical medications	neomycin sulfate bacitracin		+ / - ++ / +		
Total number of positive reactions (PT1/PT2)		4 / 1	4 / 1	2 / 1	2 / 1

Presentation of results is in accordance with the recommendations of the ICDRG criteria[24]: *-, negative reaction; +, weak positive reaction; ++, strong positive reaction; +++, extreme positive reaction; ?+, doubtful reaction. AZA, azathioprine; csa, cyclosporin A; mtx, methotrexate; myf, mycophenolic acid; PT1, patch test conducted prior to dupilumab treatment; PT2, patch test conducted during dupilumab treatment; dupi, dupilumab.* [a]reaction apparent after 7 days.

Vehiculum: nickel sulfate hexahydrate (5%, petr.); cobalt (II) chloride hexahydrate (1%, petr.), fragrance mix (8%, petr.), fragrance mix II (14%, petr.), balsam of Peru (25%, petr.), isoeugenol (1%, petr.), idopropynyl butylcarbamate (0.2%, vas.), imidazolidinyl urea (2%, petr.), methyldibromo glutaronitrile (0.5%, petr.), paraben mix (16%, petr.), thimerosal (0.1%, petr.), carbamix (3%, petr.) lanolin alcohol (30%, petr.), clove (10%, vas.), curry (10%, vas.), p-phenylenediamine (1%, petr.), colophony (20%, petr.), benzophenone-4 (2%, vas.), potassium dichromate (0.5%, petr.), methylchloroisothiazolinone (0.02%, water), 2-mercaptobenzothiazole (2%, petr.), mercapto mix (2%, petr.), textile dye mix (6.6%, petr.), amerchol L 101 (50%, petr.), bisphenol A epoxy resin (1%, petr.), budesonide (0.01%, petr.), hydrocortisone-17-butyrate (1%, petr.), neomycin sulfate (20%, petr.), sesquiterpenelactone mix (0.1%, petr.), bicycle handlebar (s=), gold sodium thiosulfate (0.5%, petr.), cinnamic aldehyde (1%, petr.), 1,3-diphenylguanidine (1%, petr.), bacitracin (20%, petr.)

first PT, 2 patients were being treated with systemic immunosuppressants (patient 2: azathioprine 100mg once daily, patient 7: cyclosporin A 2.8mg/kg). The median time between the first and second PT was 5.5 years (IQR 2-8; range 2-17).

In the second PT, a median prevalence of 0.5 (IQR 0-1; range 0-3) positive patch test reactions per patient was found. A total of 13 different allergens elicited sixteen + or stronger patch test reaction in 10 patients, namely: bacitracin, balsam of peru, carbamix, colophony, fragrance mix I, fragrance mix II, mercaptobenzothiazole, mercapto mix, methyldibromo glutaronitrile, methylisothiazolinone, nickel sulfate hexahydrate, potassium dichromate, and sesquiterpene lactone (Table 2). One delayed reaction (day 7) to colophony was found in patient 7. Three allergens were responsible for three indeterminate reactions (benzophenone 4, textile dye mix, and nickel sulfate hexahydrate). The second PT was conducted after a mean of 36 weeks (SD 15) of continuous dupilumab treatment. At that time, 3 patients were still using concomitant systemic immunosuppressants next to dupilumab treatment: cyclosporin A (patient 15, 0.7mg/kg in tapering schedule), methotrexate (patient 7, 10mg/wk) and mycophenolic acid (patient 4, 360mg twice-daily), respectively. During the second PTs, 11 patients had recalcitrant eczematous lesions (11/20=55%) (Table 1). Recalcitrant lesions while on dupilumab treatment were mainly located in the head-neck area (7/11=64%), followed by hands (n=2), feet (n=2), and generalized (n=1). Seven out of the 10 patients with a positive reaction in the second PT were having recalcitrant lesions.

Table 3 shows that 37 of the 56 (66%) reactions that were initially positive (first PT) turned negative at re-testing (second PT). Twelve (12/37=32%) of these reactions changed from ++ to -. In addition, 25 (25/37=68%) reactions showed a change from + to - (Table 3). The categories of allergens in which ≥75% of the reactions turned from positive to negative were: wool alcohols (5/5=100%), food ingredients

Table 3. Results of epicutaneous patch tests conducted prior to (PT1) and during dupilumab treatment (PT2) – stratified by results of PT1

		Patch test during dupilumab (PT2)					
		-	+	++	+++	?+	Total
Patch test prior to dupilumab (PT1)	+	25	6	0	0	3	34
	++	12	7	1	0	0	20
	+++	0	0	2	0	0	2
Total		37	13	3	0	3	56

Presentation of results is in accordance with the recommendations of the ICDRG criteria: *-, negative reaction; +, weak positive reaction; ++, strong positive reaction; +++, extreme positive reaction; ?+, doubtful reaction*

(2/2=100%), hair products (1/1=100%), fragrances (10/13=77%), and topical medications (4/5=80%). In contrast, the following allergens turned negative in <75% of the tests: metals (6/10=60%), preservatives (5/7=71%), rubber (2/6=33%), fabric dyes (0/1=0%), and adhesives (1/3=33%). Of the other 19 reactions that did not turn negative during the second PT, 7 showed similar reactions prior to and during dupilumab (+ to +: n=6, ++ to ++: n=1). Additionally, 9 reactions showed a decrease in intensity from +++ to ++ (n=2) and ++ to + (n=7) (Table 2). Three reactions that were determined positive in the first PT, turned into an indeterminate (?+) reaction in the second PT. None of the patients had stronger patch test reactions during dupilumab treatment. The reproducibility rate for reactions which were determined extreme positive (+++) in the first PT was 100% (2/2), although reactions turned out to be weaker (both strong positive: ++) in the second PT (Table 3). In the group of strong positive reactions (++, n=20) in the first PT, 40% (8/20) remained positive in the second PT, with a weak positive reaction (+) in 88% (7/8). The weak positive reactions (+, n=34) in the first PT showed a lower reproducibility rate in the second PT, namely 18% (6/34). Patients who had recalcitrant lesions during dupilumab treatment showed higher reproducibility rates (36%) compared to patients without recalcitrant lesions (17%).

DISCUSSION

Twenty AD patients who had a positive reaction in an epicutaneous PT conducted prior to dupilumab treatment were re-tested with prior positive-tested allergens while undergoing dupilumab treatment. In the first PT conducted prior to dupilumab treatment, 37 allergens elicited a + or stronger reaction, resulting in 56 positive reactions (Table 2, Table 3). Strikingly, only 16 of these 56 (16/56=29%) positive reactions could be replicated upon repeated patch testing during dupilumab treatment. The reproducibility rate was higher for reactions that were determined as extreme (+++, 100%) or strong positive (++, 40%) in the first PT, in comparison to reactions that were determined as weak positive (+, 18%) in the first PT. However, 56% (9/16) of the positive reactions were weaker in the second PT compared to the first PT.

The reliability of patch testing in patients treated with systemic immunosuppressants or systemic immunomodulators has not been fully elucidated. Several papers reported positive patch test reactions in patients using dupilumab and conventional systemic immunosuppressants.[18, 20, 25, 26] However, the effect of these drugs on the accuracy of patch testing has not been well established. The high percentage

(71%) of positive patch test reactions that could not be replicated during dupilumab treatment in our patients might be the result of the anti-inflammatory effect of dupilumab treatment, resulting in false-negative patch test reactions. Although Dhingra et al reported on distinct T-cell polarization responses to different allergens, we did not observe different reaction patterns between allergens thought to be Th1/Th17 or Th2 inducing.[16] Our observation that weak positive reactions (+) showed a lower reproducibility rate compared to stronger reactions (++,+++) is in line with results from a recent study.[8] However, Dittmar et al reported a much higher persistence rate of positive patch test reactions in AD (64.6%) compared to our study.[8] This observation was confirmed for the reproducibility of individual allergens or categories of allergens (Table S1).

Recent literature shows variable clinical effects of dupilumab on ACD. Three publications, reporting on eight ACD patients, showed almost complete clearance of ACD symptoms with dupilumab treatment, even after discontinuation of allergen avoidance.[18, 27, 28] However, there were also AD patients with comorbid ACD treated with dupilumab suffering from generalized flares (n=1) or localized, recalcitrant dermatitis (n=1) after exposure to known allergens.[18, 20] Although the immunological pathways underlying ACD and AD are not the same, they are largely overlapping, which may explain why targeting the shared Th2 pathway reduces ACD severity. These results suggest there could be a therapeutic role for dupilumab in the treatment of patients with (comorbid) ACD who are not able to avoid their allergens fully e.g. due to work circumstances. However, in our opinion, allergen avoidance strategies should not be omitted during dupilumab treatment. Future studies investigating patch test reactions in patients who discontinued dupilumab treatment after long term use and evaluation of the effect of dupilumab in patients with recalcitrant ACD (i.e. contact allergens of clinical relevance) would be of added value.

Limitations of this study are the retrospective and unblinded design, the absence of a control group, the different test sites, and the variable period of time between the PTs. However, the period of time between repeated PTs does not (statistically) influence reproducibility rates according to available literature.[8] Additionally, evidence on reproducibility after different periods of time for individual allergens is lacking. In our study, patients with a shorter time between the patch tests, seem to show relatively higher reproducibility rates. However, even the patients with a shorter time between patch tests showed a reproducibility rate which is much lower than reproducibility rates from literature. Furthermore, allergens with high general reproducibility rates (i.e. preservatives and rubbers) have been tested

relatively frequent in patients who have been re-tested within 3 years after the first patch test, whilst allergens with lower general reproducibility rates (i.e. metals, fragrances, and corticosteroids) were more commonly tested after a longer period of time (Table S2).[7, 8] Additionally, a possible limitation could be that PTs prior to and during dupilumab were not always conducted in the same clinic. However, we found similar results in the subset of patients that were tested in the Erasmus MC University Medical Center and Northwestern Medicine prior to and during dupilumab treatment (n=12, 28% of positive reactions in first PT reproducible) compared to the group in which the first PT was conducted in a referral center (n=8, 30% of positive reactions in first PT reproducible). Additionally, similar allergens and occlusion times were applied at our centers and referral centers. This suggests that our findings could not be explained by a discrepancy in applied reading qualities or - techniques. Although allergens tested in the first PT slightly differ between Chicago and Rotterdam, there were only 4 allergens tested solely in Chicago (1,3-diphenylguanidine, bacitracin, cinnamic aldehyde, and gold sodium thiosulfate) of which only 1 allergen (bacitracin) remained positive at re-testing. Although patients with recalcitrant lesions showed higher reproducibility rates (36%) compared to patients without recalcitrant lesions (17%), none of the positively tested allergens was unavoidable or of relevance in daily life for these patients which made a relevant contact allergy as a source for these recalcitrant lesions unlikely. Additionally, patients were instructed to avoid patch-proven contact allergens after the first PT. Since the majority of our patients is suffering from recalcitrant lesions, it might be suggested that patients suffering from recalcitrant lesions are more likely to undergo re-testing compared to patients without complaints and as a result an ascertainment bias could not be ruled out.

We showed that only 29% of positive patch test reactions observed before dupilumab treatment, could be re-elicited in AD patients using dupilumab treatment. Consequently, this study suggests that patch test reactions in dupilumab treated AD patients might be suppressed, possibly leading to false-negative reactions. Further prospective studies are warranted to elucidate the effect of dupilumab and other systemic immunosuppressive agents on patch testing in patients with AD.

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Alicia Overduin: informing patients, study procedures

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Table S1. Persistence rates of individual allergens or categories of allergens

	Persistence rates	
	Our cohort	**Literature[a]**
Categories		
metals	40%	62%
fragrances	23%	54%
preservatives	29%	78%
rubbers	67%	77%
corticosteroids	0%	44%
Individual allergens [b]		
nickel sufate hexahydrate	29% (n=2/7)	54-87%; 61% (n=27)
cobalt (II) chloride hexahydrate	0% (n=0/1)	35-57%; 35% (n=6)
fragrance mix I	20% (n=1/5)	63-64%; 64% (n=9)
p-phenylenediamine	0% (n=0/1)	69% (n=9)
potassium dichromate	100% (n=1/1)	63-100%; 100% (n=11)
carba mix	66% (n=2/3)	80% (n=8)
colophony	100% (n=2/2)	78% (n=7)
mercaptobenzothiazole	100% (1/1%)	56% (n=5)
balsam of Peru	25% (n=1/4)	63% (n=5)

[a] Dittmar D et al. Persistence of contact allergy: a retrospective analysis. Contact Dermatitis 2018; Nielsen N H et al. Persistence of contact allergy among Danish adults: an 8-year follow-up study. Contact Dermatitis 2001; Jensen CD et al. Course of contact allergy in consecutive eczema patients patch tested with TRUE Test panels 1 and 2 at least twice over a 12-year period. Contact Dermatitis 2005 [b] individually reported allergens in published articles.

Table S2. Tested categories in patient groups with different periods of time between patch tests

	Time between patch tests		
	≤3 years	**3-8 years**	**≥8 years**
Categories (no.)			
metals	2	8	-
fragrances	3	4	6
corticosteroids	-	1	1
preservatives	3	1	3
rubbers	3	3	-
Total number	11	17	10
metals, fragrances, corticosteroids[a]	5 (5/11 = 45%)	13 (13/17 = 76%)	7 (7/10 = 70%)
preservatives, rubbers[b]	6 (6/11 = 55%)	4 (4/17 = 24%)	3 (3/10 = 30%)

[a] known to have high general reproducibility rates, [b] known to have lower general reproducibility rates

Chapter 8

Presence of joint complaints during dupilumab treatment in atopic dermatitis patients: an undiscovered side effect?

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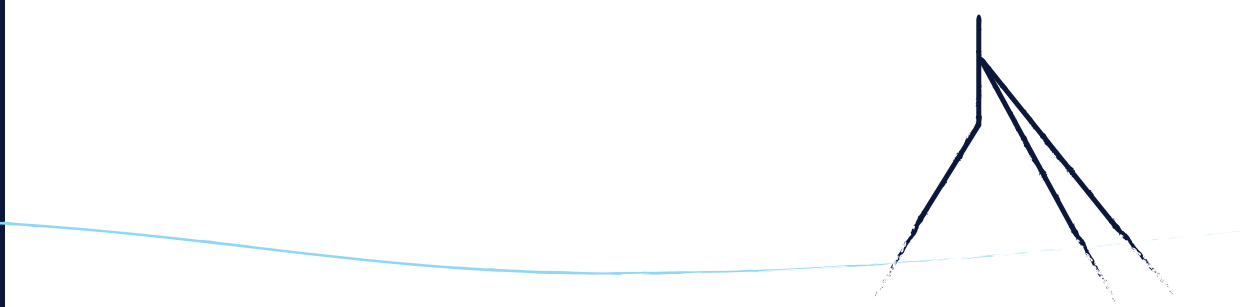
Submitted



ABSTRACT

Background Although joint complaints are increasingly observed in dupilumab treated atopic dermatitis (AD) patients in daily practice, little is known about this potential side effect.

Objectives To investigate the proportion and nature of joint complaints in dupilumab treated AD patients.

Methods We conducted a cross-sectional survey-based retrospective cohort study in all AD patients who started dupilumab treatment in the Erasmus MC. All patients received an online 10-item survey about the presence, timing, nature and treatment of their possible joint complaints. In addition, we reported in detail on all patients who consulted a rheumatologist because of their symptoms. Characteristics and diagnostic results of these patients were summarized.

Results Fifty-four (33%) of the 165 included patients reported joint complaints. Twenty-one of these patients consulted a physician (e.g. rheumatologist, or general practitioner) because of their complaints. Starting pain- and/or stiffness were the most frequently reported symptoms (n=35). Radiological and laboratory abnormalities suggestive of inflammatory rheumatologic diseases were absent in 11/12 (92%) patients who consulted a rheumatologist.

Conclusions Our results might suggest an association between rheumatologic symptoms and dupilumab treatment in AD patients. Although additional studies are warranted to further investigate this association, dermatologists should be aware of this possible side effect.

INTRODUCTION

Atopic dermatitis (AD) is a common, chronic inflammatory skin disease which is characterized by severe itch and recurrent eczematous skin lesions.[1] Abnormalities in structure and functioning of the epidermis and cutaneous inflammation due to immunological dysregulation are hallmarks in the pathogenesis of AD. T-helper-2 (Th2) cytokines interleukin-4 (IL-4) and interleukin-13 (IL-13) are thought to play a central role in this immunopathogenesis. Although acute AD is characterised by a Th2 dominant inflammatory response, chronic lesions show increased expression of Th1 cytokines.[1-3]

Dupilumab, the first biologic registered for the treatment of AD, binds to the α-subunit of the IL-4 receptor, thereby inhibiting signalling of IL-4 and IL-13. Dupilumab has shown good efficacy and effectiveness, and a favorable safety profile in AD patients in clinical trials and daily practice.[4-9] The most frequently reported side effects in clinical trials were conjunctivitis (4.5%-9.8%), injection-site reactions (8.5%-13.6%), nasopharyngitis (3.4%-10%), headache (1.7%-10.2%), and viral upper respiratory tract infections (3%-15%).[4-6] Several side effects that are (frequently) noted and reported in daily practice, were infrequently reported in clinical trials. These include conditions such as paradoxical, sharply demarcated head and neck erythema, alopecia areata, rosacea, weight gain, and psoriasiform dermatitis.[10-17]

We recently reported on a patient who developed an acute-onset mono-arthritis of the ankle and generalized polyarthralgia shortly after starting dupilumab treatment.[18] After this first case, we increasingly observed rheumatologic symptoms in AD patients treated with dupilumab in daily practice. Inflammatory arthritides, such as rheumatoid arthritis (RA) and psoriatic arthritis, are known to be mainly Th1-cell driven with tumour necrosis factor alpha (TNFα) and IL-6 as most important pro-inflammatory cytokines.[19-21] Until now, there have only been a few reports on a potential association between rheumatologic symptoms and dupilumab treatment, and the prevalence and nature of this possible side effect remains unknown.[18,22,23]

Therefore, we aimed to investigate the proportion and nature of joint complaints by conducting an online survey in dupilumab treated AD patients in daily practice.

METHODS

Study design and patient population

This cross-sectional, survey-based retrospective cohort study was conducted at the Department of Dermatology at the Erasmus MC University Medical Center (Rotterdam, the Netherlands). All adult patients with AD who started dupilumab treatment between October 2017 and December 2020 were eligible for this study. In December 2020, eligible patients received an online survey. This 10-item survey was designed by a team consisting of dermatologists and a rheumatologist. The survey included questions about presence and nature of joint complaints during dupilumab treatment, consultations with physicians because of these symptoms, therapy for joint complaints, dupilumab dose adjustments, co-medication (including other immunosuppressants), and patients' medical history with a special focus on joint complaints (Table S1). The survey included instructions to contact the treating dermatologist when patients had joint complaints. Patients could optionally opt out for participation. Patients who did not respond to our initial invitation were sent a maximum of 2 reminders. Patients who completed the survey and gave consent to publish (pseudonymized) information relating to them were included in this study. In addition, patient characteristics of the patients who completed the survey (including demographics, comorbidities and therapeutic history) were recorded using information from electronic health records (EHR). As second part of this study, we assessed EHR of dupilumab treated AD patients who consulted a rheumatologist. Patient characteristics, history of rheumatologic diseases, family history of RA, experienced joint complaints during dupilumab and their courses, results of physical examination, results of laboratory tests and radiological imaging, and treatment were recorded.

Our primary outcome was the proportion of AD patients reporting joint complaints during dupilumab treatment. Patients were classified as new-onset joint complaints, or (worsening of) pre-existent joint complaints. Additional characteristics assessed in the survey were analysed.

(Statistical) analyses

We only included patients who completed the online survey in the analyses. We performed an additional best case scenario analysis (i.e. sensitivity analysis) in which we assumed that all non-responders to our survey would not have reported joint complaints and we subsequently based the proportions on this assumption. Present complaints were classified as follows: starting problems (pain and/or stiffness) lasting >30 minutes, joint swelling, pain at rest, and pain during exertion.

Intersections within these 4 sets of symptoms were visualized using UpSet plots.[24] UpSet uses perceptually efficient visual encoding which enables understanding of relationships and facilitates accurate reading of the data.[25] In order to statistically compare baseline characteristics, we used Wilcoxon Rank Sum Tests for continuous, non-paired variables in a skewed distribution. For non-paired categorical variables, a Chi-Square Test was used. A p-value of $\alpha < 0.05$ determined statistical significant difference between the groups.

Ethical approval

Our study was exempted from evaluation by the local medical research ethics committee (MEC-2020-0814) and was conducted in accordance with the Declaration of Helsinki.[26]

RESULTS

Population

Patient characteristics are presented in Table 1. In total, 165 of the 227 eligible patients completed our survey and were included in this study, reflecting a response rate of 73% (165/227) (Table S2). Nineteen patients partially completed questionnaires, 7 patients opted out, and 36 patients did not respond to our questionnaire despite 2 reminders. Analysis of patient characteristics of responders and non-responders showed that non-responders were significantly younger compared to responders (p=0.014), and asthma was more prevalent in responders (p=0.048) (Table S2). Twenty-eight of the 54 patients who reported joint complaints (52%) were female, with a median age of 48 years (IQR 32-56) and median BMI of 26.6 kg/m2 (IQR 24.0-29.8) (Table 1). Patients who did not report joint complaints had a statistically significant lower BMI (23.5 kg/m2, p=0.003) and lower age (32 years (IQR 23-48), p=0.001) compared to the patients with joint complaints (Table 1). Most patients reported at least 1 comorbid atopic or allergic condition and had previously been treated with ≥1 systemic immunosuppressive agent. The median duration of dupilumab treatment at the time of study completion was 106 weeks (IQR 55-142).

Table 1. Patient characteristics

	Total group (n=165)	Presence of joint complaints (n=54)	Absence of joint complaints (n=111)	Significance#
Female sex – no. (%)	82 (50)	28 (52)	54 (49)	0.699
Age – median (IQR)	37 (26-52)[3]	48 (32-56)	32 (23-48)[3]	0.001*
Race – no. (%)				0.181
Caucasian	132 (80)	47 (87)	85 (77)	
Black	13 (8)	2 (4)	11 (10)	
Asian	7 (4)	3 (6)	4 (4)	
Missing	13 (8)	2 (4)	11 (10)	
BMI – median (IQR)	24.6 (22.1-27.6)[4]	26.6 (24.0-29.8)[1]	23.5 (21.8-26.4)[8]	0.003*
Age at onset AD, years - median (IQR)	0 (0-4) [5]	0 (0-12)[2]	0 (0-3)[9]	0.136
Atopic/allergic conditions – no. (%)				
Asthma	113 (69)[6]	36 (67)	77 (69)[6]	0.665
Allergic (rhino)conjunctivitis	127 (77)[2]	40 (74)	87 (78)[2]	0.288
Allergic contact dermatitis	80 (49)[7]	28 (52)[1]	52 (47)[10]	0.171
Therapeutic history AD – no. (%)				
Cyclosporin A	148 (90)	50 (93)	98 (88)	0.393
Methotrexate	59 (36)	23 (43)	36 (32)	0.201
Azathioprine	33 (20)	8 (15)	25 (23)	0.245
Mycophenolic acid	57 (35)	26 (48)	31 (28)	0.010*
Weeks of dupilumab treatment at the time of survey completion – median (IQR)	104 (65-139)	106 (55-142)	104 (70-137)	0.998
Use of concomitant immunosuppressants – no. (%)	107 (65)	34 (63)	73 (66)	0.724

Missing values: [1]n=9, [2]n=4, [3]n=11, [4]n=32, [5]n=10, [6]n=1, [7]n=42, [8]n=23, [9]n=6, [10]n=33; # Presence of joint complaints versus absence of joint complaints; * statistically significant

Survey results

Fifty-four patients (54/165=33%) reported presence of ≥1 joint complaint (Table 2). Half of these patients (n=27) reported new-onset joint complaints, and the other half (n=27) reported pre-existing joint complaints. In the latter group, 16 patients reported worsening of pre-existing joint complaints. Twenty-one patients consulted a physician because of their joint complaints during dupilumab treatment, which concerned new-onset or worsened joint complaints in 15 patients. The majority of these patients (n=12) consulted a rheumatologist. Other patients visited a general practitioner (GP) (n=7) or orthopedic surgeon (n=2). Nine patients with joint complaints were treated with medication, including analgetics (n=2), (non-)steroidal anti-inflammatory drugs (NSAIDs) (n=2), prednisone (n=2), or combinations of these drugs (n=3) (Table 2). Three patients discontinued dupilumab treatment because of a combination of joint complaints and insufficient effectiveness. An extended dupilumab interval (>2 weeks) was tried in 2 patients but did not result in improvement of joint complaints.

Table 2. Joint complaints – survey results

	Total group (n=165)
Presence of joint complaints during dupilumab – no. (%)	
Total	54 (33)
New-onset complaints	27 (16)
Pre-existent complaints / which worsened during dupilumab	27 (16) / 16 (10)
Time to onset of joint complaints after starting dupilumab treatment, weeks – median (IQR)	11 (1-42)
Consultation of rheumatologist, orthopedist or GP – no. (%)	21 (13)
Subclassification of symptoms – no. (%)	
Starting problems (pain or stiffness >30 minutes)	35 (21)
Pain at rest	24 (15)
Pain during exertion	23 (14)
Swelling	19 (12)
Course of symptoms – no. (%)[a]	
Recovered	2 (4)
Recovered with residual symptoms	2 (4)
Recovering	0 (0)
Alternately present	37 (69)
Continuously present	9 (17)
Worsening	4 (7)
Duration of symptoms	
Weeks – median (IQR)	68 (32,111)
Presence >6 weeks – no. (%)[a]	52 (96)

Table 2. Joint complaints – survey results (*continued*)

	Total group (n=165)
Presence <6 weeks – no. (%)[a,b]	2 (4)
Initiated medication because of joint complaints – no. (%)[a,c]	
Analgetics[d]	2 (4)
NSAID	2 (4)
Prednisone	2 (4)
DMARD	0 (-)
bDMARD	0 (-)
Combination[e]	3 (6)
Adjustment of dupilumab therapy – no. (%)[a]	
None	49 (91)
Extended interval	2 (4)
Discontinuation	3 (6)

[a] number of applicable patients divided by all patients with complaints (n=54); [b] n=1 is continuously suffering from rheumatologic symptoms for <6 weeks; [c] 4 patients were pre-existently using medication: paracetamol, NSAID and DMARD (n=1); NSAID (n=2); NSAID and tramadol (n=1); [d] n=1: paracetamol, n=1: paracetamol/tramadol; [e] paracetamol, NSAID and DMARD; paracetamol and NSAID; NSAID and tramadol

Among the 54 patients who reported joint complaints, subclassification of joint complaints showed that starting problems (i.e. starting pain or -stiffness which lasts ≥30 minutes) were the most frequently reported symptoms (n=35), followed by pain at rest (n=24), pain during exertion (n=23), and joint swelling (n=19). As illustrated in figure 1, the most frequently reported (combinations of) complaints are: starting problems alone (n=12), starting problems combined with joint swelling (n=7); starting problems combined with pain, either in rest and during exertion (n=6); and starting problems, joint swelling, and pain at rest and during exertion (n=6). Other less frequently reported combinations can be found in figure 1. The median dupilumab treatment duration until onset of joint complaints was 11 weeks (IQR 1-42). The majority of patients (37/54=69%) reported symptoms that were intermittently present, for a median duration of 68 weeks (IQR 32-111) at the time of survey completion. Symptoms disappeared in 4 patients, and 2 patients reported recovery with residual symptoms. To summarize, 54 of 165 (33%) AD patients who are using dupilumab had joint complaints. Of those patients, 80% (n=43) reported new onset or worsening of pre-existent joint complaints. Due to these complaints, 12 patients visited a rheumatologist.

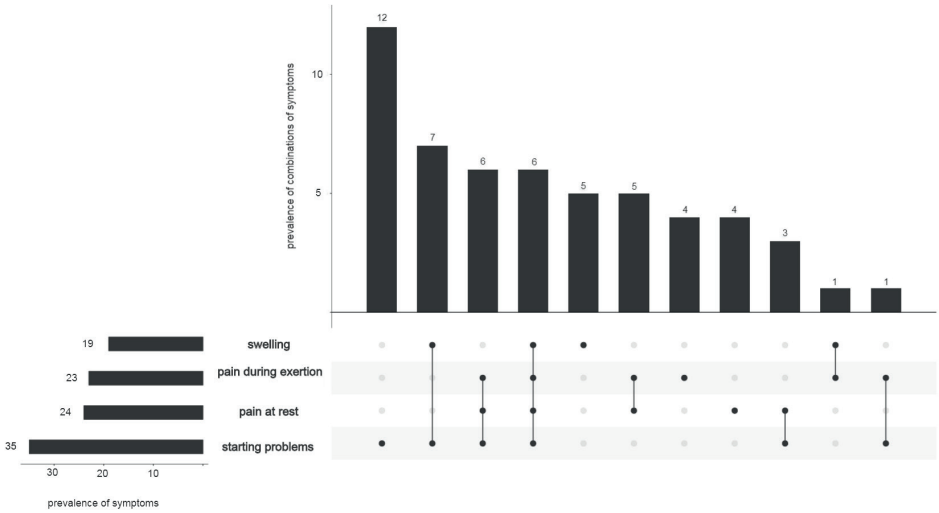


Figure 1. UpSet plot of joint complaints in dupilumab treated atopic dermatitis patients
Intersections within 4 sets of symptoms, with prevalence of symptoms on the horizontal axis and prevalence of combinations of symptoms on the vertical axis.

Patients who visited a rheumatologist

In total, 12 patients visited a rheumatologist due to worsening of pre-existent complaints (n=6), or new-onset symptoms (n=6) (Table 3). This included 7 female and 5 male patients, with an age range of 32-73 years. Although symptoms were pre-existent in 6 patients, three of these patients reported no history of rheumatologic disease. Two patients reported having a first-grade family member diagnosed with RA. Radiological imaging of the affected joints was performed in 10 patients, showing abnormalities suggestive of arthrosis in 6 patients. Serum levels of inflammatory markers (CRP, BSE); Anti-cyclic citrullinated peptide (anti-CCP) and rheumatoid factor (RF); HLA-B27; and TSH were determined in 11, 7, 1, and 8 patients, respectively. Levels of CRP/BSE, HLA-B27, and TSH were considered normal in all patients. A clinically relevant elevation of Rheumafactor IgM alone was found in one patient, and a combination of anti-CCP and Rheumafactor IgM in another patient. The last patient was diagnosed with RA. In summary, clinical symptoms combined with physical examination and radiological imaging were suggestive of joint complaints that might be related to dupilumab treatment in 10 patients (10/165=6%). A dupilumab-induced cause was unlikely in patient 6 and 10, although the use of dupilumab might have accelerated the onset of RA in patient 10.

Table 3. Case series of consultations with rheumatologists

Patient no.	1	2	3	4
Sex, age	Male, 54	Female, 67	Female, 66	Female, 54
Current AD treatment	Dupilumab[a], MTX	Dupilumab[a]	Dupilumab[a]	Dupilumab[a]
Clinical effectiveness dupilumab for AD[b]	Good	Good	Good	Good
History of rheumatologic disease(s)	Yes, unspecified	No	No	Bursitis, enthesitis
Family history rheumatoid arthritis	No	No	No	Yes, brother
Rheumatologic symptoms				
Starting problems (>30 min)	+	+	-	+
Pain at rest	*unknown*	*unknown*	-	-
Pain during exertion	*unknown*	*unknown*	+	+
Time to onset after starting dupilumab	Pre-existent[c]	Pre-existent[c]	Pre-existent[c]	Pre-existent[c]
Duration of symptoms	Multiple years	Multiple years	Multiple years	Multiple years
Location				
Small joints	+	+	+	+
Large joints	+	+	+	+
Entheses	*unknown*	*unknown*	*unknown*	*unknown*
Physical examination				
Swelling	-	-	+ (knee)	-
Movement restriction	-	-	-	+ (bending feet)
Heberden or Bouchard nodes	*unknown*	*unknown*	*unknown*	+
Pain at pressure	*unknown*	*unknown*	*unknown*	+
Serum levels				
CRP (<10 mg/L)	9.6	9.6	0.7	0.5
BSE (0-30 mm/h)	19	-	8	3

Table 3. Case series of consultations with rheumatologists (*continued*)

Patient no.	1	2	3	4
Anti CCP (<4.0 U/mL)	-	-	-	1.0
Rheumafactor IgM (<3.5 IU/mL)	-	-	-	4.0
HLA-B27 (neg)	-	-	-	-
TSH (varying)	0.56	0.835	2.26	1.51
Radiology[d]	MRI feet, hands, knees, shoulder: normal	None	X-ray feet: pes planus, arthrosis	X-ray feet: normal X-ray hands: arthrosis
Related to dupilumab treatment	Possible	Possible	Possible	Possible
Treatment	Physiotherapist	None	Analgetics, NSAID, physiotherapist	Analgetics, physiotherapist

Patient no.	5	6	7	8
Sex, age	Male, 51	Male, 57	Female, 32	Female, 57
AD treatment	Dupilumab[a]	Dupilumab[a]	Dupilumab[a]	Dupilumab[a]
Clinical effectiveness dupilumab for AD[b]	Good	Intermediate	Good	Intermediate
History of rheumatologic disease(s)	No	Yes, arthrosis	No	No
Family history rheumatoid arthritis	No	No	No	No
Rheumatologic symptoms				
Starting problems (>30 min)	+	+	-	+
Pain at rest	+	*unknown*	-	+
Pain during exertion	+	+	+	-
Time to onset after starting dupilumab	New-onset, 8 months	Pre-existent[c]	New-onset, 0 weeks	New-onset, 0 weeks
Duration of symptoms	Multiple years	Multiple years	Multiple years	Multiple years
Location				
Small joints	+	-	-	-

Table 3. Case series of consultations with rheumatologists (*continued*)

Patient no.	5	6	7	8
Large joints	+	+	+	+
Entheses	-	-	-	*unkown*
Physical examination				
Swelling	-	-	-	-
Movement restriction	-	-	-	-
Heberden or Bouchard nodes	+	+	-	+
Pain at pressure	-	-	-	-
Serum levels				
CRP (<10 mg/L)	1.9	-	0.3	9.9
BSE (0-30 mm/h)	3	-	3	18
Anti CCP (<4.0 U/mL)	0.5	-	0.5	-
Rheumafactor IgM (<3.5 IU/mL)	2.1	-	0.7	-
HLA-B27 (neg)	-	-	-	neg
TSH (varying)	1.24	-	-	-
Radiology[d]	X-ray elbows, knees, feet: normal	None	X-ray knees: normal	X-ray lumbar spine: Degenerative signs
Related to dupilumab treatment	Possible	Unlikely	Possible	Possible
Treatment	Analgetics, NSAID, physiotherapist	Analgetics, physiotherapist	Physiotherapist	Physiotherapist

Table 3. Case series of consultations with rheumatologists (*continued*)

Patient no.	9	10	11	12
Sex, age	Female, 58	Female, 67	Male, 56	Male, 73
AD treatment	Dupilumab[a]	Dupilumab[a]	Dupilumab[a]	Dupilumab[a]
Clinical effectiveness dupilumab for AD[b]	Low	Good	Good	Good
History of rheumatologic disease(s)	No	No	No	No
Family history rheumatoid arthritis	No	Father, grandmother	Unknown	No
Rheumatologic symptoms				
Starting problems (>30 min)	+	+	+	+
Pain at rest	+	+	+	*unknown*
Pain during exertion	+	+	+	+
Time to onset after starting dupilumab	Pre-existent[c]	New-onset, 10 months	New-onset, 5 months	New-onset, 5 months
Duration of symptoms	Multiple years	Multiple years	Multiple years	5 months
Physical examination - location				
Small joints	+	+	+	+
Large joints	+	+	+	+
Entheses	-	+	+	-
Physical examination				
Swelling	-	+	-	+
Movement restriction	-	-	-	+
Heberden or Bouchard nodes	*unknown*	*unknown*	*unknown*	*unknown*
Pain at pressure	-	*unknown*	*unknown*	+
Serum levels				
CRP (<10 mg/L)	5.2	7.4	<3	-
BSE (0-30 mm/h)	14	24	9	21
Anti CCP (<4.0 U/mL)	1.9	144.0	<1	1.1

Table 3. Case series of consultations with rheumatologists (*continued*)

Patient no.	9	10	11	12
Rheumafactor IgM (<3.5 IU/mL)	<0.4	4.1	3	17
HLA-B27 (neg)	-	-	-	-
TSH (varying)	1.19	1.28	0.94	-
Radiology	X-ray hands: normal X-ray knees: arthrosis	X-ray hands: arthrosis X-ray feet: arthrosis	US shoulder: biceps tendinitis; X-ray spine: arthrosis; X-ray shoulder, hands: normal	X-ray wrists: normal
Related to dupilumab treatment	Possible	Unlikely	Possible	Possible
Treatment	None	Leflunomide[d] + NSAIDs	None	None

AD atopic dermatitis, MTX methotrexate, US ultrasound - [a] 300mg Q2W, subcutaneous - [b]good:EASI-75 (or EASI<3), intermediate: EASI 50, low: other, [c]worsened from start of dupilumab treatment, [d] because of diagnosed rheumatoid arthritis

Sensitivity analysis

In our sensitivity analysis (i.e. best case scenario analysis), we assumed that all AD patients using dupilumab that did not respond to our survey (n=62) would not have joint complaints. This resulted in a proportion of 24% (54/227) of the patients experiencing joint complaints (Table S3). Furthermore, 19% (43/227) of patients had new onset or worsening of pre-existent joint complaints. Due to these complaints 5% (12/227) visited a rheumatologist. Finally, in 4% (10/227) of patients the arthralgia might be dupilumab-induced according to the treating rheumatologist.

DISCUSSION

We aimed to investigate the proportion and nature of joint complaints in dupilumab treated AD patients. In this survey-based cohort study, 33% of the dupilumab treated AD patients (n=54/165) reported joint complaints. Twenty-one patients (21/54=39%) consulted a physician because of their symptoms, resulting in prescription of drugs in 9 patients. Consultations with rheumatologists (n=12) mostly revealed arthralgia which might be dupilumab-induced.

Literature about the potential association between rheumatologic symptoms and dupilumab treatment is scarce. The incidence of arthralgia in dupilumab phase III trials was not reported in particular.[4,27] Yet, arthralgia has been described as a possible adverse event (frequency unknown) in the Summary of Product Characteristics of dupilumab, since it was noticed in unspecified postmarketing reports.[28] Strikingly, a meta-analysis of adverse events of dupilumab treatment in AD patients reported a higher incidence of musculosketetal pain or back pain in the placebo group compared to the dupilumab treated group (p=0.27 and p=0.05, respectively).[29] Until now, only a few reports on rheumatologic symptoms associated with dupilumab treatment in AD patients in daily practice have been published.[18,23] These reported on 2 female and 3 male AD patients, aged 38-68 years, who initiated dupilumab treatment because of moderate-to-severe AD (EASI: 20.6-43.0). Although AD disease severity improved in all patients, they developed arthralgia within the first 16 weeks of dupilumab treatment. Physical examination and radiological imaging revealed (poly)enthesitis in 4 patients, associated with polyarthropathy in small and large joints in 3 patients.[22,23] One patient was diagnosed with monoarthritis of the ankle, combined with polyarthralgia.[18] Autoimmune serology (i.e. anti-CCP, RF) was negative in all patients. Most patients experienced residual rheumatologic symptoms despite adequate treatment (e.g. celecoxib, naproxen, prednisone and/

or methotrexate). Three patients discontinued dupilumab treatment and reported residual rheumatologic symptoms 4 months after discontinuation.

Epidemiological studies have suggested that AD patients, regardless of therapy, may have a higher risk of developing RA.[30] The effect of systemic AD therapies on this association remains unknown. In our cohort, 50% of the patients who reported symptoms during dupilumab treatment experienced pre-existent rheumatologic symptoms. Although only 5 patients have been diagnosed with arthritis prior to dupilumab initiation, it should be mentioned that the majority of the included patients were using conventional immunosuppressive agents in the previous years. This might have masked pre-existent rheumatologic symptoms. However, patients who had pre-existent symptoms, reported worsening after initiation of dupilumab in 60% (16/27) of the cases. In 3 of these 16 cases, joint complaints worsened after discontinuation of concomitant immunosuppressants (cyclosporin A, azathioprine, prednisone), which might play a role in worsening of pre-existent symptoms.

In addition, an association between development of inflammatory rheumatologic disease and obesity has been suggested.[31] In our study, we found a statistically significant increased BMI (24.6 versus 26.6 kg/m2) in patients who reported joint complaints. Although median BMI levels of both groups do not reflect obesity (BMI>30), we could not rule out the impact of increased BMI on the proportion of joint complaints.

Dupilumab has shown not only to suppress expression of Th2 cytokines and type 2 inflammation regulated genes, but also reduces expression of Th22 and – to a lower extent - Th17 related genes.[32] In addition, Guttmann-Yassky et al. showed that dupilumab had no effect on the expression of Th1 markers in the skin of dupilumab treated patients. This suggests that dupilumab may induce a balance shift with increased Th1/Th17 inflammation. Other paradoxical reactions that have been described during dupilumab treatment, such as psoriasiform dermatitis, alopecia areata, and rosacea may also be explained by this shift.[11,14,15,17,33,34] Conversely, in patients with psoriasis and other Th1-driven diseases who were treated with biologics (anti TNF-α therapy) a shift to a Th-2 medicated disease such as eczema has been shown.[35]

Bakker et al. recently investigated whether dupilumab induced long-lasting T- and B-cell polarization, but found no evidence for Th-cell skewing after 1 year of dupilumab treatment.[36] However, in some patients (n=4/10) IL-17 production exceeded baseline levels after 1 year of dupilumab treatment.[36] This suggests that a balance

shift in individual patients cannot be ruled out. Another possible explanation for the development or worsening of rheumatologic symptoms during dupilumab treatment, was suggested by Bridgewood et al..[37] They reported that IL-4 and IL-13, may play a protective role in the entheseal induction of the IL-23-IL-17 axis. IL-4, which might thus be required for tissue homeostasis and repair, was able to attenuate activation of enthesis stroma (i.e. fibroblasts), which is thought to be an early trigger of disease.[37] In addition, IL-4 is thought to inhibit the production of pro-inflammatory cytokines including TNF-α, IL-1, and IL-6, which play a key role in RA and in the wider field of inflammatory arthritis.[37]

This is the first study reporting on the proportion and nature of joint complaints in AD patients treated with dupilumab in daily practice. All patients treated with dupilumab received an online survey, which was completed by 73% of our patients, suggesting a fair external validity. Our study is in absence of a control group, which should ideally include moderate-to-severe AD patients without systemic therapy. A future prospective study should include this control group to rule out the effect of the increased prevalence of joint complaints in AD patients in general. A recall bias due to the retrospective design of the study might have affected our results. Future studies with a prospective design would be of added value. In addition, patients who noticed joint complaints during dupilumab treatment might be more motivated to complete this survey due to personal interest (i.e. selection bias). However, additional sensitivity analyses revealed that even if all non-responders would have reported absence of joint complaints, the proportion would still be 24% (54/227) with 9% of all dupilumab treated patients (21/227) consulting a physician because of these complaints. Finally, an appropriate standardized and validated questionnaire to assess joint complaints as a possible side effect of dupilumab treatment was not available. Therefore, a team consisting of dermatologists and a rheumatologist designed a survey which was considered appropriate to answer our research question(s).

The results of this study might suggest an association between joint complaints and dupilumab treatment in AD patients. Although additional prospective, post-marketing studies with long-term follow-up are warranted to further investigate this association, dermatologists should be aware of this possible side effect.

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Table S1. Survey instrument

Part 1: rheumatologic signs and symptoms during dupilumab treatment
Question 1: Did you notice any of the following symptoms after you started dupilumab treatment? (multiple answers possible)
o No, I did not notice any of this symptoms *(patients were directed to question 7)*
o Yes, at least 1 joint was swollen (or red/warm)
o Yes, my finger or toe was swollen and painful for no apparent reason
o Yes, a painful heel
o Yes, painful joint(s) when I am in rest
o Yes, painful joint(s) after getting up (when waking up or after sitting for a while), which gets better during the day
o Yes, painful joint(s) at movements
o Yes, stiffness after waking up which lasts for longer than 30 minutes
o Yes, painful joint(s) which wakes me during the nights
Question 2: For how long have you been treated with dupilumab when you first noticed these symptoms? *[…]* weeks of dupilumab treatment
Question 3: How did these symptoms develop in time?
o Recovered (*subquestion: For how long were they present?)*
o Recovered with residual symptoms *(subquestion: For how long were they present?)*
o Recovering
o Alternately present
o Continuously present
o Worsening
Question 4: Were changes applied to your dupilumab treatment because of these symptoms?
o No
o Yes, my interval was extended to >2 weeks.
o Yes, I discontinued dupilumab treatment
Question 5: Did you consult a rheumatologist or your general practitioner for these symptoms?
o No
o Yes *(subquestion: did he/she mention that you are having arthritis?)*
Question 6: Did you use drugs for these symptoms?
o No, I did not use drugs for these symptoms
o Yes, analgetics (paracetamol)
o Yes, nonsteroidal anti-inflammatory drugs (NSAID) (Diclofenac, Ibuprofen, Naproxen, Etoricoxib (Arcoxia), or Meloxicam (Movicox))
o Yes, Disease-modifying antirheumatic drug (DMARD) (methotrexate leflunomide, hydroxychloroquine, sulfasalazine)
o Yes, biologics (including adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, toclizumab)
Part 2: rheumatologic signs and symptoms prior to dupilumab treatment

Question 7: Did you notice any of the following symptoms before you started dupilumab treatment? (multiple answers possible)

o No, I did not notice any of this symptoms *(patients were directed to the end of the questionnaire)*

o Yes, at least 1 joint was swollen (or red/warm)

o Yes, my finger or toe was swollen and painful for no apparent reason

o Yes, a painful heel

o Yes, painful joint(s) when I am in rest

o Yes, painful joint(s) after getting up (when waking up or after sitting for a while), which gets better during the day

o Yes, painful joint(s) at movements

o Yes, stiffness after waking up which lasts for longer than 30 minutes

o Yes, painful joint(s) which wakes me during the nights

Question 8: Did these symptoms got worse during dupilumab treatment?

o No

o Yes

Question 9: Did you ever consult a rheumatologist or general practitioner for these symptoms?

o No

o Yes *(subquestion: did he/she mention that you are having arthritis?)*

Question 10: Did you ever use drugs for these symptoms?

o No, I did not use drugs for these symptoms

o Yes, analgetics (paracetamol)

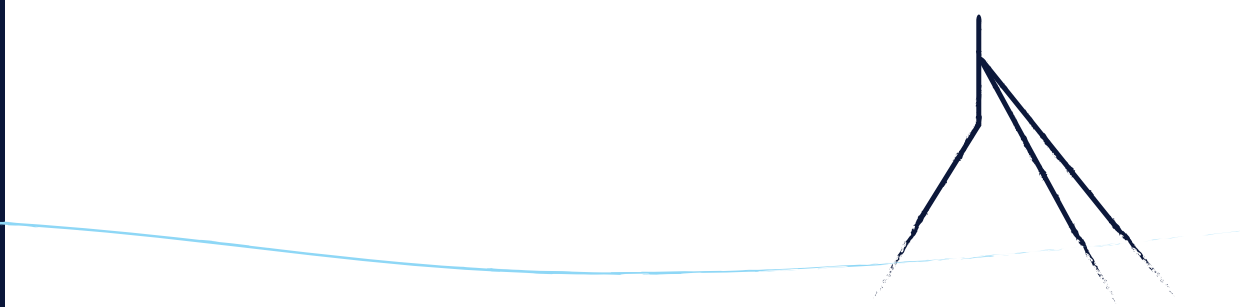
o Yes, nonsteroidal anti-inflammatory drugs (NSAID) (Diclofenac, Ibuprofen, Naproxen, Etoricoxib (Arcoxia) en Meloxicam (Movicox))

o Yes, Disease-modifying antirheumatic drug (DMARD) (methotrexaat, leflunomide, hydroxychloroquine, sulfasalazine)

o Yes, biologics (including adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, toclizumab)

Chapter 9

General discussion



Atopic dermatitis (AD) is a chronic inflammatory skin disease associated with a high disease burden.[1] Abnormalities in structure and functioning of the epidermis and cutaneous inflammation due to immunological dysregulation are believed to be hallmarks in the pathogenesis of AD.[2] Acute AD is characterized by a Th2 dominant inflammatory response with a central role for interleukins(IL)-4 and IL-13. Chronic lesions show progressive immune activation of Th1, Th2, Th17 and Th22-subsets.[3, 4]

Until recently, treatment of patients with moderate-to-severe AD was limited to conventional systemic immunosuppressants, UVB, topical corticosteroids (TCS), topical immunomodulators (TIM), and moisturizers.[5, 6] This armamentarium remained unchanged for several decades. Due to major advances in the understanding of AD and development of new targeted therapies, we recently entered a new era in treatment of patients with moderate-to-severe AD.[7-9] Novel therapies including biologics and small molecules are now starting to fill the large unmet need in the treatment of AD. However, evidence about the effectiveness and drug safety in daily practice should be extensively considered and compared between therapies before we can legitimately call this a therapeutic revolution.[10, 11] Dupilumab was the first new drug that was approved for treatment of moderate-to-severe AD in 2017.[12, 13] First experiences with dupilumab treatment in daily practice are discussed in this thesis.

Over the past decades, core values in management of chronic diseases changed. We shifted from a paternalistic model towards provision of people-centered care with e.g. increased attention for shared decision making.[14, 15] In order to tailor AD care to patients' needs, especially considering the many emerging therapeutic options, we investigated the needs and preferences of patients in the management of AD.

Main conclusions regarding the needs and preferences of AD patients (**Chapter 2**), the effectiveness of dupilumab in daily practice (**Chapter 3-6**), and the (unexpected) side effects of dupilumab (**Chapter 7-8**) are discussed in this chapter (**Chapter 9**: general discussion). In addition to this, clinical implications, current (ethical) considerations, and future perspectives regarding these topics will be discussed.

WHAT DOES A PATIENT NEED AND PREFER IN TERMS OF ATOPIC DERMATITIS CARE?

AD is associated with the highest disease burden among all skin disorders.[1, 16] In our qualitative study, described in **Chapter 2**, patients reported the need for a physician's increased recognition of the physical and psychological burden of their chronic disease. Besides, a trustful relationship with their physician was considered very important. Patients in our study reported that adequate communication, empathy, and a physician using a personal approach towards patients are essential in order to build a good doctor-patient relationship. In addition, people-centered healthcare (i.e. "care that is respectful of, and responsive to, individual preferences, needs and values of patients") and involvement of patients in their treatment process are promoted as some of the key targets for management of long-term conditions by agencies such as the World Health Organization.[14, 17, 18] Remarkably, many physicians consider soft interpersonal aspects less crucial in the evaluation of the doctor-patient relationship.[19] They rather consider this relationship in a more pragmatic manner with emphasis on knowledge and technical expertise. This discrepancy might be influenced by the present healthcare system which is associated with high workloads combined with rapid technological and biomedical progress. These new developments might not be adequately placed into context within a healthcare system characterized by understanding, compassion and empathy.[17] Studies have shown that many physicians are not aware of this, possibly leading to overestimation of their communication skills.[20] Therefore, creating awareness and increased implementation and improvement of formal training in communication skills in the medical curriculum might be necessary, especially for healthcare providers who are treating patients with chronic diseases.[21]

In addition to a trustful relation with an empathic physician, some patients expressed the need for more profound psychosocial support. A recent review confirmed the hypothesis that the presence of psychosocial stress increases symptoms and severity in AD patients.[22] On the other hand, (psycho)social support, adequate coping strategies, and educational interventions were found to improve the severity of symptoms, disease management, and quality of life in AD.[22-24] This support or education could possibly be provided by specialized nurses.[25] They are often able to build strong and long-term relations with patients, which promotes among others trust, self-management, treatment adherence, and as a result quality of life of patients.[25]

AD is a chronic, fluctuating disease and only snapshots of the disease course are observed in consultations with physicians. Patients in our qualitative study (**Chapter 2**) reported the need for being more actively involved in their disease management in order to provide a more realistic perspective of their disease severity and treatment effect. Tools for patients to indicate the disease impact and disease control on the long term could address these needs. Patient Reported Outcome Measures (PROMs) are used to ascertain patients' views on their signs and symptoms, their functional status, and their health related quality of life.[26] PROMs can be generic (e.g. EQ-5D-5L), dermatology-specific (e.g. Dermatology Life Quality Index, DLQI), or disease-specific (Patient-Oriented Eczema Measure, POEM).[27-29] Most PROMs are self-administered, take a short time to complete, and are easily scored. Therefore, they are very useful for routine care. PROMs should be repeatedly taken to give insight into the disease course on the long term and to enable the comparison of the outcomes at different time points.[26] PROMs are beneficial for patients, physicians, regulators, and other stakeholders in healthcare.[26, 30-32] The use of PROMs might improve involvement of patients in their treatment process, which could promote communication, patient engagement, and self-efficacy. For physicians, PROMs might help to better understand patients' experiences regarding disease impact and symptoms. This will result in detection of otherwise unrecognized problems and could consequently influence clinical decision making. On a population level, aggregated PROM data might be used as indicator for quality of care facilitating transparency of outcomes of care. In the ideal situation, patients should complete PROMs frequently in a strict routine, or at least prior to every consultation. Questionnaires should be filled out in an online system, ideally linked to the electronic patient file, enabling the physician to review patients' scores. During the consultation, practical barriers (i.e. deviant or striking values) that were identified in PROMs should be discussed and this should result in treatment optimization based on patient-centered treatment goals.

In the current healthcare system, patients visit the out-patient clinic on a regular base with consultations that are planned e.g. 3 months ahead. This does not always fit for patients with a highly fluctuating disease severity. In the acute situation of a disease flare, the current system usually is insufficiently responsive to patients' needs, and long waiting lists limit quick access to care. In this context, frequently administered PROMs would also enable early recognition of increased disease severity. This might facilitate on demand care which is responsive to increased disease severity. The need for a more flexible and accessible system was also highlighted by patients in our qualitative study, described in **Chapter 2**. Previous studies have shown that better accessibility of care led to optimized use of diagnostic and

therapeutic services and optimized resource utilization in other chronic inflammatory conditions.[33, 34] Solutions to enable quick access to healthcare, such as virtual care are increasingly available and have proven to be (cost-)effective.[35] In addition, tools for self-management including personal health records, flare self-assessment, and written eczema action plans with individualized guidance on e.g. treatment use have been shown to help in AD and other allergic diseases.[35-37] Using early signs to detect disease flares and improving the patients' ability to self-manage their disease would also facilitate in the complex challenge of providing high-quality care while keeping health care systems accessible and affordable.[38, 39] However, socioeconomic inequalities have been found to influence the access to and use of for instance personal health records.[40] Several factors of influence for the access to and use of PHR such as desire to access, not having physical access or digital skills, and intentions to regularly use PHR have been identified. Therefore, attention should also be paid to patients who are not able to exploit the potential of digital technology (e.g. elderly, migrants) in order to advance health equity.

Prior to the implementation of novel therapies such as dupilumab, AD was already associated with a high economic burden due to direct and indirect costs (e.g. absenteeism at work).[16] The recent implementation of novel, costly therapies will increase the global economic burden.[41] In addition, it will also increase the personal financial burden in countries with poor reimbursement circumstances. However, opposite to increasing direct costs, indirect costs and counterfactuals (i.e. the costs the patient would have incurred had they not been treated with biologics) are likely to decrease after implementation of effective new drugs.[42] Dupilumab was globally approved in 2017 for use in patients with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable.[12, 43] However, stricter eligibility criteria for dupilumab treatment were implemented in the Netherlands due to the high costs of dupilumab, i.e. drug costs of €17 000 per year. In order to be eligible for dupilumab treatment, AD patients must have failed on at least 1 systemic immunosuppressant after treatment in an adequate dose for 4 months, unless contraindicated.[44] These criteria are different from country to country, with for instance Eczema Area and Severity Index (EASI) ≥24 combined with insufficient effectiveness or contraindication for cyclosporine A treatment as a requirement for dupilumab treatment in Italy, while in Germany dupilumab is the first step when topical therapy and/or UVB have failed.[45, 46] Many of these approaches are restrictive and not receptive to the interpretation of patient and physician. According to patients in our qualitative study, described in **Chapter 2**, physicians should be able to make patient-dependent exceptions on applied guidelines when the disease highly interferes with patients'

daily life. On the other hand, attention should be paid to patients and healthcare providers who might not be aware of the existence of new medicines, although they would be eligible according to the applied criteria. This may be the result of the unprecedented speed of innovation after years of absence of novel systemic therapies. Therefore, education of general practitioners and dermatologists on (anticipated) drug approvals and treatment guidelines is very important to optimize the referral route of patients with moderate-to-severe AD.

In addition to the factors described above, the therapeutic decision making process was evaluated in our qualitative study, described in **Chapter 2**. In order to create a (therapeutic) patient journey that suits the patient best, patients in our study reported that the decision making process should be patient-centered. The process should be optimized through e.g. consideration of the patient's personal situation regarding eligibility and feasibility of therapies, and the patient's right and ability to make their own choices after being adequately informed (i.e. self-determination). The need for shared clinical decision making was acknowledged by an international panel of physicians, nurses, and patients who reached an expert consensus on the first treat-to-target approach for patients with moderate-to-severe AD.[47] Comparable approaches were already established in other immune-mediated conditions.[48, 49] The treat-to-target approach for AD among others aims to guide decisions about continuation, discontinuation, or modification of treatment(s) in patients requiring systemic therapy. According to the treat-to-target algorithm for AD, decisions should be based on changes in the patient's global assessment combined with changes in at least one specific domain (e.g. EASI, POEM, NRS itch) measured with validated outcome measures, both physician and patient-reported. In addition to such algorithms supporting therapeutic decisions, patient decision aids (e.g. decision cards: 1-page overviews of possible treatment options) for patients could also be helpful and were already implemented in routine care at the Erasmus MC University Medical Center.[50] These tools are particularly useful for improving patients' knowledge, risk perception and to enable consideration of different therapeutic options at home.

Yet, to be able to inform patients on benefit-risk ratios and guide patients in therapeutic decisions, more insight into the effectiveness and safety profile of novel therapies in daily practice is highly needed. These insights regarding dupilumab, the first registered biologic for treatment of AD, are discussed in the next paragraph of **Chapter 9**.

WHAT IS THE EFFECTIVENESS OF DUPILUMAB TREATMENT IN DAILY PRACTICE?

The differences between large clinical trials and daily practice

There may be differences between treatment effect found in clinical trials (i.e. efficacy) and daily practice (i.e. effectiveness), most probably due to the controlled conditions in clinical trials.[51] In general, the measured effect of a therapy is not only determined by the treatment itself, but also by many other contributing factors including patient characteristics and adherence.[52] This varying effectiveness and safety of a treatment across a patient population is known as the "heterogeneity of treatment effect". Therefore, the use of appropriate eligibility criteria in clinical trials to identify a population that is representative of a real-world population is very important. This would enhance replication of data and generalizability in daily practice (i.e. external validity).

Unfortunately, differences between patient populations in real world registries and clinical trials do exist.[51] There are limited data available quantifying the differences between AD populations in large clinical trials versus daily practice. Compared to patients in the clinical trials with dupilumab, patients in the daily practice studies that are reported in this thesis (**Chapters 3 and 4**) used a relatively high number of systemic (immunosuppressive) therapies prior to dupilumab treatment. This suggests a long history of severe disease. Additionally, the nature of comorbidities and the number of patients with these comorbidities are different between clinical trials and daily practice studies in other immune-mediated diseases such as psoriasis.[53] Strikingly, only 30% of the patients receiving systemic therapy for psoriasis in a Spanish daily practice cohort would have been eligible for psoriasis clinical trials, confirming the differences in patient populations and therefore questionable generalizability.[54]

Another important difference between clinical trials and daily practice is the wash-out period for therapies that is applied in trials. Patients with severe AD who are not able to wash-out topical and systemic therapies for 2 and 4 weeks (resp.) prior to randomization, are deemed ineligible for participation in the dupilumab phase 3 trials (i.e. screen failures).[55] However, these patients suffering from severe AD are likely to be the first candidates for dupilumab treatment in daily practice. Interestingly, the number of screen failures due to unfeasible wash-out periods are not reported in specific in dupilumab phase 3 trials, although it is encouraged to document screen failure information according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[56] More transparency about screen failures,

including numbers and reasons, is highly needed in order to adequately indicate whether the trial population is representative of the patients who start dupilumab treatment in daily practice.

Furthermore, differences in treatment adherence between clinical trials and daily practice are often present.[57] Treatment adherence in clinical trials is often increased due to administration of drugs or placebos in the presence of a healthcare provider during study visits. Besides, the so-called "white coat compliance" results in an increased treatment adherence around consultations with physicians, which occur frequently in clinical trials.[57] Last, the use of concomitant AD therapy is often restricted in trials in order to have the ability to investigate the effectiveness of monotherapy and limit the influence of possible confounders. As a result, the difference in effect between the investigational drug and the placebo will become bigger.

In clinical trials, primary endpoints are mostly based on Investigator Global Assessment (IGA) scores, as advocated by agencies like the US Food and Drug Administration (FDA).[58] In most trials, the primary endpoint is defined as IGA 0 (i.e. clear) or 1 (i.e. almost clear). This indicates induction of remission and is mostly determined at a certain predefined time point (e.g. 12 or 16 weeks of treatment), regardless of the disease severity in the days to weeks before the primary endpoint. However, an effective treatment should result in sustained disease control (i.e. effective maintenance therapy). To adequately measure disease control, advanced primary endpoints more adapted to the acute relapsing and remitting nature of AD and incorporating repeated measures would be more appropriate. Although PROMs are measured in clinical trials, it could also be discussed whether a more prominent role for PROMs in trials should be pursued. Although AD is not lethal it has a high burden of disease and with treatment, we strive to achieve disease control. Disease control includes not only improvement of signs, but also symptoms and quality of life. These factors are best judged by patients themselves. The use of PROMs was also promoted in the definition of 'a clinically relevant response' as defined by Ariens et al.[59] A clinically relevant response could be achieved through physician- or patient reported endpoints. Strikingly, although 89% of the patients treated with dupilumab in daily practice (n=129) reached a clinically relevant improvement in at least one domain, only 55% reached clinically relevant response for at least one PROM and one physician-reported outcome. In addition, 27% of the patients reported a clinically relevant response, whereas the physician-reported endpoint was not achieved. This confirms the added value of PROMs. The Harmonising Outcome Measures for Eczema (HOME) initiative also emphasizes the importance

of these scores in the Core Outcome Set for clinical trials and clinical practice.[60, 61] In addition, the FDA and European Medicines Agency (EMA) published regulatory guidance documents in which they reflect on the place that PROMs may have in the drug evaluation process.[62, 63] The FDA stated that PROMs (when proven valid, reliable, and able to detect changes), could provide optimal information about the patient's perspective. They are currently urging the use of systematically and rigorously collected PROM data in drug development and evaluation, as part of FDA's Patient-Focused Drug Development efforts.[62, 64]

The importance of international registries and observational studies

The aforementioned important differences between clinical trials and daily practice could lead to a difference in treatment effect observed in trials versus daily practice. This might be concerning, since clinical recommendations and guidelines for these novel therapies (i.e. evidence-based medicine) are frequently based on scientific evidence derived from these rigorously designed trials because daily practice data are not yet available.[65] In addition to the treatment effect, data on side effects, the effect on comorbidities, and the benefits and harms of combination therapies in daily practice are essential to get better insights into therapies and to perform evidence-based medicine, based on robust (subgroup) analyses. This emphasizes the importance of observational studies in a real-world setting in order to evaluate the benefits and harms of a therapy in a wider population. Data collection of these observational daily practice studies should be organised in (inter)national registries to increase the number of included patients and be able to conduct robust analyses.

In the Netherlands, different AD daily practice registries were established and they were boosted shortly after the introduction of dupilumab.[66, 67] However, combining results in international collaborations is essential for increasing the registries' power and impact. This initiative is already set in psoriasis (and psoriatic arthritis) with registries such as the PSONET registry (2008) and British Association of Dermatologists Biologic and Immunomodulators Register (BADBIR) (2012).[68] These are respectively international and national, independent population-based registries including patients who are treated with systemic agents. These registries resulted in robust analyses of e.g. combination of biologics and conventional systemic agents, or persistence with biologic therapies.[69, 70] Because novel AD therapies have only recently been introduced, duration of the follow-up of treatment response is limited and datasets are relatively small. However, with the lessons learned from psoriasis, which is considered as the forerunner of AD when it comes to innovative systemic therapies, we should increasingly collaborate in order to be able to generate robust evidence in a very early stage of the AD therapeutic revolution.

In conclusion, evidence-based medicine derived from clinical trials and collaborations of daily practice registries should be combined with physician's expertise and experience, provided that patients' preferences and needs are taken into consideration as well, in order to provide optimal healthcare for every individual patient.

Dupilumab treatment in daily practice

In **Chapter 3**, we evaluated the effectiveness and side effects of dupilumab treatment in daily practice in all AD patients who started treatment in two Dutch University Hospitals. Studying data on patients treated in a real-world setting comes with several (methodological) challenges. In clinical trials, patients visit the outpatient clinics in strict time windows with the same number of visits for every patient. However, timing of visits in daily practice is usually more flexible and often personalized according to e.g. concomitant medication, effectiveness, and tolerability of treatment in every individual patient. This results in unbalanced repeated measurements which cannot be adequately analyzed by statistic models that are used in clinical trials. To adequately analyze all data, we used Linear Mixed-Effects (LME) models in our studies which are described in **Chapter 3**. The use of these models allows for the analysis of unbalanced repeated measures and is therefore most suitable for analyzing data that is collected in daily practice.[71]

In our prospective observational cohort studies, short-term (**Chapter 3.1**) and long-term (**Chapter 3.2**) effectiveness of dupilumab treatment in daily practice were evaluated using LME models. We visualized the disease course in time up to 16 and 84 weeks of dupilumab treatment and included all repeated patient- and physician-reported measurements in the analyses. Dupilumab showed a clinically relevant and sustained improvement of all signs, symptoms, and quality of life, apparent from the first weeks of dupilumab treatment. Extension of the dosing interval in case of adequate effectiveness did not result in deterioration of the effect, as described in **Chapter 5**. Overall, dupilumab was generally well-tolerated, apart from eye complaints. Eye complaints were reported in up to 62% of the patients. About 20% of dupilumab treated AD patients were referred to an ophthalmologist, or started treatment with ophthalmological medicines, other than artificial tears or antihistamine eye drops.

One of the secondary aims of **Chapter 3** was to compare effectiveness of dupilumab in daily practice with efficacy in clinical trials.[55, 72, 73] Compared with patients who are included in dupilumab phase 3 trials, we included patients with a more extensive therapeutic history in our daily practice studies (**Chapter 3.1** and **3.2)**. In our studies, around 70% of the patients were previously treated with two or

more immunosuppressants, whereas a maximum of 31% of the patients in the SOLO 1 and 2 trials were treated with at least 1 conventional systemic immunosuppressant.[55] The LIBERTY AD CAFÉ study population consisted of patients who inadequately responded to cyclosporine A (~65%) (or in whom this treatment was inadvisable: ~35%).[73] Although patients in our daily practice cohorts were found to have lower baseline EASI scores (18.6 and 21.4) compared to phase 3 trials (28.6 and 30.4), PROM scores at baseline (POEM: 21.4 and 25.9) were comparable or even worse compared to clinical trials (POEM: 21.0 and 21.0). These relatively high baseline PROM scores in our cohort indicate more severe disease as experienced by patients. The combination of these scores and the extensive therapeutic history with many systemic immunosuppressants reflects a history of severe disease in our patients treated in daily practice.

It should be mentioned that adequate direct and statistical comparison of the treatment effect in clinical trials and daily practice is complicated due to the different study designs and methodologies used to analyze the data. In addition, our cohort contains of a relatively small number of patients in comparison with large daily practice registries in for instance psoriasis. Yet, for comparison of the short-term treatment effect in our cohort (**Chapter 3.1**) with clinical trials for dupilumab, LIBERTY AD CAFÉ might be the best representative clinical trial when taking into account the inclusion and exclusion criteria.[73] Compared to the LIBERTY AD CAFÉ trial, the relative change in EASI scores from baseline to 16 weeks of treatment is smaller in our cohort (-61% versus -80%, resp.), but absolute EASI scores after 16 weeks of treatment are similar and indicate mild disease. The differences in relative change might result from the 2-4 weeks wash-out period for topical and systemic therapy in clinical trials resulting in worse baseline scores. The relative changes in NRS pruritus (-57% versus -54%) and absolute changes in POEM scores (-11.3 versus -11.9) were comparable. Similar results were found when comparing our long-term effectiveness study (**Chapter 3.2**) with the LIBERTY AD CHRONOS trial.[72]

As described in **Chapter 6**, we found that tapering immunosuppressants after the start of dupilumab results in a seamless transition between therapies, without new side effects emerging from the use of these combinations. Our results have shown that this approach leads to a favourable disease course in the first months of dupilumab treatment. Patients who did not follow our transition regimen more often experienced a rebound phenomenon which was not observed in the patients who slowly tapered their immunosuppressants during dupilumab therapy. We therefore proposed to taper immunosuppressants guided by the degree of disease control which should be determined through shared decision making between patient

and physician. The importance and advantages of shared decision making were discussed in **Chapter 2** as well. The use of strict cut-off levels for achieving disease control such as EASI75 was considered to be inadequate, because we wanted to take into account the many personal factors that might interfere in determining achievement of disease control (e.g. current symptoms, season, patient's mental state, relative patient burden of signs and symptoms, and experiences with tapering the immunosuppressant). Additional tools that could be useful to support clinical findings in the assessment of disease control include PROMs such as the Atopic Dermatitis Control Tool (ADCT) or the Recap of atopic eczema (RECAP).[74] In some cases, disease control is not reached during dupilumab treatment and discontinuation of concomitant immunosuppressants is not feasible. In these patients topical therapy should be optimized and continuation of concomitant immunosuppressants at the lowest possible effective dose, or discontinuation of dupilumab treatment should be considered. These patients could be transitioned to other targeted therapies within the fast expanding arsenal of AD therapeutic options. In addition to the importance of patient-centered care with respect for a patient's autonomy in determining disease control, the importance of personalized medicine becomes more evident especially because of the highly accelerating drug development pipeline. Therefore, future studies evaluating the prediction of treatment response to certain therapies, including the use of predictive (serum) biomarkers, would be very helpful.

The importance of determining treatment effect and disease control in a patient-centered way is also underlined by the conclusion of our study described in **Chapter 4**. The effectiveness of dupilumab treatment in Japan versus the Netherlands was evaluated in this comparative study. This study was initiated because of known ethnic- or geography dependent clinical and immunological heterogeneity.[75-77] The impact of cultural and racial impact on outcome measures in AD is largely unknown. However, studies which are conducted in routine care are particularly suitable for evaluating such context-dependent influences. Although the mean estimated baseline EASI score was higher in Japanese patients, baseline PROMs were significantly higher in Dutch patients. The mean estimated EASI scores of Dutch and Japanese patients both decreased quickly to a score indicating mild disease, with a comparable trajectory from 12 weeks until the end of follow-up. Strikingly, PROMs showed different trajectories with relatively high levels and clinically relevant, better outcomes for PROMs in Japanese patients. Important differences between Japan and the Netherlands in terms of healthcare organization and therapeutic management of AD were discussed in **Chapter 4**. The most important factors possibly contributing to the observed differences in PROM

scores include differences in patient characteristics (e.g. richer therapeutic history in the Netherlands), concomitant topical therapy (better compliance in Japan), personal financial strain associated with dupilumab treatment (higher in Japan), and coping- and sociocultural differences. In general, Japanese patients are known to show bettercoping and resilience, and lower absenteeism at work and school, compared to Western countries.[78] This might also apply for coping with AD signs and symptoms. It is known that cultural characteristics and behavior determine the perception of health and illness and therefore this might explain the low PROM scores indicating less signs and symptoms as experienced by patients.[79] This shows that, in addition to racial disease-specific differences, healthcare system- or culture related characteristics might contribute to differences in physician- and patient reported outcome measures between countries. Therefore, we propose to consider this in the evaluation of treatment effect in both clinical trials and in daily practice (studies) with attention for PROMs, healthcare system related characteristics, and culture-related characteristics in particular. In addition, more objective outcome measures such as biomarkers which are not subjected to behavior would be highly valuable.

WHAT ARE THE (UNEXPECTED) SIDE EFFECTS OF DUPILUMAB TREATMENT IN DAILY PRACTICE?

Dupilumab was the long-awaited drug for many patients with severe AD, and it was proven successful in clinical trials and daily practice studies. Overall, dupilumab showed a remarkably good tolerability profile in clinical trials. Conjunctivitis, herpes infections, and injection-site reactions were the most frequently observed side effects.[55, 72, 73] However, a relatively small number of selected patients was studied for a limited period of time in these clinical trials. In comparison to biologics used for other chronic inflammatory (skin) diseases in routine care, dupilumab seems to have unique safety profile (e.g. laboratory testing not required according to local protocols). However, several side-effects of dupilumab treatment that were described in this thesis (**Chapter 7 and 8**) were not reported or reported at a much lower frequency in clinical trials. Therefore, further pharmacovigilance studies (i.e. drug safety) are still needed in order to understand and prevent certain side effects.[80] In this context, daily practice registries with structured reporting of side effects are highly valuable.

In **Chapter 7.1** we describe a paradoxical head and neck erythema, affecting about 30% percent of dupilumab treated AD patients in daily practice. We found that this

paradoxical erythema was clinically and histopathologically heterogeneous, but most suggestive of a dupilumab-induced skin reaction. If patients had pre-existent eczema in the head and neck region, this was notably different from the head and neck erythema that was found after 10-39 weeks of dupilumab treatment. Moreover, symptoms (e.g. itch, burning) were absent in most patients. In general, visible lesions in the head and neck area are associated with higher patient-perceived importance of almost or complete skin clearance.[81] However, patients in our study were still very satisfied with their dupilumab treatment and rated their overall satisfaction 9 out of 10. This was also reflected by the total EASI scores that showed a clinically relevant improvement in all patients, but worsening of the subscores of the head and neck region.

In skin biopsies taken from this paradoxical erythema, spongiosis and eosinophils were largely absent. Histopathology showed a psoriasiform dermatitis, with a perivascular lymphocytic infiltrate, ectatic capillaries in the papillary dermis, and epidermal hyperplasia with elongation of rete ridges. As dupilumab targets the IL-4 receptor alpha chain, it blocks the key signaling pathway for Th2 T-cell differentiation. Blocking the Th2 pathway could hypothetically result in a balance shift towards a more Th1-, Th17-and Th22-dominated response, which could explain the observed psoriasiform reaction pattern.[82,83] However, specific clinical and histopathological hallmarks of psoriasis were absent.[84] Other etiologies that were considered, mostly because of the typical distribution, include *Malassezia furfur*-associated head and neck dermatitis, *Demodex*-associated rosacea-like dermatosis, a drug-induced photosensitivity reaction, and allergic contact dermatitis (ACD). However, clinical presentation and histological features were not deemed indicative of any of these diagnoses. Although we were one of the first to report on this phenomenon, an increasing number of publications on this topic suggests that it is now increasingly observed by physicians.[85] These physicians might now recognize this erythema earlier, whereas prompt identification of this erythema was initially delayed because it was not reported in literature. The large number of possible etiologies that were suggested, reflect the clinical and histopathological heterogeneity. Further research on the underlying mechanisms is ongoing.

Distinction of ACD from other causes in patients with facial erythema or a general sub-optimal response might be important. However, evidence on the reliability of patch test reactions in dupilumab treated patients was scarce and conflicting. We hypothesized that these tests might be unreliable, as investigated in our study described in **Chapter 7.2**. In general, allergy patch testing should be reasonably reproducible as long as methodologic inconsistencies are minimized.[86-88] Wee et

al. reported on the questionable reliability of patch testing in patients who are treated with conventional systemic immunosuppressive agents.[89] In our study, only 29% of the positive reactions could be replicated upon repeated patch testing during dupilumab treatment. We believe that the patch test reactions might be suppressed during dupilumab treatment, possibly leading to false-negative reactions. This might be explained by the largely overlapping underlying immunological pathways in ACD and AD that are suppressed when targeting the Th2 pathway with dupilumab.[90] This could also suggest a therapeutic role for dupilumab in treatment of ACD patients who are not able to fully avoid their allergens (e.g. due to work circumstances). Future prospective studies are warranted to investigate ACD as an indication for dupilumab treatment.

Another possible side-effect associated with a dupilumab induced immunological balance shift was described in **Chapter 8**. The results of our questionnaire study suggested an association between rheumatologic symptoms and dupilumab treatment in AD patients. One out of 3 dupilumab treated AD patients (33%) reported joint complaints, which started (50%) or worsened (50%) during dupilumab treatment. Thirty-nine percent of these patients required a physician's evaluation for their complaints. These consultations mostly revealed arthralgia in absence of clinical, radiological, and laboratory abnormalities suggestive of inflammatory rheumatologic diseases. Factors that might contribute to the etiology of rheumatologic signs and symptoms during dupilumab treatment, which are usually Th1 driven, might include the possible balance shift with increased Th1/Th17 inflammation. In addition, IL-4, which is suppressed by dupilumab treatment, may be required for homeostasis and repair of entheseal tissue. IL-4 is also thought to inhibit the production of pro-inflammatory cytokines including TNF-α, IL-1 and IL-6, which play a key role in RA and in the wider field of arthralgia and inflammatory arthritis.[91] Yet, other factors might play a role in the high proportion of patients experiencing joint complaints during dupilumab treatment. These include the increased risk of developing RA in AD patient regardless of therapy, the previous use of systemic immunosuppressive therapy which might have masked pre-existent rheumatologic symptoms, and the higher BMI (26.6 kg/m2) in patients who reported joint complaints.[92, 93] Although we do believe that dermatologists should be aware of this possible side effect, prospective long-term pharmacovigilance studies are needed to further investigate this association.

As discussed, both the paradoxical head and neck erythema and joint complaints might be explained by a balance shift with a relatively increased expression of Th1/Th17 proteins. This shift might also explain other side effects that emerged in daily

practice, including psoriasiform dermatitis, alopecia areata, and rosacea.[94-96] An immunological balance shift has also been described in e.g. patients with psoriasis treated with biologics (eg. anti TNF-α therapy). In these patients a shift in the opposite direction, i.e. towards a Th2 mediated disease such as eczema was found.[97] However, this balance shift might be present in only a subgroup of patients, as supported by small laboratory studies.[83, 98] It remains to be seen whether these side effects are also associated with emerging targeted therapies such as drugs selectively blocking IL-13 or Janus kinase (JAK). Whereas biologics (e.g. dupilumab, tralokinumab, nemolizumab) inhibit certain cytokines which are for instance Th2 specific, JAK inhibitors (JAKi) inhibit a signaling pathway (i.e. JAK-signal transducer and activator of transcription (STAT) pathway) and are considered less specific compared to biologics. Consequently, side effects which might be caused by skewing of the immune system may be less prominent in patients who are treated with JAKi. In addition, musculoskeletal complaints which are thought to be partially caused by inhibition of IL-4 might be less prevalent in patients treated with tralokinumab which selectively blocks IL-13. Besides, investigating whether and when balance shifts are reversible after switching between drugs would be an interesting topic for future research.

FUTURE PERSPECTIVES AND CONCLUDING REMARKS

As mentioned throughout this general discussion, findings presented in this thesis bring perspective for future research.

To evaluate benefits and harms of new therapies in a wider population, observational studies in a real-world setting are necessary. Data collected in daily practice should ideally be organized in (inter)national registries in order to increase the number of patients and consequently be able to conduct robust (subgroup) analyses. Although dupilumab seems to have an uniquely good safety profile, pharmacovigilance studies and studies specifically investigating side effects such as the paradoxical head-neck erythema and joint complaints are indicated.

In addition, the importance of personalized medicine becomes more evident due to the fast expanding arsenal of AD therapeutic options. Therefore, future studies evaluating the prediction of treatment response to certain therapies, including the use of predictive (serum) biomarkers, would be very helpful. These biomarkers could also be helpful as objective disease severity measures.

Last, the revolution of biomedical and technical developments in medicine will fill unmet needs. However, this should not outweigh the heart of a physician's profession which is characterized by compassion and empathy. In addition, the patient should be treated as an autonomous person and healthcare should be centered to that individual "patient-as-person".

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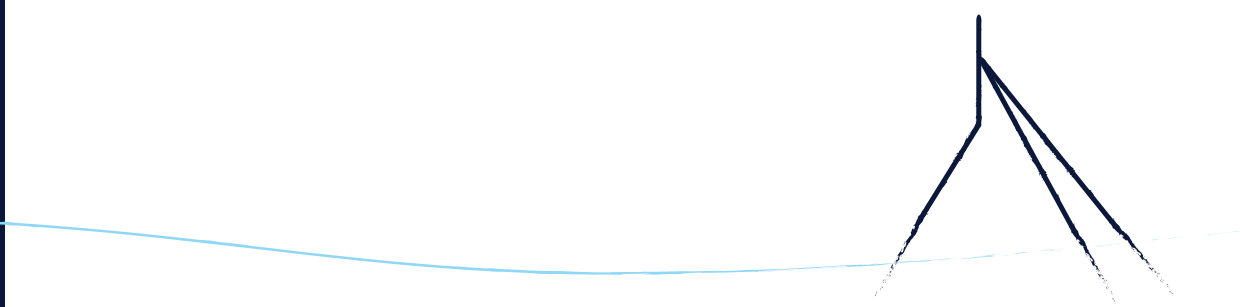
Chapter 10

Summary / Samenvatting



Chapter 1 is the general introduction and outlines the aims of this thesis. Atopic dermatitis (AD) is a very heterogeneous chronic inflammatory skin disease which is associated with a high physical and (psycho)social burden. At present, there is no cure for AD and the main goal of treatment is therefore to establish sustained disease control with an increased quality of life, by providing patient-centered care. AD treatment consists of avoidance of triggering factors, improvement of skin barrier impairment, and anti-inflammatory treatment. Anti-inflammatory treatment follows a step-up or step-down approach using topical therapy, phototherapy, conventional systemic immunosuppressants, or targeted therapies (including biologics and small molecule antagonists). Dupilumab is the first biologic that has been approved for treatment of moderate-to-severe AD and was proven efficacious in clinical trials. However, controlled situations in clinical trials might lead to differences in treatment effect in clinical trials versus daily practice. This emphasizes the importance of observational studies in a real-world setting in order to evaluate the benefits and harms of a therapy in a wider population.

In a qualitative focus group study described in **Chapter 2** we investigated the needs and preferences of patients in AD care. We identified the need for a more patient-tailored approach as an overarching theme in AD care. In addition, patients expressed specific needs and preferences regarding consultations with physicians, AD care organisation, and the therapeutic decision making process. With regard to consultations, patients stressed the need for a personal approach, a certain amount of patients' autonomy in determining disease severity and treatment effect, and an increased recognition of the disease impact. In relation to the organisation of AD care, the need for psychosocial and medical supportive care as well as quick access to healthcare during disease flares were emphasized. Within the context of the decision making process, patients indicated that the provided information, the role of the patient and physician, whether or not treatment goals should be set, and decisive factors for indication and feasibility of novel therapies should be tailored to the needs and preferences of every individual patient. In conclusion, this study demonstrated that AD patients have a variety of needs and preferences regarding AD care which should be considered in order to provide patient-centered care.

In **Chapter 3.1** the effectiveness and side effects of dupilumab treatment in daily practice were evaluated in all AD patients who started treatment in 2 Dutch University Hospitals. Linear mixed-effects (LME) models were used to analyse outcome measures which were prospectively collected in daily practice during the first 16 weeks of dupilumab treatment. The majority of patients that were included in this observational cohort study were using systemic immunosuppressants at the

start of dupilumab treatment, which were often continued and tapered during dupilumab treatment. During follow-up, the estimated mean Eczema Area and Severity Index score (EASI) (0–72) decreased from 18.6 (95% confidence interval (CI) 16.0–21.4) to 7.3 (95% CI 5.4–10.0), and the estimated mean patient-reported outcome measures (PROMs) showed a decrease of 41–66%. Five patients discontinued dupilumab treatment due to side-effects or ineffectiveness. Eye symptoms were the most frequently reported side effects (62%). Overall, dupilumab treatment in daily practice showed a clinically relevant improvement of physician-reported scores and PROMs, which is in line with efficacy data from clinical trials. Besides the frequently reported eye symptoms, there were no apparent safety concerns.

In **Chapter 3.2**, the long-term effectiveness and safety of dupilumab were investigated in daily practice. In total, 221 patients who started dupilumab treatment in 2 Dutch University Hospitals were included and data collected up to 84 weeks of dupilumab treatment were analysed using LME models. We found a sustained good effectiveness of dupilumab treatment with continuation of improvement in time, as expressed by physician- and patient reported outcome measures. Dupilumab treatment was generally well-tolerated, apart from 45 patients who experienced severe eye complaints requiring ophthalmologic examination or medication other than antihistamines and indifferent eye drops. In conclusion, dupilumab treatment 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.

In **Chapter 4** the effectiveness of dupilumab in AD patients in the Netherlands versus Japan was evaluated over a period of 80 weeks of treatment. A longitudinal comparative cohort study revealed important differences in baseline characteristics including sex, disease onset, body mass index, and therapeutic history between patients in the Netherlands versus Japan. Physician-reported severity scores at baseline were higher (i.e. worse) in Japan, while baseline PROMs were worse in the Netherlands. Dupilumab showed significant, comparable and sustained improvement of physician-reported scores in patients in Japan and the Netherlands. However, PROMs showed different trajectories in time with better scores in Japan. This might be explained by cultural differences in coping mechanisms and the perception of disease. Therefore, we believe that in addition to racial disease-specific differences, healthcare system- or culture related characteristics should be considered when interpreting patient-reported outcome measures in clinical trials. Additionally, more objective outcome measures such as biomarkers which are not subjected to behavior would be highly valuable.

In **Chapter 5**, the effect of adjusted dose regimens of dupilumab on disease severity in daily practice in time was evaluated in a retrospective observational study. Dose regimens were adjusted upon expert opinion due to reasons such as sustained effectiveness or side effects. These adjustments were in accordance with the patients' preferences. LME models were used to assess the effect of extended dose regimens. An extended interval has shown sustained effectiveness, similar to patients with a standard interval. However, a causal and signal effect could not be distinguished in this retrospective study. Therefore, a future study with uniform dose adjustment criteria and strategies is warranted.

In **Chapter 6**, we proposed an approach for the transition from conventional systemic immunosuppressants to dupilumab in AD patients. We found that immunosuppressants can be tapered after 8 weeks of dupilumab treatment, guided by the degree of disease control. Disease control should be determined through shared decision making, assisted by validated tools assessing disease control. Our approach resulted in a seamless transition between therapies, without new side effects emerging from the use of these combinations. Patients who did not follow the transition regimen more often experienced a rebound phenomenon in the first months of dupilumab treatment. Patients who were unable to taper and discontinue systemic immunosuppressants should continue in the lowest possible dose or should discontinue dupilumab treatment and switch to other new targeted therapies within the fast expanding arsenal of AD therapeutic options.

In **Chapter 7.1** we reported on a paradoxical head-neck erythema which appeared 10 to 39 weeks after starting dupilumab treatment. Patients presented with a relatively sharp demarcated, patchy erythema in the head and neck area that was mostly asymptomatic and showed no or less scaling compared to their usual eczema. Lesional biopsies showed ectatic capillaries, a perivascular lymphohistiocytic infiltration, and epidermal hyperplasia with elongation of rete ridges. Spongiosis and eosinophils were largely absent. In conclusion, this phenomenon was both clinically and histopathologically heterogeneous and most suggestive of a drug induced skin reaction. Further research on the underlying mechanisms is ongoing.

Distinction of ACD from other causes in patients with head and neck erythema or a general sub-optimal response might be important. In **Chapter 7.2**, we assessed the reliability of patch testing during dupilumab treatment. We found out that only 29% of positive patch test reactions observed before dupilumab treatment, could be re-elicited in AD patients using dupilumab treatment. Consequently, this study suggests that patch test reactions in dupilumab treated AD patients might be sup-

pressed, possibly leading to false-negative reactions. Further prospective studies are warranted to elucidate the effect of dupilumab on patch testing in patients with AD and the therapeutic effect of dupilumab in ACD patients.

Patients treated with dupilumab in daily practice frequently reported presence of joint complaints. Therefore we performed a cross-sectional survey-based retrospective cohort study to investigate the proportion and nature of joint complaints in dupilumab treated AD patients, as described in **Chapter 8**. Thirty-three percent of the included patients (n=54/165) reported joint complaints, with starting pain or starting stiffness being the most frequently reported symptoms. Half of these patients experienced pre-existent joint complaints, but these complaints worsened in most patients. Medical assessments revealed arthralgia in absence of abnormalities suggestive of inflammatory rheumatologic diseases in most patients. Our results might suggest an association between rheumatologic symptoms and dupilumab treatment in AD patients. Although additional studies are warranted to further investigate this association, dermatologists should be aware of this possible side effect.

Hoofdstuk 1 vormt de algemene introductie en toont de doelen van mijn promotie onderzoek. Atopisch eczeem is een heterogene chronisch inflammatoire huidziekte. Atopisch eczeem is geassocieerd met een hoge fysieke en (psycho)sociale draaglast. Aangezien we de ziekte niet kunnen genezen, vormen het bereiken van ziektebeheersing en een hogere kwaliteit van leven de belangrijkste behandeldoelen. Dit willen we bereiken middels het leveren van zogenaamde patiëntgerichte zorg. De behandeling van atopisch eczeem bestaat uit het vermijden van uitlokkende factoren, het verbeteren van de huidbarrière en anti-inflammatoire behandeling. Anti-inflammatoire behandeling wordt trapsgewijs toegepast waarbij topicale therapie, lichttherapie, conventionele systemische immunosuppressiva en de nieuwere generatie medicijnen, namelijk "targeted therapies", elkaar opvolgen. Dupilumab is de eerste biologic die is goedgekeurd voor de behandeling van matig tot ernstig atopisch eczeem. Dupilumab bleek effectief in de grote geneesmiddelenstudies. Toch weten we dat de sterk gereguleerde situaties in deze studies kunnen leiden tot een verschil in behandeleffect in vergelijking met de realiteit in de dagelijkse praktijk. Dit benadrukt het belang van observationele studies in een dagelijkse praktijksetting om zodoende de voor- en nadelen van een behandeling in een grote en meer gevarieerde populatie te kunnen evalueren.

Om in de toekomst goede patiëntgerichte eczeemzorg te kunnen leveren, onderzochten we in een kwalitatieve focusgroep studie die werd beschreven in **Hoofdstuk 2** de wensen en behoeften van patiënten in de huidige eczeemzorg. We identificeerden de algemene behoefte aan een aanpak die meer wordt afgemeten aan individuele patiënten. Daarnaast deelden patiënten specifieke wensen en behoeften met betrekking tot de consulten met zorgverleners, de organisatie van de eczeemzorg en het therapiekeuze proces. Patiënten gaven aan dat er in consulten sprake moet zijn van een persoonlijke benadering met erkenning van de ziektelast. Daarnaast zouden patiënten meer autonomie moeten krijgen en voelen bij het bepalen van de ernst van de ziekte en het behandeleffect. Als het gaat om de organisatie van de eczeemzorg werd er benadrukt dat er aandacht geschonken moet worden aan ondersteunende zorg op zowel psychosociaal als medisch vlak. Daarnaast moet zorg ten tijde van opvlammingen van de ziekte snel bereikbaar zijn. Patiënten gaven aan dat het therapiekeuze proces vooral aangepast moet worden naar de wensen en behoeften van de individuele patiënt. Dit geldt voor het verschaffen van informatie, de rol van arts en patiënt, het wel of niet bespreken van behandeldoelen en het bespreken van meewegende factoren en praktische haalbaarheid bij de keuze voor een behandeling. Concluderend liet deze studie zien dat patiënten met atopisch eczeem een variëteit aan wensen en behoeften hebben binnen de eczeem zorg. Deze wensen en behoeften moeten in

overweging genomen worden om op die manier patiëntgerichte zorg te kunnen leveren.

In **hoofdstuk 3.1** werden de effectiviteit en bijwerkingen van dupilumab behandeling in de dagelijkse praktijk geëvalueerd in alle patiënten met atopisch eczeem die zijn gestart met dupilumab in 2 Nederlandse Universitaire Ziekenhuizen (n=95). Linear mixed-effects (LME) modellen werden gebruikt om de uitkomstmaten te analyseren. Data werden prospectief verzameld in de dagelijkse praktijk gedurende de eerste 16 weken van de dupilumab behandeling. De meerderheid van de patiënten die werden geïncludeerd in deze observationele studie gebruikten systemische immunosuppressiva bij de start van dupilumab behandeling. Deze immunosuppressiva werden vaak gecontinueerd en afgebouwd gedurende de behandeling met dupilumab. Gedurende de behandeling daalde de gemiddelde Eczema Area and Severity Index (EASI) score (0-72) van 18.6 (95% betrouwbaarheidsinterval (BI) 16.0-21.4) naar 7.3 (95% BI 5.4-10.0). De patiënt-gerapporteerde uitkomstmaten daalden met 41-66% vanaf start van dupilumab behandeling. Vijf patiënten stopten met dupilumab vanwege bijwerkingen of onvoldoende effectiviteit. Oogklachten bleken de meest gerapporteerde bijwerkingen (62%). Samenvattend zorgde dupilumab behandeling in de dagelijkse praktijk voor een klinisch relevante verbetering van de arts- en patiënt-gerapporteerde uitkomstmaten. Deze verbetering was vergelijkbaar met de verbetering in de grote geneesmiddelenstudies. Met uitzondering van de gerapporteerde oogklachten werd de behandeling goed verdragen door de patiënten.

In **Hoofdstuk 3.2** werd de effectiviteit en veiligheid van behandeling met dupilumab op de langere termijn in de dagelijkse praktijk onderzocht. In totaal werden er in deze studie 221 patiënten die zijn gestart met dupilumab behandeling in 2 Nederlandse Universitaire Ziekenhuizen geïncludeerd. De uitkomstmaten die werden verzameld tot 84 weken behandeling werden geanalyseerd met behulp van LME modellen. We vonden een aanhoudende, goede effectiviteit van dupilumab behandeling met een voortgaande verbetering over de tijd. Dit werd weergegeven middels zowel arts- als patiënt-gerapporteerde uitkomstmaten. Dupilumab behandeling werd goed verdragen door de patiënten, alhoewel er 45 patiënten ernstige oogklachten rapporteerden. Deze oogklachten behoefden beoordeling door een oogarts of werden met medicatie anders dan indifferente- of antihistaminica oogdruppels behandeld. Op basis van deze studie concludeerden we dat dupilumab een effectieve behandeling is voor de lange termijn, tot ten minste 84 weken. Deze behandeling, eventueel gecombineerd met topicale therapie of gelijktijdige behandeling met systemische immunosuppressiva, toonde een aanhoudende verbetering van huidafwijkingen, symptomen en kwaliteit van leven.

In **Hoofdstuk 4** werd de effectiviteit van dupilumab in eczeempatiënten in Nederland vergeleken met de effectiviteit in patiënten in Japan, gedurende 80 weken behandeling. Een longitudinale, vergelijkende cohort studie toonde belangrijke verschillen tussen Japan en Nederland als het gaat om patiëntkarakteristieken zoals geslacht, leeftijd van ontstaan van eczeem, BMI en therapeutische voorgeschiedenis. Arts-gerapporteerde uitkomstmaten bij start van de behandeling waren hoger (en dus slechter) in Japan, terwijl de patiënt-gerapporteerde scores bij start van behandeling juist slechter waren in de Nederlandse populatie. Dupilumab toonde een significante, aanhoudende verbetering van arts-rapporteerde uitkomstmaten die vergelijkbaar was in Japan en Nederland. Desalniettemin toonden de patiënt-gerapporteerde uitkomstmaten verschillende trajecten in beide landen, met betere scores in Japan. Dit zou mogelijk verklaard kunnen worden door culturele verschillen in coping mechanismen en ziektebeleving. Hierdoor zouden kenmerken geassocieerd met het gezondheidssysteem of de cultuur in overweging genomen moeten worden bij het interpreteren van uitkomsten in (geneesmiddelen)studies. Daarnaast zouden objectievere uitkomstmaten zoals biomarkers, die niet onder invloed staan van bijvoorbeeld gedrag, van toegevoegde waarde zijn.

In **Hoofdstuk 5** werd het effect van aangepaste doseringsintervallen op de ziekte-ernst geëvalueerd in de dagelijkse praktijk middels een retrospectieve observationele studie. Doseringsintervallen werden aangepast gebaseerd op de inschatting van arts en patiënt om redenen zoals stabiele ziektebeheersing, onvoldoende effectiviteit of aanwezigheid van een opvlamming in de tweede week van het standaard doseringsinterval. LME modellen werden gebruikt om het effect van deze aanpassingen op de ziekte ernst weer te geven. Een verlengd interval toonde een aanhoudende effectiviteit die vergelijkbaar was met patiënten die werden behandeld in het standaard doseringsinterval van 2 weken. Gezien het retrospectief en niet-standaardiseerd observationeel karakter van deze studie kan er geen onderscheid gemaakt worden in een causaal- en signaaleffect. Daarom is een toekomstige prospectieve studie met uniforme criteria voor aanpassing van het doseringsinterval nodig om een duidelijke uitspraak te kunnen doen over de effectiviteit van deze aanpassingen.

In **Hoofdstuk 6** werd er een aanpak voor de transitie van conventionele systemische immunosuppressiva naar dupilumab in eczeempatiënten besproken. Er werd gevonden dat immunosuppressiva kunnen worden afgebouwd na 8 weken dupilumab behandeling, op geleide van de mate van ziektebeheersing. Ziektebeheersing kan worden bepaald middels overeenstemming tussen arts en patiënt, waarbij ondersteunende vragenlijsten gebruikt kunnen worden. Deze aanpak toonde een

goede overgang tussen beide therapieën waarbij er geen nieuwe bijwerkingen ontstonden door de tijdelijke combinatie van beide therapieën. Patiënten die niet werden behandeld volgens deze aanpak maakten vaker een opvlamming van hun ziekte door in de eerste maanden van dupilumab behandeling vergeleken met de mensen die wel volgens de voorgestelde aanpak behandeld werden. Er werd aanbevolen dat patiënten die geen ziektebeheersing konden bereiken de immunosuppressiva erbij konden blijven gebruiken in de laagst mogelijke dosering, dan wel dupilumab zouden moeten staken. Deze patiënten zouden dan kunnen starten met een nieuwe therapie binnen het snel uitbreidende behandelarsenaal voor constitutioneel eczeem.

In **Hoofdstuk 7.1** werd er gerapporteerd over een paradoxaal hoofd-hals erytheem wat zichtbaar werd na 10-39 weken dupilumab behandeling. Patiënten toonden een relatief scherp omschreven erytheem in het hoofd-hals gebied. Het erytheem was asymptomatisch in de meeste gevallen waarbij er niet of nauwelijks sprake was van squamatie. Lesionale huidbiopten toonden ectatische capillairen, perivasculaire lymfohistiocytaire infiltraten en epidermale hyperplasie met verlengde retelijsten. Concluderend kan er gesteld worden dat er sprake was van een klinisch en histopathologisch heterogeen beeld. Het fenomeen was het meest suggestief voor een dupilumab-geïnduceerde reactie. Aanvullend onderzoek naar de onderliggende mechanismen wordt op dit moment uitgevoerd.

Om meer te weten te komen over de onderliggende oorzaak van de genoemde roodheid is het uitsluiten van een contactallergie belangrijk. In **Hoofdstuk 7.2** werd de betrouwbaarheid van plakproeven gedurende dupilumab behandeling onderzocht. Uit dit onderzoek bleek dat slechts 29% van de reacties die voorafgaand aan dupilumab behandeling positief waren, opnieuw opgewekt konden worden tijdens dupilumab behandeling. Dit suggereert dat reacties in epicutaan allergologisch onderzoek mogelijk onderdrukt worden in eczeem patiënten die met dupilumab behandeld worden, wat kan leiden tot fout-negatieve reacties. Aanvullende prospectieve studies zijn nodig om het onderdrukkend effect van dupilumab en andere immunsuppressiva op plakproeven bij patiënten met eczeem te onderzoeken.

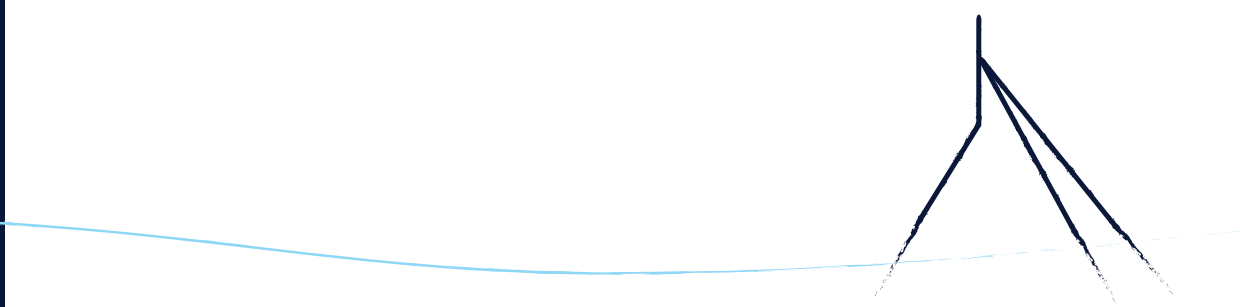
Patiënten die werden behandeld met dupilumab in de dagelijkse praktijk rapporteerden aanwezigheid van gewrichtsklachten. Daarom voerden we een retrospectief cross-sectioneel vragenlijstonderzoek uit om de proportie en aard van de gewrichtsklachten in eczeempatiënten die met dupilumab werden behandeld te onderzoeken. Deze studie werd beschreven in **Hoofdstuk 8.** Drieëndertig procent

van de deelnemers aan de enquête (n=54/165) rapporteerden gewrichtsklachten, waarbij startpijn of startstijfheid de meest gerapporteerde symptomen vormden. De helft van deze patiënten hadden deze klachten pre-existent opgemerkt, alhoewel de klachten toenamen in ernst gedurende dupilumab behandeling. Medische beoordeling toonde artralgie zonder inflammatoire kenmerken in de meeste patiënten. Deze resultaten zouden mogelijk een associatie tussen reumatologische symptomen en dupilumab behandeling in eczeempatiënten kunnen suggereren. Ondanks dat aanvullende studies nodig zijn om deze bevinding verder te onderzoeken, zouden dermatologen zich bewust moeten zijn van deze mogelijke bijwerking.

Appendices

Abbreviations

Publications
Contributing authors
PhD portfolio
Curriculum vitae
Dankwoord



ABBREVIATIONS

ACD	allergic contact dermatitis
AD	atopic dermatitis
ADCT	Atopic Dermatitis Control Tool
AE	adverse event
AZA	azathioprine
BMI	body mass index
CI	confidence interval
CsA	cyclosporin A
DLQI	Dermatology Life Quality Index
EASI	Eczema Area and Severity Index
HOME	Harmonizing Outcome Measures for Eczema
HSV	Herpes Simplex virus
ICDRG	International Contact Dermatitis Research Group
IGA	Investigator Global Assessment
IL	Interleukin
IQR	interquartile range
JAK	Janus kinase
JAKi	Janus kinase inhibitor
JAK-STAT	Janus kinase - signal transducer and activator of transcription
LME	linear mixed-effects
MTX	methotrexate
MYF	mycophenolic acid
MMF	mycophenolate mofetil
No.	number
NRS	Numeric Rating Scale
POEM	Patient-Oriented Eczema Measure
PROM	Patient-Reported Outcome Measure
RECAP	Recap of atopic eczema
RF	Rheumatoid factor
SD	standard deviation
Th	T-helper
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
UV	ultraviolet

PUBLICATIONS

In this thesis

L.E.M. de Wijs, C.R.G. Schreurs, T. Nijsten, P.H.P. de Jong, D.J. Hijnen
Presence of joint complaints during dupilumab treatment in atopic dermatitis patients: an undiscovered side effect?
Submitted

L.E.M. de Wijs, S. van Egmond, A.C.A. Devillers, T. Nijsten, D.J. Hijnen, M.Lugtenberg
Needs and preferences of patients regarding atopic dermatitis care in the era of new therapeutic options: a qualitative study.
Submitted

L.E.M. de Wijs, J.I. Olydam, J. van Rosmalen, T. Nijsten, D.J. Hijnen
Adjusted dosing regimens in dupilumab treatment for atopic dermatitis: daily practice experiences
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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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L.E.M. de Wijs, C.R.G. Schreurs, T. Nijsten, D.J. Hijnen
Baricitinib for atopic dermatitis patients who responded inadequately to dupilumab treatment: first daily practice results
Submitted

L.E.M. de Wijs, M.M. Joustra, J.I. Olydam, T, Nijsten, D. Hijnen
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EASI p-EASI: predicting disease severity in atopic dermatitis patients treated with tralokinumab
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A. Ragamin, **L.E.M. de Wijs**, D.J. Hijnen, N.J.T. Arends, M.L.A. Schuttelaar, S.G.M.A. Pasmans, M.B. Bronner
Care for children with atopic dermatitis in the Netherlands during the COVID-19 pandemic: Lessons from the first wave and implications for the future.
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A.L. Bosma, **L.E.M de Wijs**, M.H. Hof, B.R. van Nieuwenhuizen, L.A.A. Gerbens, M.A. Middelkamp-Hup, D. Hijnen, P.I. Spuls
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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Numbers on injectable treatments in the Netherlands in 2016
J Eur Acad Dermatol Venereol. 2018 Aug; 32(8): e328-e330

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Basic Introduction course on SPSS, MolMed	2018	1.0 ECTS
Introduction to data-analysis, NIHES	2018	0.9 ECTS
Basis Regelgeving en Organisatie voor Klinisch Onderzoek (BROK)	2018	1.5 ECTS
Biomedical English Writing, MolMed	2018	2.0 ECTS
The Coure on R, MolMed	2018	1.8 ECTS
Pubmed literature search course	2018	0.3 ECTS
Workshop Open Clinica	2019	0.2 ECTS
Workshop Gemstracker	2019	0.2 ECTS
Research integrity, Erasmus MC	2020	0.3 ECTS
Entrepreneurship Awakening program (Erasmus Centre for Entrepreneurship)	2021	1.0 ECTS
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10th Georg Rajka International Symposium on Atopic Dermatitis, Utrecht	2018	1.0 ECTS
6th PhD weekend Dermatology Erasmus MC, Breda	2018	1.0 ECTS
Scientific meeting of the NVDV, Rotterdam	2018	0.3 ECTS
20th NVED conference, Lunteren	2019	1.0 ECTS
7th PhD weekend Dermatology Erasmus MC, Den Haag	2019	1.0 ECTS
28th Congress of the EADV, Madrid	2019	1.0 ECTS
21st NVED conference, Lunteren	2020	1.0 ECTS
11th Georg Rajka International Symposium on Atopic Dermatitis, digital	2021	1.0 ECTS
8th PhD weekend Dermatology Erasmus MC, Leiden	2021	1.0 ECTS
30th Congress of the EADV, digital meeting	2021	1.0 ECTS
Oral presentations		
Dupilumab treatment in daily practice, NVED conference	2019	1.0 ECTS
Regional AD meetings (twice a year)	2019	1.0 ECTS
Paradoxical head-neck erythema, 28th Congress of the EADV	2019	1.0 ECTS

Paradoxical head-neck erythema, NVED conference	2020	1.0 ECTS
Introduction to AD research in Rotterdam, Osaka Habikino Medical Center	2020	1.0 ECTS
Regional AD meetings (twice a year)	2020	1.0 ECTS
Regional AD meetings (twice a year)	2021	1.0 ECTS
The doctor-patient relationship, 30th Congress of the EADV	2021	1.0 ECTS
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Research fellowship ISAD (amount: €10 000)	2020	2.0 ECTS
Teaching		
ICK teaching: Atopic dermatitis for medical students	2018-19	0.5 ECTS
Research education meetings Department of Dermatology (4 times)	2018-21	1.0 ECTS
Training colleagues in AD care and organization	2019-21	1.0 ECTS
Master thesis of medical student José vd Waa	2018	1.0 ECTS
Master thesis of medical student Tan Nguyen	2019	1.0 ECTS
Master thesis of medical student Maaike Joustra	2020	1.0 ECTS
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Research meetings Dept. of Dermatology, Erasmus MC	2018-21	3.5 ECTS
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Next Generation Forum, Leo Pharma	2021	0.5 ECTS

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Linde Elisabeth Maria de Wijs is geboren op 6 februari 1993 te Echt. Na het behalen van haar Gymnasium diploma op het Trevianum te Sittard, werd ze in 2011 toegelaten tot de geneeskunde opleiding aan de Universiteit van Maastricht. Tijdens haar coschappen werd de liefde voor Dermatologie geboren, waarna ze haar keuze coschap en haar semi-stages doorliep binnen dit vakgebied. Na het behalen van haar artsexamen is ze gestart als arts-assistent niet in opleiding op de afdeling Dermatologie in het Maasstad Ziekenhuis. Na hier ruim een half jaar met veel plezier gewerkt te hebben, maakte ze in februari 2018 de overstap naar de afdeling Dermatologie in het Erasmus MC te Rotterdam. Hier is ze gestart met haar promotieonderzoek op het gebied van atopisch eczeem, een ziektebeeld wat haar interesse heeft gewekt vanaf de eerste kennismaking met de Dermatologie. Ze doorliep haar promotietraject onder begeleiding van promotor prof. dr. T. Nijsten en copromotor dr. D.J. Hijnen. Gedurende deze periode heeft ze met veel overgave meegewerkt aan het opzetten van nieuwe onderzoekslijnen, het opzetten van een biobank, het uitvoeren van klinische trials, het uitbreiden en optimaliseren van de eczeemzorg, en sociale commissies. Gedurende haar promotietraject bezocht ze het Osaka Habikino Medical Center in Japan in het kader van een Research Fellowship, mogelijk gemaakt door een toegekende beurs van de International Society of Atopic Dermatitis. Daarnaast heeft zij gedurende 2 jaar met veel plezier deel uitgemaakt van het landelijk bestuur van Stichting Medical Business. In januari 2022 begon ze aan de specialisatie tot dermatoloog in het Erasmus Medisch Centrum te Rotterdam.

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