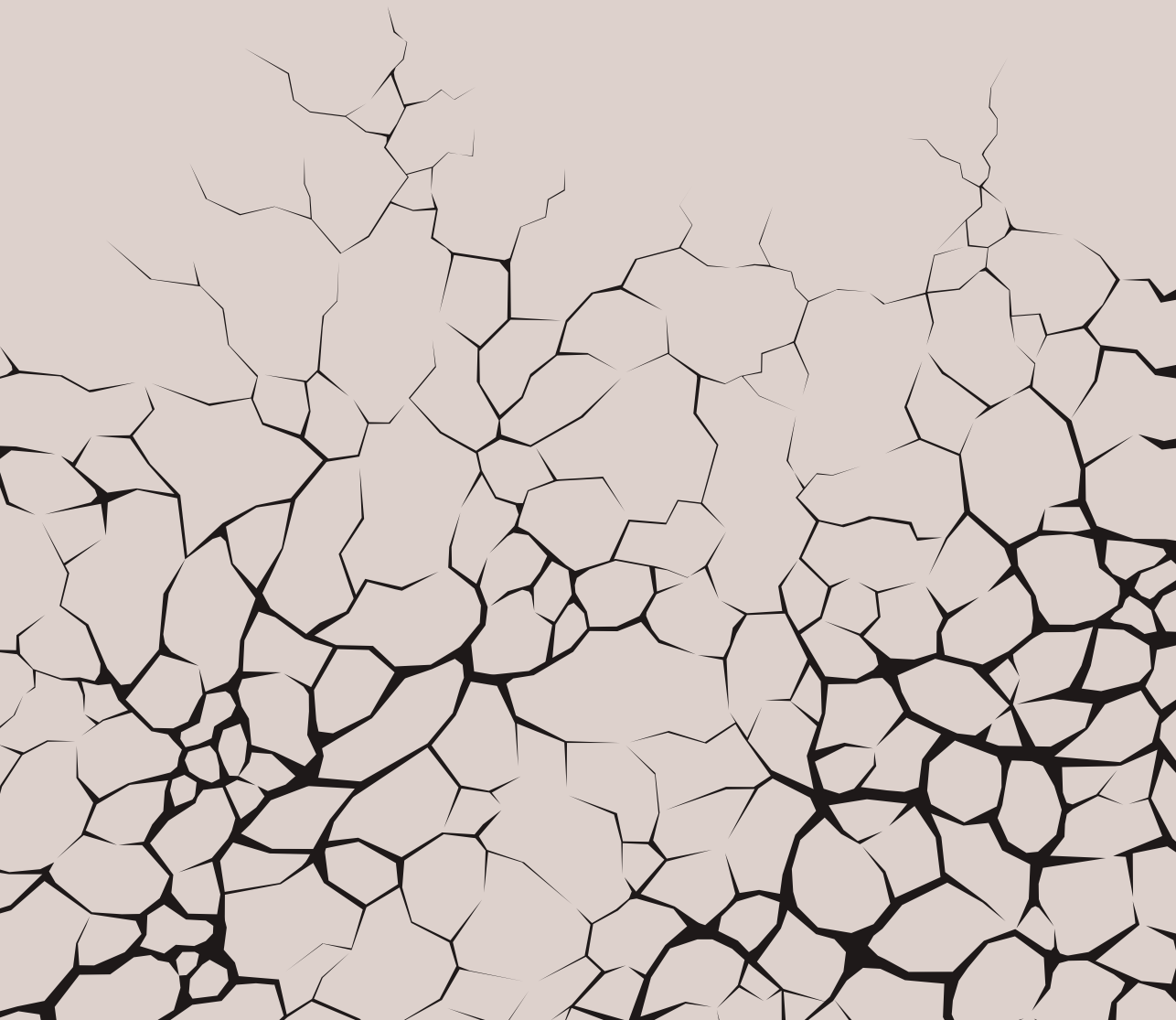
Optimal management of patients with atopic dermatitis at the edge of a new era of advanced systemic treatments

Lieneke Ariëns



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PhD thesis, Utrecht University, the Netherlands

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Optimal management of patients with atopic dermatitis at the edge of a new era of advanced systemic treatments

Behandeling van patiënten met constitutioneel eczeem in een nieuw tijdperk met doelgerichte therapieën
(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
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ingevolge het besluit van het college voor promoties
in het openbaar te verdedigen op

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Chapter 1

General introduction

Atopic dermatitis

Atopic dermatitis (AD) is the most common chronic inflammatory skin disease worldwide with an increasing prevalence up to 20% in children and 10% in adults in developed countries.[1, 2] While AD may occur at any age, it usually starts in early childhood, typically at the age of 3-6 months.[3] The course of AD can be continuous after initiation, but can also show a relapsing-remitting nature. In early birth cohort studies, high percentages of improvement or clearance of AD up to 70% until late childhood have been demonstrated.[4] However, recent studies show a high prevalence of AD in adults, including patients with a persistent course, with relapses after a long symptom free interval, and with new adult-onset forms.[4] These data show that AD is a lifelong condition characterized by intermittent disease activity and various clinical phenotypes. Atopic dermatitis is characterized by cutaneous inflammation, intense pruritus, and causes a profound impact on the quality life of patients and their relatives due to the associated sleep deprivation and social stigmatization.[5, 6]

The pathogenesis of AD is multifactorial and involves a complex interplay between genetic, environmental, and immunological factors with epithelial barrier disruption and a predominantly type 2 skewed immune dysregulation as two main factors (Figure 1). Lesional skin of patients with AD shows a hyperactive immune system characterized by a t-cell infiltrate (predominantly characterized by CD4 expression), dendritic cells, eosinophils, mast cells and immunoglobulin E (IgE)-producing plasma cells. AD is considered as a primarily T helper 2 (Th2) cell-driven disease with a high expression of Th 2 related markers (including interleukin (IL)-4, IL-5, IL-13, IL31, and TARC/CCL17) in lesional skin and the peripheral blood of patients with AD.[7-9] Although AD is thought to be a primarily Th 2 driven disease, recent research has demonstrated the role of other immune pathways including Th1, Th22 and Th17 in the pathogenesis of AD.[10] During the past decade, the new understanding in disease pathogenesis and the key drivers of AD has led to the development of a considerable number of promising targeted therapeutic options for the treatment of AD including biologics blocking the Th2/Th22 pathways and small molecules targeting the Janus kinase - signal transducer and activator of transcription (JAK-STAT) pathway. [11]

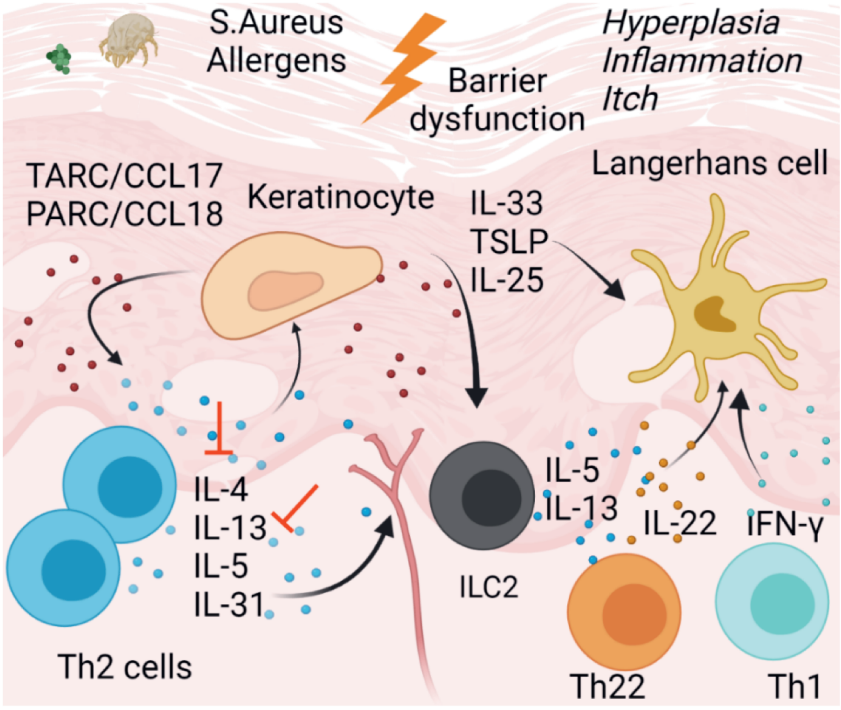

Figure 1. Atopic dermatitis is T cell-meadiated inflammatory disease of the skin. Patients often have a disturbed skin microbial composition. Figure adapted from "Immune monitoring and treatment in immune-mediated inflammatory diseases" by van Wijk F et al. 2022, Nature Communications 2022 13:1 [Internet]. 2022 Jun 7 [cited 2022 Jun 23]; Available from: https://www.nature.com/articles/s41467-022-30891-7.

Atopic dermatitis is associated with many comorbid conditions including an increased cardiovascular risks as well as cutaneous and extra-cutaneous-, multi-organ- and systemic infections.[12] The association with these comorbid conditions is likely multifactorial with immune dysregulation, skin-barrier dysfunction, chronic sleep disturbance, decreased physical activity, and iatrogenic factors such as increased alcohol consumption and cigarette smoking as contributing factors.[12] Patients with AD, particularly moderate-to-severe AD, are also at higher risk of depressive symptoms, clinical depression and suicidality.[13] The comorbid conditions, high rates of anxiety and depression, patient-reported symptoms and lower health-related quality of life (HrQoL) causes a major burden in patients with moderate-to-severe AD.[14] Since many of these factors are directly related to the severity of AD and inadequate disease control, these data imply the high unmet needs in this patient population.

In addition, AD also has a substantial socioeconomic impact derived from direct costs of treatment and indirect costs caused by missed work and school and reduced work productivity.[15] Several studies attempted to quantify the costs associated with AD, however, reported costs varies widely due to different treatment settings and different AD severities. In addition, studies used different definitions of directs and indirect costs and due to the variability in healthcare systems across different countries estimated costs in studies are difficult to compare.[5, 16, 17]

With currently new more-targeted therapeutics being approved for the treatment of moderate-to-severe AD and many promising therapeutics currently being studied in clinical trials [18], more information on the economic burden and impact on HrQoL in the group of AD patients indicated for these treatments is needed. It is expected that these new treatments will increase drug acquisition costs, which may, in part, be compensated by the impact of these treatments on the HrQoL and costs of productivity losses.

Conventional therapeutic options and unmet medical needs

The majority of the AD patients can be adequately controlled with topical corticosteroids, topical immunomodulators, or ultraviolet (UV) light therapy. However, in patients with difficult-to-treat AD in which controlled disease cannot be reached with safe amounts of topical corticosteroids and adequate instructions and self-management training, treatment with systemic immunosuppressive drugs may be required.[19] Until recently, the last breakthrough in the treatment of difficult-to-treat AD was reported in 1991 for the use of cyclosporine A.[20] For many years, cyclosporine A was the only registered oral immunosuppressive drug for the treatment of AD in European countries. Although treatment with cyclosporine A is very effective, nearly half of the patients has to discontinue treatment due to side effects (mostly nephrotoxicity and hypertension) and/or ineffectiveness.[21] In the United States (US), oral corticosteroids were the only approved systemic drugs for the treatment of AD for many years. However, due to the potential side effects and the risk of severe rebound flares after discontinuation, the use of oral corticosteroids should be limited to short-term use.[22] Several other broad immunosuppressants including methotrexate (MTX), azathioprine (AZA), and mycophenolate mofetil (MMF) are commonly used off-label for the treatment of difficult to treat AD in daily practice. Although these drugs are not officially registered for the treatment of AD, most of them are incorporated in international guidelines. However, studies have shown that these drugs are only effective in about half of the AD patients and

treatment is discontinued in many patients due to side effects and/or ineffectiveness.[21, 23] Thus, there has been a large unmet need for effective and safe long-term systemic treatment for moderate-to-severe AD patients.

New era of advanced systemic treatments in atopic dermatitis

In the past decade, the improved understanding of the underlying immune pathogenesis of AD have led to the development of new, more targeted therapies. Dupilumab, a fully human monoclonal antibody targeting the IL-4 receptor alpha, thereby blocking the IL-4 and IL-13 pathway, is the first antibody-based treatment that has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for moderate-to-severe AD. Dupilumab is currently registered in the United States, Europe, and Japan for moderate-to-severe AD patients and was recently also approved for children aged 6 years and older and adolescents inadequately controlled with topical treatment or in whom topical therapies are not advisable.[24] In consensus based European clinical guidelines, the use of dupilumab is additionally recommended for patients in whom other systemic treatments are not advisable.[25, 26] Phase III clinical trials including patients with moderate-to-severe AD showed significantly improved disease severity measured by the Eczema Area and Severity Index (EASI) and Investigator's Global Assessment (IGA), and HrQoL of dupilumab treatment with or without concomitant topical corticosteroids until 16 and 52 weeks.[27-30] The latest phase III open-label extension study demonstrated that dupilumab treatment was effective and well tolerated up to 76 weeks.[31] Overall, dupilumab was well tolerated in all clinical trials and has shown a favorable safety profile with mostly mild side effects being observed. Patients treated with dupilumab showed higher rates of injection-site reactions and localized herpes simplex infections (only in the first trials) compared to the placebo-treated patients.[27-31] Dupilumab treated groups also showed a higher incidence of conjunctivitis (5–28%) compared to the placebo-treated groups (1–11%). In the clinical trials, the development of conjunctivitis was associated with severe AD or coexisting allergic conjunctivitis.[32] The pathogenesis of conjunctivitis occurring during dupilumab treatment remains unknown. Higher rates of conjunctivitis were not reported in clinical trials studying dupilumab for the treatment of asthma or nasal polyposis, suggesting an AD-specific underlying mechanism. [33-35]

Recently, tralokilumab, a fully human monoclonal antibody that potently and specifically neutralizes IL-13 and janus kinase (JAK) inhibitors abrocitinib, baricitinib, and upadacitinib were approved for the treatment of moderate-severe AD. [36-41] The

introduction of these new, more targeted treatment options for AD and more therapeutics in the pipeline is currently expanding the field of AD treatment and changing the treatment algorithm for moderate-severe AD patients, as proposed in Figure 2.

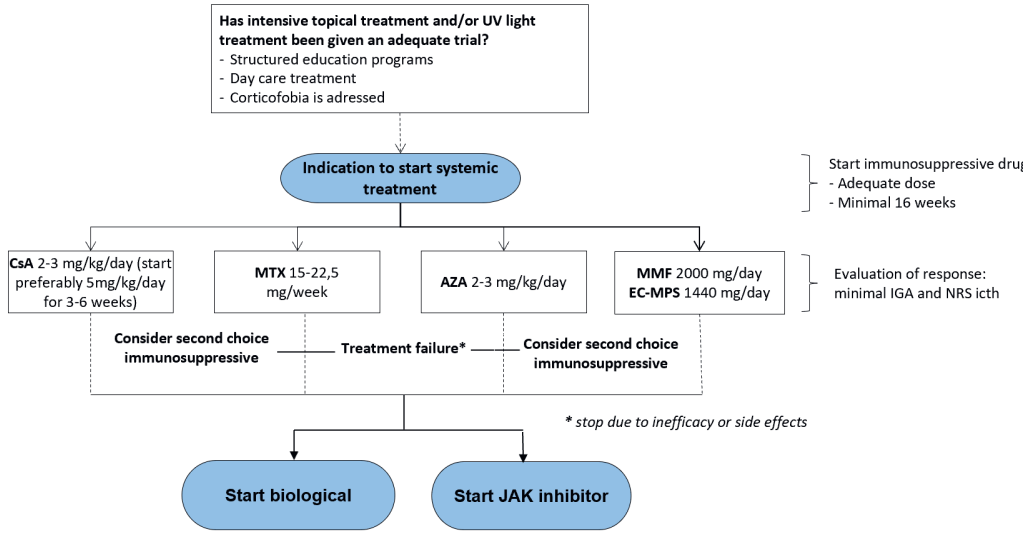

Figure 2. Proposed treatment alcorithm for currently available systemic treatment of atopic dermatitis (AD) in Europe. The introduction of biologics and small molecules will highly change the current treatment algorithm. Figure adapted from "Dupilumab in atopic dermatitis: rationale, latest evidence and place in therapy" by Lieneke Ariens et al. 2018, Ther Adv Chronic Dis. 9(9): 159-170. AZA, azathioprine; CsA, cyclosporine A; EC-MPS, enteric-coated mycophenolate sodium; IGA, Investigator Global Assessment; MMF, mycophenolate mofetil; MTX, methotrexate; NRS, Numeric Rating Scale

From clinical trial to daily practice: the importance of real-life registries

Extensive clinical trial programs have been globally conducted to evaluate the clinical efficacy and safety of dupilumab in patients with AD. Dupilumab was studied as monotherapy, in combination with concomitant topical corticosteroids, and after failure of cyclosporine A treatment in >3000 adult patients with moderate-to-severe AD in one phase I, two phase II and four phase III clinical trials. [27, 28, 32, 42, 43] This clinical trial program in adults was followed by an extensive clinical trial program in children and adolescences.[44-46] In addition, long-term dupilumab treatment was studied in open-label extension studies including patients who had previously participated in phase 1-3 clinical trials. [31, 44, 47] In AD history it was the first time that such an extensive clinical trial program was enrolled for a new systemic therapy. Nowadays, large

multicenter randomized placebo controlled trials are required before a new drug is registered. Patients included in randomized controlled trials are usually carefully screened based on predefined strict in- and exclusion criteria and represent a rather homogeneous population. However, in the real-world the patient population is less homogeneous because of the presence of comorbidities which were excluded in clinical studies, lower treatment compliance, concomitant medication use or higher age. [48, 49] Therefore, despite the extensiveness of a clinical trial program and the high quality of clinical trials, results may not be generalizable to daily practice.

In a real-life setting, the balance between effectiveness and side effects determines whether treatment will be continued. In addition, the availability of alternative treatment options and patients' adherence also influence the treatment success in daily practice. Furthermore, the main outcomes on the efficacy of dupilumab in AD clinical trials were fixed endpoints such as the proportion of patients achieving a ≥75% reduction in EASI score from baseline (EASI-75). However, these fixed endpoints do not capture the full range of clinical benefits since treatment effects both clinician- (including EASI and IGA) and patients-reported (including pruritus and HrQoL) outcomes. Therefore, based on these fixed endpoints, patients might be considered as non-responders, while they experience clinical relevant improvement in patient-reported outcomes. Registration of real-life data will offer new possibilities for further research on the definition of a treatment responder based on a combination of both patient- and clinician-reported outcomes.

Registration of real life treatment results using prospective registries are useful to access the long-term safety and effectiveness of new therapeutics such as dupilumab. Furthermore, after the availability of other new therapeutics, the prospective registries will also address the need for further research on the comparison between different therapeutics by drug-survival analysis and may help to increase the knowledge on efficacy and safety of treatment options related to patient characteristics.

The BioDay Registry

The BioDay Registry is a prospective multicenter registry in which patients treated with new systemic treatments for AD are enrolled. The BioDay Registry aims to address the need for daily practice data regarding the effectiveness and safety of new systemic treatment options in patients with AD and the effect of these new therapies on other atopic co-morbidities in a multicenter setting. The coordinating

centers of the BioDay Registry are the National Expertise center for Atopic Dermatitis from the Department of Dermatology and Allergology of the University Medical Center Utrecht (UMCU) and the department of Dermatology of the University Medical Center Groningen (UMCG). These two centers started prospective registration of data in 2018. In June 2022 the registry was implemented in four academic centers (UMCU, UMCG, Radboud University Medical Center Nijmegen, Maastricht University Medical Center) and 11 non-academic centers. One of the strengths of the registry is the flexibility, the registry can easily be adjusted; for example, with modules for new therapeutic options or modules that focus on collection of information regarding new side effects. In addition, much attention is paid to the collection of high quality data with on-site training, monitoring, and selection of centers experienced in the treatment of patients with atopic diseases. Outcome measures in line with the core outcomes for eczema recommended by the global Harmonising Outcome Measures for Eczema (HOME) initiative are used to be able to merge data with other registries in future. [50] Patients treated in the UMCU are also asked to participate in a biobank in which blood, tape strips, and skin biopsies at different treatment time points are stored.

Outline of this thesis

The first aim of this thesis was to study the economic burden and impact on the quality of life in patients with moderate-to-severe AD indicated for systemic treatment who are also candidates for newly introduced systemic treatments for AD. As the new more targeted treatments are rather expensive, more information on the economic burden of patients indicated for these new drugs is important. In a cohort moderate-to-severe AD patients indicated for systemic treatment that is described in **chapter 2**, the economic burden, including direct- and costs of productivity loss, and impact on HrQoL was studied in a daily practice setting.

Secondly, in this thesis, we studied the effectiveness and safety, and impact on the economic burden of dupilumab treatment in patients with moderate-to-severe AD treated in a daily practice setting, by using data derived from the BioDay registry. In addition, we compared the effectiveness and safety of dupilumab treatment with conventional oral immunosuppressive drugs in the treatment of AD. In **chapter 3**, the relative effectiveness of dupilumab versus cyclosporine A was assessed in adult patients with moderate-to-severe AD. The clinical effectiveness and safety, and the impact on disease severity-related serum biomarkers of 16 weeks of dupilumab treatment in patients with moderate-to-severe AD was studied in a large daily

practice cohort in **chapter 4**. In **chapter 5**, the long-term effectiveness and safety of dupilumab treatment was demonstrated in a prospective, observational 52-week study, including a large cohort of patients treated with moderate-to-severe AD in a real-life setting. The impact of 52 weeks dupilumab treatment on absenteeism, presenteeism and related costs was investigated in a large prospective real-life cohort from the BioDay registry including adult patients with difficult-to-treat AD in **chapter 6**. In **chapter 7**, we primarily assessed the two-year drug survival of dupilumab and secondarily compared drug survival of dupilumab with other oral immunosuppressive drugs (cyclosporine A and methotrexate) in two historical daily practice cohorts of moderate-to-severe AD patients before the introduction of dupilumab.

The third aim of this thesis was to further identify side effects occurring during dupilumab treatment in daily practice, and to describe clinical characteristics and elucidate the underlying pathomechanism of these side effects. The first experience with 13 moderate-to-severe AD patients who developed conjunctivitis during dupilumab treatment including clinical characteristics and treatment options is described in **chapter 8**. In **chapter 9**, we studied the histopathological characteristics of conjunctivitis occurring during dupilumab treatment in conjunctival biopsies of six AD patients. In a case report presented in **chapter 10**, we described a clinically relevant adrenal insufficiency as a result of abrupt discontinuation of topical corticosteroid treatment in a patient successfully treated with dupilumab for severe AD.

The implications and future perspectives of our findings are discussed in **chapter 11**.

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Chapter 2

The economic burden of adult patients with moderate to severe atopic dermatitis indicated for systemic treatment

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ABSTRACT

Given the introduction of new therapies targeting specific activated immune pathways for atopic dermatitis (AD), information on the economic burden of AD patients is needed. Direct costs (medication use and healthcare resource utilization) and costs of productivity loss were studied in 90 adult AD patients indicated for systemic treatment. Costs were calculated for patients with controlled (Investigator Globel Assessment (IGA) 0-2) and uncontrolled (IGA 3-5) disease at inclusion. Total direct costs were €5,190 (SD €3,888) per patient per year (PPY), €4,401 (SD €2,784) for patients with controlled- versus €6,993 ((SD €4,861); p=0.003) for patients with uncontrolled-AD. Costs of productivity loss were €10,040 (SD €19,005) PPY for, €6,886 (SD €11,976) PPY for patients with controlled- versus €13,702 (SD €25,247) for patients with uncontrolled-AD (p=0.100). Total costs (direct+costs of productivity loss) were €15,231 (SD €20,214) PPY for the total group, €11,287 (SD €13,340) for patients with controlled- versus €20,695 ((SD €26,373); p=0.034) for patients with uncontrolled AD. AD patients using systemic immunosuppressive treatment incur considerable direct costs and costs of productivity loss.

INTRODUCTION

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by intense pruritus and a relapsing and remitting course. With a prevalence of 4.4%. among adults in the European Union, AD is one of the most common skin diseases[1, 2] AD has a significant effect on the quality of life of patients and their families due to intense pruritus and resulting sleep loss and concentration problems, and its psychosocial impact.[3, 4] In addition to the psychosocial burden, AD also has a substantial economic burden caused by costs directly related to treatment (direct costs) including in- and outpatient visits, diagnostic tests, transportation costs and medication costs.[5] Indirect costs, caused by productivity losses also substantially contribute to the economic burden.[4]

Several studies have attempted to quantify the economic burden of AD. However, studies are often difficult to compare as they focused on variable costs in specific patient populations and used different definitions of direct and indirect costs.[4-10] Additionally, studies were performed in various healthcare systems across different countries and costs were based on claims or patient-reported data leading to a high risk of recall bias. A recent study using data from the 2013 US National Health and Wellness Survey demonstrated that patients with AD have significantly higher health care resource utilization and direct costs compared with non-AD controls.[6] Another study performed in the US showed that patients with AD have a significantly higher work absenteeism rate and activity impairment rate compared with non-AD controls.[4] This impact of AD on work productivity and activity impairment may lead to substantial indirect medical costs.

During the past decade, the increasing knowledge of the underlying immune pathogenesis of AD has led to the development of new therapies targeting specific activated immune pathways.[11] Dupilumab, a fully human monoclonal antibody targeting the interleukin (IL)-4α receptor, thereby blocking the IL-4 and IL-13 pathway, is the first biologic treatment to be developed. It is approved for the treatment of moderate to severe AD patients defined as patients who are candidates for systemic treatment including broad immunosuppressive drugs (cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil) and newly developed therapies targeting specific activated immune pathways.[12-14] Given the introduction of these new therapies targeting specific activated immune pathways for moderate to severe AD, more information on the economic burden and impact on the quality of life in the group of AD patients indicated for systemic treatment is needed.

In this study, we aimed to investigate the economic burden, including direct and costs of productivity loss, and impact on quality of life in moderate to severe AD patients indicated for systemic treatment in a daily practice setting. In a subgroup analysis, a distinction between patients with controlled versus patients with uncontrolled AD has been made. The secondary aim of this study was to investigate differences in (economic) burden of patients with controlled and uncontrolled AD.

METHODS

Design

This observational cohort study included patients who attended the National Expertise Center for Atopic Dermatitis in the University Medical Center (UMC) Utrecht, the Netherlands between January 2016 and September 2017.

This study did not fall under the scope of the Medical Research Involving Human Subjects Act which was confirmed by the local Medical Research Ethics Committee (METC 16/757).

Patient population

All adult patients with moderate to severe AD defined as patients treated, or starting with systemic treatment, including oral immunosuppressive drugs (cyclosporine A (CsA), methotrexate (MTX), azathioprine (AZA), enteric-coated mycophenolate sodium (EC-MPS) and mycophenolate mofetil (MMF)), visiting the specialized, multidisciplinary, eczema outpatient clinic of the UMC Utrecht were included. Patients were concomitantly treated with topical corticosteroids and received instructions from a specialized dermatology nurse. AD was diagnosed by a dermatologist, according to commonly used criteria.[15, 16] Exclusion criteria were age below 18 years, treatment with oral immunosuppressive drugs for an indication other than AD and lack of available/essential data from the electronic patient file and/or pharmacist list.

Outcomes

Questionnaires and disease severity measures

Burden of disease and quality of life was assessed at the moment of inclusion (baseline) by validated questionnaires including the Skindex-29[17-19], Patient-Oriented Eczema Measure (POEM)[20], Hospital Anxiety and Depression Scale (HADS)[21] and 5-level EQ-5D, 5-dimension EuroQoL scale.[22] For the HADS questionnaire, the proportion of patients with HADS-anxiety (HADS-A) and HADS-depression (HADS-D) scores of 8 or higher (the cutoff for identifying patients with anxiety or depression) at baseline were reported. The outcomes of the EQ-5D-5L were dichotomized into 'no problems' (level 1) and 'problems (levels 2-5). The cutoff scores used to define severely impaired health-related quality of life (HRQL) based on the Skindex were >44 for the overall score, ≥37 for functioning, ≥39 for emotions, and ≥52 for symptoms.[19]

Work productivity and activity impairment was measured according to the Work Productivity and Activity Impairment questionnaire (WPAI). The WPAI questionnaire is a validated self-administered instrument to measure impairments in work and activities across 4 domains in the past 7 days; 1) absenteeism or work time missed due to health problem, 2) presenteeism or percent impairment while working due to health, 3) percentage of overall work impairment (absenteeism + presenteeism) and 4) percentage of activity impairment due to the health problem.[23] AD severity was determined at the moment of inclusion by trained healthcare professionals using the Eczema Area and Severity Index (EASI)[15] and Investigator's Global Assessment (IGA) score.[24]

Recourse utilization and (in)direct costs

The numbers of outpatient visits at the dermatology department or other departments in the UMCU, telephone consultations, days of hospitalization and the number of diagnostic- and laboratory tests in the year prior to the baseline visit were retrospectively extracted from the electronic patient files. Included patients signed consent to request medication use over the previous year at the patients' pharmacy. Google Maps was used to determine the geographical distance between the patients' residence and the UMC Utrecht.

Yearly direct costs and costs of productivity loss were calculated for the year prior to the baseline visit according to the Dutch guideline for economic evaluations in

healthcare.[25] Cost analyses were performed from a societal perspective in which all costs are included, irrespective of who bears those costs or to whom the benefits go. Medication costs were calculated using the Pharmacy Purchase Price which is published by the Z-index.nl.[26] Total medication costs included costs generated by oral immunosuppressive drugs, topical treatment, treatment for other atopic diseases and other AD-related treatment (including antibiotics). Costs for diagnostics and laboratory tests were calculated using the local unit prices.

Direct-, productivity loss-, and total costs were calculated per patient per year (PPY) for the total group and separately for patients with controlled AD (IGA 0-2) and uncontrolled AD (IGA 3-5) at inclusion. Direct costs included costs in the past 12 months related to outpatient visits, hospitalizations, diagnostic and laboratory tests, medication use and parking and transportations costs. Costs of productivity loss included costs due to productivity losses from being absent from work (absenteeism) and being less productive at work (presenteeism). Costs were valued by the human capital approach. Weekly costs due to reduced productivity and missed work time were extrapolated to calculate the yearly lost wages.

Statistical analysis

All statistical analyses were performed using SPSS statistics 21 (Version 21.0.0.0, SPSS Inc., Chicago, IL, USA). Descriptive statistics were used to describe baseline characteristics and direct costs and costs of productivity loss for the total group of patients. For the sub analysis of patients with controlled and uncontrolled AD, t-tests were used for comparisons of means between the two groups. Pearson's X^2 test was used for differences of proportions between patients with controlled and uncontrolled AD. A P value of <0.05 was considered statistically significant.

All costs were calculated per patient per year (PPY) for the total group and for patients with controlled and uncontrolled AD. Prices were adjusted for Inflation (September 2018) using the Consumer Price Index (CPI-U) as presented by the Bureau of Labor Statistics. The formulas used to calculate the yearly total- direct- and costs of productivity loss are shown in table 1.

Table 1. Formulas used to calculate the yearly total direct costs and costs of productivity loss

Yearly total direct costs	yearly healthcare resource costs (visits to a dermatologist (n)* €169.07 + visits to a dermatology nurse (n) * €50.70 + visits to a social worker (n) * €67.42 + Telephone consultation dermatologist (n) * 53.94 + Telephone consultation dermatology nurse (n) * 17.63 + days of hospitalization for AD treatment (n) * €665.90 + visits to other medical specialists (n) * €169.07) + medication costs (standard price for 14-day prescription * (duration of treatment (days)/14)) + diagnostic tests costs (number of diagnostic tests * unit price) + laboratory tests costs (number of laboratory tests * unit price) + parking costs (number of visits with parking costs to a medical specialist or nurse in the UMCU * €3.08 (unit costs per parking)) + transportation costs (distance UMCU and residence (km) * €0.20 (unit costs per km))
Yearly total costs of productivity loss	yearly productivity losses for employed patients= ((**Absenteeism**, days per month ((percent work time missed due to health/100) * number of work days per month) + **presenteeism**, days per month ((percent impairment while working due to health/100) * number of work days per month)) * **6.78** (average number of working hours per day) * **€35.53** (value of productivity loss per hour)) *12 (months)

RESULTS

Patient characteristics

Patient characteristics are shown in table 2. A total of 90 patients indicated for systemic treatment were included for analysis. For the disease control sub analysis, in total 84 patients were included of which 51 patients with controlled AD (61%) and 33 patients with uncontrolled AD (39%). Six patients were excluded from the disease control sub analysis due to missing IGA values. These patients did not differ in baseline characteristics compared to the total group of patients.

Table 2. Baseline characteristics

	Total group (n=90)	Severity groups (n=84) Controlled AD (n=51)	Uncontrolled AD (n=33)	p-value
Age, mean (SD) years	44.6 (17.4)	44.8 (15.7)	43.8 (20.2)	0.797
Male sex, n (%)	59 (65.6)	33 (64.7)	23 (69.7)	0.636
Atopic/allergic diseases at baseline, n (%)				
Allergic rhinitis	48 (57.8)	26 (54.2)	19 (61.3)	0.532
missing	2 (2.2)	3 (5.9)	2 (6.1)	
Asthma	49 (56.3)	26 (53.1)	20 (62.5)	0.402
missing	3 (3.3)	2 (3.9)	1 (3.0)	
Allergic conjunctivitis	23 (46.9)	13 (48.1)	10 (47.6)	0.971
missing	41 (45.6)	24 (47.1)	12 (36.4)	
Disease activity				
EASI, mean (SD)	9.40 (9.1)	3.8 (2.7)	16.2 (10.1)	0.000
missing, n (%)	9 (10.0)	4 (7.8)	0 (0.0)	
IGA, mean (SD)	2.2 (1.1)	1.5 (0.6)	3.3 (0.5)	0.000
missing, n (%)	6 (6.7)	0 (0.0)	0 (0.0)	
POEM, mean (SD)	12.1 (7.3)	9.5 (6.0)	15.5 (7.6)	0.000
missing, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
HADS depression (HADS-D) score ≥8, n(%)	6 (6.8)	0 (0.0)	6 (11.8)	0.003
HADS anxiety (HADS-A) score ≥8, n(%)	21 (23.3)	11 (21.6)	9 (27.3)	0.549
Impact on HRQL based on the Skindex-29				
Overall, severely impaired (>44), n (%)	26 (32.5)	10 (20.8)	14 (51.9)	0.039
missing, n (%)	10 (11.1)	3 (5.9)	6 (18.2)	
Symptoms, severely impaired (>52), n (%)	52 (59.1)	25 (50.0)	23 (69.7)	0.159
missing, n (%)	2 (2.2)	1 (2.0)	0 (0.0)	
Emotions, severely impaired (>39), n (%)	24 (27.9)	9 (18.0)	15 (48.4)	0.035
missing, n (%)	4 (4.4)	1 (2.0)	2 (6.1)	
Functioning, severely impaired (>37), n (%)	18 (20.9)	5 (12)	12 (38.7)	0.048
missing, n (%)	4 (4.4)	1 (2.0)	2 (6.1)	
EQ-5D-5L dimension, n(%)				

EQ-5D-5L dimension, n(%)					
Mobility	No problems	74 (83.1)	41 (80.4)	28 (84.8)	0.734
	Problems	15 (16.9)	9 (17.6)	5 (15.2)	
	Missing	1 (1.1)	1 (2.0)	0 (0.0)	
Self-care	No problems	81 (92)	3 (5.9)	4 (12.1)	0.423
	Problems	7 (8.0)	47 (92.2)	28 (84.8)	
	Missing	2 (2.2)	1 (2.0)	1 (3.0)	
Usual activity	No problems	52 (59.1)	32 (65.3)	18 (54.5)	0.327
	Problems	36 (40.9)	17 (34.7)	15 (45.5)	
	Missing	2 (2.2)	2 (3.9)	0 (0.0)	
Pain/discomfort	No problems	21 (23.6)	34 (66.7)	5 (15.2)	0.084
	Problems	68 (76.4)	16 (31.4)	28 (84.8)	
	Missing	1 (1.1)	1 (2.0)	0 (0.0)	
Anxiety/depression	No problems	59 (66.3)	34 (66.7)	19 (57.6)	0.333
	Problems	30 (33.7)	16 (31.4)	14 (42.4)	
	Missing	1 (1.1)	1 (2.0)	0 (0.0)	
EQ-5D-5L VAS, mean (SD)		71.4 (13.1)	73.9 (10.7)	66.7 (15.7)	0.014
Hospitalized for inpatient AD treatment, n(%)		12 (13.3)	4 (7.8)	8 (24.2)	0.036
Number of previous oral immunosuppressive treatments					
≤ 1 oral immunosuppressive treatments, n(%)		40 (44.4)	24 (47.1)	14 (42.4)	0.823
≥2 oral immunosuppressive treatments, n(%)		50 (55.6)	27 (52.9)	19 (57.6)	
Work status					
Employed, n (%)		60 (66.7)	38 (74.5)	19 (57.6)	0.105
Number of hours working per week, mean (SD)		31.2 (15.2)	31.8 (14.0)	30.6 (18.1)	0.783
Hours missed due to health problems, mean (SD)*		1.4 (5.5)	0.2 (0.9)	3.7 (9.2)	0.023
Hours missed other reasons, mean (SD)*		4.5 (9.7)	5.7 (11.4)	2.8 (4.4)	0.172

* in the past 7 days, Controlled AD (IGA 0-2), Uncontrolled AD (IGA 3-5)
AD, Atopic Dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; POEM, Patient Oriented Eczema Measure; HADS, Hospital Anxiety and Depression Scale; HRQL, Health Related Quality of Life; EQ-5D-5L, 5-level EQ-5D version; VAS, visual analogue scale of 0-100

Disease severity

Disease severity was measured at the moment of inclusion; that is, at the point when the patient received or started oral immunosuppressive treatment. Among the total group of patients, the mean EASI score at baseline was 9.4 (SD 9.1) and the mean POEM at baseline was 12.1 (SD 7.3). Out of the 90 patients, 50 (55.6%) patients had received ≥2 prior immunosuppressive treatments at baseline.

For the disease control groups, all baseline severity measures were significantly higher among patients with uncontrolled AD compared to patients with controlled AD (table 1).

Quality of life outcomes

Out of the 90 patients, 6 (6.8%) reported a baseline HADS-D and 21 (23.3%) a baseline HADS-A sub score of 8 or more, indicating anxiety and/or depression. For the EQ-5D-5L, patients reported 'problems' most frequently for the dimensions: usual activity (36 patients (40.9%)), pain and discomfort (68 patients (76.4%)) and anxiety and depression (30 patients (33.7%)). HRQL based on the Skindex was severely impaired in 26 patients (32.5%) for the overall score, in 52 patients (59.1%) for Symptoms, in 24 patients (27.9%) for Emotions and in 18 patients (20.9%) for Functioning. For the disease control groups, significantly more patients with uncontrolled AD reported a sub score of 8 or more on the HADS-D scale compared to patients with controlled AD (6 patients (11.8%) vs 0 patients (0%), p=0.003). Significantly more patients with uncontrolled AD scored a severely impaired HRQL based on the Skindex for the overall score (51.9% vs 20.8%, p=0.039), for emotions (48.4% vs 18.0%, p=0.035) and for functioning (38.7% vs 12.0%, p=0.048) compared to patients with controlled AD.

Work productivity and activity impairment

Out of the 90 patients, 60 (66.7%) were employed at the moment of inclusion (Table 2). Among the employed patients the mean number of working hours per week was 31.2 (SD 15.2). For the employed patients, the mean reported absenteeism over the past 7 days was 4.7% (SD 15.7) and mean reported presenteeism was 21.5% (SD 26.4) (Figure 1). Percent overall work impairment due to health yielded 23.1% (SD 28.2) and the percent activity impairment due to health was 30% (SD 27.6).

Compared to patients with controlled AD, patients with uncontrolled AD reported higher absenteeism (11.1% vs 0.6%, p=0.020), presenteeism (32.1% vs 14.6%, p=0.015), overall work impairment (33.5% vs 15.8%, p =0.024) and activity impairment (38.8% vs 22.4%, p=0.006).

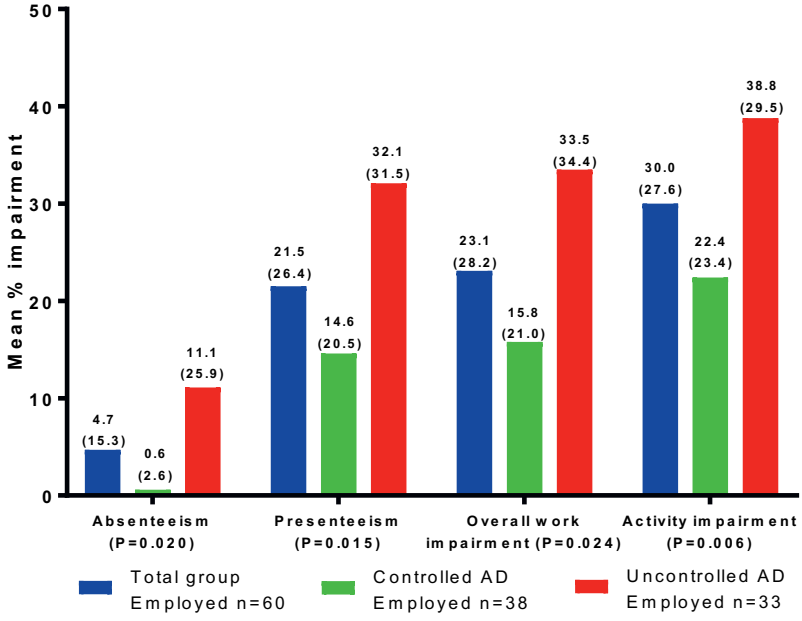

Figure 1: Weekly productivity and activity impairment (mean percent ± standard deviation) in the total group and patients with controlled and uncontrolled AD

Healthcare utilization

Yearly Annual healthcare resource utilization and associated unit costs are shown in table 3. Compared with controlled AD patients, patients with uncontrolled AD used significantly more health care resources including number of visits to a dermatologist (5.5 vs 4.4 p=0.028) and days of hospitalization for AD treatment (3.2 vs 0.9 (p=0.027)).

	Total group (90)			Severity groups (n=84) Controlled disease (51)		Uncontrolled disease (33)		p-value
	Volumes, mean (± SD)		Unit costs (€)	Volumes, mean (± SD)		Volumes, mean (± SD)		
Direct costs								
Hospitalizations and outpatient visits dermatology department								
Visit to a dermatologist	4.8	(2.1)	€ 169.07	4.4	(2.0)	5.5	(2.3)	0.028
Telephone consultation with a dermatologist	2	(2.5)	€ 53.94	1.6	(2.2)	2.8	(2.9)	0.042
Visit to a dermatology nurse	0.9	(1.7)	€ 150.70	0.8	(1.6)	1.2	(2.0)	0.329
Telephone consultation with a dermatology nurse	0.1	(0.4)	€ 17.63	0.02	(0.1)	0.2	(0.7)	0.044
Visit to a social worker	0.1	(0.3)	€ 67.42	0.1	(0.4)	0.03	(0.2)	0.318
Number of hospitalizations for AD treatment	0.14	(0.4)		0.08	(0.3)	0.3	(0.5)	0.027
Days of hospitalization for AD treatment	1.7	(4.5)	€ 665.90	0.9	(3.3)	3.2	(6.0)	0.027
Outpatient visits other hospital departments (UMCU)								
Visit to a medical specialist	0.2	(0.4)	€ 169.07	0.2	(0.4)	0.3	(0.5)	0.113
Visits with transportation and parking costs to a medical specialist or nurse in UMCU (unit costs per parking)	6.0	(2.9)	€ 3.08	5.4	(2.4)	7.2	(3.4)	0.006
Distance UMCU and residence (unit costs per km)	64	(39.6)	€ 0.20	61.9	(41.7)	68	(37.6)	0.500
Costs of productivity loss								
Work impairment employed patients								
Absenteeism, days per year (unit costs value of productivity loss per hour)	12.19	(40.82)	€ 35.53	1.5	(6.9)	28.9	(67.3)	0.020
Presenteeism, days per year (unit costs value of productivity loss per hour)	54.79	(65.81)	€ 35.53	40.1	(54.1)	77.1	(75.4)	0.058

AD, Atopic Dermatitis; UMCU, University Medical Center Utrecht

Table 3. Healthcare resource utilization and associated unit costs for the total group and patients with controlled and uncontrolled AD (€)

Yearly direct costs and costs of productivity loss

Mean total costs including direct costs and costs of productivity loss for the total group of patients was €15,231 PPY (SD €20,214). The mean total costs were significantly higher in patients with uncontrolled AD compared to patients with controlled AD (€20,695 (SD €26,373) vs €11,287 (SD €13,340), p=0.034) (table 4).

Mean total direct costs (including costs derived from healthcare resource utilization, AD related medication, diagnostics, laboratory tests and transportation and parking) PPY were estimated at €5,190 (SD €3,888) (table 4).

Mean total direct costs PPY were significantly higher for patients with uncontrolled AD compared to patients with controlled AD (€6,993 (SD €4,861) vs €4,401 (SD €2,784), p=0.006). Higher mean total direct costs PPY for patients with uncontrolled AD was mainly caused by significantly higher healthcare resource costs (€3,345 (SD €4,261) vs €1,528 (SD €2,215), p=0.012) arising from higher healthcare resource use compared to patients with controlled AD.

Costs of productivity loss were extrapolated from weekly costs derived from the WPAI to calculate the yearly lost wages. Costs of productivity loss made up the largest portion of the total costs with an estimated mean of €10,040 (SD €19,005) PPY. Costs of productivity loss were higher among patients with uncontrolled AD compared to patients with controlled AD. However, despite the large variance, this difference was not statistically different (€13,702, (SD €25,247) vs €6,886 (SD €11,976), p=0.100).

Table 4: Direct costs and costs of productivity loss (€) for the total group and patients with controlled and uncontrolled AD

	Total group (n=90)	Severity groups (n=84)		Mean difference (SE)	95 % CI*	p-value
		Controlled AD (n=51)	Uncontrolled AD (n=33)			
Total direct costs, mean (± SD) (€)	**€ 5,190 (3,888)**	**€ 4,401 (2,784)**	**€ 6,993 (4,861)**	**2,593 (834)**	**+933, +4,252**	**0.003**
Healthcare resource costs, mean (± SD) (€)	€ 2,144 (3,189)	€ 1,528 (2,215)	€ 3,345 (4,261)	1,817 (709)	+406, +3,228	0.012
Medication costs, mean (± SD) (€)	€ 2,699 (2,287)	€ 2,548 (1,800)	€ 3,244 (2,925)	696 (515)	-329, +1,721	0.180
Diagnostic tests costs, mean (± SD) (€)	€ 9 (23)	€ 6 (19)	€ 11 (24)	5 (5)	-5, +14	0.353
Laboratory tests costs, mean (± SD) (€)	€ 248 (171)	€ 241 (168)	€ 276 (184)	35 (39)	-42, +113	0.368
Transportation + parking costs, mean (± SD) (€)	€ 91 (63)	€ 77 (53)	€ 117 (72)	40 (14)	+13, +67	0.005
Total indirect costs (€), mean (± SD) (€)	**€ 10,040 (19,005)**	**€ 6,886 (11,976)**	**€ 13,702 (25,247)**	**6,816 (4,096)**	**-1,333, +14,965**	**0.100**
Yearly productivity losses, mean (± SD) (€)	€ 10,040 (19,005)	€ 6,886 (11,976)	€ 13,702 (25,247)	**6,816 (4,096)**	1,333, +14,965	0.100
Total direct + indirect costs, mean (± SD) (€)	**€ 15,231 (20,214)**	**€ 11,287 (13,340)**	**€ 20,695 (26,373)**	**9,408 (4,355)**	**+745, +18,071**	**0.034**

*Confidence intervals were calculated by a bootstrap method with 1,000 iterations. SD, standard deviation; SE, Standard error; CI, Confidence interval

DISCUSSION

This study estimated disease burden and direct costs and costs of productivity loss associated with AD in patients with moderate to severe AD indicated for systemic treatment in a real life Dutch setting. Moderate to severe AD patients using systemic immunosuppressive treatment incur considerable disease burden and direct costs as well as costs of productivity loss regardless of their level of disease control. Indirect costs due to productivity losses made up the largest portion of the total costs, especially in patients with uncontrolled AD. Total direct costs due to higher resource utilization use were significantly higher in patients with uncontrolled AD compared to patients with controlled AD.

Limited data is available about the economic impact of AD in a well-defined patient population of patients with difficult to treat AD requiring systemic treatment in a real-life setting in the Netherlands. Recently, new therapies targeting specific activated immune pathways have become available for AD patients, indicated for systemic treatment. Dupilumab is one of the first biologics that has been developed for AD and has been approved for the treatment of moderate to severe AD, indicated for systemic treatment. Besides Dupilumab, other biologics and small molecule therapies are currently under investigation. As the new therapies targeting specific activated immune pathways will be rather expensive, more information on the economic burden of patients indicated for these new drugs is important.[27]

Several studies have attempted to quantify the economic burden of AD. However, costs vary widely and comparing absolute costs across healthcare systems and different countries is difficult.[4-10] The economic burden in patients with AD requiring systemic treatment has not been previously described. The patient population in this study can therefore be regarded as unique

Costs due to lost productivity and work absenteeism made up the largest portion of the total costs due to impairments in work and daily activities associated with AD. Reduced work productivity and activity in AD patients was also demonstrated in a study performed by *Eckert et al.*[28] In this study, data from the 2013 US National Health and Wellness Survey was used to establish the burden of AD in US adults. *Eckert et al.* showed that compared with employed matched non-AD controls, employed patients with AD reported significantly higher absenteeism (9.9% vs 3.6%, $p<0.001$), presenteeism (21.1% vs 16.1%, $p=0.037$) and overall work impairment (25.6% vs 18.1%, $p=0.004$). The mean annual costs of productivity loss for employed

patients were estimated at $8,907 (vs $6,517 for non-AD controls, p=0.024). However, the diagnosis of AD in this study was patient-reported (mainly mild to moderate) and therefore this population is not completely comparable to our population of patients with difficult to treat AD requiring systemic treatment. Nevertheless, the overall conclusions are comparable with the findings of our study indicating substantial impairment in work productivity and absenteeism in patients with AD with associated costs due to lost wages. These findings provide an indication of the potential societal burden of AD due to productivity losses. It is expected that the introduction of new, effective therapies such as Dupilumab will reduce the burden of the disease and will lower costs caused by the absence from work and reduced productivity while at work.[27, 29-31]

In this study we categorized patients based on their level of disease control (measured with IgA score) in patients with controlled AD and uncontrolled AD. Despite adequate treatment with topical corticosteroids or oral immunosuppressive drugs, 39% of the included patients had an uncontrolled AD at the moment of inclusion, emphasizing the as yet unmet need for safe and effective therapies in patients with difficult to treat AD. Remarkably, patients with controlled AD also had relatively high scores for work productivity and activity impairment measured according to the WPAI and substantial costs of productivity loss as well as direct costs. A possible explanation might be that clinicians often have to search for the optimal oral immunosuppressive drug, which regularly requires a period of trial and error. Therefore, in patients with controlled and uncontrolled forms, frequent consultations are often necessary for monitoring and dose adjustments.

This study has several limitations. Costs of productivity loss were calculated by using scores for work productivity and activity impairment measured according to the WPAI. The WPAI was completed once, at the moment of inclusion, no repeated measurements were available. Weekly costs due to reduced productivity and missed work time were extrapolated to calculate yearly lost wages. The extrapolation of weekly data may have influenced the reliability of the estimated costs of productivity loss. However, the WPAI was completed at different time points within the inclusion period (between January 2016 and September 2017) which should have minimized the risk of bias due to seasonal influences.

The number of outpatient visits and hospitalization days were only available if they took place in the UMC Utrecht. There were no data available concerning the number of visits to the physician or other healthcare professionals at other hospitals or clinics. In addition, no data were available addressing out-of-pocket costs for patients (for example emollients). Literature shows AD is associated with considerable out-of-pocket costs for health care which can contribute substantially to total AD associated costs.[7] A US population-based study demonstrated that adults with AD had $371 to $489 higher out-of-pocket costs per person-year compared to patients without AD. The missing data concerning outpatient visits and hospitalization days outside the UMC Utrecht and missing out-of-pocket costs in our population may have led to an underestimation of the total AD related costs.

In conclusion, our study illustrates that moderate to severe AD patients indicated for systemic immunosuppressive treatment incur considerable direct costs as well as costs of productivity loss, with patients with uncontrolled AD incurring significantly higher direct costs than controlled AD patients. Costs due to productivity losses were the major cost contributor, especially in patients with uncontrolled AD. Additionally, moderate to severe AD presents a substantial burden on the quality of life among patients indicated for systemic treatment. Further research is needed to study whether the introduction of the new therapies targeting specific activated immune pathways can reduce the negative impact on quality of life and costs of productivity loss, which may partly compensate the expected increase in drug acquisition costs of these new treatments.

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Chapter 3

Dupilumab versus cyclosporine for the treatment of moderate-to-severe atopic dermatitis in adults: indirect comparison using the eczema area and severity index

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ABSTRACT

Background: Dupilumab is approved to treat adults with inadequately controlled moderate-to-severe atopic dermatitis (AD). Cyclosporine is approved in certain countries for up to a year. Given a lack of comparative evidence, the relative efficacy of dupilumab vs cyclosporine by indirect comparison was studied.

Methods: Regression models, based on pooled patient-level data, were used to estimate responders (defined as EASI 50 or EASI 75 at Weeks 12–16 and 24–30) to treatment with dupilumab 300 mg every 2 weeks (data source: CHRONOS clinical trial, NCT02260986) or cyclosporine (source: University Medical Center [UMC], Utrecht). Treatment was the focal regressor; baseline covariates included sex, EASI, and thymus and activation-regulated chemokine level.

Results: 106 patients were treated with dupilumab (+ topical corticosteroids [TCS]), and 57 with cyclosporine (+ TCS). Among UMC patients, estimated proportions of EASI-50 responders to dupilumab vs cyclosporine treatment were 91% vs 77% ($P = 0.038$; Weeks 12–16) and 96% vs 67% ($P < 0.0001$; Weeks 24–30). For EASI-75 responders to dupilumab vs cyclosporine, estimated proportions were 78% vs 56% ($P = 0.016$; Weeks 12–16) and 80% vs 47% ($P < 0.001$; Weeks 24–30). Among CHRONOS patients, estimated proportions of EASI-50 responders to dupilumab vs cyclosporine were 90% vs 74% ($P < 0.038$; Weeks 12–16) and 92% vs 53% ($P < 0.0001$; Weeks 24–30), and for EASI-75 were 75% vs 52% ($P = 0.016$; Weeks 12–16) and 74% vs 40% ($P < 0.001$; Weeks 24–30). The relative efficacy of dupilumab vs cyclosporine significantly improved over time for the EASI-50 response.

Conclusions: This analysis suggests that dupilumab has a higher relative efficacy than cyclosporine in treating patients with moderate-to-severe AD.

INTRODUCTION

Atopic dermatitis (AD) is a common chronic inflammatory skin disease, which is prone to disease exacerbations. In adults, the estimated prevalence of AD is between 2% and 5%, depending on region.[1] In the majority of patients, AD can be treated adequately with topical agents and/or ultraviolet (UV) light.[2] However, in a subpopulation of patients with moderate-to-severe AD, the disease remains inadequately controlled despite these treatments, with patients still experiencing signs (e.g., lesions, redness) and symptoms (e.g., itch, sleep disturbance). For these patients, systemic immunomodulating treatment is indicated. The decision to start systemic medication should be based on the severity of skin lesions; symptoms such as itch, pain, and sleep disturbance; and the impact on quality of life.[2]

Cyclosporine A is the only oral immunosuppressant approved for the treatment of severe AD in some European countries and in Japan.[3, 4] The clinical efficacy of cyclosporine in moderate-to-severe AD was supported by a systematic review of 14 randomized controlled trials, although no conclusion could be drawn about long-term safety.[5] Furthermore, many of the studies were conducted in the early 1990s, and well-validated efficacy outcome measures, such as the Eczema Area and Severity Index (EASI), had not yet been developed. In a more recent study of 356 patients with AD who were receiving long-term treatment with cyclosporine, nearly half of the patients cited lack of efficacy and/or side-effects as their reason for discontinuation of treatment.[6] Treatment response to cyclosporine has been met with various levels of success.[6, 7] Other immunosuppressant agents, including azathioprine and mycophenolate mofetil, are only recommended for use in adults by the European guidelines if cyclosporine A is either not effective or is contraindicated.[8] There remains a high unmet need for efficacious and safe therapeutics for inadequately controlled, moderate-to-severe AD.

Dupilumab is a fully human VelocImmune®-derived monoclonal antibody directed against interleukin (IL)-4 receptor alpha that inhibits signaling of IL-4 and IL-13 cytokines, key drivers of type 2 immune diseases, such as AD, asthma, allergic rhinitis, and eosinophilic esophagitis.[9, 10] Dupilumab is approved in the European Union (EU), USA, Japan, and other countries for treatment of inadequately controlled moderate-to-severe AD in adults. The clinical efficacy and safety of dupilumab ± topical corticosteroids (TCS) have been demonstrated in clinical trials of 16 weeks' (SOLO 1 & 2) and 52 weeks' (CHRONOS) duration, as well as in patients for whom cyclosporine failed or was contraindicated (CAFÉ).[11-13]

Both cyclosporine and dupilumab are approved in most European countries for patients whose disease cannot be controlled by, or who are intolerant of, topical treatment. However, there is a lack of head-to-head data comparing these 2 agents.[3, 14]

The aim of this study was to assess the relative effectiveness of dupilumab vs. cyclosporine in adult patients with moderate-to-severe AD. This comparison was achieved by estimating the proportions of patients with treatment responses based on improvements from baseline in EASI score of 75% (EASI-75; primary endpoint of CHRONOS) or 50% (EASI-50; secondary endpoint of CHRONOS).

METHODS

Study design and patient population

Patient-level data on dupilumab and cyclosporine treatment of AD were obtained from 2 different data sources. Dupilumab data were obtained from the phase 3 trial LIBERTY AD CHRONOS (CHRONOS), the design and results of which have been reported elsewhere.[12] CHRONOS was a global, randomized, double-blind, placebo-controlled trial conducted in 14 countries in Europe, Asia-Pacific, and North America between 3 October 2014, and 31 July 2015. Adult patients (aged ≥ 18 years) with moderate-to-severe AD and an inadequate response to medium- or higher-potency TCS treatment were included. The trial evaluated 2 dupilumab dose regimens: 300 mg every week (qw) plus concomitant TCS, 300 mg every 2 weeks (q2w) plus concomitant TCS, or placebo plus TCS. This analysis focused on the dupilumab 300 mg q2w plus TCS treatment arm, the dose regimen approved by the European Medicines Agency. Key inclusion criteria for the CHRONOS study included the presence of AD for ≥ 3 years before screening; a documented history within 6 months before screening of inadequate response to medium-to-high-potency TCS (with or without topical calcineurin inhibitor, as appropriate) or documented systemic treatment within the previous 6 months, or both; and an Investigator's Global Assessment (IGA) score of ≥ 3 (moderate-to-severe, on a scale of 0–4) and an EASI score of ≥ 16 at screening and baseline.[12]

Patient-level data on cyclosporine were obtained from patients treated with cyclosporine in daily practice at the Department of Dermatology and Allergology, University Medical Center (UMC) Utrecht, the Netherlands. SAS enterprise (https://sas.com) was used to extract all patients treated with cyclosporine A between

January 2015 and September 2017 in the UMC Utrecht with a diagnosis of "atopic dermatitis". Most patients were treated with cyclosporine as the first choice of systemic treatment, according to the local treatment protocol. This involved treatment initiation at a high dose, 5 mg/kg/day, for a 3–6-week induction phase, followed by gradual tapering of the dose based on clinical response to a dose of 2–3 mg/kg/day in the maintenance phase. Tapering of the cyclosporine dose was undertaken in all patients to balance the long-term safety/effectiveness profile and to establish the lowest dose at which cyclosporine remained therapeutically effective. This approach reflects how cyclosporine is used in real-world practice, because of its known toxicity profile. Concomitant use of TCS was permitted as needed for all patients treated with cyclosporine.

Baseline data recorded for the UMC Utrecht patients included age, sex, EASI score, and thymus and activation-regulated chemokine (TARC) level at the date of cyclosporine initiation. EASI scores were available at weeks 3, 12–16, and 24–30 after the index date. Data on treatment duration, reason for discontinuation, and the cyclosporine dose were also collected at these time points. Patients treated with cyclosporine were included in the analysis if they had been treated with cyclosporine between January 2015 and September 2017 for a duration of ≥ 3 weeks, and if baseline characteristics (EASI, serum TARC level, sex, and age) and at least one follow-up EASI value were available. Outcomes for the analysis included EASI-50 and EASI-75. Patients reaching the given EASI improvement outcomes (EASI-50 or EASI-75) were defined as "responders," while those not meeting EASI-50 or EASI-75 were defined as "non-responders."

Because the cyclosporine population was treated in daily practice without fixed clinic visits, the analysis of EASI-50 and EASI-75 spanned 2 different time periods, between weeks 12 and 16 and between weeks 24 and 30. In contrast, CHRONOS patients were treated in a clinical trial setting, with EASI outcomes assessed at specific time points rather than ranges. To facilitate a comparison with outcomes in the cyclosporine population, EASI-50 and EASI-75 scores for patients in the CHRONOS study are reported here as those obtained at weeks 16 and 28.

Statistical analysis

Age, sex, EASI score, and TARC level were available at baseline for both populations. For continuous variables (age, EASI, and TARC), data were presented as means, medians, and standard deviations (SD). For categorical variables, data were presented as frequencies and percentages of patients. The 2 populations were compared using t-tests for continuous variables and $\chi 2$ tests for categorical variables. A threshold of $p < 0.05$ was used to define statistical significance.

Logistic regression analysis was performed to assess the efficacy outcomes for each endpoint. The dependent variable was EASI-50/EASI-75 (achieved or not achieved), and the focal regressor was a treatment indicator for cyclosporine vs. dupilumab use. Missing EASI values were imputed by means of the last observation carried forward (LOCF) method for both treatment populations. The other regressors in the model were sex, baseline EASI, and baseline TARC level, and adjusted-weighting was done according to these baseline data. Patients with missing baseline TARC levels or EASI scores were excluded from the analysis.

Coefficients from the adjusted regression models were used to estimate the mean predicted rate of responders under each treatment scenario (treatment with dupilumab vs. with cyclosporine) for the CHRONOS and UMC Utrecht populations separately. This enabled the prediction of responder rates for dupilumab and cyclosporine within each of the study populations. Standard errors for the estimated proportion of EASI responders were calculated using a bootstrapping technique with re-sampling (number of iterations = 1,000). The variance estimates (i.e. standard errors) were thereby generated instead of under parametric distribution assumptions around the predicted EASI responder rates. p-values for the treatment indicator (dupilumab vs. cyclosporine) in each model were reported.

The relative improvement in efficacy/effectiveness of dupilumab vs. cyclosporine over time between weeks 12–16 and weeks 24–30 was tested statistically with confidence intervals (CI) calculated by a bootstrap method with 1,000 iterations.

RESULTS

A total of 163 patients were included in the analysis. Out of 105 patients in the database at the UMC Utrecht, 48 were excluded from further analysis based on the following exclusion criteria: other treatment indication than atopic dermatitis, treatment duration < 3 weeks, missing baseline characteristic (EASI, serum TARC level, sex, age) and < 1 available follow-up EASI value, leading to 57 treated with cyclosporine + TCS. A total of 106 patients with dupilumab q2w + TCS in CHRONOS were included in the analysis. Of the 57 cyclosporine-treated patients, 40 (70%) had no history of previous treatment with oral immunosuppressive drugs. Of 17 (30%) patients who had previously received one or more immunosuppressive drugs, 6 (35%) had received metho-trexate, 12 (71%) cyclosporine, 3 (18%) azathioprine, and 1 (6%) mycophenolic acid. In contrast, 43 (41%) of the dupilumab-treated patients had previously received non-steroidal immunosuppressants to treat AD. Of these patients, 8 (19%) had received methotrexate, 33 (77%) cyclosporine, 8 (19%) azathioprine, and 8 (19%) mycophenolic acid.

Age and sex did not significantly differ between cyclosporine-treated and dupilumab-treated patients (Table I). Baseline EASI score and baseline serum TARC level were significantly higher in patients treated with dupilumab (EASI: 33.6 ± 13.3, $p < 0.0001$; TARC: 9,767 ± 19,410, $p < 0.05$) than in cyclosporine-treated patients (EASI: 19.3 ± 8.4, TARC: 5,176 ± 9,726).

Table 1. Baseline characteristics.

	CsA patients (UMC Utrecht) n = 57	Dupilumab patients (CHRONOS) n = 106	*P* value
Age, mean ± SD, years	35.3 ± 13.0	39.6 ± 14.0	0.06
Male, n (%)	34 (59.6)	62 (58.5)	0.89
Baseline EASI, mean ± SD	19.3 ± 8.4	33.6 ± 13.3	< 0.0001
Baseline TARC, mean ± SD, pg/mL	5176 ± 9726	9767 ± 19 410	< 0.05

T-tests were used to compare continuous variables. Chi-squared tests were used to compare categorical variables. CsA, cyclosporine A; EASI, Eczema Area and Severity Index; SD, standard deviation; TARC, thymus and activation-regulated chemokine; UMC, University Medical Center.

During the follow-up period of 24–30 weeks, 5 (8.8%) patients discontinued cyclosporine treatment. Reasons for discontinuation were side-effects (3 patients; 5.3%), ineffectiveness (1 patient; 1.8%), and pregnancy (1 patient; 1.8%). The median (interquartile range) cyclosporine dose at the different time points was 4.8 (0.8) mg/kg at baseline, 3.3 (0.7) mg/kg after 12–16 weeks' treatment, and 3.0 (0.9) mg/kg after 24–30 weeks' treatment. Treatment characteristics of the patients treated with cyclosporine are shown in Table II.

Of the 106 patients treated with dupilumab, 8 (7.5%) discontinued dupilumab treatment within the follow-up period of 28 weeks. Reasons for discontinuation of treatment were withdrawal by subject (4 patients; 3.8%), physician decision (2 patients; 1.9%), adverse event (1 patient; 0.9%), and protocol violation (1 patient; 0.9%) (Table II).

Table 2 Treatment characteristics of the UMC Utrecht patients who received cyclosporine (A) and the CHRONOS patients who received dupilumab (B)

(A)

	Cyclosporine patients (N = 57)
CsA dose mg/kg, median (IQR)	
At baseline	4.8 (0.8)
12–16 weeks	3.3 (0.7)
24–30 weeks	3.0 (0.9)
Patients who remained on CsA at different time points, n (%)	54 (94.7)
12–16 weeks	52 (91.2)
24–30 weeks	
Reasons for discontinuation, n (%)	5 (8.8)
Ineffectiveness	1 (1.8)
Side effects	3 (5.3)
Other (pregnancy)	1 (1.8)

CsA, cyclosporine A; IQR, interquartile range.

(B)

	Dupilumab patients (n = 106)
Patients who remained on dupilumab treatment at different time points, n (%)	
16 weeks	99 (93.4)
28 weeks	98 (92.5)
Reasons for discontinuation at 28 weeks, n (%)	
Adverse event	1 (0.9)
Physician decision	2 (1.9)
Protocol violation	1 (0.9)
Withdrawal by subject	4 (3.8)

Table III shows the adjusted regression-estimated proportions of responders to each treatment for the UMC Utrecht and CHRONOS patients; these data are presented graphically in Figs 1 and 2. Both the UMC Utrecht and CHRONOS patients had a higher estimated proportion of EASI responders with dupilumab than with cyclosporine treatment. Among UMC Utrecht patients, the estimated proportions of EASI-50 responders to dupilumab vs. cyclosporine treatment were, respectively, 91% vs. 77% ($p = 0.038$) in weeks 12–16 and 96% vs. 67% ($p < 0.0001$) in weeks 24–30; the estimated proportions of EASI-75 responders were 78% vs. 56% ($p = 0.016$) in weeks 12–16 and 80% vs. 47% ($p < 0.001$) in weeks 24–30. Among the CHRONOS trial patients, the estimated proportions of EASI-50 responders to dupilumab vs. cyclosporine treatment were, respectively, 90% vs. 74% ($p < 0.038$) in weeks 12–16 and 92% vs. 53% ($p < 0.0001$) in weeks 24–30; the estimated proportions of EASI-75 responders were 75% vs. 52% ($p = 0.016$) in weeks 12–16 and 74% vs. 40% ($p < 0.001$) in weeks 24–30. For all outcome measures at all time points, the actual (observed) percentages of patients who responded to cyclosporine in the UMC Utrecht study were the same as those estimated from the model. Likewise, in the CHRONOS study, the observed proportions of patients responding to dupilumab were identical to the estimated proportion of responders (Table III)

Table 3 Adjusted regression results: estimating proportions of treatment responders to dupilumab and cyclosporine based on EASI improvement

Population	EASI improvement outcome	Time point, weeks	Intervention	Observed proportion of EASI responders	Estimated proportion of EASI responders (SE)	*P* value
UMC Utrecht (n = 57)	EASI-50	12 to 16	CsA	0.77	0.77 (0.06)	.038*
			Dupilumab	–	0.91 (0.04)	
		24 to 30	CsA	0.67	0.67 (0.06)	< .0001*
			Dupilumab	–	0.96 (0.03)	
	EASI-75	12 to 16	CsA	0.56	0.56 (0.07)	.016*
			Dupilumab	–	0.78 (0.06)	
		24 to 30	CsA	0.47	0.47 (0.07)	< .001*
			Dupilumab	–	0.80 (0.05)	
CHRONOS (n = 106)	EASI-50	12 to 16	CsA	–	0.74 (0.08)	.038*
			Dupilumab	0.90	0.90 (0.03)	
		24 to 30	CsA	–	0.53 (0.09)	< .0001*
			Dupilumab	0.92	0.92 (0.03)	
	EASI-75	12 to 16	CsA	–	0.52 (0.08)	.016*
			Dupilumab	0.75	0.75 (0.04)	
		24 to 30	CsA	–	0.40 (0.08)	< .001*
			Dupilumab	0.74	0.74 (0.04)	

*P < .05; P values represent the significance level of the intervention coefficient in each logistic regression model. Estimated EASI-50 and EASI-75 proportions were calculated using the predicted probabilities of EASI response across patients for the given study population. SE for estimated EASI-50 and EASI-75 proportions were calculated by bootstrap method with 1,000 iterations. Predicted probabilities of EASI response were estimated for each patient by using a separate logistic regression model for each outcome (EASI-50 or EASI-75) at each time point (Weeks 12–16 or 24–30).

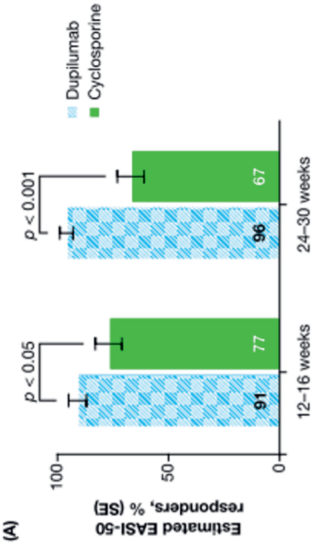

Figure 1 The estimated proportions of EASI-50 (A) and EASI-75 (B) responders in the UMC Utrecht population (n = 57). The solid colour represents observed values and hatched colours represent the estimated values. EASI, Eczema Area and Severity Index; SE, standard error; UMC, University Medical Center.

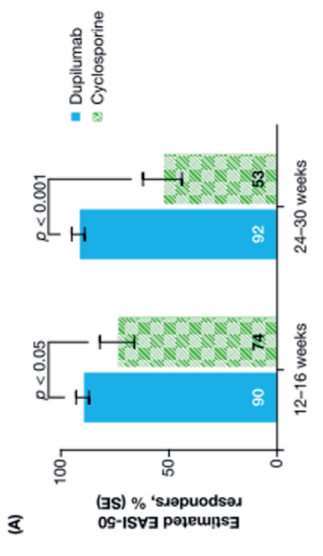

Figure 2 The estimated proportions of EASI-50 (A) and EASI-75 (B) responders in the CHRONOS population (n = 106). The solid colour represents observed values and hatched colours represent the estimated values. EASI, Eczema Area and Severity Index; SD, standard error; UMC, University Medical Center.

According to the EASI-50 criterion, the differences in responder rates of dupilumab vs. cyclosporine treatment during weeks 12–16 were 14% (UMC Utrecht population) and 16% (CHRONOS population). By weeks 24–30, these differences had increased to 29% (UMC Utrecht population) and 39% (CHRONOS population). A similar trend in treatment difference was observed for EASI-75. The EASI-75 responder rates for dupilumab vs. cyclosporine treatment during weeks 12–16 differed by 22% (UMC Utrecht population) and 23% (CHRONOS population). By weeks 24–30, these differences had increased to 33% (UMC Utrecht population) and 34% (CHRONOS population).

The proportion of EASI-50 responders to dupilumab increased slightly between weeks 12–16 and weeks 24–30 in the UMC Utrecht population (from 91% to 96%) and the CHRONOS population (from 90% to 92%). In contrast, the proportion of EASI-50 responders to cyclosporine decreased between weeks 12–16 and weeks 24–30 in the UMC Utrecht population (from 77% to 67%) and the CHRONOS population (from 74% to 53%). The proportion of EASI-75 responders to dupilumab increased slightly or remained stable between weeks 12–16 and weeks 24–30 in both the UMC Utrecht (from 78% to 80%) and CHRONOS (from 75% to 74%) populations. The proportion of patients with EASI-75 responders to cyclosporine decreased between weeks 12–16 and weeks 24–30 in both the UMC Utrecht (from 56% to 47%) and CHRONOS (from 52% to 40%) populations.

The relative increase in the proportion of EASI-50 responders to dupilumab vs. cyclosporine from weeks 12–16 to weeks 24–30 was statistically significant in both the UMC Utrecht (15%; 95% CI 2%, 29%) and the CHRONOS (23%; 95% CI 5%, 40%) populations (Table IV). However, the change in proportion of EASI-75 responders to dupilumab vs. cyclosporine from weeks 12–16 to weeks 24–30 was not statistically significant in either the UMC Utrecht (11%; 95% CI −3%, 25%) or the CHRONOS (12%; 95% CI −4%, 26%) populations

Table 4 Adjusted regression results: relative differences in proportions of treatment responders to dupilumab vs cyclosporine over time

Population	EASI improvement outcome	Intervention	Time point, weeks	Estimated proportion of EASI responders (SE)	Difference in EASI responders over time (24/30 week – 12/16 week)	Relative difference in EASI responders (dupilumab - cyclosporine)	CI
UMC Utrecht (n = 57)	EASI-50	CsA	12 to 16	0.77 (0.06)	−0.11	+0.15	+0.02, +0.29*
			24 to 30	0.67 (0.06)			
		Dupilumab	12 to 16	0.91 (0.04)	+0.05		
			24 to 30	0.96 (0.03)			
	EASI-75	CsA	12 to 16	0.56 (0.07)	−0.09	+0.11	−0.03, +0.25
			24 to 30	0.47 (0.07)			
		Dupilumab	12 to 16	0.78 (0.06)	+0.02		
			24 to 30	0.80 (0.05)			
CHRONOS (n = 106)	EASI-50	CsA	12 to 16	0.74 (0.08)	−0.21	+0.23	+0.05, +0.40*
			24 to 30	0.53 (0.09)			
		Dupilumab	12 to 16	0.90 (0.03)	+0.02		
			24 to 30	0.92 (0.03)			
	EASI-75	CsA	12 to 16	0.52 (0.08)	−0.13	+0.12	−0.04, +0.26
			24 to 30	0.40 (0.08)			
		Dupilumab	12 to 16	0.75 (0.04)	−0.01		
			24 to 30	0.74 (0.04)			

*Values are statistically significant because the CI values do not include 0.

Estimated proportions of EASI-50 and EASI-75 responders were calculated using the predicted probabilities of EASI response across patients for the given study population. Confidence intervals were calculated by a bootstrap method with 1,000 iterations.

CI, confidence interval; CsA, cyclosporine A; EASI, Eczema Area and Severity Index; SE, standard error; TARC, thymus and activation-regulated chemokine; UMC Utrecht, University Medical Center, Utrecht.

DISCUSSION

This analysis suggests a higher relative efficacy of dupilumab compared with cyclosporine effectiveness in the treatment of moderate-to-severe AD, as assessed by 50% and 75% improvements in patients' EASI scores. A direct-comparison (head-to-head) trial between dupilumab and cyclosporine for the treatment of moderate-to-severe AD would be the most rigorous means of comparing the clinical efficacy and safety of both therapies. No such published data were available. A systematic review of the literature suggested that, in the few trials assessing the efficacy of cyclosporine in AD, sample size is generally lower than 30, EASI is often not considered, and outcomes available are often reported at much earlier time points (4–8 weeks) than in dupilumab trials. The lack of adequate evidence and "networks" for comparison of dupilumab vs. cyclosporine efficacy based on published trials precluded us from using the conventional indirect comparison approach of network meta-analysis. Hence, we used patient-level data to conduct an indirect comparison of the efficacy of the 2 agents in the treatment of AD.

The relative efficacy of dupilumab vs. efficacy/effectiveness of cyclosporine improved significantly over time, on the basis of the EASI-50 response. Patients who received cyclosporine were treated, according to a defined protocol, with a high starting dose (5 mg/kg/day) over 3–6 weeks and a stepwise tapering to a maintenance dose of 2–3 mg/kg/day. The cyclosporine dose was adjusted on the basis of individual factors, including effectiveness and side-effects. Tapering of the dose reflects real-world practice and is required to avoid unwanted side-effects, while maintaining a dose with sufficient clinical effectiveness over a prolonged treatment period. Most patients have an adequate response to a high dose, but may relapse after dose reduction. Because the dose of cyclosporine is tapered stepwise, the effect of the high starting dose may continue until the first time point, weeks 12–16. Patients treated with dupilumab, on the other hand, were given 300 mg dupilumab q2w without dose adjustment. The dose reduction after the 3–6 week induction phase in patients treated with cyclosporine may have contributed to the trend in improvement in relative efficacy/effectiveness that was observed for dupilumab vs. cyclosporine over time. However, it should be noted that clinicians at UMC Utrecht are highly experienced with cyclosporine treatment and the need to taper the dose on the basis of balancing maximal effectiveness while limiting safety issues.

Blauvelt et al. reported a lower week 16 EASI-50 response rate (80%) for the dupilumab q2w arm (post hoc analysis) compared with the 90% response rate reported in this study (Table III).[12] This difference can be explained by the use of a highly conservative non-responder imputation in the CHRONOS analysis reported by Blauvelt et al. (12). In that publication, patients were defined as non-responders in cases of missing EASI values and after rescue treatment initiation or study withdrawal. In the present analysis, a LOCF analysis was performed in cases of missing follow-up EASI values. The analyses used patient-level data, which enabled select baseline characteristics to be adjusted in the regression models.

Adjustment in the multivariate regression models was possible only for available baseline characteristics that were common to both study populations, and the models did not adjust for unknown or unmeasured characteristics. Because patients were from different settings it is possible that unobserved confounders may exist that are not accounted for in the model.

The efficacy of cyclosporine in published clinical trials of AD has been reported at much earlier time points than the primary endpoint (16 weeks) in dupilumab trials.[15, 16] Also, none of the cyclosporine trials used EASI as an endpoint, which limited the ability to perform a network meta-analysis or matching-adjusted indirect comparison of the efficacy of cyclosporine with an emergent systemic therapy, such as dupilumab. However, it should be noted that the proportions of patients with EASI-50 (51%) and EASI-75 (34%) after 3–6 months' treatment with cyclosporine A in 35 patients from the German Atopic Eczema Registry are lower than that observed in our study, although mean baseline EASI values were similar.[17]

Safety was not the primary objective of this comparison, and is a difficult factor to compare in a retrospective design. Furthermore, the proactive recording of safety signals in a clinical trial setting is more rigorous than the spontaneous nature of safety reporting typical in daily practice. Therefore, adverse events were not reported in this analysis. To provide some measure of comparison, the reasons for treatment discontinuation due to side-effects have been reported for each population.

There are a number of limitations to the current study, including the fact that, since patients were not randomized, causality cannot be inferred from the findings. In addition, the overall sample size was relatively small for the purposes of an indirect comparison, and replication of the analysis with a larger sample may be warranted. Furthermore, as the data represent a convenience sample from already-collected

data, no power calculations were conducted a priori, which may have increased the likelihood of statistical type 2 errors. Regarding the logistic regression model, it is also possible that all relevant predictors of treatment response may not have been included.

The differences between the 2 population types can also be considered a limitation: CHRONOS was a global randomized controlled trial, whereas the UMC Utrecht study was conducted at one local site. It is therefore possible that unobserved differences in practice patterns or patient characteristics may have contributed to some of the study findings. Furthermore, patients participating in clinical trials are usually screened on the basis of precise inclusion and exclusion criteria, and therefore have similar characteristics. However, patients treated in daily practice often differ in characteristics such as comorbidities and medication use. In a real-life setting the balance between effectiveness and side-effects determines whether treatment will be continued or dose adjustment is necessary. Differences in patient characteristics and dosage adjustment based on clinical characteristics and effectiveness in the patients treated with cyclosporine might therefore have influenced the results. Disease history was not verified independently of the patients' self-report and is not reported here due to a high chance of recall bias. A final limitation of the study concerns collection of the data. The time point at which EASI was reported in patients treated with cyclosporine spanned a multi-week interval, as would be anticipated in daily practice, so there was no granularity in the exact timing of its assessment. By contrast, data from the CHRONOS patients were taken from a specific assessment point, as specified in the clinical trial protocol.

In conclusion, despite the several inherent limitations of an indirect comparison, our findings suggest that dupilumab has greater relative efficacy than cyclosporine in the treatment of moderate-to-severe AD in adult patients, as captured using a well-validated outcome measure, improvement in EASI score. Furthermore, the relative efficacy benefit in favor of dupilumab for EASI-50 increased over time.

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Institutional Review Board (IRB) Approval Statement. The CHRONOS study was conducted in accordance with the provisions of the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines (version R1), and applicable regulatory requirements. All patients provided signed written informed consent. The protocol and all relevant study forms of the CHRONOS study were approved by all relevant institutional review boards and an independent ethics committee. An independent data monitoring committee monitored patient safety.

Regarding the UMC Utrecht study, the Medical Research Ethics Committee confirmed that the Medical Research Involving Human Subjects Act (WMO) does not apply to the above-mentioned study and therefore an official approval of this study by the Medical Ethics Research Committee of UMC Utrecht was not required under the 1999 Medical Research Involving Human Subjects Act.

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Chapter 4

Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry

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ABSTRACT

Introduction: Dupilumab has recently been approved for the treatment of moderate to severe atopic dermatitis (AD) in adults. Daily practice data on dupilumab treatment are scarce.

Objective: To study the effect of 16 weeks treatment with dupilumab on clinical response and serum biomarkers in adult patients with moderate-severe AD in daily practice.

Methods: Data were extracted from the BioDay registry, a prospective multicenter registry. Sixteen-week clinical effectiveness of dupilumab was expressed as number of patients achieving EASI-50 (Eczema Area and Severity Index) or EASI-75, as well as patient reported outcomes measures (Patient-Oriented Eczema Measure, Dermatology Life Quality Index, Numeric Rating Scale pruritus). Twenty-one biomarkers were measured in patients treated with dupilumab without concomitant use of oral immunosuppressive drugs at 5 different time points (baseline, 4, 8, 12, and 16 weeks).

Results: In total, 138 patients treated with dupilumab in daily practice were included. This cohort consisted of patients with very difficult-to-treat AD, including 84 (61%) patients who failed treatment on ≥2 immunosuppressive drugs. At week 16, the mean percent change in EASI score was 73%. The EASI-50 and EASI-75 was achieved by 114 (86%) and 82 (62%) patients after 16 weeks of treatment. The most reported side effect was conjunctivitis, occurring in 47 (34%) patients. During dupilumab treatment, disease severity related serum biomarkers (TARC, PARC, periostin, and IL-22), eotaxin-1, and eotaxin-3 significantly decreased.

Conclusion: Treatment with dupilumab significantly improved disease severity and decreased severity related serum biomarkers in patients with very difficult-to-treat AD in a daily practice setting.

INTRODUCTION

Dupilumab is a fully human monoclonal antibody directed against the interleukin (IL)-4 receptor alpha that blocks the binding of IL-4 and IL-13, which are the key drivers of Th2 immune diseases including AD. IL-4 and IL-13 have a direct effect on the epidermis by effecting the keratinocyte differentiation, production of fillagrin and cell adhesion molecules. Furthermore, IL-4 and IL-13 induce Th2 cell activation and survival, promote IgE class switching, and stimulate eosinophil recruitment. Dupilumab is the first biologic agent that has been approved in the EU, USA, Japan, and other countries for the treatment of patients with inadequately controlled moderate to severe AD. The clinical efficacy and safety of dupilumab ± topical corticosteroids (TCS) have been demonstrated in phase 3 clinical trials at 16 weeks and 52 weeks in adult patients with moderate to severe AD[1-3]. Overall, dupilumab has shown a favorable safety profile in clinical trials. However, higher rates of conjunctivitis (9-28%) have been reported in patients treated with dupilumab compared to placebo.[1-3]

Limited data on dupilumab treatment in a daily practice setting are available. Patients participating in randomized controlled trials are often carefully screened based on predefined inclusion and exclusion criteria. In contrast, patients treated in a real-life setting are unselected and therefore probably less compliant and may have more co-morbidities.[4] Therefore, data derived from clinical trials might not be generalizable to a population treated with dupilumab in a real-life setting. In a daily practice setting, the balance between effectiveness and side effects determines whether treatment will be continued or not.

In this study we evaluated the clinical effectiveness and safety of 16-weeks of dupilumab in adult patients with difficult-to-treat AD in a real-life setting. Our secondary aim was to study which biomarkers are affected by dupilumab treatment and if they correlate to pathways involved in the pathogenesis of AD.

METHODS

Study design

A prospective, observational cohort study was performed including patients who started dupilumab treatment from October 2017 to February 2018 at the National Expertise Center for Atopic Dermatitis from the University Medical Center Utrecht (UMCU), the department of Dermatology, University Medical Center Groningen (UMCG) and the department of Dermatology, Radboud University Medical Center Nijmegen (Radboud UMC). All patients were aged ≥18 years and fulfilled the criteria for dupilumab treatment established by the Dutch Society of Dermatology and Venereology (NVDV). Data were extracted from an online Good Clinical Practice database called BioDay registry. The BioDay registry includes a prospective cohort of adult patients with moderate to severe AD treated with dupilumab in daily practice. Patients included in the BioDay registry gave written informed consent. Physicians in the participating hospitals were trained by members of the registry team in clinical scoring. This study did not fall under the scope of the Medical Research Involving Human Subjects Act which was confirmed by the local Medical Research Ethics Committee (METC 18/239). The study has been performed according to the declaration of Helsinki.

Patients and outcome measures

All 138 patients were assed prior to initiation and for 16 weeks during dupilumab treatment. At baseline, all patients received a loading dose of dupilumab 600 mg subcutaneously administered by a clinician, followed by subcutaneous dupilumab 300 mg every other week (mostly self-administered). Systemic immunosuppressive treatment was discontinued before starting dupilumab treatment in most patients, or a shared decision on continuation of systemic immunosuppressive treatment during dupilumab treatment was made. Concomitant treatment with TCS was allowed. At baseline, and after 4, 8, 12, and 16 weeks of treatment, disease severity was assessed by the Eczema Area and Severity Index (EASI). Additionally, patient reported outcomes including the Patient-Oriented Eczema Measure (POEM), weekly average Numeric Rating Scale (NRS) pruritus, Dermatology Life Quality Index (DLQI), and generic five-dimension five-level EuroQoL scale (EQ-5D-5L) were collected. Clinical endpoints (all at week 4, 8, 12, and 16, unless otherwise indicated) included the mean percent change from baseline in EASI, NRS pruritus, DLQI (at week 16), and POEM, proportions of patients with ≥50%, ≥75% or ≥90% improvement from

baseline in EASI score (EASI-50, EASI-75 or EASI-90), achieving ≥4-point reduction in weekly average NRS pruritus, reporting 'no problem' on the EQ-5D-5L pain/discomfort and anxiety/depression subscales (week 16), achieving ≥4-point improvement in DLQI score (minimal clinically important difference (MCID) at week 16), and achieving ≥4-point improvement in POEM score (MCID); change over time for number of days with itch because of eczema (POEM item 1) and number of nights that sleep was disturbed in the past week (POEM item 2). In addition, the proportion of patients using systemic immunosuppressive drugs during dupilumab treatment was monitored.

Clinically relevant response

A clinically relevant response was defined based on thresholds in one or more outcomes of the three major AD domains (signs, symptoms and quality of life)[5]. Clinically relevant response was measured via analysis of proportion of patients who achieved EASI-75 or improvement (reduction) in weekly average NRS pruritus ≥4 points from baseline or improvement (reduction) in DLQI score ≥4 points from baseline.

Safety

Side effects during the use of dupilumab were evaluated every visit. Patients were asked whether they had experienced subjective side effects and safety laboratory parameters (blood count, serum creatinine, liver enzymes) were monitored.

Serum biomarkers

Patients using oral immunosuppressive drugs at one of the five time points, and patients using oral immunosuppressive drugs within 2- (fast acting drugs) or 4- (slow acting drugs) weeks before screening were excluded. Twenty-one biomarkers associated with different disease pathways were measured: severity-associated markers (IL-22, thymus- and activation-regulated chemokine (TARC), pulmonary and activation-regulated chemokine (PARC), and periostin), Th2-associated markers (IL-4, IL-13 and thymic stromal lymphopoietin (TSLP)), Th17-associated markers (IL-6, IL-17, IL-21, IL-22, IL-23 and IL-26), Th22-associated markers (IL-20, IL-22, IL-26), a Th1-related marker (IL-12), an inflammation-related marker (tumor necrosis factor (TNF) alpha) a pruritus related marker (IL-31), eosinophil markers (IL-5, eotaxin-1, eotaxin-3), and neutrophil markers (elastase, IL-8) (supplementary Table 1). Biomarkers were

measured before initiation of dupilumab treatment (screening) and after 4, 8, 12, and 16 weeks of treatment using multiplex immunoassays as previously described.[6]

Super responders and development of conjunctivitis at week 16

Patients were stratified by the achievement of a clinically relevant improvement in all of the 3 key domains at week 16 (super-responders) and the development of conjunctivitis. Clinical characteristics were compared in the total group between patients who did or did not achieve a clinically relevant improvement at week 16 and patients with and without conjunctivitis at week 16. Baseline and changes over time in serum biomarkers were compared between patients included in the biomarker subgroup who did or did not achieve a clinically relevant improvement at week 16 and patients with and without conjunctivitis at week 16.

Statistical analysis

Data was analyzed at baseline and 4, 8, 12, and 16 weeks after initiation of dupilumab treatment, except for patients with discontinuation of dupilumab treatment, which are described separately. Clinical outcome measures at each follow-up time-point were compared using the Wilcoxon signed-rank test. Serum biomarker levels were normalized by a log-transformation. Differences in biomarker levels between T0 (baseline) and T1 (4 weeks), and between T1 (4 weeks) and T4 (16 weeks) were compared using the Wilcoxon signed-rank test. P-values <0.05 were considered statistically significant. Differences in baseline characteristics and serum biomarkers between subgroups stratified by treatment response and development of conjunctivitis at week 16 were analyzed by using a T-test for normally distributed data, Mann–Whitney test for variables with a non-normal distribution, and Chi square test for categorical variables. All statistical analyses were conducted using SPSS (for Windows, version 25.0, SPSS Inc.) and Prism (version 7.4; Graphpad).

RESULTS

Patients and baseline characteristics

Between November 2017 and September 2018, 138 consecutive patients treated with dupilumab were included with a median EASI score of 19.9 (Inter Quartile Range (IQR 13.6-28.3)) at baseline (Table 1). Weekly average pruritus NRS was 7 (IQR 6.0-8.0). Patients reported high scores on the POEM (median 20.0 (IQR 16.0-23.0)) and DLQI (median 12.5 (IQR 8.0-19.0). Most patients reported problems on usual activity (88 patients (64.7%)), pain/discomfort (116 patients (85.3%)) and anxiety/depression (78 patients (57.4%)) dimensions of the EQ-5D-5L questionnaire. Before initiation of dupilumab treatment, 136 patients (99%) were treated with oral immunosuppressants for AD (Table 1). Most patients (84 (61%)) had a history of ≥2 oral immunosuppressive treatments before starting dupilumab treatment indicating difficult-to-treat AD. None of the patients were previously treated with dupilumab in clinical trials or daily practice.

Table 1. Baseline characteristics

		Total group (n=138)	Biomarker sub-group (n=35)	P-value
Age (years), mean (SD)		43.4 (15.4)	39.8 (13.1)	0.12
Men, n (%)		86 (62.3)	25 (71.4)	0.20
Atopic/allergic diseases at baseline, n (%)				
Allergic rhinitis		100 (72.5)	27 (77.1)	0.47
Asthma		90 (65.2)	24 (68.6)	0.63
Food allergy		70 (50.7)	21 (60.0)	0.20
Allergic conjunctivitis		89 (64.5)	27 (77.1)	0.18
Previous use of systemic immunosuppressants for atopic dermatitis, n (%)		136 (98.6)	35 (100.0)	0.68
History of ≥2 oral immunosuppressive treatments, n(%)		84 (60.9)	22 (62.9)	0.78
Previous use of cyclosporin A, n (%)		131 (94.9)	34 (97.1)	0.49
Previous use of methotrexate, n (%)		55 (39.9)	11 (31.4)	0.24
Previous use of azathioprine, n (%)		46 (33.3)	13 (37.1)	0.58
Previous use of mycophenolate mofetil / enteric-coated mycophenolate sodium, n (%)		40 (39.0)	11 (31.4)	0.71
EASI score, median (IQR)		19.9 (13.6-28.3)	24.4 (16.8-31.9)	0.19
missing, n (%)		3 (2.2)	2 (5.7)	-
Weekly average pruritus NRS, median (IQR)		7 (6.0-8.0)	7 (5.0-8.0)	0.57
POEM score, median (IQR)		20 (16.0-23.0)	20 (16.0-25.0)	0.86
missing, n (%)		3 (2.2)	1 (2.9)	-
DLQI score, median (IQR)		12.5 (8.0-19.0)	10 (7.5-19.0)	0.52
missing, n (%)		2 (1.4)	2 (5.7)	-
EQ-5D-5L dimension, n(%)				
missing, n (%)		2 (2.2)	1(2.9)	-
Mobility	No problems	106 (77.9)	27 (79.4)	0.81
	Problems	30 (22.1)	7 (20.6)	
Self-care	No problems	114 (84.4)	28 (82.4)	0.70
	Problems	21 (15.6)	6 (17.6)	
Usual activity	No problems	48 (35.3)	15 (44.1)	0.21
	Problems	88 (64.7)	19 (55.9)	
Pain/discomfort	No problems	20 (14.7)	5 (14.7)	1.00
	Problems	116 (85.3)	29 (85.3)	
Anxiety/depression	No problems	58 (42.6)	15 (44.1)	0.84
	Problems	78 (57.4)	19 (55.9)	

EASI, Eczema Area and Severity Index; NRS, Numeric rating scale; IQR, Interquartile range; POEM, Patient Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; EQ-5D-5L, Generic five-dimension five-level EuroQoL scale

Effectiveness

After 16 weeks of treatment, the mean percent change in EASI score was -73%. At week 16, the EASI-50, EASI-75 and EASI-90 were achieved by 114 (86%), 82 (62%) and 32 (24%) patients, respectively (supplementary Figure 1). The proportion of patients achieving EASI ≤7 (clear-mild AD) at week 16 was 71% (Table 2). The weekly average NRS pruritus significantly decreased from baseline (NRS pruritus mean = 6.9, SD = 2.1) to week 16 (NRS pruritus mean = 3.1, SD = 2.2) (p <0.001) (supplementary Figure 1). At week 16, 79 patients (57%) achieved ≥4 points improvement (reduction) in weekly average pruritus NRS. Treatment with dupilumab also improved other patient reported outcomes including the health-related quality of life, symptoms of AD, pain/discomfort, sleep and symptoms of anxiety and depression (Table 2). The DLQI score significantly decreased from baseline (mean = 13.4, SD = 7.2) to week 16 (mean = 4.3, SD = 4.2) (p <0.001) with 78% of the patients achieving a ≥4-point improvement in DLQI score after 16 weeks of treatment. The POEM score significantly decreased from baseline (mean = 19.7, SD = 5.5) to week 16 (mean = 7.7, SD = 5.9) (p <0.001). The proportion of patients reporting 'no problems' on the EQ-5D-5L pain/discomfort and anxiety/depression subscale increased from baseline (15% and 43%) to week 16 (48% and 70%).

In 129 patients, data including the NRS pruritus, EASI and DLQI score after 16 weeks of treatment with dupilumab was available to define whether a clinically relevant response was achieved. The proportion of patients achieving a clinically relevant improvement in at least one of the 3 key domains (EASI-75 or NRS ≥4-point improvement or DLQI ≥4-point improvement) after 16 weeks of dupilumab treatment was 89% (115 out of 129 patients). In 11% (14 out of 129 patients) no clinically relevant improvement in at least one of the key domains was achieved (Figure 1).

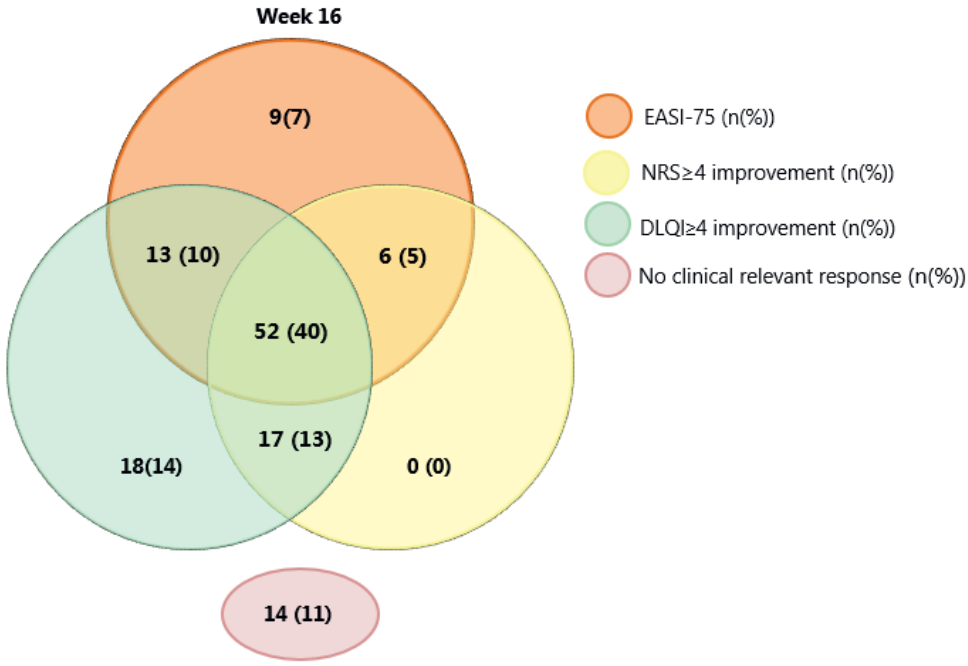
Table 2. Effectiveness outcomes during dupilumab treatment in 138 patients

	Baseline (n = 138)	Week 4 (n = 138)	Week 8 (n = 138)	Week 12 (n = 138)	Week 16 (n = 136)
Concomitant use of systemic prednisone, n (%)	37 (26.8)	23 (16.8)	14 (10.2)	11 (8.0)	9 (6.6)
Accumulated dose of systemic prednisone (mg), median (IQR)	12.5 (7.5-25.0)	10.0 (5.0-11.3)*	5.0 (3.5-10.0)*	5.0 (3.5-10.0)*	2.5 (2.0-10.0)*
EASI score, median (IQR)	19.9 (13.6-28.3)	7.8 (5.6-13.5)*	6.2 (3.1-9.1)*	4.5 (2.2-8.5)*	4.0 (2.0-7.6)*
Missing, n (%)	3 (2.2)	1 (0.7)	4 (2.9)	2 (1.4)	0 (0)
ΔEASI from baseline, mean (SD)	-	-12.1 (9.9)	-15.0 (10.6)	-15.7 (10.7)	-16.3 (10.9)
ΔEASI % from baseline, mean (SD)	-	-51.1 (31.4)	-64.8 (32.2)	-68.4 (35.5)	-73.1 (26.5)
EASI-50, n (%)	-	84 (62.7)	107 (81.7)	110 (82.7)	114 (85.7)
EASI-75, n (%)	-	27 (20.1)	58 (44.3)	74 (55.6)	82 (61.7)
EASI-90, n (%)	-	4 (3.0)	17 (13.0)	31 (23.3)	32 (24.1)
EASI≤7, n (%)	8 (5.9)	57 (41.6)	78 (58.2)	94 (69.1)	96 (70.6)
Weekly average pruritus NRS, median (IQR)	7.0 (6.0-8.0)	4.0 (2.0-6.0)*	3.0 (2.0-5.0)*	3.0 (1.0-5.0)*	3.0 (1.0-5.0)*
Missing, n (%)	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	0 (0)
ΔWeekly average pruritus NRS % from baseline, mean (SD)	-	-38.3 (41.3)	-45.3 (46.2)	-48.8 (48.0)	-53.5 (35.0)
Weekly average pruritus NRS, proportion of patients who achieved improvement (reduction) ≥4 points from baseline, n(%)	-	52 (37.7)	67 (48.6)	75 (54.3)	79 (57.2)
DLQI score, median (IQR)	12.5 (8.0-19.0)	-	-	-	3.0 (2.0-6.0)*
Missing, n (%)	2 (1.4)	-	-	-	1 (0.7)
ΔDLQI from baseline, mean (SD)	-	-	-	-	-9.2 (6.3)
Proportion of patients with ≥4-point improvement in DLQI score, n(%)	-	-	-	-	102 (77.9)
POEM score, median (IQR)	20.0 (16.0-23.0)	10.0 (5.0-15.5)*	8.0 (4.0-13.0)*	7.0 (3.0-12.5)*	7.0 (3.0-12.0)*
Missing, n (%)	3 (2.2)	9 (6.5)	4 (2.9)	5 (3.6)	0 (0)
ΔPOEM from baseline, mean (SD)	-	-8.9 (6.0)	-11.0 (7.0)	-11.6 (7.0)	-12.0 (6.6)
Proportion of patients with ≥4-point improvement in POEM score, n(%)	-	102 (83.6)	117 (92.9)	116 (93.5)	119 (93.0)
ΔPOEM item 1 (itch) from baseline, mean (SD)	-	-1.4 (1.4)	-1.7 (1.5)	-1.8 (1.5)	-1.9 (1.5)
ΔPOEM item 2 (sleep) from baseline, mean (SD)	-	-1.5 (1.5)	-1.7 (1.5)	-1.8 (1.5)	-1.8 (1.6)

EQ-5D item 4 (pain/discomfort): proportion of patients reporting 'no problem', n(%)	20 (14.7)	-	-	-
Missing, n (%)	2 (1.4)	-	-	-
EQ-5D item 5 (anxiety/depression): proportion of patients reporting 'no problem', n(%)	58 (42.6)	-	-	-
Missing, n (%)	2 (1.4)	-	-	-

Data were analyzed by using a Wilcoxon matched-pairs signed rank test (* statistically significant ($p < 0.05$) compared to baseline).
mg, milligram; IQR, Interquartile range; EASI, Eczema Area and Severity Index, NRS, Numeric rating scale; SD, Standard deviation; DLQI, Dermatology Life Quality Index; POEM, Patient Oriented Eczema Measure; EQ-5D, Generic five-dimension five-level EuroQoL scale

Figure 1. Characterization of the patients with a clinically relevant response: proportion of patients achieving EASI-75 or NRS ≥4-point improvement or DLQI ≥ 4-point improvement after 16 weeks of dupilumab treatment



Outcomes were available in 129 patients.
EASI, Eczema Area and Severity Index; EASI-75, ≥75% improvement in EASI score; NRS, Numeric Rating Scale; DLQI, Dermatology Life Quality Index.

Safety

Two patients discontinued dupilumab treatment during the 16 weeks follow-up period. One patient with a history of pellucid marginal degeneration (PMD) of both eyes and amblyopia of the left eye, developed conjunctivitis of both eyes during dupilumab treatment. Due to the development of a limbal stem cell deficiency in this predisposed patient, treatment with dupilumab was discontinued after 12 weeks. Another patient with a history of atopic keratoconjunctivitis, developed hyperemia of the conjunctiva with visual complaints. Ophthalmological examination showed a progressive PMD of the left eye. Since involvement of dupilumab in the development of this rapid progressive eye disorder could not be excluded, dupilumab treatment was discontinued after 12 weeks.

The most reported side effects during dupilumab treatment were eye irritation in 34 patients (25%) (including symptoms of dry eyes, itch and tearing) and conjunctivitis in 47 patients (34%) (symptoms and signs including hyperemia of the conjunctiva) (Table 3).

Table 3. Side effects during dupilumab treatment in 138 patients

Number of patients with, n (%)	
Conjunctivitis (total)	47 (34.1)
Mild conjunctivitis	20 (14.5)
Moderate-severe conjunctivitis (ophthalmologist confirmed, anti-inflammatory eye drops/ointment)	27 (19.6)
Blood eosinophilia (≥0.45×10x9/L)	
Screening	45 (32.6)
4 weeks	67 (48.6)
8 weeks	78 (56.5)
12 weeks	76 (55.1)
16 weeks	78 (56.5)
Eye irritation	34 (24.6)
Headache	14 (10.1)
Injection-site reaction	7 (5.1)
Gastro-intestinal complaints	7 (5.1)
Fatigue	6 (4.3)
Hair loss	5 (3.6)
Herpes Simplex	4 (2.9)
Blepharitis	4 (2.9)
Flu like symptoms	3 (2.2)

Patients were diagnosed with mild conjunctivitis when signs and symptoms could be controlled with artificial tears, antihistamine eye drops or topical treatment with anti-inflammatory ointment on the eyelids. Patients who needed treatment with ocular anti-inflammatory eyedrops or ointment were diagnosed with a moderate to severe conjunctivitis by an ophthalmologist. Out of the 47 patients developing conjunctivitis during treatment with dupilumab, 20 patients (15%) had mild-, and 27 patients (20%) had moderate to severe conjunctivitis. Treatment characteristics are described in Table 4.

Table 4. Treatment characteristics of patients developing (allergic) conjunctivitis during dupilumab treatment

	n(%)
Conjunctivitis, n (%)	47 (34.1)
Time to registration of conjunctivitis as adverse event (days), median (IQR)	56 (31-84)
Presence of preexisting conjunctivitis, n (%)	35 (76.1)
missing, n(%)	1 (2.1)
Mild conjunctivitis, n (%)	20 (42.6)
Presence of preexisting conjunctivitis, n(%)	13 (65.0)
Conjunctivitis treatment, n(%)*	
Ketotifen 0.025 mg/ml eye drops	7 (35.0)
Antibiotic eye drops	3 (15.0)
Tacrolimus 1 mg/g ointment eyelids	3 (30.0)
No treatment/artificial tears	8 (40.0)
Moderate-severe conjunctivitis (treated with anti-inflammatory eyedrops/ointment)	27 (57.4)
Presence of preexisting conjunctivitis, n(%)	22 (84.6)
Conjunctivitis treatment, n(%)*	
Dexamethasone 1 mg/ml eye drops	16 (59.3)
Oxytetracycline 5 mg/g and hydrocortisone 10 mg/g eye ointment	3 (11.1)
Tobramycin 3 mg/ml and dexamethasone 1 mg/ml eye drops	1 (3.7)
Fluorometholone Liquifilm 1 mg/ml eye drops	11 (40.7)
Tacrolimus 0.3 mg/g eye ointment	7 (25.9)
Cyclosporin A 1 mg/ml eye drops	3 (11.1)

*multiple treatments per patient

Other relatively frequently reported side effects included headache in 14 patients (10%), injection-site reaction in 7 patients (5%) and gastro-intestinal complaints in 7 patients (5%).

The proportion of patients with a blood eosinophilia (≥0.45×10x9/L) increased from screening (45 patients (33%) to week 16 (78 patients (57%)). Increased blood eosinophil levels were not associated with symptoms and did not result in dose adjustment or treatment discontinuation of dupilumab. No other laboratory abnormalities were observed during treatment with dupilumab in this study.

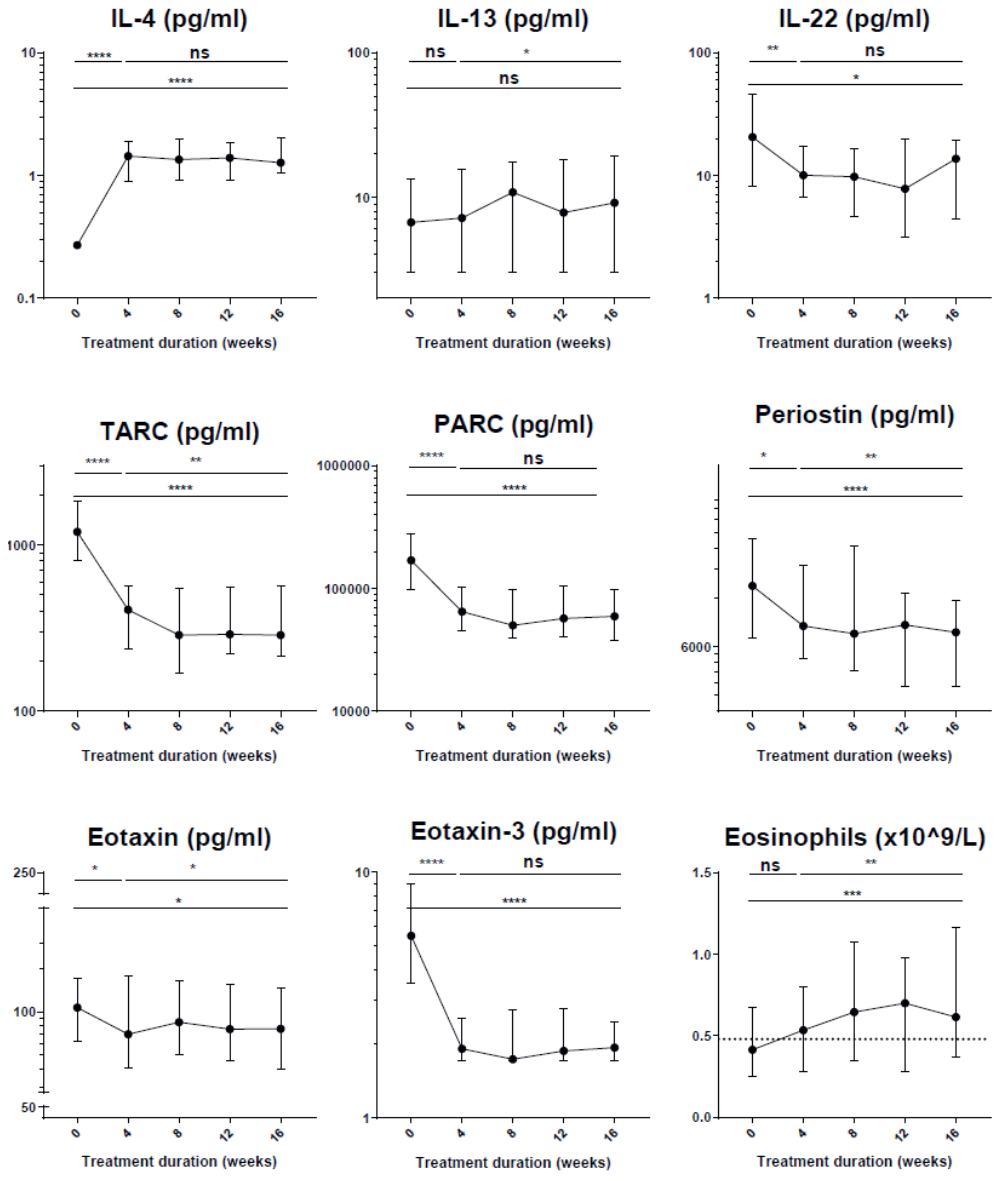
Biomarkers

For the biomarker analysis, twenty-one biomarkers (supplementary Table 1) were measured in a subgroup of 35 patients without concomitant use of oral immunosuppressive drugs at 5 different time points (screening, after 4, 8, 12, and 16 weeks of treatment with dupilumab). Baseline characteristics were not significantly different between the patients included for the biomarker analysis and the total group of patients (Table 1).

Dupilumab treatment significantly reduced severity related serum biomarkers TARC, PARC, periostin, and IL-22 from screening through week 4. TARC and periostin further decreased from week 4 through week 16 (Figure 2). IL-4 showed a significant increase from screening (median 0.27 pg/ml, IQR 0.27-0.27) through week 4 (median 1.44 pg/ml, IQR 0.90-1.88) ($p < 0.0001$). IL-13 was stable from screening to week 4, but then increased significantly from week 4 (median 7.16 pg/ml, IQR 3.00-15.61) through week 16 (median 9.13 pg/ml, IQR 3.02-19.18) ($p = 0.037$). Dupilumab treatment significantly decreased serum levels of eotaxin-1 and eotaxin-3 from screening through week 4 (from median 103.33 pg/ml (IQR 78.33-130.01) to 83.52 pg/ml (IQR 63.57-133.55) at week 4 $p = 0.038$, and from median 5.51 pg/ml (IQR 3.54-8.89) to 1.91 pg/ml (IQR 1.70-2.52), $p < 0.0001$, respectively).

No significant changes were found in the levels IL-5, IL-6, IL-8, IL-12, IL-17, IL-20, IL-21, IL-23, IL-26, IL-31, TNF-a, TSLP, and elastase during dupilumab treatment (supplementary Figure 2).

Figure 2. Serum biomarkers and blood eosinophil levels showing significant change over time during dupilumab treatment



Biomarkers were measured in a subgroup of 35 patients treated with dupilumab.
Median biomarker levels during dupilumab treatment. Error bars represent inter quartile range. Median biomarkers were compared between baseline (t0) and week 16 (t4) by using a Wilcoxon matched-pairs signed rank test (ns=P > 0.05; *P≤0.05; **P≤0.01; ***P≤0.001; ****P≤0.0001).

Super responders and development of conjunctivitis at week 16

The baseline EASI score was significantly higher among patients who achieved a clinically relevant improvement in all of the 3 key domains of the clinically relevant response compared to patients who did not achieve a clinically relevant improvement in all of the 3 domains (median EASI (IQR) 23.5 (16.5-31.8) vs 18.3 (12.6-26.5), p=0.024). Other baseline characteristics (total group and biomarker subgroup and baseline serum biomarkers (biomarker subgroup) did not significantly differ between patients who did or did not achieve a clinically relevant improvement in all of the 3 key domains of the clinically relevant response and patients with or without conjunctivitis (supplementary Table 2-6). Changes over time in EASI and serum biomarkers did also not significantly differ between patients with or without conjunctivitis at week 16 (supplementary Table 6).

DISCUSSION

This study demonstrates that treatment with dupilumab significantly improves signs and symptoms of AD as well as patient reported outcomes including pain/discomfort, itch, anxiety and depression and HrQoL (health related quality of life) in a vast majority of difficult-to-treat AD patients in a daily practice setting. Treatment with dupilumab also significantly suppressed disease severity-related serum biomarkers TARC, PARC, periostin, and IL-22, and eosinophil related markers eotaxin-1, and eotaxin-3.

The clinical effectiveness of dupilumab treatment in this daily practice cohort was consistent with the results observed in clinical phase 3 AD trials.[1, 2, 7] The primary outcome EASI-75 used in phase 3 clinical trials was achieved by 62% of the patients after 16 weeks of treatment in this daily practice cohort. In the phase 3 clinical trials, the EASI-75 was achieved by 44-69% after 16 weeks of dupilumab. Results derived from prospective daily practice registries such as the BioDay registry are important to translate clinical trial results into a real world setting. In clinical trials patients are often carefully screened based on strict in- and exclusion criteria. Patient characteristics including co-morbidities, susceptibility to side effects and earlier treatment failure may influence the treatment success in a real world setting. In this study, 61% of the patients had a history of ≥2 oral immunosuppressive treatments which implies that these patients have a very difficult-to-treat AD. Despite earlier

treatment failure, dupilumab was still very effective in this patient group with comparable results to clinical trials.

Recently, Faiz et al. described the effectiveness of dupilumab treatment in a cohort of 241 AD patients treated with dupilumab in daily practice.[8] Characteristics of the patients included in the study of Faiz et al. were similar to our patients in terms of age, sex, atopic comorbidities, disease severity and previous systemic treatments. The EASI-75 was achieved by 48.8% of the patients which is lower compared to 62% of the patients included in our study. Our study confirms the effectiveness of dupilumab treatment in a cohort of difficult to treat AD patients in daily practice. A limitation of the study by Faiz et al. is the retrospective study design leading to missing data concerning outcome measures including the EASI score which was only measured in 34% of the patients. In the BioDay registry we collect high quality prospective data including a large set of validated outcome measures with limited missing data. Moreover, we measured serum biomarkers reflecting several biomarker pathways, which have not been studied in a daily practice cohort before.

The main outcomes in dupilumab AD clinical trials were fixed endpoints such as the proportion of patients achieving EASI-75. However, since dupilumab treatment affects both clinicians reported outcomes (EASI) and patient reported outcomes (pruritus, HrQoL), these endpoints do not capture the full range of clinical benefits in daily practice. For instance, patients might be considered as non-responders based on EASI scores, while they experience clinically relevant improvement in patient-reported outcomes including pruritus and HrQoL. In our view, a combination of clinical scores and patient reported outcomes should be used to decide on treatment continuation. We defined clinically relevant responses based on thresholds of commonly used tools to assess the major AD domains: signs, symptoms and HrQoL. A large majority of the dupilumab-treated patients (89%) reported clinically relevant improvement in at least one of the three domains (EASI-75 or NRS ≥4-point improvement or DLQI ≥4-point improvement). The use of a clinically relevant response may help to identify super-responders (improvement in all domains) and non-responders (improvement in none of the domains) to treatment. In future, the clinically relevant response may also help to differentiate between very good responders and non-responders based on biomarker profile. Due to the small sample size of non-responders, a responder non-responder comparative analysis was not possible in the present study.

The proportion of patients developing new onset or worsening of conjunctivitis (34%) was higher compared to previous phase 3 clinical trials (9-28%).[1, 2, 7] This might be explained by an increased awareness of conjunctivitis. In the study by Faiz et al. conjunctivitis was also the most reported side effect in 38.2% of the patients which is comparable with the conjunctivitis rates in this study. The proportion of patients who discontinued dupilumab treatment due to ophthalmological events was higher in the study by Faiz et al. (10 patients (4.2%) compared to our study (2 patients 1.4%)).[8] Moderate-severe conjunctivitis needing treatment with anti-inflammatory eyedrops/ointment was observed in 27 patients (20% of total patient group) of whom the majority had a history of preexisting conjunctivitis (83%). However, in all patients, signs and symptoms significantly worsened and anti-inflammatory treatment was initiated during dupilumab treatment. In this cohort patient reported history of conjunctivitis and severity of AD at baseline were no predictors for the development of conjunctivitis during dupilumab treatment. In a previous study, we described the clinical characteristics of 13 moderate to severe dupilumab-treated AD patients developing conjunctivitis with inflammation of the conjunctiva and hyperemia of the limbus as prominent features.[9] Nodular swelling of the limbus was present in the most severe cases. In addition, we described a remarkable scarcity of conjunctival goblet cells accompanied by an inflammatory T-cell- and eosinophilic infiltrate in six dupilumab treated patients with an ophthalmologist-confirmed conjunctivitis requiring anti-inflammatory treatment.[10] We hypothesized that the IL-13 blocking effect of dupilumab might lead to reduction of goblet cells and mucin production in a subpopulation of patients with AD, which may potentially result in irritative conjunctivitis. Given the high proportion of patients developing new-onset or worsening of conjunctivitis during dupilumab in daily practice, potentially leading to serious ocular complications, optimal treatment and risk management is necessary. Remarkably, increased incidence of conjunctivitis was not observed in asthma and sinusitis trials with dupilumab, suggesting a disease specific predisposition in a subpopulation of AD patients.[11-13] A prospective study on ocular co-morbidity in moderate to severe AD patients before and during dupilumab treatment is already initiated in our center.

We observed elevated eosinophil levels in the peripheral blood during treatment with dupilumab. The proportion of patients with observed elevated eosinophil levels in our study was comparable with the patients included in the study by Faiz et al. However, in our study none of the patients discontinued dupilumab treatment due to eosinophilia compared to 5 patients (2.1%) in the study by Faiz et al. [8] Transient

eosinophilia was also observed in clinical trials including patients treated with dupilumab for asthma, AD and chronic sinusitis and nasal polyposis.[7, 11-14] This supports the hypothesis that dupilumab inhibits the migration of eosinophils into the tissues by suppressing the IL-4 and IL-13 stimulated production of eotaxins without influencing the production or migration from the bone marrow. Eotaxins are released from endothelial cells that have been stimulated with IL-4 and IL-13 and attract eosinophils and other inflammatory cells. Eosinophils stimulate the production of Th2-associated cytokines by T-lymphocytes which in turn prolong the survival and mediate the activation and migration of eosinophils.[15] Previous studies have shown that dupilumab decreased eotaxin-2 and eotaxin-3 levels locally in nasal polyp tissue, nasal secretion and serum from chronic rhinosinusitis patients.[11, 16] In this study, we show that serum concentrations of eotaxin-1 and eotaxin-3 chemokines decreased during dupilumab treatment. These data suggests that dupilumab suppresses eosinophil chemokines both systemically and locally.

Dupilumab has shown to normalize the RNA expression of Th2-related inflammatory molecules and reverse skin barrier abnormalities in biopsies from 18 AD patients treated with dupilumab in phase 1 studies.[17] A recent study including 54 patients treated with dupilumab in a clinical trial showed a significant decrease of Th2 related serum biomarkers TARC, PARC, and periostin after 16 weeks of treatment.[18] Both studies included a subgroup of patients from clinical trials, there is no data available on biomarkers in dupilumab treated AD patients in daily practice. Moreover, only a selective group of biomarkers reflecting Th2 activation was studied, while it is known that besides Th2 signaling, activation of Th22, Th17 and Th1 are also observed in patients with AD.[19] In this study, we showed that treatment with dupilumab significantly decreased serum biomarkers that have been implicated as biomarkers of AD severity and treatment response, including TARC, PARC, periostin, and IL-22. An interesting finding of this study was the increase of Th2 cytokines IL-4 and IL-13 during treatment with dupilumab, although levels were still relatively low. Since other Th2 related biomarkers (TARC, PARC, periostin) did decrease, we hypothesize that IL-4 receptor alpha blockade with dupilumab might result in an increase of unbound circulating IL-4 and IL-13 levels. The increase of IL-4 and IL-13 might be a temporary phenomenon, since it is likely that long-term suppression of IL-4Rα will lead to a decreased production of IL-4 and IL-13 by T cells. Dupilumab treatment significantly decreased serum IL-22 levels. No effect on Th17 related biomarkers was observed. Nevertheless, it is questionable whether the Th17 pathway plays a role in our population of European AD patients, since Th17 activation has been strongly

associated with mainly Asian and pediatric AD subtypes, and in European-American populations with only the intrinsic AD subtype.[20] The Th22 pathway is commonly activated in all major subtypes of AD.[20]

In conclusion, treatment with dupilumab significantly improved signs and symptoms of AD in patients with very difficult-to-treat AD in a daily practice setting with the majority of patients achieving a clinically relevant response after 16 weeks of treatment. Dupilumab treatment significantly suppressed disease severity related serum biomarkers and systemically suppresses eosinophil chemokines. The most reported side effect in this daily practice cohort was conjunctivitis. Future, long-term daily practice data derived from the BioDay registry will provide important information on the long-term effectiveness and safety of dupilumab.

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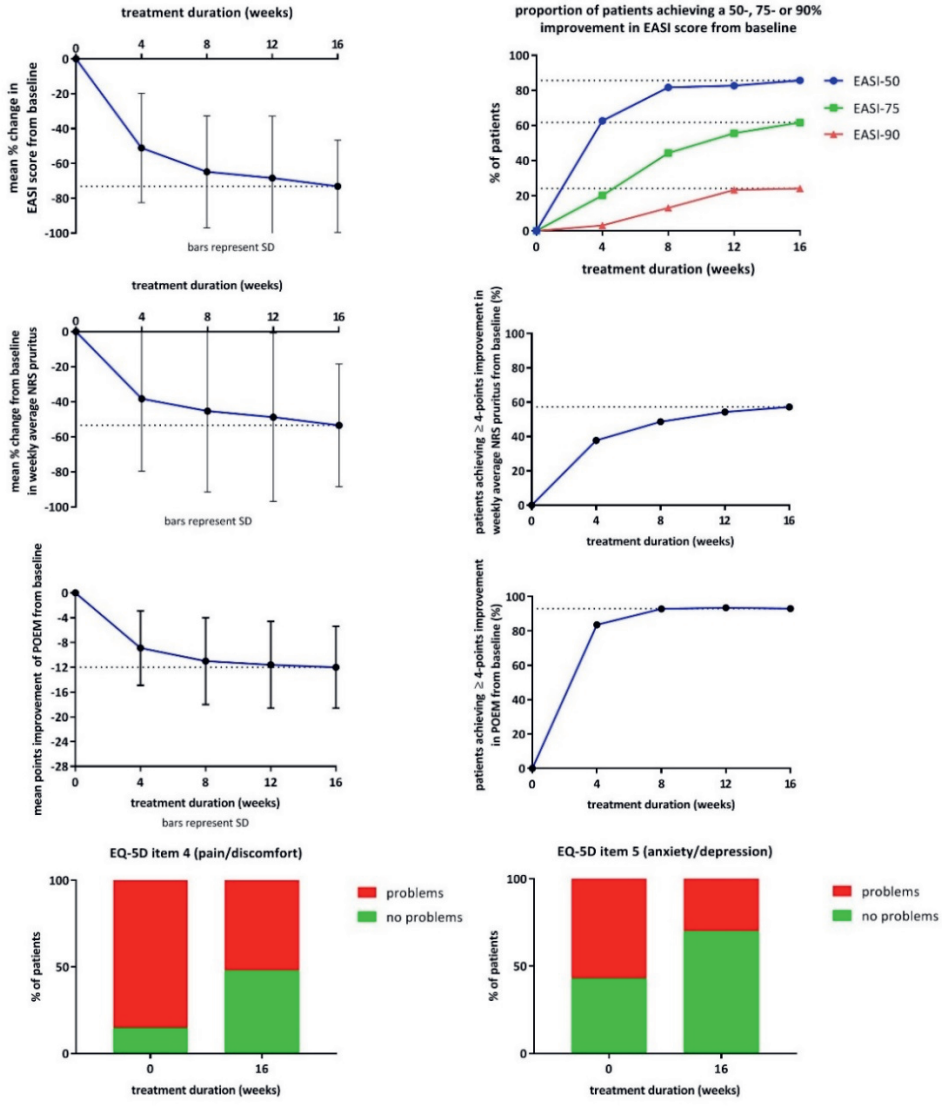
SUPPLEMENTAL FIGURES

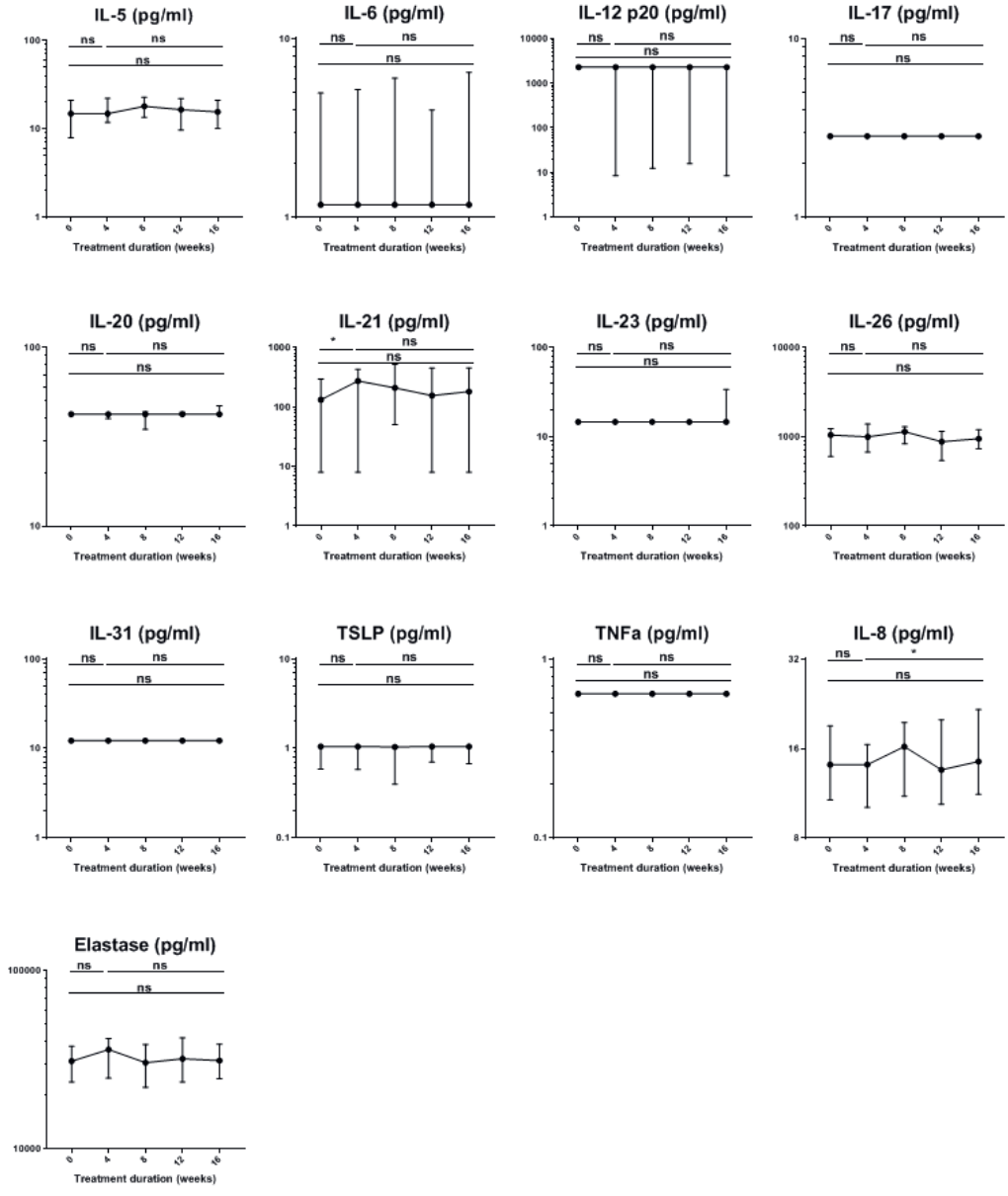
Supplementary Figure 1. Clinician-reported outcomes and patient-reported outcomes



Clinician-reported outcomes and patient-reported outcomes during dupilumab treatment were measured in 138 patients.

EASI, Eczema Area and Severity Index; SD, standard deviation; EASI-50, ≥50% improvement in EASI score; EASI-75, ≥75% improvement in EASI score; EASI-90, ≥90% improvement in EASI score; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; EQ-5D-5L, five-dimension five-level EuroQoL scale

Supplementary Figure 2. Serum biomarkers without significant change over time in 35 patients treated with dupilumab



Median biomarker levels during dupilumab treatment. Error bars represent inter quartile range. Data were analyzed using a Wilcoxon matched-pairs signed rank test (ns=p>0.05; *P≤0.05; **P≤0.01; ***P≤0.001; ****P≤0.0001).

Supplementary table 1. Biomarker panel

Severity markers	Th1 associated markers	Th2 associated markers	Th17 associated markers	Th22 associated markers	Pruritus associated markers	Eosinophil associated markers	Neutrophil associated markers
IL-22	IL-12	IL-4	IL-6	IL-20	IL-31	IL-5	Elastase
TARC	TNF-α	IL-5	IL-17	IL-22		Eotaxin1	IL-8
PARC		IL-13	IL-21	IL-26		Eotaxin3	
Periostin		Periostin	IL-22				
		TSLP	IL-23				
		TARC	IL-26				
		PARC					

Supplementary table 2. Baseline characteristics in patients with and without conjunctivitis at week 16

	Conjunctivitis at week 16		p-value
	Yes (n=47)	No (n=91)	
Age (years), mean (SD)	45.6 (14.5)	42.2 (15.7)	0.220†
Men, n (%)	26 (55)	60 (66)	0.223‡
Atopic/allergic diseases at baseline, n (%)			
Allergic rhinitis	37 (79)	63 (69)	0.237‡
Asthma	34 (72)	56 (62)	0.207‡
Food allergy	29 (62)	41 (45)	0.064‡
Allergic conjunctivitis	35 (75)	54 (60)	0.058‡
Baseline EASI score, median (IQR)	24.2 (14.1-32.4)	19.0 (13.5-27.4)	0.122§
Δ EASI score between week 0 - week 16, mean (SD)	-18.0 (10.8)	-15.5 (10.9)	0.220†
Concomitant use of systemic prednisolone at baseline, n (%)	13 (28)	24 (26)	0.872‡
Blood eosinophilia (≥0.45×10x9/L) at screening, n (%)	12 (26)	33 (36)	0.202‡

†Independent sample T-test; ‡Chi Square Test; §Mann-Whitney Test

Supplementary table 3. Baseline characteristics in patients who did or did not achieve a clinically relevant improvement in all of the 3 key domains (EASI-75 or NRS ≥4-point improvement or DLQI ≥4 point improvement) at week 16 (super-responders)

	Clinically relevant improvement in 3 key domains		P-value
	Yes (super-responders) (n=52)	No (n=77)	
Age (years), mean (SD)	44.4 (15.8)	41.8 (14.6)	0.331†
Men, n (%)	30 (58)	52 (68)	0.255‡
Atopic/allergic diseases at baseline, n (%)			
Allergic rhinitis	41 (79)	53 (69)	0.210‡
Asthma	38 (73)	48 (62)	0.204‡
Food allergy	29 (56)	37 (48)	0.390‡
Allergic conjunctivitis	37 (71)	46 (60)	0.331‡
Baseline EASI score, median (IQR)	23.5 (16.5-31.8)	18.3 (12.6-26.5)	0.024§
Concomitant use of systemic prednisolone at baseline, n (%)	10 (19)	23 (30)	0.174‡
Blood eosinophilia (≥0.45×10x9/L) at screening, n (%)	16 (31)	27 (35)	0.612‡

†Independent sample T-test; ‡Chi Square Test; §Mann-Whitney Test

Supplementary table 4. Baseline characteristics and baseline serum biomarkers in patients included in the biomarker subgroup with and without conjunctivitis at week 16

	Conjunctivitis at week 16		Adjusted P-value
Age (years), mean (SD)	42.9 (13.2)	37.2 (12.8)	0.930†
Men, n (%)	10 (63)	15 (79)	0.930‡
Atopic/allergic diseases at baseline, n (%)			
Allergic rhinitis	12 (75)	15 (79)	0.930‡
Asthma	10 (63)	14 (74)	0.930‡
Food allergy	11 (69)	10 (53)	0.930‡
Allergic conjunctivitis	13 (81)	14 (74)	0.930‡
Baseline EASI score, median (IQR)	20.9 (12.1-29.7)	25.3 (17.7-32.9)	0.962§
Biomarker level at baseline (median (IQR))			
Elastase (pg/ml)	30629.8 (22519.4-39287.8)	33155.7 (23690.9-37589.5)	0.930§
Eotaxin-1 (pg/ml)	120.0 (91.9-144.9)	95.8 (69.9-103.9)	0.467§
Eotaxin-3 (pg/ml)	4.9 (3.6-8.7)	7.0 (2.5-10.0)	0.930§
IL-12 (pg/ml)	2295.0 (7.5-2295.0)	2295.0 (2295.0-2295.0)	0.280§
IL-13 (pg/ml)	7.0 (3.2-13.4)	5.5 (3.0-13.3)	0.930§
IL-17 (pg/ml)	2.9 (2.7-2.9)	2.9 (2.9-2.9)	0.930§
IL-20 (pg/ml)	42.4 (41.8-42.4)	42.4 (42.4-42.4)	0.930§
IL-21 (pg/ml)	210.3 (10.7-433.6)	8.1 (8.1-218.3)	0.658§
IL-22 (pg/ml)	18.2 (7.7-34.9)	21.9 (8.4-47.5)	0.930§
IL-23 (pg/ml)	14.7 (14.7-14.7)	14.7 (14.7-14.7)	0.930§
IL-26 (pg/ml)	721.6 (121.7-1080.8)	699.3 (595.2-1332.3)	0.930§
IL-31 (pg/ml)	12.2 (12.2-12.2)	12.2 (12.2-12.2)	1.00§
IL-4 (pg/ml)	0.27 (0.27-0.27)	0.27 (0.27-0.27)	0.930§
IL-5 (pg/ml)	16.1 (9.6-21.4)	13.9 (6.8-21.1)	0.930§
IL-6 (pg/ml)	4.5 (1.2-7.2)	1.2 (1.2-3.7)	0.67§
IL-8 (pg/ml)	12.9 (10.7-20.7)	14.4 (11.7-17.3)	0.935§
PARC (pg/ml)	187121.7 (101151.0-240605.5)	156390.8 (86804.6-587594.9)	0.930§
Periostin (pg/ml)	7266.1 (6411.4-8378.8)	7032.2 (5879.0-7860.4)	0.930§
TARC (pg/ml)	1168.1 (560.3-1826.0)	1308.2 (822.5-1836.8)	0.930§
TNF-alpha (pg/ml)	0.6 (0.6-0.6)	0.6 (0.6-0.6)	0.930§
TSLP (pg/ml)	0.9 (0.6-1.1)	1.1 (0.5-1.1)	0.930§

P-values were adjusted for multiple testing using the Benjamini-Hochberg procedure, which controls False Discovery Rate (FDR). FDR adjusted P values <0.05 were considered statistically significant rate

†Independent sample T-test; ‡Chi Square Test; ᶜMann-Whitney Test

Supplementary table 5. Baseline characteristics and baseline serum biomarkers in patients included in the biomarker subgroup who did or did not achieve a clinically relevant improvement in all of the 3 key domains (EASI-75 or NRS ≥4-point improvement or DLQI ≥4 point improvement) at week 16.

	Clinically relevant improvement in 3 key domains		Adjusted P-value
	Yes (super-responders) (n=12)	No (n=20)	
Age (years), mean (SD)	39.4 (13.7)	39.0 (12.8)	0.949[a]
Men, n (%)	7 (58)	15 (75)	0.919[b]
Atopic/allergic diseases at baseline, n (%)			
Allergic rhinitis	11 (92)	14 (70)	0.919[b]
Asthma	9 (75)	14 (70)	0.919[b]
Food allergy	8 (67)	12 (60)	0.919[b]
Allergic conjunctivitis	10 (83)	15 (75)	0.919[b]
Baseline EASI score, median (IQR)	24.6 (17.2-30.9)	20.0 (16.4-31.9)	0.919[c]
Biomarker level at baseline (median (IQR))			
Elastase (pg/ml)	30629.8 (24043.9-37248.6)	30070.4 (19317.8-36503.7)	0.919[c]
Eotaxin-1 (pg/ml)	110.1 (69.8-120-9)	100.0 (72.2-133.6)	1.00[c]
Eotaxin-3 (pg/ml)	4.9 (3.6-8.3)	6.3 (2.9-9.8)	0.919[c]
IL-12 (pg/ml)	2295.0 (583.6-2295.0)	2295.0 (2295.0-2295.0)	0.919[c]
IL-13 (pg/ml)	8.4 (3.0-16.2)	6.1 (3.2-11.3)	0.919[c]
IL-17 (pg/ml)	2.9 (2.9-2.9)	2.9 (1.8-2.9)	0.919[c]
IL-20 (pg/ml)	42.4 (41.8-55.1)	42.4 (42.4-42.4)	0.919[c]
IL-21 (pg/ml)	175.4 (8.1-488.3)	107.7 (8.1-278.0)	0.919[c]
IL-22 (pg/ml)	12.1 (7.7-26.5)	22.3 (8.2-49.3)	0.919[c]
IL-23 (pg/ml)	14.7 (14.7-14.7)	14.7 (14.7-14.7)	0.919[c]
IL-26 (pg/ml)	1173.5 (725.3-1327.8)	895.1 (593.6-1145.7)	0.919[c]
IL-31 (pg/ml)	12.2 (12.2-12.2)	12.2 (12.2-12.2)	1.000[c]
IL-4 (pg/ml)	0.3 (0.3-0.3)	0.3 (0.3-0.3)	1.000[c]
IL-5 (pg/ml)	19.1 (7.9-23.8)	14.4 (9.8-18.4)	0.919[c]
IL-6 (pg/ml)	2.6 (1.2-5.4)	1.2 (1.2-4.9)	0.919[c]
IL-8 (pg/ml)	12.2 (10.7-14.2)	14.5 (10.2-19.3)	0.919[c]
PARC (pg/ml)	110139.1 (80911.9-229555.7)	210304.7 (109694.7-387814.2)	0.919[c]
Periostin (pg/ml)	7416.4 (6621.0-8971.7)	7075.9 (5947.6-7973.7)	0.919[c]
TARC (pg/ml)	1127.4 (565.2-1477.9)	1144.0 (494.5-1979.3)	0.919[c]
TNF-alpha (pg/ml)	0.6 (0.6-0.6)	0.6 (0.6-0.6)	0.919[c]
TSLP (pg/ml)			0.919[c]

P-values were adjusted for multiple testing using the Benjamini-Hochberg procedure, which controls False Discovery Rate (FDR). FDR adjusted P values <0.05 were considered statistically significant

[a]Independent sample T-test; [b]Chi Square Test; [c]Mann-Whitney Test

Supplementary table 6. Changes over time in EASI and serum biomarkers in patients included in the biomarker subgroup with or without conjunctivitis at week 16

	Conjunctivitis at week 16		P-value
	Yes (n=16)	No (n=19)	
Δ EASI score between week 0 - week 16, mean (SD)	-18.0 (9.9)	-19.2 (14.8)	0.917
Δ Biomarker level between week 0 - week 16, mean (SD)			
Elastase (pg/ml)	-4259.3 (18541.4)	269.8 (23092.6)	0.821
Eotaxin-1 (pg/ml)	19.0 (37.7)	9.2 (24.0)	0.761
Eotaxin-3 (pg/ml)	6.2 (11.3)	6.1 (8.6)	1.00
IL-12 (pg/ml)	609.7 (1358.2)	254.2 (739.7)	0.761
IL-13 (pg/ml)	-9.2 (18.5)	-1.2 (7.2)	0.741
IL-17 (pg/ml)	-0.4 (0.9)	-0.5 (1.5)	0.917
IL-20 (pg/ml)	-9.4 (33.2)	1.4 (10.4)	0.741
IL-21 (pg/ml)	-391.7 (913.7)	-42.6 (276.5)	0.741
IL-22 (pg/ml)	10.3 (30.9)	12.2 (21.7)	0.917
IL-23 (pg/ml)	-98.5 (218.9)	-3.0 (64.5)	0.741
IL-26 (pg/ml)	-1645.1 (6397.1)	1296.0 (5676.3)	0.741
IL-31 (pg/ml)	-521.9 (2021.3)	-157.2 (579.0)	0.794
IL-4 (pg/ml)	-1.2 (0.7)	-1.2 (0.8)	0.917
IL-5 (pg/ml)	-0.2 (6.3)	-1.5 (6.6)	0.821
IL-6 (pg/ml)	-2.4 (8.0)	-570.9 (2423.9)	0.761
IL-8 (pg/ml)	85.4 (353.5)	-494.5 (2099.5)	0.761
PARC (pg/ml)	107036.2 (128201.9)	4248345735.2 (10980880893.0)	0.741
Periostin (pg/ml)	978.0 (1129.1)	843.5 (1134.5)	0.917
TARC (pg/ml)	772.8 (566.1)	949.3 (644.2)	0.761
TNF-alpha (pg/ml)	-0.1 (0.3)	-1.1 (4.8)	0.761
TSLP (pg/ml)	0.0 (0.0)	0.0 (0.0)	1.00

P-values were adjusted for multiple testing using the Benjamini-Hochberg procedure, which controls False Discovery Rate (FDR). FDR adjusted P values <0.05 were considered statistically significant

p-values were calculated by using the independent sample T-test

Chapter 5

Dupilumab shows long-term effectiveness in a large cohort of treatment-refractory atopic dermatitis patients in daily practice: 52-weeks results from the Dutch BioDay registry

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ABSTRACT

Background: Real-life data on long-term effectiveness and safety of dupilumab in atopic dermatitis patients is limited.

Objective: To study 52-weeks effectiveness and safety of dupilumab in a prospective multi-center cohort of adult patients with treatment-refractory atopic dermatitis.

Methods: Patients treated with dupilumab participating in the Dutch BioDay-registry were included. Clinical effectiveness and safety were evaluated.

Results: 210 atopic dermatitis patients were included. Mean percent change in EASI after 16 weeks was -70.0% (SD 33.2) and further decreased to -76.6% (SD 30.6) by week 52. EASI-75 was achieved by 59.9% at week 16 and 70.3% at week 52. The most reported side effect was conjunctivitis (34%). Limited patients (17 (8.1%)) discontinued dupilumab treatment.

Limitations: Due to the lack of a control-group and observational design, factors of bias may have been induced.

Conclusion: Treatment with dupilumab resulted in a rapid improvement in clinical outcome measures, and effectiveness further improved during the 52-week follow-up period.

INTRODUCTION

Dupilumab, a fully monoclonal-antibody that targets the shared receptor component for IL-4 and IL-13, is the first biologic approved for the treatment of patients with moderate-to-severe atopic dermatitis (AD). In phase-3 clinical trials including patients with moderate-to-severe AD, dupilumab ± concomitant topical corticosteroids (TCS) significantly improved disease-severity and health-related quality of life until 16-and 52 weeks.[1-4] The most recent phase-3 open-label extension study showed that dupilumab treatment was effective and well-tolerated up to 76 weeks.[5]

Data derived from daily-practice provides important information, in addition to data from clinical trials, since there may be considerable differences in patient population and treatment conditions. Results from dupilumab treatment in daily practice shows clinically relevant improvement of physician-reported outcome-measures and patient-reported outcome measures after 3-6 months, which is in line with data from clinical trials.[6-8] The proportion of patients developing conjunctivitis during dupilumab treatment was higher in daily practice (34-38%) compared to previous phase-3 clinical trials (9-28%).[1-3, 6-8] However, real-life data on the long-term effectiveness and safety of dupilumab treatment is limited and prospective large cohort studies are scarce.[9, 10]

In this prospective real-life registry study, 52-weeks effectiveness and safety of dupilumab was studied in a multi-center cohort of adult patients with treatment-refractory AD.

METHODS

Study design

This prospective multicenter observational longitudinal cohort study consecutively included all adult patients who (a) started dupilumab for treatment-refractory AD, according to the criteria established by the Dutch Society of Dermatology and Venereology (NVDV) (treatment ≥4 months with ≥1 conventional systemic therapy in an adequate dose), from October 2017 to September 2018 and (b) participated in the Dutch BioDay-registry.[8] At baseline, all patients received a loading dose of dupilumab 600mg subcutaneously, followed by dupilumab 300mg every other week.

Interval adjustment was allowed in case of severe side effects or insufficient response. If possible, systemic immunosuppressive treatment was discontinued before starting dupilumab treatment. The BioDay-registry was considered as non-interventional by the local Medical Ethics Committee and collection of data was performed according to the Helsinki Declaration. All patients provided written informed consent. ClinicalTrials.gov identifier: NCT03549416.

Patients and outcome measures

Patient characteristics were extracted from the BioDay-registry. All patients were assessed at baseline until 52 weeks of treatment. Disease severity was assessed at baseline, after 4, 16, 28, 40, and 52 weeks (maximal visit window 4 weeks) of treatment, by the Eczema Area and Severity Index (EASI: 0-72) and serum thymus and activation-regulated chemokine (TARC) levels.[11, 12] Patient-reported outcomes, including the Patient-Oriented Eczema Measure (POEM: 0-28), weekly average Numeric Rating Scale (NRS: 0-10) pruritus, Dermatology Life Quality Index (DLQI: 0-30), and generic five-dimension five-level EuroQoL scale (EQ-5D-5L: 0-5 for each dimension) were collected.[13-16] To study longitudinal improvement and course of individual patients, the proportion of patients achieving absolute cut-off scores indicating controlled disease (EASI≤7 and NRS≤4) (week 16, 28, 40 and 52) and relative changes over time (EASI-50, EASI-75, NRS≥4 points improvement from baseline) at 0/4, ≥1/4, ≥2/4, ≥3/4, and 4/4 follow-up visits were analyzed. Patients with baseline EASI<7 and NRS<4 were excluded from this analysis.

Safety

Patients were asked about side effects and medication use during every visit. Ocular side effects and ocular medication use were assessed by standardized questionnaires during every visit, and included severity of redness/itching/tearing/pain/photophobia/burning sensation/blepharitis of the eyes. In case of conjunctivitis with insufficient response to artificial tears and/or topical tacrolimus skin ointment on the eye-lids, patients were referred to an ophthalmologist for standardized examination and ophthalmological follow up. Laboratory parameters were monitored.

Statistical analysis

Clinical outcome measures were compared using the Wilcoxon signed-rank test. Missing data in patients who discontinued treatment during follow-up were imputed by last observation carried forward (LOCF) method. Statistical analyses were conducted using SPSS (for Windows, version 25.0, SPSS Inc.) and Prism (version 7.4; GraphPad).

RESULTS

Population

210 patients with moderate-to-severe AD were included (mean (SD) age 43.2 years (15.5); 61.4% male). The majority of patients had been previously treated with oral immunosuppressive drugs (n=208(99.0%))(table 1). Two patients did not use prior oral immunosuppressive drugs because of contra-indications. Treatment with oral immunosuppressive drugs (excluding systemic corticosteroids) was discontinued in almost all patients before start of dupilumab treatment (99.5%). One patient was concomitantly treated with methotrexate (indication rheumatoid arthritis).

Table 1. Baseline characteristics

	Total group (n=210)
Age (years), mean (SD)	43.2 (15.5)
Men, n (%)	129 (61.4)
Atopic/allergic diseases at baseline, n (%)	
Allergic rhinitis	145 (69.0)
missing	4 (1.9)
Asthma	124 (59.0)
missing	4 (1.9)
Food allergy	101 (48.1))
missing	4 (1.9)
Allergic conjunctivitis	125 (59.5)
missing	5 (2.4)
EASI score, median (IQR)	19.0 (12.6-27.7)
IGA score, median (IQR)	3 (3.0-4.0)
Weekly average pruritus NRS, median (IQR)	7 (6.0-8.0)
POEM score, median (IQR)	20 (16.0-23.5)
DLQI score, median (IQR)	12 (8.0-18.0)
Previous use of oral immunosuppressive drugs for atopic dermatitis*, n (%)	208 (99.0)
History of ≤ 1 oral immunosuppressive drug, n (%)	100 (47.6)
History of ≥ 2 oral immusuppressive drugs, n(%)	110 (52.4)
Previous use of cyclosporine, n (%)	201 (95.7)
Previous use of methotrexate, n (%)	70 (33.3)
Previous use of azathioprine, n (%)	59 (28.0)
Previous use of mycophenolate mofetil / enteric-coated mycophenolate sodium, n (%)	48 (22.9)
Use of oral corticosteroids at start of dupilumab, n (%)	53 (25.2)

* Treatment with oral immunosuppressive drugs for ≥4 months.

SD, standard deviation; EASI, Eczema Area and Severity Index; IQR, Interquartile range; IGA, Investigator's Global Assessment; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measure; DLQI, Dermatology Life Quality Index

Effectiveness of dupilumab treatment

Mean EASI significantly improved from baseline (19.0(IQR 12.6-27.7)) to week 16 (3.6(IQR 1.8-7.2), p<0.001) and week 52 (2.7(IQR 1.4-5.4), p<0.001). Mean percent change in EASI from baseline to week 16 was -70.0% (SD 33.2) and further improved to -76.6% (SD 30.6) in week 52 (Table 2). The proportion of patients achieving the EASI-50, EASI-75, and EASI-90 was 84.2%(n=170), 58.9%(n=119) and 21.9% (n=46) respectively at week 16 and 90.1%(n=182), 70.3%(n=142) and 34.7%(n=70) respectively at week 52 (figure 1). Median serum TARC levels significantly decreased from baseline (2231.0 pg/ml (IQR 810.0-4747.0)) to week 16 (s439.0(IQR 241.5-766.0)) (p=<0.001) and week 52 (360.0(IQR 226.0-559.5)) (p=<0.001).

Weekly average NRS pruritus significantly decreased from baseline (median 7.0(IQR 6.0-8.0)) to week 16 (3.0 (IQR 1.3-4.0)) (p=<0.001) and week 52 (2.0 (IQR 1.0-5.0)) (p=<0.001). A ≥4-point reduction in weekly average pruritus NRS was achieved by 60.2% (109/185 patients (patients with NRS<4 at baseline were excluded) at week 16 and 62.1% (110/185 patients) at week 52. DLQI score significantly decreased from baseline (median 12.0(IQR 8.0-18.0)) to week 16 (median 3.0 (IQR 1.0-6.0) (p<0.001)) and to week 52 (median 3.0(2.0-5.0)). POEM score significantly decreased from baseline (median 20.0(IQR 16.0-23.5)) to week 16 (median 7.0(IQR 3.0-11.0)) (p<0.001) and to week 52 (median 6.0(IQR 3.0-11.0)) (p<0.001). The proportion of patients reporting "no problems" on the EQ-5D-5L pain/discomfort and anxiety/depression subscale increased from baseline (16.1% and 49.4%) to week 52 (59.8% and 72.0%).

At baseline, 53 patients (25.2%) were treated with systemic corticosteroids. Use of concomitant systemic corticosteroids was successfully tapered and discontinued in the majority of patients (table 2). At week 52, eight patients (3.8%) were still using systemic corticosteroids; two patients due to inadequately controlled AD, three patients because of a tertiary adrenal insufficiency and three patients for the indication asthma.

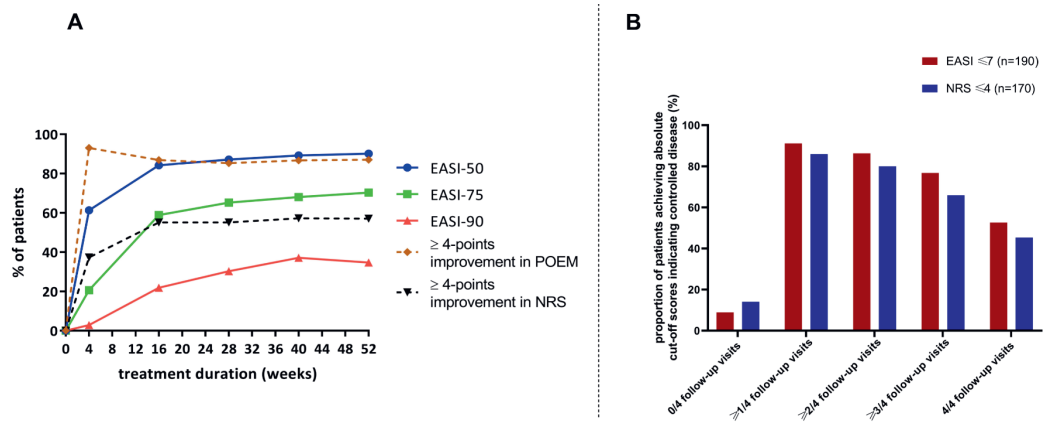
Table 2. Effectiveness outcomes during dupilumab treatment in 210 patients

	Baseline	Week 4	week 16	week 28	week 40	week 52
EASI score, median (IQR)	19 (12.6-27.7)	7.5 (4.8-12.4)***	3.6 (1.8-7.2)***	3.4 (1.6-6.4)***	2.7 (1.2-6.2)***	2.7 (1.4-5.4)***
missing	4 (1.9)	2 (1.0)	5 (2.4)	5 (2.4)	11 (5.2)	3 (1.4)
ΔEASI % from baseline, mean (± SD)	-	-48.9 (37.4)	-70.0 (33.2)	-72.5 (33.0)	-75.0 (33.4)	-76.6 (30.6)
EASI-50, n (%)	-	125 (61.3)	170 (84.2)	175 (87.1)	173 (89.2)	182 (90.1)
missing	-	6 (2.9)	8 (3.8)	9 (4.3)	16 (7.6)	8 (3.8)
EASI-75, n (%)	-	42 (20.6)	119 (58.9)	131 (65.2)	132 (68.0)	142 (70.3)
missing	-	6 (2.9)	8 (3.8)	9 (4.3)	16 (7.6)	8 (3.8)
EASI-90, n (%)	-	6 (2.9)	46 (21.9)	61 (30.3)	72 (37.1)	70 (34.7)
missing	-	6 (2.9)	8 (3.8)	9 (4.3)	16 (7.6)	8 (3.8)
Proportion of patients with EASI≤7, n(%)	15 (7.3)	92 (44.2)	151 (73.3)	157 (76.6)	161 (81.3)	167 (81.1)
missing	4 (1.9)	2 (1.0)	4 (1.9)	5 (2.4)	12 (5.7)	4 (1.9)
Serum TARC levels, median (IQR)	2231.0 (810.0-4747.0)	652.0 (374.5-1164.5)***	439.0 (241.5-766.0)***	389.0 (256.5-681.5)***	410.0 (252.5-559.0)***	360.0 (226.0-559.5)***
Weekly average pruritus NRS, median (IQR)	7.0 (6.0-8.0)	4.0 (2.0-6.0)***	3.0 (1.3-4.0)***	3.0 (1.0-4.0)***	3.0 (1.0-5.0)***	2.0 (1.0-5.0)***
missing	8 (3.8)	7 (3.3)	6 (2.9)	7 (3.3)	16 (7.6)	9 (4.3)
Weekly average pruritus NRS, proportion of patients who achieved improvement (reduction) ≥ 4 points from baseline, n (%) (n=185)	-	75 (41.2)	109 (60.2)	109 (60.9)	107 (61.8)	110 (62.1)
missing	-	3 (1.6)	4 (2.2)	6 (3.2)	12 (6.5)	8 (4.3)
Proportion of patients with NRS ≤4, n (%)	31 (15.3)	118 (58.1)	146 (71.6)	154 (76.2)	142 (74.3)	148 (75.5)
missing	8 (3.8)	7 (3.3)	6 (2.9)	8 (3.8)	19 (9)	14 (6.7)
DLQI score, median (IQR)	12.0 (8.0-18.0)	-	3.0 (1.0-6.0)***	-	-	3.0 (2.0-5.0)***
missing	10 (4.8)	-	8 (3.8)	-	-	24 (11.4)
Proportion of patients with ≥ 4-point improvement in DLQI score, n(%) (n=186)	-		155 (84.7)			145 (86.8)
missing			3 (1.6)			19 (10.2)
Proportion of patients with DLQI≤5, n (%)	28 (14.0)		152 (75.2)			189 (97.4)
missing	10 (4.8)		8 (3.8)			16 (7.6)

POEM score, median (IQR),	20.0 (16.0-23.5)	7.0 (4.0-11.0)***	7.0(3.0-11.0)***	6.0 (2.8-11.0)***	6.0 (2.8-11.0)***	6.0 (3.0-11.0)***
missing	9 (4.3)	19 (9.0)	12 (5.7)	12 (5.7)	24 (11.4)	18 (8.6)
Proportion of patients with ≥ 4-point improvement in POEM score, n (%) (n=200)	-	173 (93.5)	166 (87.4)	163 (85.8)	156 (87.2)	161 (87.5)
missing		15 (7.5)	10 (5.0)	10 (5.0)	21 (10.5)	16 (8.0)
ΔPOEM item 1 (itch) from baseline, mean (± SD)	-	-1.5 (1.4)	-1.8 (1.5)	-1.9 (1.5)	-1.9 (1.5)	-1.9 (1.5)
ΔPOEM item 2 (sleep) from baseline, mean (± SD)	-	-1.5 (1.5)	-1.8 (1.6)	-1.8 (1.6)	-1.8 (1.5)	-1.9 (1.6)
Proportion of patients with POEM≤7, n (%)	7 (3.5)	108 (56.5)	99 (50.0)	110 (55.6)	99 (53.5)	111 (57.5)
missing	9 (4.3)	19 (9.0)	12 (5.7)	12 (5.7)	25 (11.9)	17 (8.1)
EQ-5D item 4 (pain/discomfort): proportion of patients reporting 'no problem', n(%)	32 (16.1)	-	-	-	-	113 (59.8)
missing	11 (5.2)	-	-	-	-	21 (10.0)
EQ-5D item 5 (Anxiety/depression): proportion of patients reporting 'no problem', n (%)	86 (49.4)	-	-	-	-	136 (72.0)
missing	10 (4.8)					21 (10.0)
Concomitant use of systemic prednisone, n (%)	53 (25.2)	24 (11.4)	11 (5.2)	12 (5.7)	11 (5.2)	8 (3.8)

Data were analyzed by using a Wilcoxon matched-pairs signed-rank test. *, **, *** = p< 0.05,p < 0.01, p< 0.001 to baseline.
Missing data in patients who discontinued dupilumab treatment during follow-up were imputed by last observation carried forward (LOCF) method
SD, standard deviation; EASI, Eczema Area and Severity Index; IQR, Interquartile range; IGA, Investigator's Global Assessment; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; EQ-5D-5L: generic five-dimension five-level EuroQoL scale

Figure 1. Clinician-reported outcomes, patient-reported outcomes and longitudinal treatment effect of dupilumab



A: Relative changes over time in clinician-reported outcomes and patient-reported outcomes during dupilumab treatment (n=210)
B: Longitudinal treatment effect was evaluated by the proportion of patients achieving absolute cut-off scores indicating controlled disease. N: number of patients with available outcome measure.
Patients with baseline EASI<7, NRS<4 and POEM<7 were excluded from this analysis.
EASI, Eczema Area and Severity Index; SD, standard deviation; EASI-50, ≥50% improvement in EASI score; EASI-75, ≥75% improvement in EASI score; EASI-90, ≥90% improvement in EASI score; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure

Longitudinal effectiveness of dupilumab treatment

EASI≤7 was achieved at all (4/4) follow up visits by 100/190(52.6%), at ≥3/4 visits by 146/190(76.8%), at ≥2/4 visits by 164(86.3%), at ≥1/4 by 173/190(86.3%) and at 0/4 visits by 17/190(8.9%) of patients (figure 1). NRS≤4 was achieved at 4/4 visits by 77/170(45.3%), at ≥3/4 visits by 112/170(65.9%), at ≥2/4 visits by 136/170(80.0%), at ≥1/4 visits by 146/170(85.9%) and at 0/4 visits by 24/170(14.1%) patients.

Side effects

The most common observed side effect was conjunctivitis in 34.1% (n=72) (Table 3). Fourteen patients (6.6%) were diagnosed with mild conjunctivitis defined as signs and symptoms that could be controlled with artificial tears, antihistamine eye drops, or topical treatment with anti-inflammatory ointment on the eyelids. Patients were diagnosed with moderate-to-severe conjunctivitis if treatment with ocular anti-inflammatory therapy was prescribed by an ophthalmologist (n=58 (27.5%)). Conjunctivitis during dupilumab treatment was associated with significantly higher EASI scores (p=0.004) and serum TARC levels (p=0.045) at baseline; there were no other predictive factors (supplementary table 1).

Other reported side effects included headache (n=20(9.4%)), muscle or joint pain (n=16(7.6%)), fatigue (n=10(4.7%)), gastro-intestinal complaints (n=10(4.7%)), injection-site reaction (n=7(3.3%)), hair loss (n=6(2.8%)), and red face (n=6(2.8%)). The proportion of patients with blood eosinophilia (≥0.45 × 10 × 9/L) increased from baseline (n=67(33.0%)) to week 16 (n=108(54.5%)) and then decreased (n=72(40.2%)) at week 52. No other clinically significant changes in laboratory parameters were observed during dupilumab treatment.

Dupilumab dose adjustment

Dupilumab interval was prolonged in 12 patients (7.0%) because of side effects (300mg/3 weeks: n=8 (3.8%); 300mg/4 weeks: n=4 (1.9%)). In 10/12 patients dupilumab interval was prolonged because of persistent conjunctivitis despite treatment with ocular anti-inflammatory therapy. In 2 patients (1.2%), dupilumab interval was prolonged because of severe muscle or joint pain. Dupilumab interval was shortened in 2 patients (300mg/weekly) due to ineffectiveness.

Discontinuation of dupilumab treatment

Seventeen patients (8.1%) discontinued dupilumab treatment during follow-up (Supplementary table 2). Eight (3.8%) due to side effects of which 5 (2.4%) were due conjunctivitis during dupilumab treatment. Other side effects resulting in discontinuation of dupilumab included joint and muscle complaints (0.5%), enlargement of lymphoid cells (0.5%), and flare of rosacea (0.5%). Nine patients (4.3%) discontinued dupilumab treatment because of ineffectiveness.

Table 3. Side effects during dupilumab treatment in 2010 patients

Number of patients with, n(%)	
Headache	20 (9.4)
Fatigue	16 (7.6)
Gastro-intestinal complaints	10 (4.7)
Injection-site reaction	10 (4.7)
Hair loss	7 (3.3)
Facial redness	6 (2.8)
Herpes Simplex	6 (2.8)
Herpes Zoster	3 (1.4)
Nasopharyngitis	1 (0.5)
Skin infection	1 (0.5)
Conjunctivitis	1 (0.5)
Mild conjunctivitis	14 (6.6)
Moderate-severe conjunctivitis (treated with anti-inflammatory eyedrops/ointment	50 (27.5)
Eosinophilia (≥0.45×10x9/L)	
Baseline	67 (33.0)
4 weeks	96 (47.5)
16 weeks	108 (54.5)
28 weeks	89 (46.4)
40 weeks	82 (45.3)
52 weeks	72 (40.2)

DISCUSSION

In this prospective observational 52-week study, data on long-term effectiveness and safety during dupilumab treatment in patients with moderate-to-severe AD in a real-life setting are presented. Clinical outcome measures rapidly improved in the first 16 weeks of treatment with dupilumab and further improved until week 52. Overall, dupilumab was well tolerated with only 3.8% of patients discontinuing treatment due to side effects. However, 34% of the patients were diagnosed with new onset or worsening of conjunctivitis during dupilumab treatment.

Physician- and patient-reported outcomes at week 16 are consistent with those reported in previous phase-3 clinical trials and daily practice studies.[1-3, 6-8, 17] Concerning long-term outcome, the effectiveness in our daily practice study is comparable with clinical outcomes of the 52-week randomized, double-blinded, placebo-controlled, phase-3 study (LIBERTY AD CHRONOS).[1] In contrast to CHRONOS, nearly all clinical outcome measures, further improved after 16 weeks in the current study. Patients included in CHRONOS had a higher median (IQR) baseline EASI score (29.6(22.2–40.8)) compared to the patients included in this study (19.0(12.6-27.7)) which can be explained by the wash-out period of oral immunosuppressive drugs and TCS before the start of dupilumab in CHRONOS. In our study, follow-up visits were performed by specialized physicians and nurses paying specific and particular attention to adequate use of TCS and compliance. This might explain the slightly better performance of this daily practice cohort compared to CHRONOS.

A recently published retrospective study including 52 patients treated with dupilumab in daily practice evaluated the long-term (52-weeks) efficacy, safety and reasons for discontinuation.[9] At week 52, 54% (n=28) achieved the primary outcome of IGA 0/1 (clear-almost clear); 46% of patients were defined as 'non-responders', although dupilumab treatment was continued in these patients because of significant improvement in quality of life, pruritus and sleep. Bosma et al. published a prospective cohort study including 221 patients treated with dupilumab in daily practice.[10] Linear mixed models were used, as not all patients reached the long-term endpoints. The models showed similar results in clinical outcome measures compared to our study. After starting dupilumab treatment, 46.6% of the patients continued treatment with conventional systemic therapy, which makes the interpretation of the effectiveness of dupilumab difficult in this bridging phase. In our study we preferred discontinuation of systemic immunosuppressive drugs to

evaluate effectiveness of dupilumab in the first weeks of treatment. To avoid exacerbations despite intensive treatment with topical steroids, short courses systemic steroids were used in some patients before starting dupilumab treatment. As the number of patients using this recuse medication was rather small and the treatment period in most patients was short, this might not have large impact on our results.

This study found low discontinuation rates of dupilumab treatment after 52 weeks (8.1%), mostly due to side effects (3.8%) and ineffectiveness (4.3%). This percentage of discontinuation is slightly lower compared to the retrospective daily practice study of Jo *et al* (12%) and comparable with the discontinuation rate in the study of Bosma et al (6.1%).[9, 10] In CHRONOS, discontinuation due to adverse events was reported in 2% of patients treated with dupilumab every-other-week + TCS (n=110) at week 52.[1] Long-term effectiveness and safety data of conventional systemic immunosuppressive drugs in AD show high discontinuation rates- up to 50% - in daily practice after 1 year due to side effects and ineffectiveness.[18-20] The low discontinuation rate of dupilumab in the current study, despite the relatively high rate of conjunctivitis, might be explained by the intensive and protocolled ophthalmological care and the lack of alternative treatment options, as most patients had already failed multiple oral immunosuppressive treatments.

In this study cohort, 34% of the patients were diagnosed with conjunctivitis. Literature on patients treated with dupilumab in daily practice shows incidences of conjunctivitis up to 38% which is higher compared to clinical trials.[6-8, 21] Higher conjunctivitis rates during daily practice treatment with dupilumab can be explained by an increased awareness, but can also be related to the differences in AD severity at baseline. The patient population treated with dupilumab shortly after market access represents a rather severe AD population. In this study, conjunctivitis during dupilumab treatment was associated with significantly higher EASI baseline scores and serum TARC levels, which is in accordance with the clinical trials data. In contrast to trial data, conjunctivitis was not associated with history of conjunctivitis in this study. Despite the fact that moderate-to-severe conjunctivitis, indicated for ocular anti-inflammatory treatment, was observed in 58 (27.5%) patients, dupilumab was discontinued in only 5 (2.4%) patients. The other patients were able to continue dupilumab treatment, but remained dependent on ocular anti-inflammatory treatment. The pathogenesis of dupilumab related conjunctivitis is still unknown. Notably, in asthma and nasal polyp patients, dupilumab treatment was not

associated with higher conjunctivitis rates compared to placebo treated patients.[22] It is therefore likely that AD-specific factors contribute to the higher prevalence of conjunctivitis in AD during dupilumab treatment. As ocular comorbidities are highly prevalent in patients with AD compared to the general population, it is possible that pre-existing ocular comorbidities predispose to higher conjunctivitis rates in AD patients during dupilumab.[23] Previously, we described a remarkable scarcity of conjunctival goblet cells and an extensive cellular infiltrate, mainly existing of CD4+ T-cells in the conjunctival stroma, in 6 patients with conjunctivitis during dupilumab.[24]

Comparable with clinical trials, we observed an asymptomatic and transient eosinophilia during dupilumab treatment, which was independent of concomitant treatment with systemic corticosteroids. [1-3, 25-27] The increase of eosinophil levels in the peripheral blood is consistent with the hypothesis that blockage of IL-4 and IL-13 inhibits the production of eotaxins and migration of eosinophils into tissue, but does not inhibit the production and migration from the bone marrow. This mechanism results in a transient increase in circulating eosinophils. Recently, we demonstrated that serum concentrations of eotaxin-1 and eotaxin-3 chemokines significantly decreased during dupilumab treatment.[8] In addition, previous studies in patients with chronic rhinosinusitis patients showed that dupilumab decreased eotaxin-2 and eotaxin-3 levels locally in nasal polyp tissue, nasal secretion, and serum.[25, 28]

Several limitations result from the daily practice setting of this study. Due to the lack of a control group and observational design, factors of bias may have been induced. Additionally, due to the lack of an ophthalmological examination before starting dupilumab treatment, pre-existing specific signs and symptoms of conjunctivitis could not be determined.

In conclusion, this observational 52-week daily-practice study showed long-term effectiveness in a large cohort of treatment-refractory AD patients. Treatment with dupilumab resulted in a rapid improvement of all clinical outcome measures in the first 16 weeks of treatment, and clinical effectiveness was sustained or even improved during the total 52-week follow-up period. A limited number of patients (17 (8.1%)) discontinued dupilumab treatment, with only 8 patients (3.8%) discontinuing dupilumab treatment due to side effects, and 9 (4.3%) due to ineffectiveness. In this study, conjunctivitis was the most common side effect, but this rarely resulted in discontinuation of dupilumab treatment. Future daily practice data derived from the

BioDay-registry will provide further important information on the long-term effectiveness and safety of dupilumab treatment.

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SUPPLEMENTAL DATA

Supplementary table 1. Baseline characteristics in patients with and without conjunctivitis at week 52

	Conjunctivitis at week 52		P-value
	Yes (n=72)	No (n=138)	
Age (years), mean (SD)	42.2 (14.3)	43.2 (16.2)	0.998
Men, n (%)	45 (62.5)	84 (60.9)	0.818
Atopic/allergic diseases at baseline, n (%)			
Allergic rhinitis	51 (70.8)	94 (68.1)	0.876
Asthma	46 (63.9)	78 (56.5)	0.573
Food allergy	41 (56.9)	60 (43.5)	0.177
Conjunctivitis	47 (65.3)	78 (56.5)	0.413
Baseline EASI score, median (IQR)	23.4 (14.4-31.9)	17.7 (11.5-26.9)	0.004
Blood eosinophilia (≥0.45×10x9/L) at screening, n (%)	19 (26.3)	48 (34.8)	0.221
Serum TARC level (pg/ml) at baseline, median (IQR)	2890 (1406-6007)	2022 (748-4709)	0.045

*Independent sample T-test; ** Chi Square Test; *** Mann-Whitney Test

Supplementary table 2. Reasons for discontinuation of dupilumab treatment*

Discontinuation of dupilumab treatment, n (%)	17 (8.1)
Side effects, n (%)	8 (3.8)
Conjunctivitis	5 (2.4)
Joint and muscle complaints	1 (0.5)
Enlargement of lymphoid cells**	1 (0.5)
Rosacea flare	1 (0.5)
Ineffectiveness, n (%)	9 (4.3)

*Multiple reasons for discontinuation per patient

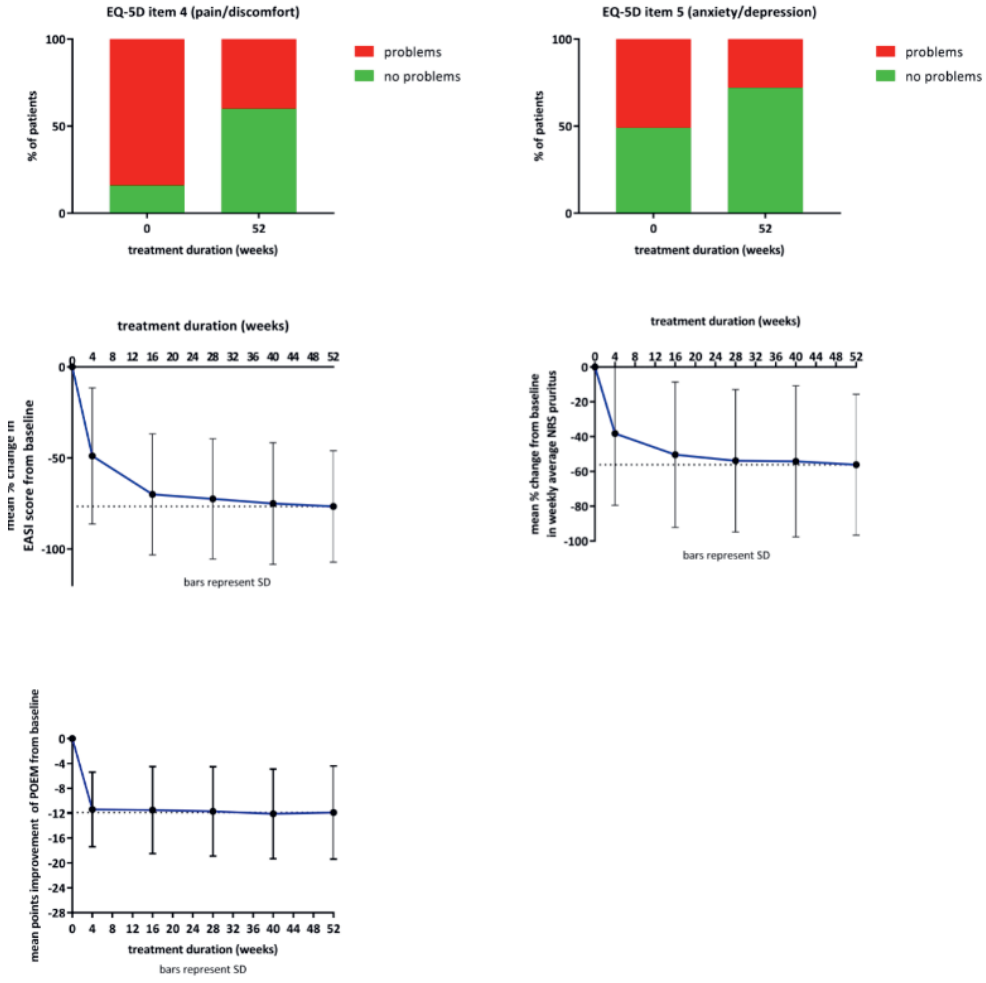
** Abnormalities in total blood count were present before starting dupilumab treatment. Dupilumab treatment was discontinued due to persistent enlargement of lymphoid cells and the suspicion of cutaneous t-cell lymphoma. Additional diagnostic tests showed a monoclonal t-cell population but no indication of cutaneous t cell lymphoma

Supplementary table 3. Effectiveness outcomes during dupilumab treatment in 138 patients without concomitant use of systemic corticosteroids

	Baseline	Week 4	week 16	week 28	week 40	week 52
EASI score, median (IQR)	19.5 (14.1-27.3)	7.5 (4.8-12.3)*	3.5 (1.6-6.8)*	3.2 (1.6-6.2)*	2.4 (0.9-5.4)*	2.4 (1.4-5.4)*
ΔEASI % from baseline, mean (± SD)	-	-51.2 (37.2)	-73.2 (29.4)	-76.7 (28.3)	-79.1 (29.8)	-79.1 (27.7)
EASI-50, n (%)	-	97 (64.7)	130 (88.4)	133 (91.1)	133 (93.0)	141 (94.0)
EASI-75, n (%)	-	34 (22.7)	92 (62.6)	103 (70.5)	108 (75.5)	108 (72.0)
EASI-90, n (%)	-	5 (3.3)	36 (24.5)	51 (34.9)	61 (42.7)	58 (38.7)
Weeky average pruritus NRS, median (IQR)	7.0 (6.0-8.0)	4.0 (2.0-6.0)*	3.0 (2.0-4.0)*	3.0 (1.0-4.0)*	3.0 (1.0-4.0)*	2.0 (1.0-5.0)*
DLQI score, median (IQR)	11.0 (8.0-17.0)	-	3.0 (1.0-5.5)*	-	-	3.0 (2.0-5.0)*
POEM score, median (IQR),	20.0 (16.0-24.0)	7.0 (4.0-12.0)*	8.0 (3.0-12.0)*	6.0 (3.0-11.0)*	6.0 (3.0-11.0)*	6.0 (3.0-11.0)*

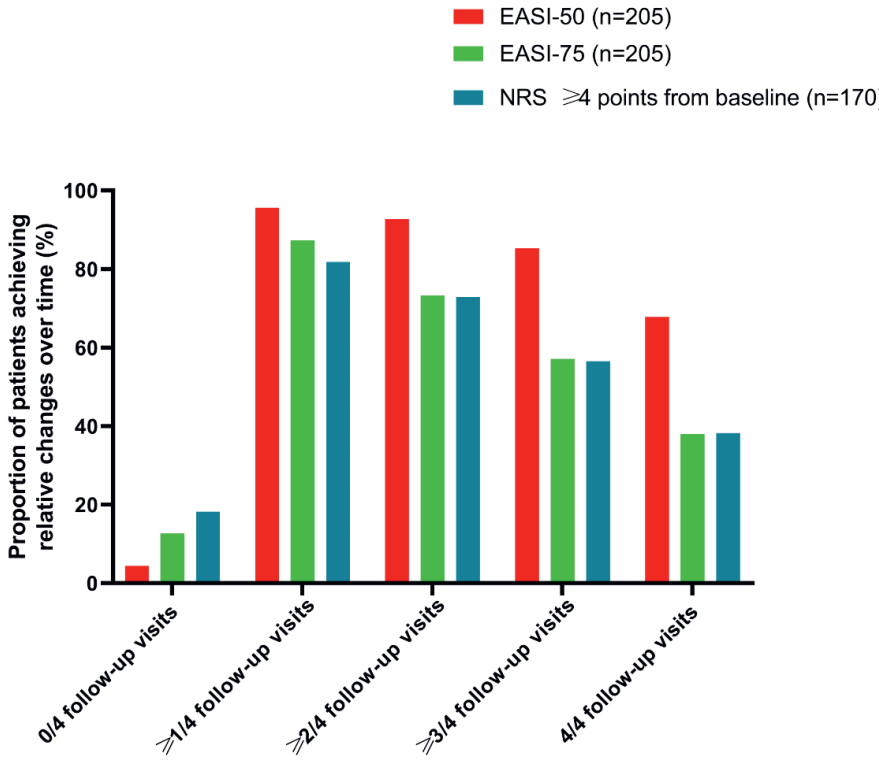
Data were analyzed by using a Wilcoxon matched-pairs signed-rank test. * Statistically significant (P < .05) compared to baseline.
Missing data in patients who discontinued dupilumab treatment during follow-up were imputated by last observation carried forward (LOCF) method

Supplementary figure 1: Clinician-reported outcomes and patient-reported outcomes during treatment with dupilumab



Clinician-reported outcomes and patient-reported outcomes during dupilumab treatment were measured in 210 patients.
EASI, Eczema Area and Severity Index; SD, standard deviation; NRS, numeric rating scale; POEM, Patient-Oriented Eczema Measure; EQ-5D-5L, five-dimension five-level EuroQoL scale

Supplementary figure 2: The proportion of patients achieving relative changes over time (EASI-50, EASI-75 and NRS≥ 4 points improvement from baseline) at 0/4, ≥1/4, ≥2/4, ≥3/4, and 4/4 follow-up visits.



This figure demonstrates the proportion of patients achieving relative changes over time to study the longitudinal treatment effect of dupilumab.
EASI, Eczema Area and Severity Index; EASI-50, ≥50% improvement in EASI score; EASI-75, ≥75% improvement in EASI score; NRS, numeric rating scale

Chapter 6

Rapid and sustained effect of dupilumab on work productivity in patients with difficult-to-treat atopic dermatitis: results from the Dutch BioDay-registry

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ABSTRACT

Dupilumab treatment improves signs, symptoms, and quality of life in moderate-to-severe atopic dermatitis patients (AD). This study evaluated the impact of dupilumab treatment on absenteeism, presenteeism, and related costs in a large multi-center cohort of adult patients with difficult-to-treat AD in daily practice. Patients treated with dupilumab participating in the Dutch BioDay-registry reporting employment were included. Absenteeism, presenteeism, and related costs at baseline and during follow-up were calculated by using the Work Productivity and Activity Impairment questionnaire. A total of 218 adult patients with moderate-to-severe AD were included. Total work impairment significantly reduced from baseline (35.5%) to week 52 (11.5%), $p<0.001$. Median weekly productivity losses significantly reduced from baseline (€379.8 (140.7-780.8)) to week 52 (€0.0 (0.0-211.0), $p<0.001$). In this study, dupilumab treatment demonstrated a significant improvement on work productivity and reduction in associated costs in a large cohort of patients with difficult-to-treat AD in daily practice.

INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases worldwide and is characterized by intense pruritus and a relapsing and remitting course.[1] Moderate-to-severe AD has been shown to have a significant impact on the quality of life (QoL) of patients due to its psychosocial impact, sleep loss, and concentration problems resulting from intense pruritus.[2, 3] Additionally, AD has a substantial economic burden caused by costs directly related to treatment and reduced work productivity.[3, 4] A recent study on work productivity in patients with inadequately controlled AD demonstrated significantly higher absenteeism, presenteeism, and overall work impairment to non-AD matched controls.[5] In addition, costs due to productivity losses have shown to be a major contributor to the economic burden of the disease in patients with moderate-to-severe AD indicated for systemic treatment.[3]

Recent insight about the underlying immune pathogenesis of AD has led to the development of novel targeted therapies.[6] Dupilumab, a fully monoclonal-antibody that targets the shared receptor component for IL-4 and IL-13, is the first biologic treatment for AD. The safety and effectiveness of dupilumab has been proven in phase III clinical trials and in daily practice.[7-14] Dupilumab treatment significantly improves signs, symptoms, and QoL in patients with moderate-to-severe AD.[7-14]

Real-life data on the effect of dupilumab treatment on absenteeism, presenteeism, and related costs in AD patients treated in daily practice are lacking. Data derived from daily practice provides important information in addition to data from clinical trials since there may be considerable differences in patient characteristics and treatment response. Patients participating in randomized controlled trials are screened by strict inclusion and exclusion criteria and treatment adherence and might not be generalizable to a wider population in daily practice.

In the present prospective real life registry study, the impact of dupilumab treatment on absenteeism, presenteeism, and related costs was studied in a large multi-center cohort of adult patients with difficult-to-treat AD.

METHODS

Patient population

Data were extracted from the BioDay-registry, a prospective multicenter observational longitudinal registry including all adult patients who started dupilumab for treatment-refractory AD, according to the criteria established by the Dutch Society of Dermatology and Venereology (NVDV) (treatment ≥4 months with ≥1 conventional systemic therapy in an adequate dose). Patients included in the BioDay-registry were followed by two protocols. In the start-up phase of the BioDay-registry, patients were followed according to the 'early access' protocol. Shortly after approval of dupilumab by The European Medicines Agency, dupilumab treatment was only available to patients included in the early access program. These patients were intensively monitored by frequent follow-up visits. After market access of dupilumab, patients were followed according to the BioDay protocol, a simplified protocol with less frequent follow-up visits. Therefore, outcomes regarding work productivity and activity impairment were available at baseline and week 52 for both cohorts, at week 16 for patients included the early access cohort and at week 28 for patients included in the BioDay cohort. The BioDay-registry was considered as non-interventional by the local Medical Ethics Committee and collection of data was performed according to the Helsinki Declaration. All patients provided written informed consent. ClinicalTrials.gov identifier: NCT03549416.

Outcomes

Patients included in this analysis were assessed at baseline, after 16 (early access protocol), 28 (BioDay protocol), and 52 weeks of dupilumab treatment. Patients who indicated active employment status at any of the assessment visits and with available scores on the Work Productivity and Activity Impairment questionnaire general health (WPAI-GH) at baseline and ≥1 of the follow-up visits were included in this analysis.

The WPAI questionnaire is a validated, self-administered instrument to measure impairments in work and activities across 4 domains in the past 7 days; 1: absenteeism or percentage work time missed due to health problems; 2: presenteeism or percentage impairment while working due to ill health; 3: percentage of overall work impairment (absenteeism + presenteeism); and 4:

percentage of activity impairment due to the health problem.[15] The WPAI questionnaire used in this study was translated in Dutch by The Mapi research institute on behalf of Reilly Associates. The Dutch version of the WPAI-GH is not validated itself. Disease severity at baseline, week 16, week 28, and week 52 were assessed by the Eczema Area and Severity Index (EASI: 0-72).[16] Patient-reported outcomes, including the Patient-Oriented Eczema Measure (POEM: 0-28), weekly average Numeric Rating Scale (NRS: 0-10), and pruritus and Dermatology Life Quality Index (DLQI: 0-30) were reported at baseline, week 16, week 28, and week 52.[17-19] In the start-up phase of the BioDay registry, the effect of dupilumab on concomitant allergic diseases was not monitored by using validated questionnaires. Therefore, these data are not available for the current cohort of patients.

Analysis

Costs of productivity losses were calculated according to the Dutch guideline for economic evaluations in healthcare.[20] Costs of productivity loss included costs due to productivity losses from being absent from work (absenteeism) and being less productive at work (presenteeism). Total productivity losses for employed patients were calculated by hours of productivity losses (hours of absenteeism + presenteeism) multiplied by the value of productivity loss per hour. Outcome measures at different follow-up visits were compared to baseline using the Wilcoxon signed-rank test. Missing data during follow-up were imputed by last observation carried forward (LOCF) method. Statistical analyses were conducted using SPSS (for Windows, version 25.0, SPSS Inc.) and Prism (version 7.4; 120 GraphPad).

RESULTS

In total, 218 patients with moderate-to-severe AD were included (mean (interquartile range (IQR) age 39.0 (28.5-51.9); 139 (65.0%) male) (table 1). Out of 218 patients, 99 (45.4%) had a history of ≥2 oral immunosuppressive treatments. At baseline, median (IQR) baseline EASI score was 18.1 (12.1-26.3). Patients reported a median (IQR) baseline POEM score of 22.0 (18.0-26.0), a median (IQR) baseline weekly averaged pruritus NRS score of 7.0 (6.0-8.0) and a median (IQR) baseline DLQI score of 12.0 (8.0-18.0).

Table 1. Baseline characteristics

	Total group (n=218)	Early access protocol (n=134)	BioDay protocol (n=84)	p-value
Age, years, median (IQR)	39.0 (28.5-51.9)	42.6 (29.4-53.9)	33.6 (28.3-48.7)	0.035
Male sex, n (%)	139 (65.0)	84 (62.7)	55 (65.5)	0.608
Atopic/allergic diseases at baseline, no. (%)				
Allergic rhinitis	152 (71.4)	92 (69.7)	60 (74.0)	0.352
missing	5 (2.3)	2 (1.5)	3 (3.6)	
Asthma	126 (59.2)	82 (62.1)	44 (54.3)	0.237
missing	5 (2.3)	2 (1.5)	3 (3.6)	
Food allergy	125 (58.7)	66 (50.0)	37 (45.7)	0.167
missing	5 (2.3)	2 (1.5)	3 (3.6)	
Allergic conjunctivitis	103 (48.4)	79 (60.3)	46 (56.8)	0.830
missing	5 (2.3)	3 (2.2)	3 (3.6)	
History of ≥2 oral immunosuppressive treatments, n (%)	99 (45.4)	65 (48.5)	34 (40.4)	0.290
Previous use of cyclosporin A, n (%)	205 (94.0)	125 (93.3)	80 (95.2)	0.553
Previous use of methotrexate, n (%)	56 (25.7)	39 (29.1)	17 (20.2)	0.145
Previous use of azathioprine, n (%)	45 (20.6)	30 (22.4)	25 (29.8)	0.421
Previous use of mycophenolate mofetil/ enteric-coated mycophenolate sodium, n (%)	41 (18.8)	29 (21.6)	11 (13.1)	0.113
EASI score, median (IQR)	18.1 (12.1-26.3)	18.9 (12.5-27.2)	17.0 (11.1-24.7)	0.325
IGA score, n (%)				
3 (moderate)	93 (43.1)	58 (43.3)	35 (42.7)	na
4 (severe)	52 (24.1)	56 (41.8)	32 (39.0)	
Weekly averaged pruritus NRS score, median (IQR)	7.0 (6.0-8.0)	7 (6.0-8.0)	7.0 (5.0-8.0)	0.643
POEM score, median (IQR)	22.0 (18.0-26.0)	23.0 (18.0-27.0)	20.0 (17.5-25.0)	0.007
DLQI score, median (IQR)	12.0 (8.0-18.0)	13.0 (8.0-18.8)	12.0 (7.5-17.0)	0.393

IQR, Interquartile range; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measure; DLQI, Dermatology Life Quality Index

Out of 218 patients, 134 (61.5%) were followed according the early access protocol and 84 patients (38.5%) were followed according the BioDay protocol. Patients included in the early access cohort were significantly older (median (IQR) 42.6 years (29.4-53.9)) compared to patients included in the BioDay cohort (median (IQR) 33.6 years (28.3-48.7)) (p=0.035). The baseline POEM score was significantly higher in the early access cohort (median (IQR) 23.0 (18.0-27.0)) compared to the BioDay cohort (20.0 (17.5-25.0)) (p=0.007). Other baseline characteristics were similar among the groups.

Dupilumab treatment resulted in a significant reduction in AD signs, symptoms, and impact on quality of life from baseline to week 4, week 16, week 28 , and improvement sustained until week 52 (data not reported).In the early access cohort, mean percentage absenteeism significantly reduced from baseline (20.8% (SD 34.4)) to week 16 (7.6% (SD 23.3), p<0.001) and to week 52 (2.7% (SD 15.0), p<0.001) (table 2). In the BioDay cohort, mean absenteeism significantly reduced from baseline (11.6% (SD 25.7)) to week 28 (3.4% (SD 11.4), p=0.008) and to week 52 (4.5% (SD 16.4), p=0.05). In the total group of patients, absenteeism significantly reduced from baseline (17.2% (SD 31.5)) to week 52 (4.5% (SD 16.4), p<0.001) (figure 1). Mean presenteeism, overall work impairment (absenteeism + presenteeism) and activity impairment also significantly reduced from baseline to week 16 (p<0.001) (access cohort), from baseline to week 28 (p<0.001) (BioDay cohort) and from baseline to week 25 (p<0.001) in both cohorts (figure 1). Mean change over time in presenteeism and total work impairment, from baseline to week 52, was significantly higher in patients without self-reported asthma at baseline compared to patients with self-reported asthma at baseline (presenteeism: -30.1% (SD 29.1) vs – 19.6% (SD 25.1) (p=0.017); total work impairment: -30.6% (SD 29.4) vs -19.9% (SD 26.3) (p=0.019)). No other differences in change over time of WPAI scores from baseline to week 52 were observed among patients with other atopic comorbidities.

Figure. 1. Weekly productivity and activity impairment (mean percent (standard deviation)) at baseline and after 52-weeks of treatment with dupilumab.

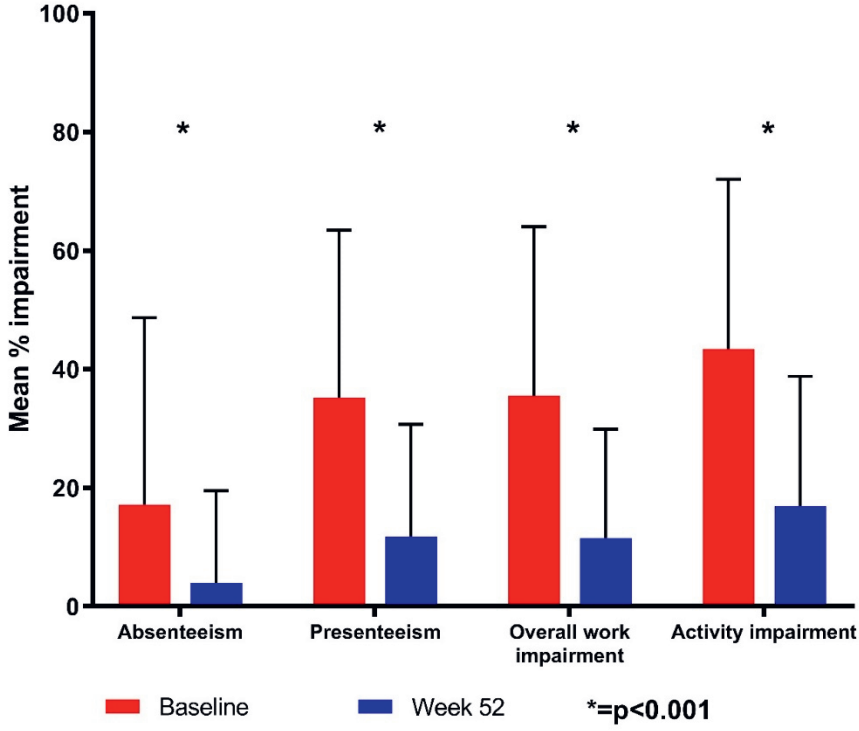

Table 2. Weekly productivity and activity impairment and disease severity

	Baseline			Week 16	Week 28	Week 52		
	Total group (n=218)	Early access protocol (n=134)	BioDay protocol (n=84)	Early access protocol (n=134)	BioDay protocol (n=84)	Total group (n=218)	Early access protocol (n=134)	BioDay protocol (n=84)
Absenteeism, %, mean (SD)	17.2 (31.5)	20.8 (34.4)	11.6 (25.7)	7.6 (23.3)***	3.4 (11.4)*	4.0 (15.5)***	2.7 (15.0)***	4.5 (16.4)*
Presenteeism, %, mean (SD)	35.2 (28.2)	36.2 (27.2)	33.9 (29.6)	15.7 (23.4)***	13.2 (21.7)***	11.8 (18.9)***	13.3 (20.0)***	9.4 (16.9)***
Overall work impairment, %, mean (SD)	35.5 (28.5)	36.0 (27.3)	34.8 (30.4)	15.9 (25.4)***	13.8 (22.8)***	11.5 (18.4)***	12.7 (19.3)***	9.5 (16.9)***
Activity impairment, %, mean (SD)	43.4 (28.6)	44.8 (29.7)	40.7 (26.3)	17.5 (23.7)***	22.4 (21.2)***	16.9 (21.9)***	15.4 (22.4)***	20.8 (20.5)***
Total EASI score, median (IQR)	18.1 (12.1-26.3)	18.9 (12.5-27.2)	17.0 (11.1-24.7)	3.6 (1.6-7.0)***	3.6 (1.4-6.9)***	2.7 (1.2-5.0)****	2.4 (1.4-5.0)***	2.8 (1.1-4.9)***
Weekly averaged pruritus NRS score, median (IQR)	7.0 (6.0-8.0)	7 (6.0-8.0)	7.0 (5.0-8.0)	3.0 (1.0-5.0)***	3.0 (1.0-5.0)***	2.0 (1.0-4.0)***	2.0 (1.0-4.0)***	2.0 (1.0-4.0)***
POEM score, median (IQR)	22.0 (18.0-26.0)	23.0 (18.0-27.0)	20.0 (17.5-25.0)	8.0 (3.0-13.0)***	7.0 (4.0-10.0)***	6.0 (3.0-11.0)***	6.0 (3.0-11.0)***	6.0 (3.0-10.5)***
DLQI score, median (IQR)	12.0 (8.0-18.0)	13.0 (8.0-18.8)	12.0 (7.5-17.0)	2.0 (1.0-5.0)***	2.0 (1.0-4.5)***	2.0 (1.0-3.0)***	2.0 (1.0-3.0)***	2.0 (1.0-3.5)***

Data were analyzed by using a Wilcoxon matched-pairs signed-rank test. *, **, *** = p< 0.05,p < 0.01, p< 0.001 to baseline.
SD, Standard Deviation, IQR, Interquartile range; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; POEM, Patient Oriented Eczema Measure; DLQI, Dermatology Life Quality Index

Mean total weekly hours of productivity loss (hours absenteeism + hours presenteeism) significantly decreased from baseline (to week 16 ($p<0.001$) (early access cohort), from baseline to week 28 ($p<0.001$) (Bioday cohort) and from baseline to week 52 ($p<0.001$) in both cohorts (table 3). Reduced productivity loss resulted in a significant decrease of related costs during dupilumab treatment compared to baseline. The weekly annual median costs (hours absenteeism + hours presenteeism * value of productivity loss per hour (€35.17)) decreased from baseline (€422.0 (IQR 140.7-747.4)) to week 16 (€0.0 (IQR 0.0-174.1), $p<0.001$) and to week 52 (€0.0 (IQR 0.0-211.0), $p<0.001$) in the early access cohort. In the BioDay cohort, median costs decreased from baseline (€281.4 (IQR 126.6-844.1)) to week 28 (€0.0 (IQR 0.0-225.1), $p<0.001$) and to week 52 (€0.0 (IQR 0.0-128.4), $p<0.001$). In the total group of patients, median weekly costs decreased from baseline (€379.8 (IQR 140.7-780.8)) to week 52 (€0.0 (IQR 0.0-211.0)). Estimated extrapolated median yearly costs due to productivity losses significantly decreased from baseline (€19751.5 (IQR 7315.4-40966.0) to week 52 (€0.0 (IQR 0.0-10973.0), $p<0.001$) in the total group of patients.

Table 3. Total weekly hours of productivity loss and related costs

	Baseline			**Week 16**	**Week 28**	**Week 52**		
	Total group (n=218)	Early access protocol (n=134)	BioDay protocol (n=84)	Early access protocol (n=134)	BioDay protocol (n=84)	Total group (n=218)	Early access protocol (n=134)	BioDay protocol (n=84)
Absenteeism + presenteesism (hours/week), mean (SD)	13.7 (12.2)	14.1 (12.2)	12.9 (12.2)	4.4 (8.0)***	5.4 (9.5)***	4.7 (9.3)***	4.4 (8.8)***	5.1 (10.2)***
Weekly productivity losses (€), median (IQR)	379.8 (140.7-780.8)	422.0 (140.7-747.4)	281.4 (126.6-844.1)	0.0 (0.0-174.1)***	0.0 (0.0-225.1)***	0.0 (0.0-211.0)***	0.0 (0.0-211.0)***	0.0 (0.0-128.4)***

Data were analyzed by using a Wilcoxon matched-pairs signed-rank test. *, **, *** = $p< 0.05$, $p < 0.01$, $p< 0.001$ to baseline.
SD, Standard Deviation, IQR, Interquartile range

DISCUSSION

This study demonstrated a rapid and sustained reduction in work absenteeism, presenteeism, and associated costs in patients with moderate-to-severe AD treated with dupilumab in daily practice.

In a previous study by our group, we demonstrated a substantial economic burden in patients with AD indicated for systemic treatment.[3] In this study, the mean (SD) reported absenteeism over the past 7 days at baseline was 15.7%, mean reported presenteeism was 26.4%, and overall work impairment due to health was 28.2% compared to 17.2%, 35.2%, and 35.5% respectively at baseline in the current study. The slightly higher percentages in the present study can possibly be explained by the fact that the study population suffered from a more severe form of AD; all patients included in this study had very difficult-to-treat AD and had failed multiple treatments with oral immunosuppressive drugs.

In our previous study, costs due to productivity losses were the major contributor to the economic burden in this group of patients. Costs of productivity loss were €10,040 (€6,260–14,012) per patient year (PPY) for the total group, €6,886 (€4,188–10,129) PPY for patients with controlled AD vs. €13,702 (€6,124–22,996) for patients with uncontrolled AD. In the present study, estimated extrapolated median yearly costs at baseline due to productivity losses were higher (€19751.5 (IQR 7315.4-40966.0)) compared to our previous study which may be explained by the inclusion of a more severely afflicted population which is also reflected by higher baseline disease severity scores. The estimated extrapolated median yearly costs due to productivity losses significantly decreased to €0.0 ((IQR 0.0-10973.0), $p<0.001$) after 52 weeks of treatment with dupilumab. Given the higher price of dupilumab treatment compared to conventional immunosuppressive treatments, direct costs related to treatment will substantially increase in patients treated with dupilumab. However, this increase in direct costs could be compensated by savings in costs due to productivity losses in patients treated with dupilumab.

Recently, pooled analysis of data from the SOLO 1 and 2 randomized, controlled clinical trials, demonstrated significant reduction in work/school absenteeism and related costs in patients with moderate-to-severe AD treated with dupilumab compared to placebo.[21] However, this study did not include the impact of dupilumab on presenteeism and associated costs, which has been demonstrated to be a major contributor to the economic burden of the disease. Therefore, the results of our study

on the impact of dupilumab on absenteeism, presenteeism, and associated costs in patients treated with dupilumab in daily practice provides important additional information.

The current study should be interpreted in the context of several limitations. Patients included in this study were followed by two different protocols. Therefore, we could not perform a pooled analysis including all patients at all follow-up visits. Additionally, shortly after approval of dupilumab by The European Medicines Agency, dupilumab treatment was only available for patients included in the early access program. Patients were indicated for treatment with dupilumab in the early access program in cases of severe AD with limited alternative treatment options. Therefore, this cohort may represent a more severe population compared to patients included in the BioDay cohort which could explain the higher baseline productivity losses in the early access cohort compared to the BioDay cohort. Another limitation of this study is the use of the WPAI-GH to calculate work impairment and related costs. The WPAI-GH is a non-disease-specific tool and observed decreases in total work impairment could also be the effect of other diseases (e.g., impact of dupilumab on allergic comorbidities). In this study, we observed a significantly higher change over time in presenteeism and total work impairment from baseline to week 52 in patients without self-reported asthma compared to patients with self-reported asthma at baseline. These data suggest that WPAI scores are also affected by the presence of allergic comorbidities, including asthma. Dupilumab has shown to improve signs and symptoms, reduce exacerbations and reduce the amount of oral corticosteroids in patients with moderate-to-severe eosinophilic or oral steroid dependent asthma.[22-24] In this study, the severity of asthma and whether patients suffered from eosinophilic or oral steroid dependent asthma was unknown. Therefore, the effect of dupilumab on concomitant asthma might be less significant compared to the effect on AD in this severe AD population. Patients with self-reported asthma at baseline might still experience signs and symptoms of active asthma at week 52, which may explain the lower change over time in WPAI outcomes.

The absence of an analysis of the direct costs is another limitation of this study. Since patients were included shortly after approval of dupilumab by the European Medicines Agency (early access cohort) and market access of dupilumab (BioDay cohort), and were intensively monitored by frequent follow-up visits and laboratory monitoring, analysis of the direct costs would not have reflected a real life setting and would have resulted in an overestimation of direct costs. However, given the high cost of dupilumab treatment compared to conventional immunosuppressive

treatments, it is likely that direct costs related to treatment may be substantially higher in patients treated with dupilumab. Future research should further investigate the effect of dupilumab treatment on direct as well as indirect costs.

In conclusion, patients with difficult-to-treat AD reporting employment demonstrated significant, rapid and sustained reductions in absenteeism, presenteeism, total work impairment and activity impairment. In addition, indirect costs due to productivity losses were significantly reduced. Future research should further investigate the direct as well as indirect costs in patient treatment with dupilumab and other new treatment options in atopic dermatitis in daily practice.

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Chapter 7

Two-year drug survival of dupilumab in a large cohort of difficult-to-treat adult atopic dermatitis patients compared to cyclosporine A and methotrexate: results from the BioDay registry

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To the editor,

Dupilumab is a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor subunit α (IL-4 Rα), the common subunit of the type 2 cytokines IL-4 and IL-13, blocking signaling of both cytokines, and consequently inhibiting the entire Th2 pathway.[1] Overall, the clinical efficacy and safety of dupilumab ± topical corticosteroids (TCS) have been demonstrated in several phase 3 clinical trials for the treatment of patients with moderate-severe AD.[2] In clinical trials, efficacy of dupilumab is tested under ideal circumstances in selected patients and therefore, results are not always generalizable to daily practice. Recent results from dupilumab treatment in daily practice show a clinically relevant improvement of physician-reported outcome measures and patient-reported outcome measures after 3-6 months, which is in line with data from clinical trials.[3, 4]

Drug survival is an analysis which gives a reflection of daily practice by analysing the time from initiation to discontinuation of therapy. Drug survival is a comprehensive outcome covering effectiveness, safety, and patients' and doctors' preferences.[5] Drug survival studies for dupilumab are scarce and studies comparing drug survival of dupilumab with conventional oral immunosuppressive drugs for AD are lacking.[6] In the current study, we primarily aim to assess the drug survival of dupilumab, and secondarily to compare drug survival of dupilumab with other oral immunosuppressive drugs (cyclosporine A (CsA) and methotrexate (MTX)) in two historical (previously published) daily practice cohorts of moderate to severe AD patients before the introduction of dupilumab.[7, 8] Patients treated with dupilumab were included in the BioDay registry; a prospective multicentre registry that contains daily practice data on the effectiveness and safety of dupilumab for the treatment of AD, including both Quality of Life (QoL) as well as clinical parameters. Patients were treated with MTX, CsA and dupilumab according to national guidelines concerning dosage and follow-up. Drug survival was determined through Kaplan Meier survival curves, and analyzed for overall drug survival (discontinuation due to well-controlled disease; side effects [with/without ineffectiveness]; ineffectiveness [with/without side effects]; and other) for dupilumab, CsA and MTX and separately for treatment failure (ineffectiveness combined with side effects). Patients, who were using dupilumab/CsA/MTX at time of data lock or were lost to follow up, were censored. For each patient, data on treatment duration and reason for discontinuation was collected, as well as other detailed patient- and treatment characteristics.

The dupilumab cohort comprised of 402 patients (39.1% female, mean age 43.3 years) with a median dupilumab treatment duration of 15.1 (Interquartile range (IQR) 8.2-20.3) months at time of data lock (480 active treatment years) (table 1). In the dupilumab cohort, 99.5% had a history of prior treatment with oral immunosuppressive drugs (93.8% CsA, 33.8% MTX, 22.9% azathioprine, 16.9% enteric-coated mycophenolate sodium) compared to 19.4% in the CsA- and 69.7% in the MTX cohort.

Table 1. Patient and treatment characteristics for treatment with dupilumab, cyclosporine A, and methotrexate

	Dupilumab (n=402)	Cyclosporine A (n=356)	Methotrexate (n=89)
Female, n (%)	157 (39.1)	167(46.9)	36(40.4)
Age (years), mean (±SD)	43.3(15.8)	37.6(14.2)	50.1(17.3)
History of prior treatment with oral immunosuppressive drugs, n (%)	400 (99.5)	69 (19.4)	62 (69.7)
Treatment duration (months), [a] median (IQR)	15.1(8.2-20.3)	7.9(3.2-14.4)	7.3(3.0-11.4)
Status of use, [c] n (%)			
Active	358(89.1)	80(22.5)	37(41.6)
Discontinued	37(9.2)	258(72.4)	45(50.5)
Lost to follow up	7(1.7)	18(5.1)	7(7.9)

[a]data lock two years after start treatment; dupilumab 15-12-2019; cyclosporine A 01-01-2014; methotrexate 01-02-2015. SD, Standard deviation; IQR, Interquartile Range.

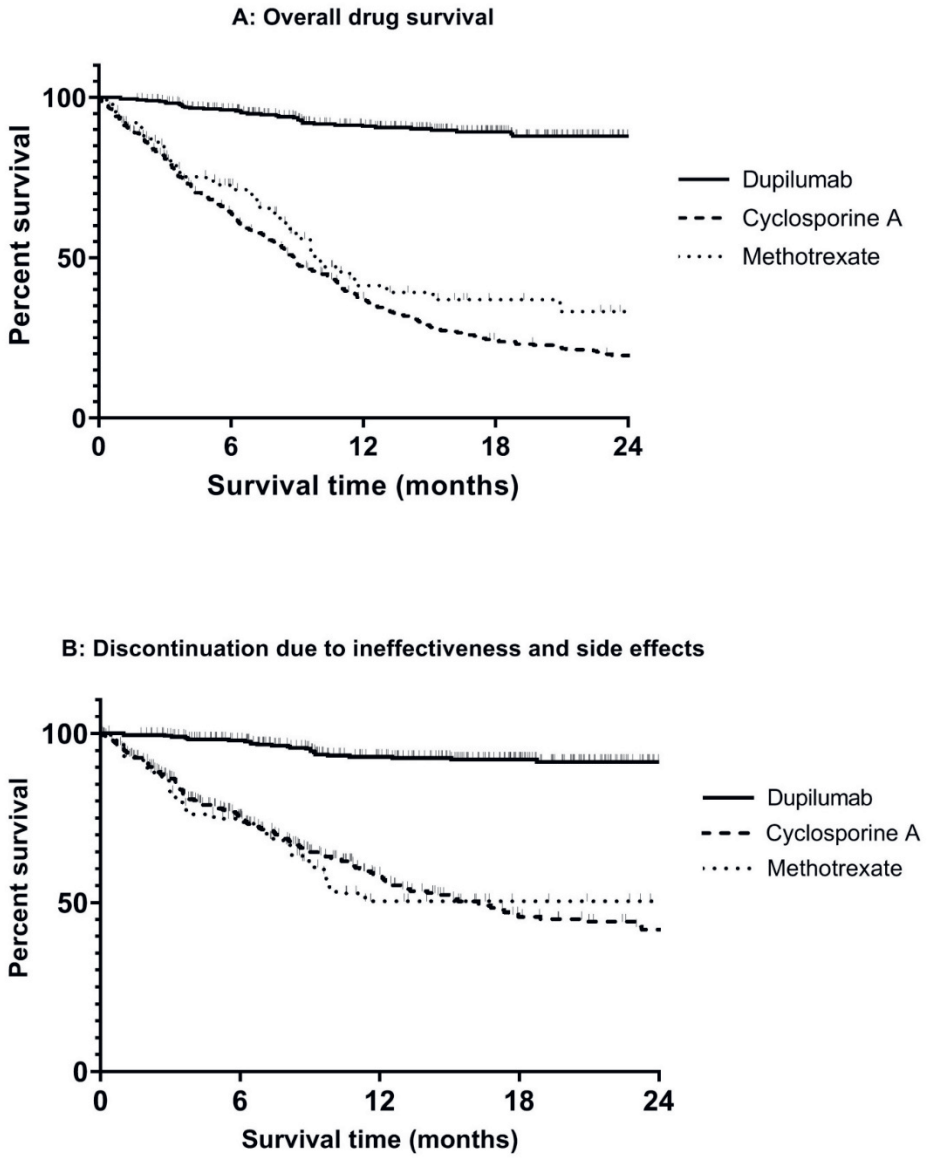
At the moment of data lock, 358 patients (89%) used dupilumab, 37 patients (9%) had discontinued dupilumab treatment and 7 patients (2%) were lost to follow-up. The most frequent reason for discontinuation of dupilumab was side effects (17 patients (4%)). Seven patients (2%) discontinued treatment because of ineffectiveness, two patients (0.5%) due to a combination of both side effects and ineffectiveness (Supplementary table 1). Regarding CsA, 356 patients were included with a median treatment duration of 7.9 (IQR 3.2-14.4) months. The majority of the patients (n=258 (73%)) discontinued treatment within two years after start of CsA, mostly because of well-controlled disease (n=79 (22%)) followed by side effects (n=72 (20%))[8]. The MTX cohort included a total of 89 patients with a median treatment duration of 7.3 (IQR 3.0-11.4) months. Half of the patients (n=45 (51%))

discontinued treatment after two years of follow-up, 22 patients (25%) due side effects and 13 patients (15%) due to ineffectiveness.[7]

The overall drug survival rates for dupilumab were 91% and 88% after 1 and 2 years, respectively. In CsA treated patients drug survival rates were 37% and 20%. This was comparable to the drug survival of MTX, which was 41% and 33%, after respectively 1 and 2 years. Drug survival of dupilumab was significantly longer compared to MTX and CsA ($p<0.0001$) (figure 1A). Approximately, half of the patients discontinued CsA and MTX because treatment failure (ineffectiveness and/or side effects); limited dupilumab patients discontinued treatment due to treatment failure (figure 1B). Due to the low number of patients discontinuing dupilumab treatment, a prediction analysis of drug survival was not possible in the present study.

A drug survival rate of 89% after 800 days (26.3 months) of treatment with dupilumab in a daily practice cohort (n=112) of AD patients treated at a Tertiary Care Center in the United States (US) was reported by Khosravi et al. Reasons for discontinuation were AD flare (5/112 (5%)), conjunctivitis (3/112 (3%)), and adequate control with phototherapy (1/112 (1%)).[6] Overall drug survival rates were comparable with the results of our study, although we found a slightly lower rate of discontinuation due to ineffectiveness (2% vs. 5%).

Figure 1. A: Overall drug survival for dupilumab, cyclosporine A and methotrexate. B: Drug survival related to discontinuation due treatment failure for dupilumab, cyclosporine A and methotrexate



Drug survival is influenced by the availability of alternative treatment options and changes in the population treated over time. None of patients were previously treated with dupilumab. Patients included in the MTX and CsA cohort, were treated before initiation of clinical trials and marketing authorization of dupilumab, and therefore the availability of dupilumab did not influence the drug survival in these cohorts. Longer drug survival of dupilumab (compared to MTX and CsA) can be explained by a persistent clinical response and lack of discontinuation due to controlled disease, but also due to the lack of availability of alternative treatment options.

In conclusion, this study shows that dupilumab has a longer drug survival compared to CsA and MTX. Only a limited number of dupilumab patients discontinued treatment due to side effects and/or ineffectiveness. Future daily practice data will provide further important information on the impact of the introduction of new biologic agents and small molecules for the treatment of AD on drug survival of dupilumab.

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SUPPLEMENTAL TABLE

Supplementary table 1. Reason for discontinuation of dupilumab, cyclosporine A, and methotrexate

	Dupilumab (n=402)	Cyclosporine A (n=356)	Methotrexate (n=89)
Reasons for discontinuation, n (%)			
Well-controlled disease	-	79(22.2)	4(4.5)
Ineffectiveness	7 (1.7)	55(15.4)	13(14.6)
Side effects	17 (4.2)	72(20.2)	22(24.7)
Both ineffectiveness and side effects	2(0.5)	19(5.3)	-
Other	11(2.7)	33(9.3)	5(6.7)

Chapter 8

Conjunctivitis Occurring in Atopic Dermatitis Patients Treated with Dupilumab - Clinical Characteristics and Treatment

J Allergy Clin Immunol Pract. 2018 Sep-Oct;6(5):1778-1780

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To the editor,

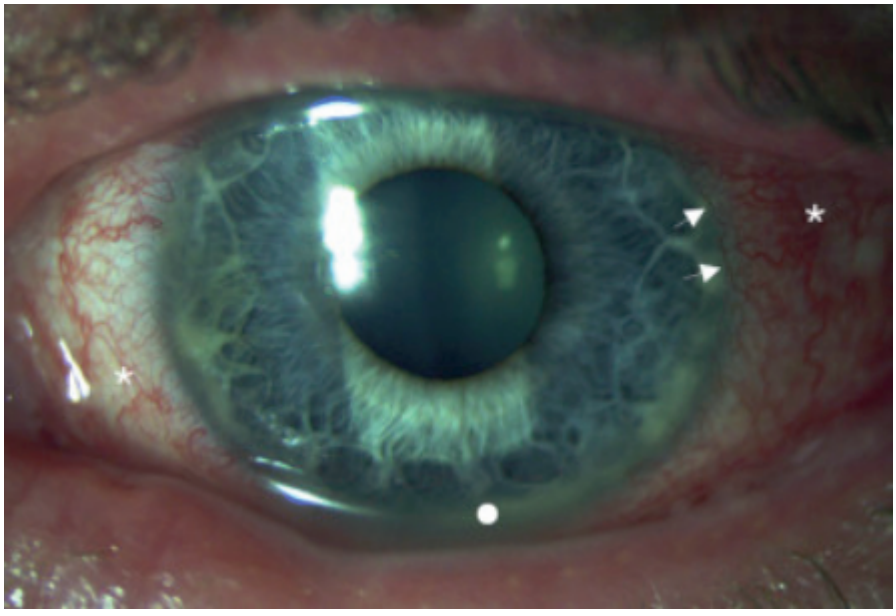
Atopic dermatitis (AD) is a common, highly pruritic, chronic, inflammatory skin disease with a high burden of disease to the patient.1 Established therapeutic options include emollient therapy, topical anti-inflammatory therapy with corticosteroids, and calcineurin inhibitors, as well as (mostly off-label) use of systemic immunosuppressive drugs.[1] Dupilumab is an antibody directed against the IL-4 receptor alpha subunit, which blocks the signaling activity of both IL-4 and IL-13. It has recently been approved by the FDA for the treatment of adult patients affected by moderate-to-severe AD. During clinical trials, conjunctivitis adverse events were reported in a minority of patients, but more often in dupilumab-treated patients (5% to 28%) compared with placebo (2% to 11%).[2-5]

It was hypothesized that the blockage of IL-4 and IL-13 would increase the activity of the specific ligands involved in atopic keratoconjunctivitis, such as the OX40 ligand, in the eye.[6] However, the pathogenesis, clinical characteristics, and treatment options of this conjunctivitis are still not characterized well. Severe AD, preexisting conjunctivitis, and low serum concentrations of dupilumab are reported to be associated with the occurrence of conjunctivitis, which is more frequently observed in AD trial patients only, but not in asthma or nasal polyposis trials.[7]

Here, we report our experience with this clinically relevant complication of dupilumab-treated AD seen in 25% and 50% of patients from our 2 centers from April 2016 to February 2017, and give treatment recommendations based on our personal experience with 13 moderate-to-severe dupilumab-treated patients with AD developing conjunctivitis as an adverse event. This conjunctivitis is reported in temporal association with dupilumab treatment, but a causal relation is not established. The prominent feature in all of these patients was redness of the conjunctiva in both eyes. In most, but not all patients, typical symptoms included itch, stinging, burning, tearing, foreign body sensation, and depending on the severity of tearing, also some decrease in bilateral visual acuity.

Specifically, the prominent feature of dupilumab-related conjunctivitis is the predominant involvement of the conjunctiva, and especially a hyperemia of the limbus (Figure 1). In the most severe cases, this included nodular swelling of the limbus resembling the picture of Tantras' dots, but being located a little more anteriorly on the limbus.

Figure 1. Dupilumab-induced conjunctivitis showing conjunctival hyperemia (white asterisks), limbal hyperemia (white triangles) and tearing (white dot).



Characteristics of conjunctivitis are summarized in Table I. Of the 13 patients, 9 did not have a history of conjunctivitis before participating in the dupilumab clinical trials. In 4 patients, conjunctivitis reoccurred or worsened after onset of dupilumab. New signs of blepharitis developed in 10 patients during dupilumab treatment. Blepharitis symptoms were mild in the majority of patients. The dupilumab-related conjunctivitis was generally manageable, and the benefit-risk profile remained largely favourable in patients who developed this condition; therefore, this was not a side effect limiting dupilumab treatment.

Table 1. Patient characteristics

Patient no.	Age, Sex	History of conjunctivitis	AD severity before dupilumab	Time to onset (d)	Conjunctivitis	Blepharitis	Limbal edema	Corneal vascularisation	Effective treatment of conjunctivitis	Clinical outcome
1	61, F	–	Severe, EASI 26.8, IGA 4	27	OU: mild palpebral	–	–	–	Tacrolimus eye ointment 0.03%	Improvement
2	28, M	–	Moderate, EASI 16.2, IGA 3	181	OU: mild bulbar OU: moderate palpebral	OU: moderate	–	–	Tacrolimus eye ointment 0.03%	Complete resolution
3	53, M	–	Severe, EASI 44.2, IGA 4	25	OU: severe bulbar and palpebral	OU: severe	OU: yes	–	Tacrolimus eye ointment 0.03%	Improvement
4	52, F	–	Severe, EASI 30.4, IGA 4	30	OU: severe bulbar	OU: mild	OU: yes	–	Tacrolimus eye ointment 0.03%	Complete resolution
5	39, M	yes	Severe, EASI 44.9, IGA 4	110	OU: mild palpebral	OU: mild	–	–	NA	Ongoing
6	44, M	–	Severe, EASI 34.5, IGA 4	20	OU: mild bulbar OU: moderate palpebral	OU: mild	–	–	Oxytetracycline and hydrocortisone eye drops	Improvement
7	35, M	yes	Severe, EASI 27.9, IGA 4	42	OU: moderate palpebral	OU: mild	–	OS: deep vascularisation	Dexamethasone eye drops	Improvement
8	33, M	–		34	OU: mild bulbar	OU: severe	–	–	NA	NA
9	42, M	–		150	OU: moderate palpebral	OU: mild	–	–	Fluorometholone Liquifilm eye drops	Improvement
10	41, F	–		150	OU: severe palpebral	OU: moderate	OU: yes	–	Fluorometholone Liquifilm eye drops	Complete resolution
11	34, M	yes		389	OU: moderate palpebral	OU: mild	OU: yes	–	Fluorometholone Liquifilm eye drops	Improvement

Patient no.	Age, Sex	History of conjunctivitis	AD severity before dupilumab	Time to onset (d)	Conjunctivitis	Blepharitis	Limbal edema	Corneal vascularisation	Effective treatment of conjunctivitis	Clinical outcome
11	34, M	yes		389	OU: moderate palpebral	OU: mild	OU: yes	–	Fluorometholone Liquifilm eye drops	Improvement
12	48, F	–		163	OU: moderate palpebral	–	OU: yes	–	Dexamethasone and Fluorometholone Liquifilm eye drops	Improvement
13	59, M	yes		210	OU: mild bulbar	–	–	–	Fluorometholone Liquifilm eye drops	Complete resolution

AD, Atopic dermatitis; OD, right eye; OS, left eye; OU, both eyes; –, no; NA, not applicable.

We have applied a number of different treatment options to our patients depending on the preference of the managing clinician in each case. In 2 patients, the severity of conjunctivitis was too mild to warrant the use of topical steroids. These patients received either hyaluronic acid eye drops or no topical treatment at all. However, in our limited experience, antihistamine eye drops and artificial tears did not confer any alleviation in this type of conjunctivitis (data not shown). In 11 patients, dupilumab-related conjunctivitis was treated with topical tacrolimus or steroids, leading to clinically significant improvement or full recovery in all 11 patients treated. Two treatment options were particularly successful, and we would recommend these for future patients.

In 5 patients, conjunctivitis was treated with fluorometholone 0.1% eye drops, leading to significant improvement. Fluorometholone was used because it is approved for allergic inflammation of the anterior eye segment and because of its relatively poor penetration into the anterior chamber of the eye compared with other available topical steroids, resulting in a lower risk of complications like cataract and glaucoma. Clinically significant improvement was achieved in all 5 fluorometholone-treated patients. In 2 patients, signs and symptoms resolved completely. In 4 patients, conjunctivitis was treated with tacrolimus 0.03% eye ointment (Supplementary table 1). A calcineurin inhibitor was chosen because this substance does not induce glaucoma or cataract even on long-term use, and the special formulation was chosen to reduce the viscosity of the resulting ointment. Signs and clinical symptoms improved significantly in all patients, and in 2 patients, full recovery of conjunctivitis was achieved. Ocular application of tacrolimus is used in the treatment of various ocular inflammatory diseases. Ocular application of tacrolimus 0.1%, 0.03%, and 0.02% have been used successfully in patients with allergic conjunctivitis and vernal keratoconjunctivitis, but preparations have not been approved.[8, 9]

Dexamethasone or hydrocortisone eye drops or antibiotic combination therapies of medium to high potency were used in 3 patients leading to clinically significant improvement of conjunctivitis symptoms. As the long-term use of ocular steroids increases the risk of complications such as glaucoma and cataract, these can be considered for short term but are not suitable for prolonged treatment. Tacrolimus 0.03% eye ointment can be safely used for prolonged treatment, as it does not influence intraocular pressure and there is no increased risk of glaucoma and cataract.

Because dupilumab is a long-term treatment option for AD, conjunctivitis occurring during dupilumab treatment may require therapy for a prolonged period of time. Therefore, we would recommend considering either fluorometholone 0.1% eye drops or off-label use of tacrolimus 0.03% eye ointment in the treatment of conjunctivitis occurring in patients with AD during dupilumab treatment.

In conclusion, a clinically characteristic inflammation of the anterior conjunctiva and hyperemia of the limbus was observed during dupilumab treatment, which can be treated successfully with fluorometholone 0.1% eye drops or tacrolimus 0.03% eye ointment.

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SUPPLEMENTAL TABLE

Supplementary table 1: Compounding instruction for Tacrolimus eye ointment 0.03%

Rp.:	
Tacrolimus ointment 0.1%	27.00 g
Cholesterol	0.63 g
Paraffinun subliq.	26.77 g
Vaselinum alb.	35.60 g
M.D.S.: Tacrolimus eye ointment	
Dispense in 5 g tubes	

Chapter 9

Goblet cell scarcity and conjunctival inflammation during treatment with dupilumab in patients with atopic dermatitis

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Dear editor,

Higher rates of conjunctivitis have been reported in atopic dermatitis (AD) patients treated with dupilumab, a human monoclonal antibody that inhibits the signaling of interleukin (IL)-4 and IL-13, versus patients treated with placebo in phase III clinical trials.[1] However, the exact pathomechanism of this potential treatment-limiting side effect has not been clarified. Given the necessity of optimal treatment and risk management in clinical practice, the aim of this study was to describe the histopathological characteristics of conjunctivitis during dupilumab treatment in AD patients.

Participants, selected from the Bioday registry, consisted of 74 moderate-to-severe AD patients treated with dupilumab for at least 16 weeks. Of these, 23% developed ophthalmologist-confirmed conjunctivitis requiring anti-inflammatory treatment. We sequentially included six patients (three male; median age 39 years, interquartile range [IQR] 29-54) in whom a diagnostic conjunctival biopsy of the inferior fornix was performed by the ophthalmologist before initiation of ocular anti-inflammatory treatment. Biopsies were fixed, paraffin-embedded and stained with haematoxylin and eosin (HE) for histological assessment, and additionally with CD3/CD4 (T helper [Th] cells) and Alcian Blue (mucus-containing goblet cells [GCs]). Conjunctival biopsies of two healthy controls were included from the local pathology database and stained with Alcian Blue. Biopsies were assessed by two independent experienced pathologists. This study did not fall under the scope of the Medical Research Involving Human Subjects Act which was confirmed by the local Medical Research Ethics Committee (METC 18/537).

The most prominent histopathological feature in conjunctival biopsies from patients with AD developing conjunctivitis during dupilumab treatment was scarcity of intraepithelial GCs. Median GC density was 3.3 cells/mm (IQR 1.1 – 4.9) (Figure 1A-B) in patients with AD with conjunctivitis vs. 28.3 and 36.3 cells/mm in the two control samples. Five patients showed a multicellular immune-cell stromal infiltrate, consisting mainly of T cells (CD3+) and eosinophils (Figure 1C). Epithelial migration of eosinophils and lymphocytes was seen in respectively four and five out of six patients.

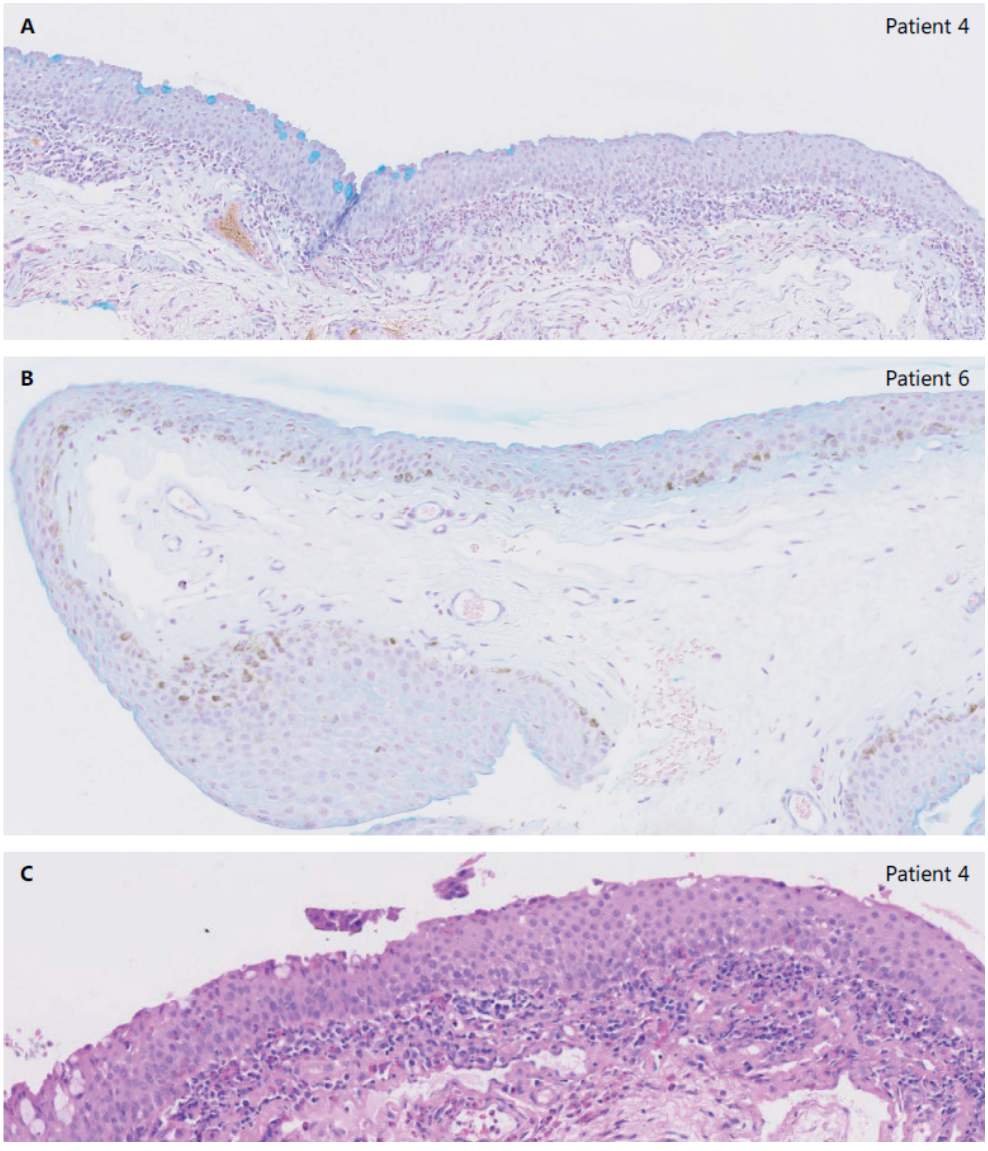

Figure 1. Alcian blue-stained histological sections of the inferior bulbar conjunctiva under light microscopy shows the presence of decreased goblet-cell density in patients with AD treated with dupilumab (original magnification × 40). **A.** Regions with no goblet cells (GCs) interspersed with smaller regions of normal GC density. **B.** In patient 6 no GC was found in the conjunctival biopsy. **C.** Haematoxylin and eosin stained histological sections of the inferior bulbar conjunctiva under light microscopy show the presence of a superficial inflammatory multicellular infiltrate in the conjunctival stroma consisting of mainly T cells and eosinophils, partially migrating into the conjunctival epithelium.

Conjunctival GCs are specialized mucus-secreting cells and are assumed to be vital for ocular surface function.[2] GC density varies between different conjunctival regions, with higher numbers in the normally covered locations of the open eye. [3] In healthy individuals lower forniceal GC counts vary between 8.8 and 30 cells/mm.[4] All patients included in our study had a marked decreased number of GCs (median of 3.3 cells/mm) vs. controls (median 32.3 cells/mm).

Mice studies have demonstrated that ocular IL-13 expression normally stimulates GC proliferation and mucus secretion.[5] By blocking IL-13, dupilumab treatment may lead to GC hypoplasia, as IL-4Rα is expressed on conjunctival epithelium. This might result in decreased mucin production, subsequent tear film instability and mucosal epithelial barrier dysfunction, leading to conjunctival inflammation in a subpopulation of (predisposed) patients with AD. Clinically, the loss of GC-produced factors may result in dry eyes, as was reported by all patients, and subsequently irritative conjunctivitis. As in this study biopsies were performed after initiation of dupilumab, GC scarcity might already be present before dupilumab treatment, although patients did not experience ocular symptoms at start of treatment.

Our histopathological findings do not correspond with the histopathology of atopic keratoconjunctivitis and allergic conjunctivitis, which is associated with an increased GC density and increased mucus production, probably due to IL-13 overexpression.[6, 7] Dupilumab treatment might theoretically be beneficial in these typical Th2 mediated ocular surface diseases.

It has been proposed that dupilumab treatment could increase *Demodex* numbers in hair follicles, causing ocular rosacea-like disease.[8] Ocular rosacea is a Th17-driven disease characterized by an inflammatory cell infiltrate, mainly consisting of CD4+ T cells, but not eosinophils.[9] The unique combination of low conjunctival GC numbers accompanied by numerous lymphocytes and eosinophils found in this study may imply a new entity of conjunctivitis in dupilumab-treated patients with AD.

Only patients with new onset of conjunctivitis symptoms or worsened symptoms in cases of pre-existing conjunctivitis were included in this study; these probably do not represent all conjunctivitis cases during dupilumab treatment. In daily practice, we experience some patients reporting improvement of conjunctivitis symptoms during dupilumab treatment, underlining the heterogeneity of the conjunctivitis.

Limitations of this study are small sample size, and collection of conjunctival biopsies at one single time point. Therefore, dynamic differences in histopathological features before and during dupilumab treatment could not be studied. Nevertheless, the histopathological features and findings were very consistent, and constitute a first clue in the underlying pathomechanism of dupilumab-associated conjunctivitis. However, the exact pathomechanism of this new entity of conjunctivitis could not be fully elucidated.

In conclusion, this study found a remarkable scarcity of conjunctival GCs accompanied by an inflammatory T-cell-and eosinophilic infiltrate in patients with AD with conjunctivitis during dupilumab treatment. We hypothesize that the IL-13 blocking effect of dupilumab might lead to reduction of GCs and mucin production in a subpopulation of patients with AD, which may potentially result in irritative conjunctivitis. A prospective study further characterizing conjunctivitis in patients with AD before and during dupilumab treatment will start soon.

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Chapter 10

Very successful treatment with dupilumab in a patient with severe, difficult to treat atopic dermatitis: beware of symptomatic adrenal insufficiency due to abrupt discontinuation of potent topical corticosteroids

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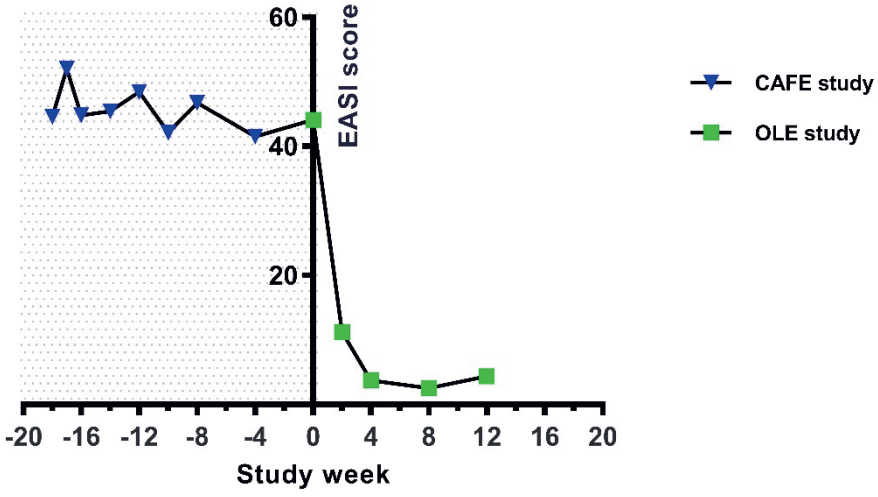
To the editor,

Topical corticosteroids are widely used in the treatment of chronic inflammatory skin diseases, including atopic dermatitis (AD).[1] Long-term treatment with potent topical corticosteroids can lead to systemic effects due to percutaneous corticosteroid absorption.[2] Potentially serious systemic effects include Cushing's syndrome and suppression of the hypothalamic-pituitary-adrenal (HPA) axis.[3] Prolonged suppression of the HPA-axis may result in tertiary adrenal insufficiency caused by adrenal atrophy, which is a potential life-threatening disorder.[3] The risk of tertiary adrenal insufficiency depends on several factors, for instance age, the quantity and potency of the topical corticosteroids, extent of the treated body surface, the condition of the skin (barrier) at the time of application and the use of concomitant (corticosteroid-containing) drugs. Topical corticosteroid induced HPA-axis suppression has been described, however the development of symptomatic adrenal insufficiency is rare.[4-6] Here, we report a case of clinically relevant adrenal insufficiency as a result of abrupt discontinuation of topical corticosteroid treatment in a patient successfully treated with dupilumab for severe AD.

A 50-year-old male with a history of inflammatory bowel disease, anxiety disorder and hypertension, was treated at our clinic for severe AD. Relevant medication use included fluoxetine (40mg/day) for panic attacks. He suffered from uncontrolled AD, despite treatment with potent topical corticosteroids in both an outpatient- as inpatient setting and treatment with various oral immunosuppressive drugs. Treatment with Cyclosporin A (CsA) was effective but had to be discontinued after several months due to kidney failure. Enteric-coated mycophenolate sodium and subsequently azathioprine were discontinued after >12 weeks of treatment due to ineffectiveness. After discontinuation of extended-release tacrolimus because of side effects, the patient was treated with high-potency topical corticosteroids and systemic corticosteroids. Severe, difficult-to-control AD was the motivation to participate in a phase 3 double-blind, placebo-controlled trial investigating the efficacy, safety and tolerability of dupilumab in patients with severe AD inadequately controlled or ineligible to treatment with CsA (CAFÉ study).[7] Treatment with systemic corticosteroids was gradually tapered off over several weeks and stopped 24 weeks before start of dupilumab. At baseline, the patient had a severe, generalized AD with an Eczema Area Severity Index (EASI) score of 44.60. During the 16-week treatment period, the patient was treated with placebo without clinical response (figure 1). In this period, the patient used medium- to high-potency topical corticosteroids

(mainly betamethasone dipropionate 0.05% ointment) 1-2 times daily with a mean amount of 150 g/week. After completing the 16-week treatment period, the patient participated in the Open-Label Extension (OLE) study in which he was treated with 300 mg dupilumab weekly. Four weeks after enrollment, disease severity improved significantly (EASI 3.70) (figure 1). The rapid clinical improvement was followed by abrupt cessation of self-supplied topical corticosteroids. Two weeks after discontinuation of topical corticosteroids the patient presented at our clinic with flu-like symptoms including dizziness, pains in the joints and muscles, lack of appetite and fatigue, suspected for adrenal insufficiency. The patient's morning serum cortisol level was 69.1 nmol/L (normal 09.00 hr plasma cortisol 150 to 802 nmol/l), which was consistent with suspected HPA axis suppression.[8]

Figure 1. EASI in CAFÉ and OLE study



Shown is the patients' Eczema Area and Severity Index (EASI) score during the CAFÉ- and OLE-study.

We diagnosed the patient with symptomatic tertiary adrenal insufficiency as a result of abrupt discontinuation of long-term use of topical corticosteroids after successful treatment with dupilumab. As recommended by the endocrinologist, oral hydrocortisone (40 mg/day) was started in tapering dose and the patient received instructions considering dosing hydrocortisone in periods of physical and emotional stress. Treatment with dupilumab was successfully continued and the patient clinically recovered from adrenal insufficiency after a few days of hydrocortisone treatment. Hydrocortisone treatment could be tapered off over a period of 6 months. After discontinuation of hydrocortisone treatment adrenocorticotropin (ACTH) stimulation testing showed recovery of the HPA axis.

In this case, several risk factors may have contributed to the development of symptomatic adrenal insufficiency. As impairment of the skin barrier facilitates the percutaneous absorption of topical corticosteroids and the potential for adrenal suppression, severity of AD and application of potent corticosteroids on large body surfaces may have increased the risk for adrenal insufficiency in this patient. Besides, the patient was treated with fluoxetine for panic attacks which is a moderate CYP3A4 inhibitor. Corticosteroids are mainly metabolized in the liver by CYP3A4 and concomitant use with CYP3A4 inhibitors might prolong the effect of corticosteroid medications and therefore increase the risk of adrenal insufficiency.

Adrenal insufficiency in this patient became clinically significant after abrupt cessation of long-term applied potent-topical corticosteroids following very strong and fast effect of dupilumab. Dupilumab is a fully human monoclonal antibody against the IL-4 receptor, inhibiting the IL-4 and IL-13 signaling pathways and is the first biologic systemic treatment for AD. Recent phase 3 studies have shown promising results of dupilumab in the treatment of moderate to severe AD.(7, 9) After recent approval by the US Food and Drug Administration (FDA) and the European Commission (EC), dupilumab will be broadly available and hence be used on a wider scale in the management of moderate-severe AD. Treatment with dupilumab may result in fast and strong clinical disease improvement in the majority of patients, resulting in rapid tapering or abrupt discontinuation of topical corticosteroid treatment. Especially patients with severe AD, using large amounts of potent-topical steroids are at risk for developing clinically significant adrenal insufficiency. In these patients, it may be considered to evaluate the risk of adrenal insufficiency by assessing morning serum cortisol levels before discontinuation of topical corticosteroid treatment. If the HPA-axis is completely suppressed, reflected by non-

measurable serum cortisol levels, the risk of tertiary adrenal insufficiency is significant and patients should receive instructions considering extra dosing of hydrocortisone in periods of stress.

In conclusion, with the availability of new very successful and strong acting systemic treatment options for AD, such as dupilumab, physicians should be aware of the risk on tertiary adrenal insufficiency as a result of prolonged HPA axis suppression by long-term use of (potent) topical corticosteroids. Patients should be informed about the risk and symptoms of adrenal insufficiency and testing should be considered, especially in patients at higher risk or presenting with nonspecific symptoms.

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Chapter 11

General discussion

Atopic dermatitis (AD) is one of the most common skin diseases with a major patient burden, as well as socioeconomic burden. Until recently, there has been a large unmet medical need in patients with moderate-to-severe AD indicated for systemic treatment. Dupilumab was the first anti-body based treatment, that entered the European market in 2018. Currently, the field of systemic treatment for AD is expanding with new biologics and small molecules being approved for the treatment of moderate-to-severe AD. The introduction of these more targeted treatment options is changing the treatment algorithm for moderate-to-severe AD patients and prescription behavior. It is expected that these new, more expensive treatment options, will impose a large financial burden on the total healthcare budgets of countries.

The research presented in this thesis aimed to:

1) study the economic burden and impact on the quality of life in patients with moderate-to-severe AD indicated for systemic treatment, who are also candidates for newly introduced systemic treatments for AD;

2) study the effectiveness and safety, the economic burden of dupilumab treatment in patients with moderate-to-severe AD, and compare the effectiveness and safety of dupilumab treatment with conventional immunosuppressive drugs in the treatment for AD;

3) identify side effects occurring during dupilumab treatment in daily practice, and to describe clinical characteristics and elucidate the underlying pathomechanism of these side effects.

The clinical implications, recommendations and suggestions for future research regarding the main findings of this thesis will be discusses in this chapter.

MAIN FINDINGS OF THIS THESIS

The (economic) burden of atopic dermatitis before and after the introduction of dupilumab

I. Moderate-to-severe atopic dermatitis patients indicated for systemic treatment incur considerable disease burden and significant total costs (including direct costs and costs of productivity loss) of €15,231 per patient per year. Costs of productivity loss had the largest impact on total costs in this patient population. – **Chapter 2**

II. A rapid and sustained reduction in work absenteeism and associated costs during 52-weeks of dupilumab treatment was demonstrated in 218 moderate-to-severe AD patients treated in daily practice. – **Chapter 6**

The effectiveness of dupilumab treatment in daily practice

I. In the absence of head-to-head clinical trials, an alternative available comparative study design including an indirect comparison suggested a higher relative efficacy of dupilumab compared with CsA based on the proportion of patients achieving EASI-50 and EASI-75. The relative efficacy of dupilumab versus CsA improved over time. – **Chapter 3**

II. Treatment with dupilumab significantly improved disease severity and decreased severity-related serum biomarkers in 138 patients with very difficult-to-treat AD in a daily practice setting. Clinically relevant improved (EASI-75 or NRS itch ≥4-point improvement or DLQI ≥4-point improvement) was achieve in the majority (89%) of patients. – **Chapter 4**

III. Dupilumab treatment resulted in a rapid improvement in clinical outcome measures, and effectiveness further improved during the 52-week follow-up period in 210 AD patients with treatment-refractory AD. – **Chapter 5**

IV. Comparative two-year drug survival showed longer drug survival of dupilumab compared to two historical cohorts of patients treated with CsA and MTX. A limited number of dupilumab patients discontinued treatment due to side effects and/or ineffectiveness. – **Chapter 7**

The safety of dupilumab treatment in daily practice

I. Inflammation of the conjunctiva and hyperemia of the limbus were observed as the first described clinical features of dupilumab treated AD patients developing conjunctivitis in a clinical trial setting. – **Chapter 8**

II. A remarkable scarcity of conjunctival goblet cells and an extensive sub-epithelial inflammatory T-cell- and eosinophilic infiltrate was observed in conjunctival biopsies in six AD patients who developed conjunctivitis during dupilumab treatment – **Chapter 9**

III. Abrupt discontinuation of potent topical corticosteroids after successful treatment with dupilumab resulted in symptomatic adrenal insufficiency in a patient with severe, difficult-to-treat AD. – **Chapter 10.**

The (economic) burden of atopic dermatitis before and after the introduction of dupilumab

Atopic dermatitis has shown to have a significantly effect on the health-related quality of life (HrQoL) of patients and their families, particularly among patients with more severe disease. The psychosocial effect of AD including social stigmatization and sleep deprivation can lead to an increased risk of depression, anxiety, and suicidality.[1, 2] Atopic dermatitis also causes a substantial economic burden in terms of direct costs including inpatient and outpatient visits, diagnostic tests, transportation and medication costs, as well as costs through lost work productivity (indirect costs).

The (economic) burden of atopic dermatitis before the introduction of new targeted treatments

In **chapter 2** we studied the impact of AD on the HrQol and economic burden in patients with moderate-severe AD indicated for systemic treatment before the introduction of targeted therapies. This study demonstrated a significant disease burden with significantly higher rates of anxiety and depression, and with a more severe impaired HrQoL in patients with uncontrolled AD compared to patients with controlled AD. These results were strengthened by a recent study by Girolomoni et al.[3] quantifying the direct and indirect costs of moderate-severe AD and studying the impact of psychosocial comorbidities by using the 2017 National Health and Wellness Survey among patients in the European Union-5 (France, Germany, Italy, Spain, and the UK). This study demonstrated that more than half of the moderate-severe AD patients has complaints of anxiety, sleep difficulties, and depression leading to a significant effect of these comorbidities on the HRQoL and reduced productivity. In line with our results, other studies also showed that psychosocial comorbidities are more frequent in patients with uncontrolled disease and adequate treatment of AD might reduce these comorbidities.[4] These findings show a large psychosocial burden and unmet medical needs in patients with moderate-severe AD prior to the introduction of the first targeted therapies for AD.

In **chapter 2**, mean total costs (direct costs and costs of productivity loss) in the total group of patients (controlled and uncontrolled AD) were €15,231 per patient per year (PPY) with the larger impact of costs of productivity loss with an estimated mean of €10,040 PPY. The study by Girolomoni et al. showed comparable results with total annual direct costs ranging from €2242 to €6924 and the larger impact of costs due

to productivity ranging from €7277 to €14,236 depending on the level of disease control. Remarkably, patients included in our study with controlled AD at the moment of inclusion also had relatively high scores on work productivity and activity impairment and related costs of productivity loss as well as high direct costs. This can be attributed to the period before initiation and in the start-up phase of systemic treatment. Clinicians often have to search for the optimal oral immunosuppressive drug and dosage and some immunosuppressant's have a delayed clinical response of several months. Hence, this requires often a period of trial and error with frequent consultations for monitoring and dose adjustments.

The economic burden of atopic dermatitis after introduction of dupilumab

Dupilumab entered the European market in 2018. Since many biologics and small molecules are expected to enter the AD market in de upcoming years [5], it is expected that these treatments will impose a large financial burden on the total healthcare budgets of countries. However, due to the high efficacy of targeted therapies, this increase in direct medication costs could be compensated by savings in costs due to productivity losses and potentially by limiting the need for hospitalizations and intensive treatment monitoring.

The first study on the impact of dupilumab treatment on work/school absenteeism and related costs including patients with moderate-severe AD treated in phase 3 clinical trials was reported by de Bruin-Weller et al.[6]. Pooled analysis of data from the SOLO 1 and 2 randomized, controlled clinical trials, demonstrated significant reductions in work/school absenteeism and related costs. However, the impact of dupilumab on presenteeism and associated costs, which have been shown to be the major contributor on total costs, were not included.[3, 7] In addition, included patients were treated in clinical trials in which patients are screened by strict inclusion and exclusion criteria and treatment adherence, therefore these results are not generalizable to a real life setting. In **chapter 6** the impact of dupilumab treatment on absenteeism, presenteeism and related costs was studied in a large, prospective, real-life multi-centre cohort of adult patients with moderate-severe AD. We demonstrated a rapid and sustained reduction in work absenteeism and presenteeism measured by the Work Productivity and Activity Impairment questionnaire general health (WPAI-GH) and associated costs during the 52-weeks follow-up period. Estimated extrapolated median yearly costs due to productivity losses significantly reduced from €19751 at baseline to €0.0 after 52 weeks of treatment with dupilumab. These finding were supported by a recent study of Bosma

et al.[8], investigating work ability and quality of working life at baseline and during dupilumab treatment in a prospective observational cohort study including patients with AD treated in daily practice. This study reported significant improvements in work ability and quality of working life according to the Work Ability Index (WAI) and the Quality of Working Life Questionnaire (QWLQ), mainly due to improvements in health-related problems. These studies imply a substantial effect of dupilumab treatment on work productivity and potential savings in indirect costs by reducing costs of productivity losses.

The impact of dupilumab treatment on direct costs in daily practice has not been studied yet. In **chapter 6,** direct costs were not included since patients were included shortly after approval of dupilumab by the European Medicines Agency and market access. These patients were intensively monitored by frequent follow-up visits and laboratory monitoring which is not required according to the label of dupilumab. Analysis of direct costs in this group of patients would therefore have led in an overestimation of direct costs.

To study the savings of indirect costs by new, targeted treatments, incorporation of validated questionnaires such as the WPAI, in real-life prospective registries, evaluating the effect of novel targeted therapies on work productivity in daily practice generates relevant data for future economic evaluations. Productivity costs and potential savings in indirect costs are costs to society and these costs are not directly reflected in the total healthcare budget. Future research should include economic evaluations taking a societal perspective in which all costs available are included, regardless of who bears those costs or to whom the benefit goes.

As a consequence of the high costs of biologics, strict reimbursement criteria for biologic treatment including dupilumab treatment for AD are formulated in many countries. Reimbursement criteria for dupilumab treatment differ across different countries. In the US and Germany, dupilumab treatment is reimbursed for patients with moderate-severe AD whose disease is not adequately controlled with topical therapies or when those therapies are not advisable. In other countries, including the Netherlands, dupilumab treatment is reimbursed when a patient has failed at least one oral immunosuppressive treatment. These differences in reimbursement criteria will influence the impact of dupilumab treatment on total healthcare budgets in different countries.

Another factor that can influence the total costs is the dosage of biologicals and small molecules that is prescribed. Based on clinical trials, the label recommends a loading dose of dupilumab 600mg followed by a maintenance dose of 300mg every other week. After achieving adequate disease control, it is unknown whether disease control could be maintained with longer dosage intervals or treatment withdrawal.

Studies in psoriasis suggest that a disease activity guided, dose reduction of biologics could lead to successful dose reduction in a part of the patients.[9-12] However, also reduced efficacy and increase of antidrug antibodies are described in patients with intermittent administration of biologics for psoriasis.[9-12] A randomized clinical trial investigating the efficacy and safety of different dupilumab regimens in maintaining clinical response after 16 weeks of initial treatment was published by Worm et al.[13] Patients with a sufficient initial response (IGA 0/1 or EASI75%) were rerandomized to continue the original regimen of dupilumab 300mg weekly or every 2 weeks or to prolong dosage interval to dupilumab 300mg, every 4 or 8 weeks. This study observed that longer dosage intervals (300mg every four or eight weeks) and placebo resulted in clinical worsening of AD. Therefore, the approved dosage of 300mg every other week for long-term treatment was recommended by this study. However, these patients were randomized in the different dupilumab treatment regimen groups after 16 weeks of treatment based on the clinical response. Randomized patients continued the dosage regimen until the end of the follow-up period regardless of the clinical response after interval prolongation. These results might not be generalizable to a daily practice setting. In daily practice patient-tailored, individual dosing could be considered depending on individual response to treatment and side effects. Data on individual dosing of dupilumab in daily practice are scarce. A very recent study from our group showed that dose reduction was successful in a subgroup of patients with controlled AD by using a patient-centered dosing regimen. These patients showed stable low disease activity and low severity biomarkers over time.[14] In future, it is expected that after dupilumab patent expiration, less expensive biosimilars will enter the market which was also observed in the field of psoriasis, rheumatoid arthritis and inflammatory bowel disease.[15, 16].

In conclusion, this thesis demonstrated a significant economic burden of moderate-severe AD patients, including direct and indirect costs with the highest impact of costs due to productivity losses. Newly introduced biologics and small molecules for the treatment of moderate-severe AD will increase drug acquisition costs. In turn, due to the high efficacy of these new treatment, the high drug acquisition costs may

be compensated by lower societal costs due to positive effects on work productivity as demonstrated in this thesis. Daily practice registries are very important to provide data on personalized and safe use of novel therapies for AD in the coming years. Future studies including validated questionnaires, evaluating the effects of novel targeted therapies on direct costs and work productivity in a real life setting are very important for future economic evaluations. In addition, effective usage and possibilities for individual dosing of novel therapies are important to prevent a high impact on total healthcare budgets.

Effectiveness of dupilumab treatment in daily practice

Cyclosporine A was the only registered oral immunosuppressive therapy for the treatment of moderate-severe AD in European countries for many years. Cyclosporine A treatment has shown to be very effective in the treatment of AD, however, many patients develop side effects (mostly nephrotoxicity and hypertension) and dose reduction, mostly because of side effects, leads to ineffectiveness. [17] Also other, broad immunosuppressant's including methotrexate, azathioprine, and mycophenolate mofetil are commonly used off label for the treatment of moderate-severe AD shows discontinuation rates of approximately 50% due to side effects and/or ineffectiveness. [17, 18] Dupilumab entered the European market for the treatment of moderate-severe AD in 2018. At the moment of approval, dupilumab was studied in an extensive clinical trials program and clinical efficacy and safety of dupilumab has been demonstrated in phase 3 clinical trials. [19-21] In LIBERTY AD CAFÉ, a phase 3 clinical trial, dupilumab treatment was studied in patients with an inadequate response to CsA or for whom CsA treatment was medically inadvisable. However, no head-to-head clinical trials comparing dupilumab with CsA have been performed. Head-to-head clinical trials are important to compare the efficacy and safety of new therapies in comparison to the currently available options.

In the absence of head-to-head evidence, we used an indirect comparison analysis to compare effectiveness of dupilumab to CsA. In **chapter 3**, the relative effectiveness of dupilumab versus CsA in adult patients with moderate-severe AD was assessed by using dupilumab data obtained from the phase 3 trial LIBERTY AD CHRONOS and CsA data from a daily practice cohort. We performed an indirect comparison by estimating the proportions of patients with treatment responses based on improvements from baseline in EASI score of 75% (EASI-75%) or 50% (EASI-50). Effectiveness was indirectly compared by using regression models comparing the proportion of patients achieving EASI-75 or EASI-50 after 12-16 and 24-30 weeks

of treatment with dupilumab or CsA. This analysis suggested a higher relative efficacy of dupilumab compared with CsA effectiveness based on 50% and 75% improvements in EASI scores of patients with moderate-severe AD. The relative efficacy of dupilumab compared to the effectiveness of cyclosporine A significantly improved over time based on the EASI-50 response. This could be explained by the effect of stepwise dose tapering of CsA based on individual factors including side effects and effectiveness, reflecting a daily practice setting. In contrast, patients with dupilumab were treated with 300mg dupilumab every other week without dose adjustment since they were participating in a clinical trial. The differences between the two treatment settings were an important limitation of this study. Adequate and statistical comparison of the treatment effects in clinical trials and daily practice is complex due to differences in study designs, study-outcomes, patient characteristics, and practice patterns. This emphasizes the relevance of head-to-head clinical trials comparing new drugs with standard of care before EMA approval and market introduction

Dupilumab treatment in daily practice. how to define successful treatment?

In **Chapter 4**, the effect of 16-weeks treatment with dupilumab on clinical response and serum biomarkers in adult patients with moderate-severe AD was studied. We demonstrated that dupilumab treatment significantly improved signs and symptoms of AD as well as patient-reported outcomes including itch, anxiety, pain/discomfort, depression and HrQoL in a very severe AD population who failed earlier treatment with ≥1 oral immunosuppressive drugs. These results were confirmed in **chapter 5** studying the 52-week effectiveness and safety of dupilumab in 210 moderate-severe patients treated in daily practice. Effectiveness of dupilumab treatment sustained or further improved during the 52-week follow-up period.

Patient- and physician reported outcomes in **chapter 4** and **chapter 5** were more or less comparable to outcomes reported in previous phase 3 clinical trials and other daily practice studies.[19, 20] The percentage of patients achieving 90% improvement in EASI (EASI-90) from baseline was lower in our studies described in **chapter 4** and **chapter 5** compared to results reported in the phase 3 clinical trials.[19, 20] Patients treated with dupilumab in **chapter 4 and chapter 5** were included in the BioDay registry shortly after approval of dupilumab by the European Medicines Agency and market access. In the start-up phase of the BioDay registry, dupilumab was started after a washout period of oral immunosuppressive drugs, comparable with patients included in the phase 3 clinical trials which might partly explain the comparable

outcomes. However, most patients included in **chapter 4** and **chapter 5** failed multiple systemic treatments indicating very severe AD and patients were treated in a less controlled setting which might explain the difference in the percentage of patients achieving EASI-90.

Relative vs absolute outcomes, holistic outcomes and disease control

In the extensive clinical trial program of dupilumab, fixed clinical endpoints including the proportion of patients achieving EASI-50 and EASI-75 were used to determine treatment effect. A disadvantage of these fixed clinical endpoints is that they do not capture the full range of clinical benefits and therefore might not be ideal to define treatment response in daily practice (table 1).

Table 1. There is no singe outcome that captures the diverse signs, symptoms and quality of life impact of atopic dermatitis.
DLQI, Dermatology Life Quality Index; EASI=Eczema and Severity Index; HADS=Hospital Anxiety and Depression Scale; IGA, Investigator's Global Assessment; MCID, minimum clinically important difference; NRS, Numerical Rating Scale; POEM, Patient-Oriented Eczema Measure

Outcome measure	MCID	Clinical signs	Symptoms	Quality of life	Disease control
IGA	n/a	✓	✗	✗	✗
EASI	6.6	✓	✗	✗	✗
Pruritus NRS	2–3	✗	✓	✗	✗
POEM	3.4	✗	✓	✗	✗
DLQI	4	✗	✗	✓	✗
HADS	n/a	✗	✗	✗	✗
ADCT	5	✗	✓	✓	✓

In **chapter 4,** we defined clinically relevant responses in order to capture the full range of clinical benefits, based on thresholds of commonly used outcomes to assess the major AD domains including signs, symptoms and HrQoL (EASI-75 or NRS itch ≥4-point improvement or DLQI ≥4-point improvement) (Figure 1).

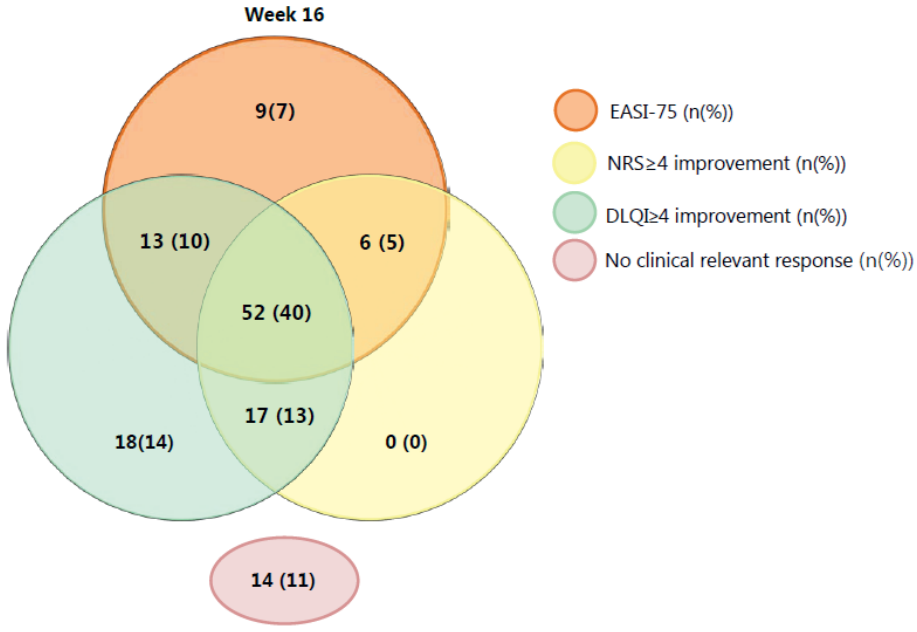

Figure 1. Characterization of the patients with a clinically relevant response: proportion of patients achieving EASI-75 or NRS ≥4-point improvement or DLQI ≥ 4-point improvement after 16 weeks of dupilumab treatment (outcomes available in 129 patients). EASI, Eczema Area and Severity Index; EASI-75, ≥75% improvement in EASI score; NRS, Numeric Rating Scale; DLQI, Dermatology Life Quality Index.*Figure adapted from "Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: First clinical and biomarker results from the BioDay registry" by Ariens et al. Allergy 2020 Jan;75(1):116-126.*

The majority (89%) of the dupilumab-treated patients reported clinically relevant improvement in at least one of the three domains after 16 week of treatment, clinically relevant improvement in all of the three domains was achieved in 40% of the patients. Clinical guidelines make no recommendations on criteria for the assessment of treatment success in patients with AD. In clinical trials, treatment success is often defined by strict clinical endpoints based on a percentage reduction in these clinical scores. However, percentage reduction of clinical scores might not be relevant for individual patients and an absolute score indicating controlled disease might be more relevant in clinical practice. With the introduction of

expensive, targeted treatment options for AD, there is a need for more guidance in the assessment of treatment success for adequate and effective usage of these treatments. In our view, a combination of clinical scores and patient-reported outcomes should be used to decide on treatment continuation and future dose tapering for adequate and effective usage of dupilumab and other new targeted treatments. A recent study by de Bruin-Weller et al. [22], sought to reach international consensus on a framework for shared decision-making on systemic treatment continuation, modification, or discontinuation in adult patients with moderate-severe AD. Using an eDelphi process, consensus was achieved on a core set of statements related to treat-to-target outcomes at two specific time points; an initial acceptable target based on reductions that represent acceptable improvements at 3 months and optimal target at 6 months. These targets are based on improvements in patient global assessment (PtGA), reflecting the patient's perception of disease activity plus at least one specific key domain measured by validated outcome measures including SCORAD, EASI, DLQI, Peak Pruritus NRS or POEM. This study provides a framework that could be used for evaluation of systemic treatment in clinical practice including both patient-reported and physician reported outcome measures.

Relative improvement in outcome measures can be used in patients starting a new systemic treatment without bridging therapy. However, in daily practice, clinicians often bridge between different systemic treatments to avoid unnecessary exacerbations. In case of bridging treatments, relative reductions in clinical outcomes measures to assess initial improvement are not useful. Therefore, during long-term treatment and switching between different treatments, the current status of disease control using a combination of absolute scores might be more relevant for patients and physicians than the improvement since baseline. Recently, some instruments have been validated to evaluate long-term disease control including the Atopic Dermatitis Control Test (ADCT), and Recap of Atopic Eczema (RECAP). [23, 24] These instruments could be used to evaluate patient-perceived AD control and regularly use of these instruments could be used to evaluate long-term treatment success.

Drug survival of dupilumab treatment

Drug survival analysis and associated predictors reflects the real life situation in daily practice without intervention of a fixed research protocol and encompasses factors including effectiveness, occurrence of side-effects, patients factors, and the availability of alternative treatment options. [25] Drug survival analysis of dupilumab

treatment provides important additional information on the long-term performance of this drug in a real life situation. In addition, with the lack of head-to-head clinical trials comparing dupilumab treatment with conventional oral immunosuppressive drugs, drug survival analysis enables comparison of dupilumab with conventional oral immunosuppressive drugs in a daily practice setting. In **chapter 7,** we assessed the two-year drug survival of dupilumab treatment and compared drug survival of dupilumab with conventional immunosuppressive drugs including CsA en MTX in two historical daily practice cohorts of moderate-severe AD patients. The overall drug survival rates for dupilumab were 91% and 88% after 1 and 2 years compared to 27% and 20% in CsA and 41% and 33% in MTX. In patients treated with CsA and MTX approximately half of the patients discontinued treatment due to treatment failure (ineffectiveness and/or side effects). In dupilumab treated patients, limited number (7%) discontinued treatment due to treatment failure. In the CsA group a relatively high percentage of patients (22%.) discontinued treatment within two years after start of CsA because of well-controlled AD. In contrast, none of the patients treated with dupilumab discontinued because of well-controlled disease which can partly explain the overall longer drug survival of dupilumab. Due to the low number of patients discontinuing dupilumab treatment, a prediction analysis of determinants of drug survival was not feasible. Dal bello et al. also studied drug survival of dupilumab in comparison with CsA, reasons for discontinuation and predictive factors of drug survival in 149 AD patients treated in daily practice. [26] Sixteen months from baseline, the drug survival rate of dupilumab was 82%, compared to drug survival of 11% in CsA treated patients. Reasons for discontinuation of dupilumab treatment were ineffectiveness in 4.7% of patients, clinical remission in 7.4%, and side effects in 2% of the patients. Older age and shorter AD duration had a negative predictive effect on drug survival of dupilumab. In contrast to our study, this study included patients treated with CsA and dupilumab within the same time frame. Therefore, it is likely that the availability of dupilumab effects the drug survival of CsA in this cohort, explaining the lower percentage of drug survival compared to our cohort.

Drug survival is influenced by the availability of alternative treatment options

After approval of dupilumab in the Netherlands in 2018, most patients who started treatment with dupilumab failed treatment with multiple conventional oral immunosuppressive drugs, as described in **chapter 4** and **chapter 5**. In most of these patients, there were no alternative treatment options in case of treatment failure of

dupilumab (ineffectiveness or side effects) and therefore, it is likely that patients continued dupilumab treatment despite side effects and/or insufficient treatment response. The field of systemic treatment for AD is expanding with currently new biologics and small molecules being approved or in the pipeline for the treatment of moderate-to-severe AD. It is likely that these new targeted treatment options for AD will influence future drug survival of dupilumab. With more targeted treatment options becoming available for moderate-to-severe AD, more patients on dupilumab treatment will switch treatment in case of side effects and/or insufficient treatment response. Therefore, it is expected that drug survival of dupilumab treatment will decrease in the coming years. Future drug survival studies will provide important information on long term performance of dupilumab, the impact of newly introduced biologics and small molecules and comparison of dupilumab with these new targeted treatment options with regard to drug survival.

In conclusion, as demonstrated in this thesis, dupilumab treatment has shown to be an effective treatment option for patients with very severe AD in daily practice. The absence of direct head-to-head clinical trials comparing new more-targeted therapeutics with the current available treatment options emphasizes the importance of the generation of daily practice data. With the availability of more, highly effective, but also more expensive treatment options for AD, there is a need for more guidance in the assessment of treatment success for adequate and effective usage of these treatments. The combination of clinical scores and patient-reported outcomes should be used to guide in the decision to continue treatment and future dose tapering.

Side effects of dupilumab treatment in daily practice

Overall, dupilumab was well tolerated in all clinical trials and showed a favorable safety profile.[19, 21, 27-29] The dupilumab-treated groups reported higher rates of injection-site reactions, localized herpes simplex infections and conjunctivitis. Due to the favorable safety profile of dupilumab demonstrated in clinical trials, laboratory testing is not required according to the label of dupilumab. However, in clinical trials the safety of dupilumab treatment is studied in a very homogeneous population due to strict in- and exclusion criteria and only for a limited treatment duration. Therefore, daily practice registries are very relevant to access the long-term safety and effectiveness of new therapeutics such as dupilumab.

Conjunctivitis during dupilumab treatment in daily practice: clinical characteristics?

Conjunctivitis was the most frequent reported side effect in clinical trials evaluating dupilumab treatment for AD. In the latest phase III clinical trial, the incidence of conjunctivitis (28 % (LIBERTY AD CAFÉ)) was higher compared to the earlier clinical trials. [19, 21, 27-30] In clinical trials, baseline AD severity and prior conjunctivitis history were associated with the development of conjunctivitis during dupilumab treatment. In daily practice, the proportion of AD patients developing conjunctivitis during dupilumab treatment was even higher (34-38%) as reported in **chapter 4** and **chapter 5**. The higher incidence of conjunctivitis in daily practice might be explained by an increase awareness of conjunctivitis among dermatologists and dupilumab treated patients.

In **chapter 8**, we described first ophthalmological findings of dupilumab treated AD patients developing conjunctivitis in a clinical trial setting.[31] Inflammation of the conjunctiva and hyperemia of the limbus were observed as prominent clinical features. Nodular swelling of the limbus was observed in the most severe patients. As the long-term use of corticosteroid eye drops increases the risk of complications such as glaucoma and cataract, there is a need for other long-term safe ocular anti-inflammatory treatment. Therefore, as described in **chapter 8**, we recommend to start anti-inflammatory treatment with tacrolimus skin ointment on the eyelids or cyclosporine eye drops. A more recent, prospective daily practice study including patients from the BioDay registry, evaluating ophthalmological characteristics and long-term treatment outcomes of ophthalmologist-confirmed conjunctivitis during dupilumab treatment was reported by Achten et al.[32] In contrast to clinical trial data[33], the conjunctivitis in this daily practice study did not resolve in most AD patients while continuing dupilumab, despite extensive treatment by an ophthalmologist. The most frequently prescribed ophthalmological treatment during follow-up included corticosteroid eye drops, tacrolimus ointment on the eyelids, and lubricant eye drops. Despite adequate treatment, limbitis was observed in a substantial (24.2%) part of the patients treated with dupilumab in this study. Dose adjustment or discontinuation of dupilumab was needed in approximately one third of the patients. Corticosteroid eye drops were needed in almost two-third of the patients developing conjunctivitis in this study.

Patients with AD have a higher prevalence and disease severity-dependent increased risk of ocular comorbidities as compared with the overall population.[34] Since conjunctivitis was not associated with dupilumab treatment in trials including

patients with other type 2 diseases, pre-existing ocular comorbidities and a disease specific interaction with dupilumab might explain the increased incidence of conjunctivitis during dupilumab treatment in patients with AD. Recently, Achten et al. studied the frequency, severity and pathogenesis of ocular surface disease in patients with moderate-severe AD before the start of dupilumab treatment.[35] Before starting dupilumab treatment, 90% of patients already had ocular surface disease. However, 25% of the patients with moderate-severe ocular surface disease did not report any symptoms. Another study by Achten et al. identified risk factors for the development of dupilumab-associated ocular surface disease in a large prospective daily practice cohort including 469 patients treated with dupilumab in daily practice. [36] In this study, a history of any eye disease, but not a history of self-reported episodic acute allergic conjunctivitis, combined with the use of ocular medication at the start of dupilumab treatment was associated with the development ophthalmological side effects, defined as dupilumab-associated ocular surface disease. The development of dupilumab-associated ocular surface disease was not associated with baseline severity of AD in this study. In contrast, in clinical trials and in our study described in **chapter 5**, we observed an association between AD baseline severity and the development of conjunctivitis during dupilumab treatment. Patients included in the study described in **chapter 5** of this thesis started dupilumab treatment ahead of market access in an Early Access program. Patients were indicated for treatment with dupilumab in the early access program in case of severe AD with limited treatment options. Therefore, this cohort may represent a more severe population with higher EASI scores at baseline compared to the patients included in the study of Achten et al.

*Pathomechanism of conjunctivitis during dupilumab treatmen*t

As conjunctivitis it the most frequent side effect in AD patients treated with duilumab, more insight is needed in the underlying pathomechanism and possibilities for risk stratification in patients that are candidates for dupilumab treatment.

In **chapter 9**, histopathological characteristics in conjunctival biopsies from 6 AD patients developing conjunctivitis during dupilumab treatment were analyzed. We observed a remarkable scarcity of conjunctival goblet cells and an extensive sub epithelial infiltrate in the conjunctival stroma, mainly consisting of CD4+ T cells and eosinophils. The histopathological findings described in **chapter 9**, do not correspond with the histopathological features in patients with other Th2-mediated ocular diseases including atopic keratoconjunctivitis and allergic conjunctivitis, which

are characterized by increased density of goblet cells and increased mucus production.[37, 38] Ocular rosacea is a Th17-driven disease that is histopathologically characterized by low density of goblet cells and an inflammatory cell infiltrate mainly consisting CD4+ cells, but not eosinophils. The combination of low numbers of conjunctival goblet cells in combination with an inflammatory infiltrate consisting lymphocytes and eosinophils observed in our study may imply a new entity of conjunctivitis developing in patients treated with dupilumab for AD.[39] A study by Bakker et al. extended the above research by using imaging mass cytometry, which enables in situ protein expression analysis of multiple markers.[40] This study showed highly activated and proliferating CD4+ and CD8+ T-cells, B-cells, monocytes, macrophages, and dendritic cells within the infiltrating cells of conjunctival biopsies from AD patients treated with dupilumab. In addition, elevated Th1 (interferon gamma (IFNγ), TNFα) and Th17 (IL-17) cytokine production and increased cytotoxic activity were observed.

Conjunctival goblet cells are specialized mucus secreting cells, which keep the ocular surface lubricated and retain water and have an immunomodulatory effect.[41] The conjunctival epithelium is normally a goblet cell rich mucosal tissue, and the Th2 cytokine IL-13 stimulates protein synthesis, proliferation and mucus secretion. Interferon gamma produced by CD4+ T cells and innate cells has showed to cause conjunctival goblet cell loss and tear dysfunction ocular have been associated with increased IFNγ expression.[42] These findings support results of mice studies suggesting that altered ratios of Th cytokines with increased levels of the Th1 cytokine IFNγ and increased ratio of Th1 cytokines (including IFNγ) to the Th2 cytokine IL-13, may cause goblet cell loss in these dry eye diseases.[42, 43] These results are in line with the findings in dupilumab-treated AD patients in the study by Bakker et al.[40] It was hypostasized that dupilumab treatment may lead to loss of conjunctival goblet cells and mucin production by inhibiting IL-13, which normally stimulated goblet cell differentiation and mucus production. The loss of conjunctival goblet cells might lead to tear film dysfunction and dry-eye like disease. The loss of immunomodulatory effects of goblet cells preventing the ocular surface from inflammation may also lead to infiltration of Th1 cytokine producing T cells and subsequently irritative conjunctivitis. The attraction of Th1 cytokine producing T cells might lead to further apoptosis of conjunctival goblet cells. In addition, the inhibition of the IL4/IL13 pathway by dupilumab may possibly induce a shift from a Th2 to a more Th1/Th17-mediated inflammatory response which further stimulates this process.

Calcineurin inhibitors including CsA have shown to decrease the production of inflammatory cytokines, improve homeostasis of the corneal barrier function and increase conjunctival goblet cells in dry eye disease. [44] These findings emphasize the use of calcineurin inhibitors in the treatment of conjunctivitis occurring during dupilumab treatment. The majority of AD patients treated with dupilumab had previously been treated with CsA and also other oral immunosuppressive drugs (**chapter 4** and **chapter 5**) which may have simultaneously treated ocular comorbidities in these patients. The mechanism of action of dupilumab in patients with a high pre-existing prevalence and risk of ocular comorbidities may explain the high numbers of conjunctivitis during dupilumab treatment, which were not observed during treatment with conventional immunosuppressive drugs. Recently, tralokinumab, a fully human monoclonal antibody that potently and specifically neutralizes IL-13 was approved for the treatment of moderate-severe AD. [45-47] In phase 3 clinical trials, the incidence of conjunctivitis was higher in patients treated with tralokinumab compared to placebo, being mild in most of the patients. In contrast to dupilumab, tralokinumab specifically binds to the IL-13 cytokine and does not block IL-4 signaling. Specific inhibition of IL-13 by tralokilumab might potentially have a less negative effect on the conjunctival goblet cells and shift in the immune system compared to inhibition of both IL-13 and IL-4 signaling by dupilumab. Recently, Hansen et al. assessed cell proliferation and the effect of cytokines on goblet cell proliferation using cells from human donors.[48] This study demonstrated that IL-13 and IL-4 promoted goblet cell proliferation, whereas IFN- γ strongly negatively influenced proliferation and viability of human goblet cells and decreased capacity of producing and secretion of mucin. Inhibition of IL-4 signaling by dupilumab may induce a Th1 cytokine milieu with increased IFN- γ production, leading to apoptosis of goblet cells and secretory dysfunction. This additional factor might theoretically exert a more negative effect on GC compared to only IL-13 inhibition.

Several other hypotheses for the underlying pathomechanism of conjunctivitis in AD patients treated with dupilumab, have been proposed. One of the proposed theories is that the dupilumab-related conjunctivitis might be caused by an increase of Demodex mites in hair follicles and cause Meibomian gland dysfunction and ocular rosacea like disease, driven by IL-17 inflammation. [49-51] Another suggested theory is that the blockage of IL-4 and IL-13 would increase the activity of specific ligands (OX40 ligand) involved in atopic keratoconjunctivitis in the eye.[49] Thyssen et al. suggested an eosinophil-mediated response as increased peripheral blood

eosinophils counts were observed during dupilumab treatment.[20, 34] Other studies suggested relative ocular undertreatment due to lower tissue distribution of dupilumab in the eyes.[21, 33] A dysregulated immune-mediated response of conjunctival associated lymphoid tissue by dupilumab treatment in patients with AD was proposed by Shen et al.[52]

In the future, the identification of patients at risk for developing conjunctivitis during dupilumab treatment before initiation of treatment may enable early or preventive treatment. In these patients' alternative treatment options could be considered. Increased risk for the development of conjunctivitis during treatment was not observed in trials studying JAK inhibitors for the treatment of AD. [53-56] Janus kinase (JAK) inhibitors inhibiting the JAK/activator of transcription (STAT) pathway are considered as more broad-acting small molecules, therefore potential side effects caused by skewing of the immune system might be less common in patients treated with JAK inhibitors compared to biologics blocking Th2 specific cytokines. Switching to treatment with these more broad-acting JAK inhibitors could be considered in patients at risk for developing conjunctivitis or in patients developing conjunctivitis during dupilumab treatment.

Side effects of dupilumab treatment in daily practice, not observed in clinical trials

Due to the life changing beneficial effect of dupilumab therapy in patients with a history of failure on multiple previous treatments, most patients are reluctant to stop therapy and side effects are potentially under-reported. Several side effects were observed in daily practice that were not reported in the dupilumab clinical trials.[57, 58] Facial redness occurring during dupilumab treatment was reported in up to 10% of patients in daily practice. [57] The clinical and histopathological features of dupilumab facial redness are different than the familiar AD in these patients.[59-61] Patients described in case-reports present with well-demarcated, erythematous and scaling patches in the head and neck, mostly not accompanied by subjective symptoms, but some patients report itchy and burning sensations.[59-61]. In a case-study by our group including patients from the Bioday registry, a heterogeneous histology was observed in two patients with histopathological features of eczema and neutrophilic dermatosis, which was contributed as a result from the Malassezia yeast.[59] These patients showed a positive response to therapy with oral itraconazole. In a case-series including skin biopsies of seven patients with dupilumab facial redness by the Wijs et al., histopathological features of a psoriasiform dermatitis and dilated capillaries and perivascular lymphocytic cell infiltrates were reported.[61] Spongiosis

was absent in all of these patients. Features of a psoriasiform dermatitis including orthokeratosis and parakeratosis in the epidermis and a lymphocytic cell infiltrate in the dermis was also reported in four cases described by Dybala et al.[60] Basal layer vacuolar degeneration and adipocyte necrosis suggesting a drug-induced psoriasiform dermatitis was also described in this study. Given the heterogeneity of the clinical and histopathological characteristics of dupilumab facial redness described in literature, a clear hypothesis of the underlying pathomechanism has not been established yet. Most case-studies suggested a psoriasiform reaction by shifting to a more Th1/Th17/Th22 dominated response by blocking the Th2 pathway with dupilumab.[57, 59-61] Larger studies on the underlying mechanism and treatment options of this new phenomena are needed.

Another recently described side effect in daily practice during dupilumab treatment are joint/muscle symptoms including various forms of arthropathy/enthesitis/ tendinopathy. In our 52-weeks follow-up study described in **chapter 5** muscle and joint pain were reported in 7.6% of the patients treated with dupilumab in daily practice. Other observational daily practice studies also reported rheumatologic symptoms including inflammatory arthritis in almost 5% of patients treated with dupilumab for AD.[62-64] A few studies report an increased risk of rheumatoid arthritis in AD patients, regardless of therapy. [65, 66] By blocking the Th2 pathway with dupilumab treatment, the shift to a more Th1/Th17 dominated immune response might contribute to the development of rheumatologic signs and symptoms during dupilumab treatment in predisposed patients. An in vitro study in entheseal fibroblasts demonstrated that IL-4 and IL-13 both attenuated the production of IL-23.[67] In addition, IL-4 also inhibited secretion of TNF/IL-17A induced stromal cell CCL20 expression in entheseal stroma. The cytokines IL-23 and IL-17 have demonstrated to play an important role in the pathogenesis of autoinflammatory arthritis.[68] Decreased levels of IL-4 by dupilumab treatment, potentially also increase levels of TNF-α and IL-6, which are important inflammatory cytokines in the pathogenesis of rheumatoid arthritis.[69] Besides the immunological shift to a more Th1/Th17 skewed cytokine milieu, masking of pre-existing comorbidities by previous treatment with more broad acting conventional immunosuppressive drugs can also play a role in the development of side effects.

In patients reporting side effects during dupilumab treatment with well-controlled AD, individual dosing including interval prolongation should be considered. With the availability of new, alternative treatment options, switching to another therapy

should also be considered in these patients. Janus Kinase inhibitors are considered as more broad-acting small molecules and therefore side effects caused by skewing of the immune system might be less common in patients treated with JAK inhibitors compared to biologics.

As demonstrated in this thesis, high rates of conjunctivitis during dupilumab treatment are reported in daily practice. Patients with AD have a high prevalence and disease severity-dependent increased risk of ocular surface disease. This predisposition in combination with the immunomodulatory effect of dupilumab on ocular goblet cells might explain the high rates of conjunctivitis during dupilumab treatment in AD patients. In future, identification of patients at risk for developing conjunctivitis is important to enable early or preventive treatment. In addition, in this thesis we described side effects of dupilumab treatment in daily practice, not observed in the extensive clinical trial program. This emphasizes the importance of prospective registries to study the safety of new systemic treatment options and to identify not previously observed side effects.

Future perspectives

Generation of real life data to evaluate the balance between effectiveness and tolerability of new therapies in an unselected AD population is necessary. Real life data of new therapies should ideally be collected in prospective, (inter)national registries containing modules to study effectiveness and safety in AD but also on the effect of treatment on other atopic comorbidities. These registries will offer possibilities for further research on the comparison between different therapeutics by drug-survival analysis and may help to increase the knowledge on effectiveness and safety of treatment options related to patients' characteristics for more personalized medicine. Since the expected impact of new therapies on drug acquisition costs, prospective registries including validated questionnaires evaluating the impact of new therapies on direct costs and work productivity are necessary for economic evaluations. In addition, real life data will address the need of effective usage and possibilities for individual dosing of novel therapies to increase tolerability and prevent an excessive impact on total healthcare budgets.

Concluding remarks

Health economics

I. Newly introduced biologics and small molecules for the treatment of moderate-to-severe AD will increase drug acquisition costs. In turn, due to the high efficacy of these new treatments, the high drug acquisition costs may be compensated by savings in indirect costs due to decreased productivity losses.

II. Future studies using data from daily practice registries including validated questionnaires, evaluating the effects of novel targeted therapies on direct costs and work productivity are very important for future economic evaluations.

III. To prevent an excessive impact on total healthcare budgets, future studies searching for possibilities for individual dosing and effective usage of novel therapies are very important.

Effectiveness in daily practice and definition of treatment success

I. In contrast to clinical trials, in daily practice, the balance between effectiveness and side effects and the availability of alternative treatment options in an unselected patient population determines whether treatment will be continued. Therefore, daily practice data evaluating the effectiveness, side effects and the effect on comorbidities of novel therapies are very important for incorporation in clinical recommendations and guidelines.

II. With the introduction of many, highly effective, more expensive treatment options for AD, there is a need for more guidance in the assessment of treatment success for adequate and effective usage of these treatments.

III. In our view, a combination of clinical scores and patient-reported outcomes should be used to decide on treatment continuation and future dose tapering for adequate and effective usage of dupilumab and other new targeted treatments.

IV. Drug survival studies using data from prospective registries are important to study long term performance of new systemic treatment options and, to compare newly introduced biologics and small molecules with the currently available treatment options for AD.

Safety in daily practice

I. Although dupilumab seems to have a uniquely good safety profile, high rates of conjunctivitis during dupilumab treatment in daily practice are reported.

II. In future, the identification of patients at risk for developing conjunctivitis during dupilumab treatment may enable early or preventive treatment.

III. In patients developing side effects during dupilumab individual dosing or alternative treatment options could be considered.

IV. Prospective registries are important to study the safety of new systemic treatment options and to identify side effects not observed in clinical trials.

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Chapter 12

English summary

Nederlandse samenvatting

English summary

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases worldwide with an increasing prevalence of up to 20% in children and 10% in adults. The pathogenesis of AD is multifactorial and occurs from a complex interaction between immunological, genetic and, environmental factors resulting in epithelial barrier dysfunction and a predominantly type 2 skewed immune dysregulation.

Atopic dermatitis, particularly moderate-to-severe AD, is associated with high rates of anxiety and depression, and lower health-related quality of life (HrQoL) causing a major burden in this patient population. In addition, moderate-to-severe AD also has a significant socioeconomic impact caused by direct costs from treatment and indirect costs caused by reduced work productivity and missed work and school. Since many of these factors are related to the severity of AD and inadequate disease control, there has been a high unmet need in patients with moderate-to-severe AD. In the last years several novel targeted therapeutic options have been developed for the treatment of AD including biologics blocking the Th2/Th22 pathways and small molecules targeting the Janus kinase – signal transducer and activator of transcription (JAK-STAT) pathway. Dupilumab, a fully human monoclonal antibody targeting the IL-4 receptor alpha, thereby blocking the IL-4 and IL-13 pathway, is the first antibody-based treatment that has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for moderate-to-severe AD.

In the studies described in this thesis we aimed to investigate the costs, the effectiveness and the safety of dupilumab in a daily practice setting.

The (economic) burden before the introduction of dupilumab

The psychosocial effects of AD including social stigmatization and sleep deprivation can lead to an increased risk of depression, anxiety and suicidality. Atopic dermatitis also incurs an substantial economic burden derived from direct costs including inpatient and outpatient visits, diagnostic tests, medication costs, as well as indirect costs caused from lost work productivity. With currently many new, and costly, targeted therapeutics being approved for the treatment of moderate-to-severe AD, and the expected impact on drug acquisition costs, more information on the

economic burden and HrQoL in patients who are candidates for these treatments is needed.

In **chapter 2** we studied direct costs derived from medication use and healthcare resource utilization, and costs of productivity loss in 90 adult AD patients indicated for systemic treatment. This study demonstrated considerable costs including total costs (direct costs and costs of productivity loss) of €15,231 per patient per year in the total group of patients. Patients with uncontrolled disease had higher costs (€20,695) compared to patients with controlled disease (€11,287). Costs of productivity loss had the largest impact on total costs. In addition, AD demonstrated to cause a significant burden on the quality of life of patients indicated for systemic treatment. Future research is needed to study whether the introduction of the new more-targeted therapeutics can improve the impact of AD on quality of life and productivity loss, which might (party) compensate the expected increase in drug acquisition costs.

Effectiveness of dupilumab treatment in daily practice

For many years, cyclosporine A was the only registered oral immunosuppressive therapy for the treatment of AD in European countries. Cyclosporine A is very effective; however, nearly half of the patients discontinue treatment due to side effects and/or ineffectiveness. Several other broad immunosuppressant's including methotrexate, azathioprine, and mycophenolate mofetil are commonly used off label for the treatment of moderate-to-severe AD. Discontinuation rates of approximately 50% due to side effects and/or ineffectiveness have been reported in daily practice. Dupilumab entered the European market for the treatment of moderate-to-severe AD in 2018 after it was studied in an extensive clinical trials program. Remarkably, despite the extensive clinical trial program, no head-to-head clinical trials were performed to compare the effectiveness and safety of dupilumab with the current available options.

In the absence of a head-to-head clinical trial comparing dupilumab with the CsA, the only registered systemic treatment of AD, we sought for an alternative comparative study design including an indirect comparison of dupilumab with CsA described in **chapter 3**. The relative effectiveness of dupilumab versus CsA was assessed by using dupilumab data obtained from the phase 3 trial LIBERTY AD CHRONOS and CsA data from a daily practice cohort. This study suggested a higher relative efficacy of dupilumab compared with CsA effectiveness based on the

proportion of patients achieving EASI-50 and EASI-75. However, comparing two treatments used in different treatment setting including a clinical trial and daily practice is highly complex due to differences in study designs, patient characteristics and practice patterns which is an important limitation of this study. The absence of direct head-to-head clinical trials comparing new more-targeted therapeutics with the current available treatment options emphasizes the importance of the generation of daily practice data. In a daily practice setting the balance between effectiveness and side effects determines whether treatment will be continued in an unselected patient population. Prospective registries including daily practice data will address the need for comparison of different therapeutics in the absence of head-to-head clinical trials.

In **chapter 4,** the clinical effectiveness and safety, and the impact on disease severity-related serum biomarkers of 16 weeks of dupilumab treatment in patients with moderate-to-severe AD was studied in a daily practice cohort including 138 patients. Dupilumab treatment significantly improved signs and symptoms of AD, as well as patient-reported outcomes including itch, anxiety, pain and discomfort, and depression and quality of life in a very severe AD population who failed previous treatment with multiple oral immunosuppressive drugs. These results were confirmed in **chapter 5** studying the long-term 52-week effectiveness and safety of dupilumab in 210 moderate-to-severe AD patients treated in daily practice. In this study, effectiveness of dupilumab treatment sustained or further improved during the follow-up period. In the extensive clinical trial program of dupilumab, fixed clinical endpoints including the proportion of patients achieving EASI-50 and EASI-75 were used to determine treatment effect. Since these fixed clinical endpoints do not fully capture the range of clinical benefits, they might not be suitable to define treatment success in daily practice. In **chapter 4**, we defined clinically relevant responses based on thresholds of commonly used outcomes (EASI-75 or NRS itch ≥4-point improvement or DLQI ≥4-point improvement). The majority of patients (89%) reported clinically relevant improvement in at least one of the three domains after 16 weeks of treatment. With the introduction of more expensive, targeted treatment options for AD, there is a need for more guidance in the assessment of treatment success for effective usage of these treatments. Future studies using a combination of clinical scores and patient-reported outcomes to define treatment success are needed to study effective usage of new treatments.

The economic impact of the introduction of dupilumab

In **chapter 2**, we demonstrated the high economic impact and costs due to productivity losses in patients with moderate-to-severe AD indicated for systemic treatment. Given the higher price of dupilumab treatment compared to conventional immunosuppressive treatments, direct costs will substantially increase in patients treated with dupilumab. However, this increase in direct costs could be, partially, compensated by savings in costs due to the effect of dupilumab on the quality of life and savings in costs due to productivity losses. The impact of 52-weeks dupilumab treatment on absenteeism, presenteeism and related costs was investigated in a prospective, real-life cohort including 210 adult patients with difficult-to-treat AD described in **chapter 6**. We demonstrated a rapid and sustained reduction in work absenteeism and presenteeism measured by the Work Productivity and Activity Impairment questionnaire general health (WPAI-GH) and associated costs during the 52-weeks follow-up period. Estimated extrapolated median yearly costs due to productivity losses significantly reduced from €19,751 at baseline to €0.0 after 52 weeks of treatment with dupilumab. Patients included in **chapter 6** were included shortly after approval of dupilumab and were intensively monitored by frequent follow-up visits and laboratory monitoring which is not required according to the label. Therefore, analysis of direct costs in this group of patients would overestimate the direct costs of dupilumab and were excluded in this study. Future research should further investigate the effect of dupilumab treatment and other new more targeted treatments on direct as well as indirect costs.

Drug survival of dupilumab compared with conventional immunosuppressive treatments

After approval of dupilumab for the treatment of adult patients with moderate-to-severe AD, prospective daily practice data was collected in the BioDay registry. The generation of a large daily practice cohort addressed the need for comparison of dupilumab treatment with conventional systemic therapies by drug survival analysis in the absence of head-to-head clinical trials. Drug survival is a real-life reflection of daily practice by analyzing the length of time until discontinuation of a drug without intervening of a fixed research protocol. The reason for discontinuation of a drug in daily practice reflects the balance between effectiveness, side effects, tolerability, and the availability of alternative treatment options. In **chapter 7**, we studied the two-year drug survival of dupilumab treatment and compared drug survival with conventional systemic treatments including CsA and MTX in two historical daily

practice cohorts. The overall drug survival rates for dupilumab were 91% and 88% after 1 and 2 years compared to 27% and 20% in CsA and 41% and 33% in MTX. In contrast to the dupilumab cohort, relatively more patients in the CsA cohort discontinued treatment because of well-controlled disease. In this study, only limited patients discontinued dupilumab treatment, therefore a prediction analysis of determinants of drug survival was not feasible. Drug survival is influenced by the availability of alternative treatment options. Since the current expanding field of systemic treatment for AD, it is likely that these new treatment options will influence future drug survival of dupilumab.

The safety of dupilumab treatment in daily practice

Dupilumab has shown a favorable safety profile with mostly mild adverse events reported in clinical trials. Conjunctivitis was the most frequent reported adverse event in clinical trials evaluating dupilumab treatment for AD (up to 28% in the CAFÉ phase 3 clinical trial). In daily practice, the proportion of AD patients developing conjunctivitis during dupilumab treatment was even higher (34-38%) compared to the latest phase III clinical trials as reported in **chapter 4** and **chapter 5**. The higher incidence of conjunctivitis in daily practice might be explained by an increased awareness of conjunctivitis among dermatologists and dupilumab treated patients. The first clinical ophthalmological findings of dupilumab treated AD patients developing conjunctivitis in a clinical trials setting were described in **chapter 8**. We observed inflammation of de conjunctiva and hyperemia of the limbus as prominent clinical features, with nodular swelling of the limbus observed in the most severe patients. There is a need for safe long-term ocular anti-inflammatory treatment options, as long-term use of corticosteroid eye drops can lead to side effects such as glaucoma and cataract. In **chapter 8** we suggested to start anti-inflammatory treatment with tacrolimus skin ointment on the eyelids or cyclosporine eye drops.

The underlying pathomechanism of conjunctivitis during dupilumab treatment in AD patients is still unknown. Conjunctivitis was not associated with dupilumab treatment in trials including patients with other type 2 diseases suggesting a disease specific interaction in a population with a high prevalence of pre-existing ocular comorbidities. In **chapter 9,** we observed a remarkable scarcity of conjunctival goblet cells and an extensive subepithelial infiltrate in the conjunctival stroma, mainly consisting of CD4+ T cells and eosinophils in conjunctival biopsies from 6 AD patients developing conjunctivitis during dupilumab treatment. The combination of low numbers of conjunctival goblet cells with an inflammatory infiltrate consisting of

lymphocytes and eosinophils observed in our study may imply a new entity of conjunctivitis developing in patients treated with dupilumab for AD. It has been demonstrated that IL-13 normally has a stimulating effect on goblet cell proliferation and mucus secretion. We hypothesized that dupilumab-associated IL-4/IL-13 signaling inhibition in combination with a local T1 skewed cytokine production induces the loss of goblet cells and their important immunomodulatory effects in the conjunctiva. This can eventually lead to dry eyes, a highly activated multicellular infiltrate and tissue damage. Future identification of patients at risk for developing conjunctivitis during dupilumab treatment before initiation of treatment may enable early or even preventive treatment.

Future perspectives

Future generation of real-life data to evaluate the balance between effectiveness and tolerability of novel therapies in an unselected AD population is essential. Prospective registries will offer possibilities for further research on comparison between different therapeutics by drug-survival analysis. Since the expected impact of new therapies on drug acquisition costs, studies evaluating the impact of new therapies on direct costs and work productivity are needed for future economic evaluations. In addition, future real-life studies are needed to address the need of effective usage and possibilities for individual dosing of novel therapies to increase tolerability and prevent an excessive impact on total healthcare budgets.

Nederlandse samenvatting

Constitutioneel eczeem (CE) is een van de meest voorkomende chronische inflammatoire huidziekten wereldwijd, met een toenemende prevalentie tot 20% bij kinderen en 10% bij volwassenen. De pathogenese van CE is multifactorieel en ontstaat door een complex mechanisme waarbij zowel immunologische, genetische als omgevingsfactoren uiteindelijk leiden tot verstoring van de huidbarrière en disregulatie van het immuunsysteem.

Constitutioneel eczeem, en dan met name matig-ernstig CE, is geassocieerd met een hoge vermelding van angst en depressieklachten, een lagere gezondheid gerelateerde kwaliteit van leven (HRQoL) resulterend in een grote ziektelast in deze patiëntenpopulatie. Daarnaast heeft matig-ernstig CE een significante sociaaleconomische impact, veroorzaakt door directe kosten voorkomend uit de behandeling en indirecte kosten door verminderde arbeidsproductiviteit en gemiste werk- en schooldagen. Aangezien veel van deze factoren gerelateerd zijn aan de ziekte ernst van CE en onvoldoende ziektecontrole, bestond er een grote behoefte aan effectieve behandelopties in deze patiëntenpopulatie.

In het afgelopen decennium zijn er verschillende nieuwe therapeutische opties ontwikkeld voor de behandeling van CE waaronder biologics die aangrijpen op de Th2/Th22 signaalroutes en Janus-kinase (JAK) remmers die aangrijpen op de signaaltransductieroute van intracellulaire eiwitten JAK en signaaltransductie en activator van transcriptie (STAT). Dupilumab is een volledig humaan monoklonaal antilichaam dat specifiek bindt aan de interleukine-4-receptor-alpha-subeenheidketen van de interleukine-4 (IL-4) en interleukine-13 (IL-13) receptoren en remt daarmee de signaaltransductie van deze cytokines. Dupilumab is de eerste geregistreerde biologic voor de behandeling van matig-ernstig CE.

De onderzoeken die in dit proefschrift zijn beschreven hebben als doel gehad om de kosten, de effectiviteit en de veiligheid van behandeling met dupilumab te evalueren in patiënten met matig-ernstig CE behandeld in de dagelijkse praktijk

De (economische) ziektelast voor de introductie van dupilumab

De psychosociale gevolgen van CE waaronder sociale stigmatisatie en slaapproblemen kunnen leiden tot een verhoogd risico op angst- en depressieklachten en suïcidaliteit. Daarnaast brengt CE ook aanzienlijke

economische lasten met zich mee, die voortvloeien uit directe kosten, waaronder opnames en poliklinische bezoeken, diagnostisch onderzoek en medicatiekosten, evenals indirecte kosten als gevolg van verloren arbeidsproductiviteit. Met het toenemende aantal geregistreerde, kostbare, doelgerichte therapieën voor de behandeling van matig-ernstig CE en de verwachte impact op het zorgbudget, is er meer informatie nodig over de economische ziektelast en gezondheid gerelateerde kwaliteit van leven van patiënten die in aanmerking komen voor deze behandelingen.

In **hoofdstuk 2** werden zowel de directe kosten als gevolge van medicatie gebruik en gebruik van medische zorgvoorzieningen als indirecte kosten door productiviteitsverlies geëvalueerd in 90 volwassen CE patiënten met een indicatie voor systemische therapie. Deze studie toonde een aanzienlijke totale economische ziektelast (directe kosten en kosten ten gevolge van productiviteitsverlies) van €15.231 per patiënt per jaar in de totale patiëntengroep. Patiënten met ongecontroleerde ziekte hadden hogere kosten (€20.695) in vergelijking met patiënten met gecontroleerde ziekte (€11.287). Kosten ten gevolge van productiviteitsverlies hadden de grootste impact op de totale kosten. Daarnaast werd een grote impact van CE gezien op de kwaliteit van leven in deze patiëntenpopulatie. Toekomstig onderzoek is nodig om te evalueren of de introductie van de nieuwe, doelgerichte therapieën de impact van CE op de kwaliteit van leven productiviteitsverlies kan verbeteren, en zo mogelijk (deels) kan compenseren voor de verwachte impact van deze geneesmiddelen op de economische ziektelast in deze patiëntenpopulatie.

Effectiviteit van dupilumab in de dagelijkse praktijk

Voor lange tijd was ciclosporine-A (CsA) als enige van de orale immunosuppressiva geregistreerd in Europese landen voor de behandeling van ernstig CE. Ciclosporine-A is zeer effectief voor behandeling voor CE, maar bijna de helft van de patiënten stopt de behandeling vanwege bijwerkingen en/of ineffectiviteit. Een aantal andere breed werkende immunosuppressiva zoals methotrexaat (MTX), azathioprine (AZA) en mycofenolaatmofetil (MMF) worden off label gebruikt voor de behandeling van matig-ernstig CE. Ook bij deze off-label therapieën wordt in ongeveer 50% van de patiënten, behandeld in de dagelijkse praktijk, de behandeling gestaakt door bijwerkingen en/of ineffectiviteit.

Dupilumab kwam in 2018 in Europa op de markt voor de behandeling van matig-ernstig eczeem nadat de effectiviteit en veiligheid intensief was bestudeerd in een

uitgebreid programma van klinische trials. Ondanks het uitgebreide trial programma, werden er geen directe vergelijkende klinische trials verricht waarbij de effectiviteit en veiligheid van dupilumab werd onderzocht in vergelijking met de beschikbare behandelopties op dat moment.

In de afwezigheid van een directe, vergelijkende klinische trial tussen dupilumab en CsA, de enige geregistreerde systemische behandeloptie voor CE, hebben wij gezocht naar een alternatief studiedesign om de veiligheid en effectiviteit van deze behandelopties te kunnen vergelijken. De resultaten van deze indirecte vergelijkende studie tussen dupilumab en CsA worden beschreven in **hoofdstuk 3**. De relatieve effectiviteit van dupilumab ten opzichte van CsA werd onderzocht door het gebruik van dupilumab data uit de fase 3 klinische studie LIBERTY AD CHRONOS en CsA data uit de dagelijkse praktijk. De resultaten uit deze studie suggereren een hogere relatieve effectiviteit van de dupilumab ten opzichte van CsA gebaseerd op het aantal patiënten die een 50% (EASI-50) of 75% (EASI-75) verbetering behaalde in EASI score. Echter is de vergelijking van twee behandelingen die zijn gebruikt in een verschillende behandelsetting complex door verschillen in studiedesigns, patiëntkarakteristieken en voorschrijfgedrag. Het ontbreken van directe, vergelijkende studies tussen nieuwe doelgerichte therapieën met de beschikbare behandelopties benadrukt het belang van het genereren van gegevens uit de dagelijkse praktijk. In de dagelijkse praktijk bepaalt de balans tussen effectiviteit en bijwerkingen of de behandeling wordt voortgezet in een heterogene patiëntenpopulatie. Toekomstige prospectieve, dagelijkse praktijk registers kunnen voorzien in de behoefte aan vergelijkende studies tussen verschillende behandelingen in de afwezigheid van directe, vergelijkende klinische trials.

In **hoofdstuk 4**, beschrijven we de klinische effectiviteit en veiligheid, en impact op ziekte ernst-gerelateerde serum biomarkers van 16 weken dupilumab behandeling in een cohort van 138 patiënten met matig-ernstig CE behandeld in de dagelijkse praktijk. Behandeling met dupilumab resulteerde in een significante verbetering van tekenen en symptomen van CE en patiënt gerapporteerde uitkomstmaten zoals jeuk, angst, pijn en discomfort, depressie en kwaliteit van leven in een populatie van zeer ernstige CE patiënten die eerder zijn behandeld met meerdere orale immunosuppressiva. De resultaten van deze studie werden bevestigd in **hoofdstuk 5** waarin de lange termijn effectiviteit en veiligheid van dupilumab behandeling gedurende 52-weken werd bestudeerd in 210 matig-ernstige CE patiënten behandeld in dagelijkse praktijk. In deze lange termijn studie werd de effectiviteit

van dupilumab behandeling behouden of verbeterde verder gedurende de follow-up van 52 weken. In het uitgebreide klinische trial programma van dupilumab werden vaste klinische eindpunten gebruikt waaronder het percentage patiënten dat een EASI-50 en EASI-75 score behaalde, om het behandeleffect te bepalen. Deze vaste, klinische uitkomstmaten reflecteren niet het volledige behandeleffect van dupilumab en zijn daarom mogelijk niet geschikt voor het definiëren van behandelrespons in de dagelijkse praktijk. In **hoofdstuk 4** hebben we getracht te zoeken naar een combinatie van veel gebruikte klinische uitkomstmaten (EASI-75 of ≥4 punten verbetering in NRS jeuk of ≥4 punten verbetering in DLQI) om een klinisch relevante response te definiëren. De meerderheid van de patiënten (89%) behaalden een klinisch relevante verbetering in tenminste een van deze 3 domeinen na 16 weken behandeling met dupilumab. Met de introductie van meer kostbare, doelgerichte behandelopties voor CE, is er behoefte aan meer richtlijnen voor het definiëren van behandelrespons voor effectief gebruik van deze middelen. Toekomstige studies die een combinatie van klinische scores en patiënt-gerapporteerde uitkomstmaten gebruiken voor de definitie van behandelrespons zijn nodig om effectief gebruik van nieuwe behandelingen te bestuderen.

De economische impact na de introductie van dupilumab

In **hoofdstuk 2** demonstreerde we een hoge economische impact en kosten door productiviteitsverlies in patiënten met matig-ernstig CE met een indicatie voor systemische behandeling. Gezien de hogere prijs van dupilumab behandeling in vergelijking met de conventionele immunosuppressieve behandelingen, zullen de directe kosten aanzienlijk toenemen in patiënten die worden behandeld met dupilumab. Deze toename in directe kosten kan echter mogelijk gedeeltelijk gecompenseerd worden door besparingen in kosten als gevolg van het effect van dupilumab op de kwaliteit van leven en besparingen in kosten als gevolg van productiviteitsverlies. De impact van dupilumab behandeling gedurende 52 weken op verzuim, productiviteitsverlies en gerelateerde kosten in 210 volwassen patiënten met moeilijk behandelbaar CE wordt beschreven in **hoofdstuk 6.** Deze studie toonde een snelle en langdurige afname in werkverzuim en productiviteitsverlies en gerelateerde kosten gedurende 52-weken gemeten door de Work Productivity and Activity Impairment (WPAI) vragenlijst. De geschatte, geëxtrapoleerde mediane jaarlijkse kosten door productiviteitsverlies nam significant af van €19.751 op baseline naar €0.0 na 52 weken behandeling met dupilumab. De patiëntenpopulatie beschreven in **hoofdstuk 6** werd geïncludeerd kort na de goedkeuring van

dupilumab en werden intensief vervolgd door frequente follow-up consulten en laboratorium monitoring die volgens de voorschriften niet nodig zijn. De analyse van directe kosten in deze patiëntenpopulatie zou leiden tot een overschatting van de directe kosten van dupilumab behandeling en zijn voor deze reden niet meegenomen in deze studie. Er is behoefte aan meer studie naar het effect van dupilumab en andere nieuwe, doelgerichte, therapieën op zowel direct als indirecte kosten.

Drug survival van dupilumab vergeleken met conventionele immunosupressieve behandelingen

Na de goedkeuring van dupilumab voor de behandeling van volwassen patiënten met matig-ernstig eczeem, werden prospectieve dagelijkse praktijkgegevens verzameld in het BioDay register. Het genereren van een groot, dagelijkse praktijk cohort voorzag in de behoefte aan vergelijking van dupilumab-behandeling met conventionele systemische therapieën door middel van drug-survivalanalyse in de afwezigheid van directe vergelijkende klinische trials. Drug survival is de tijdsduur dat een patiënt een bepaald medicament gebruikt in de dagelijkse praktijk. Drug survivalanalyse is gebaseerd op de reden van stoppen en hierdoor een reflectie van de balans tussen effectiviteit en bijwerkingen en de beschikbaarheid van alternatieve behandelopties in de dagelijkse praktijk. In **hoofdstuk 7** wordt de twee-jaar drug survival van dupilumab behandeling en vergelijking van dupilumab drug survival met conventionele systemische behandelingen zoals CsA en MTX in 2 historische dagelijkse praktijk cohorten beschreven. De algehele drug survival van dupilumab was 91% en 88% na respectievelijk 1 en 2 jaar behandeling vergeleken met 27% en 20% in het CsA cohort en 41% en 33% in het MTX cohort. In tegenstelling tot het dupilumab cohort, staakten relatief meer patiënten in het CsA cohort de behandeling vanwege goed gecontroleerde ziekte. In **hoofdstuk 7** werd behandeling met dupilumab maar in een klein aantal patiënten gestaakt waardoor een predictieanalyse naar determinanten van drug survival niet mogelijk was. Drug survival wordt onder andere beïnvloed door de beschikbaarheid van alternatieve behandelopties. Gezien de huidige uitbreiding van het aantal beschikbare, doelgerichte behandelingen van CE, is het waarschijnlijk dat deze nieuwe behandelopties invloed zullen hebben op de toekomstige drug survival van dupilumab.

De veiligheid van dupilumab behandeling in de dagelijkse praktijk

Het gunstige veiligheidsprofiel van dupilumab behandeling werd aangetoond in klinische trials. Conjunctivitis was de meest frequent gerapporteerde bijwerking in de dupilumab klinische trials in CE patiënten (tot 28% in de CAFÉ fase 3 klinische trial). Het aantal CE patiënten die conjunctivitis ontwikkelden gedurende behandeling met dupilumab in de dagelijkse praktijk, beschreven in **hoofdstuk 4** en **hoofdstuk 5**, lag nog hoger (34-38%) dan in de laatste fase 3 klinische trials. De hogere indicatie van conjunctivitis in de dagelijkse praktijk kan mogelijk worden verklaard door een verhoogd conjunctivitis tijdens dupilumab behandeling bij dermatologen en patiënten. De eerste klinische oogheelkundige bevindingen van CE patiënten die conjunctivitis ontwikkelden tijdens dupilumab behandeling in klinische trials werden beschreven in **hoofdstuk 8**. Inflammatie en hyperemie van de limbus waren de meest voorkomende klinische kenmerken. Oedeem van de limbus werd vastgesteld in de meest ernstige patiënten. Gezien het risico op steroïd-geïndiceerd glaucoom of cataract bij lange termijn behandeling met oculaire corticosteroïden is er behoefte aan veilige, lange-termijn oculaire anti-inflammatoire behandelopties. In **hoofdstuk 8** adviseren wij om te starten met anti-inflammatoire behandeling doormiddel van tacrolimuszalf op de oogleden of ciclosporine oogdruppels.

Het onderliggende pathomechanisme van het ontstaan van conjunctivitis tijdens dupilumab behandeling in CE patiënten is nog niet volledig opgehelderd. Opvallend is dat conjunctivitis niet wordt gerapporteerd in klinische studies voor andere Th2 gerelateerde aandoeningen wat een ziekte specifieke interactie suggereert in een populatie met een hoge prevalentie van pre-existerende oculaire comorbiditeiten. In **hoofdstuk 9** vonden wij een opmerkelijk laag aantal slijm producerende cellen (goblet cellen) en de aanwezigheid van een ontstekingsinfiltraat voornamelijk bestaande uit T-cellen en eosinofielen in conjunctiva biopten van 6 CE patiënten die conjunctivitis ontwikkelden tijdens dupilumab behandeling. Het is bekend dat IL-13 normaal gesproken een stimulerend effect heeft op de proliferatie van goblet cellen en slijmproductie. In **hoofdstuk 9** stelden wij de hypothese dat remming van IL-4 en IL-13 door dupilumab in combinatie met hierdoor een lokaal verhoogde productie van Th1 cytokines kan leiden tot een afname van het aantal goblet cellen en hun belangrijke immuun modulerende functie in de conjunctiva. Deze combinatie kan leiden tot droge ogen, inflammatie en schade aan de conjunctiva. Toekomstige identificatie van patiënten die risico lopen op het ontwikkelen van conjunctivitis voor

de start van dupilumab is belangrijk omdat deze patiënten mogelijk profijt hebben van vroegtijdige of preventieve anti-inflammatoire oogheelkundige behandeling.

Toekomstperspectieven

Zoals in dit proefschrift beschreven is de generatie van data uit de dagelijkse praktijk belangrijk voor het evenwicht tussen effectiviteit en verdraagbaarheid van nieuwe therapieën in een heterogene CE populatie. Prospectieve registers zullen mogelijkheden bieden voor verder onderzoek naar de vergelijking tussen verschillende therapieën door middel van drug-survivalanalyses. Gezien de verwachte impact van nieuwe therapieën op het zorgbudget is er behoefte aan meer studies naar de impact van deze middelen op directe kosten en werkproductiviteit voor economische evaluaties. Daarnaast zullen dagelijkse praktijk studies bijdragen aan het effectief gebruik en mogelijkheden voor het individueel doseren van nieuwe therapieën om de verdraagbaarheid te verhogen en een excessieve impact op het zorgbudget te voorkomen.

Chapter 13

List of abbreviations

Contributing authors

Acknowledgements

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AD	Atopic dermatitis
AZA	Azathioprine
CI	Confidence interval
CsA	Cyclosporine-A
DLQI	Dermatology Life Quality Index
EASI	Eczema and Severity Index
EMA	European Medicines Agency
EQ-5D-5L	Generic five-dimension five-level EuroQoL scale
FDA	Food and Drug Administration
GCs	Gobletcells
HADS	Hospital Anxiety and Depression Scale
HOME	Harmonizing Outcome Measurements in Eczema
HPA	Hypothalamic-pituitary-adrenal
HrQoL	Health-related Quality of Life
IGA	Investigator's Global Assessment
IL	Iterleukin
IQR	Interquartile Range
JAK	Janus-kinase
LOCF	Last observation carried forward
MCID	Minimum clinically important difference
MMF	Mycophenolate mofetil
MTX	Methotrexate
NRS	Numerical Rating Scale

NVDV	Dutch Society of Dermatology and Venereology
PARC	Pulmonary and activation-regulated chemokine
POEM	Patient-Oriented Eczema Measure
PPY	Per Patient per Year
SD	Standard deviation
TARC	Thymus and activation-regulated chemokine
TCS	Topical corticosteroids
Th	T helper
TNF	Tumor Necrosis Factor
TSLP	Thymic stromal lymphopoietin
UMCU	University Medical Center Utrecht
US	United States
WPAI	Work Productivity and Activity Impairment questionnaire

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List of publications

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Ariëns LFM, van Nimwegen KJM, Shams M, de Bruin DT, van der Schaft J, van Os-Medendorp H, De Bruin-Weller M. Economic Burden of Adult Patients with Moderate to Severe Atopic Dermatitis Indicated for Systemic Treatment. Acta Derm Venereol. 2019 Jul 1;99(9):762-768.

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Curriculum vitae

Lieneke Ariëns werd geboren op 25 maart 1989 te Nieuwegein. In 2007 behaalde ze haar atheneumdiploma (profiel Cultuur en Maatschappij) aan College de Heemlanden in Houten. Aansluitend behaalde zij haar propedeuse voeding en diëtetiek aan de Hogeschool van Amsterdam. In 2008 behaalde zij de aanvullende vakken voor het atheneum profiel Natuur en Gezondheid en begon zij in 2009 aan haar studie geneeskunde aan de Universiteit Utrecht. Haar interesse voor de dermatologie ontwikkelde zij gedurende haar coschappen en resulteerde uiteindelijk in een dedicated schakeljaar bestaande uit een bijzondere semiarts stage dermatologie en een masteronderzoek naar constitutioneel eczeem onder begeleiding van dr. Jorien van der Schaft en prof. dr. Marjolein de Bruin-Weller op de afdeling Dermatologie en Allergologie. Na het behalen van haar artsenexamen in 2015 begon zij in 2016 als trial-arts op de afdeling Dermatologie en Allergologie van het Universitair Medisch Centrum (UMC) te Utrecht). Na een jaar startte zij met haar promotietraject op dezelfde afdeling onder begeleiding van prof. dr. De Bruin-Weller, en co-promotoren dr. Jorien van der Schaft en dr. Judith Thijs. De bevindingen van haar onderzoek hebben geleid tot dit proefschrift. In 2019 is zij begonnen met de opleiding tot dermatoloog in het UMC Utrecht onder leiding van Feiko Rijken. Lieneke woont samen met Paul Bart en hun 2 kinderen in Doorn.