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

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Summary

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

Objectives To evaluate dupilumab treatment in daily practice in patients with AD.

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

Results Ninety-five patients were included. Of these, 62 patients were using systemic immunosuppressants at baseline; the use of systemic immunosuppressants was continued during dupilumab treatment in 43 patients. From baseline to 16 weeks of treatment, the estimated mean Eczema Area and Severity Index score (0–72) decreased from 18·6 [95% confidence interval (CI) 16·0–21·4)] to 7·3 (95% CI 5·4–10·0), and the estimated mean PROMs showed a decrease of 41–66%. Investigator's Global Assessment 0 or 1 (clear/almost clear) was reached in 38% of the patients. Five patients discontinued dupilumab treatment due to side-effects or ineffectiveness. Eye symptoms and orofacial (nonocular) herpes simplex virus (HSV) reactivation were reported in 62% and 8% of the patients, respectively.

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

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Conflicts of interest
L.E.M. de W., A.L.B., N.S.E., L.M.H., L.A.A.G., A.C.M.K. and T.E.C.N. declare no conflicts of interest. M.A.M.-H. consults for Sanofi and Pfizer. P.I.S. has consulted on an unpaid basis in the past for Sanofi (11 October 2017) and AbbVie (4 December 2017) and, in the past > 5 years, has received contract support to perform clinical trials for many pharmaceutical companies that manufacture drugs used for the treatment of, for example, psoriasis and atopic dermatitis, with financial compensation paid to the department/hospital. D.J.H. is an investigator for LEO Pharma, MedImmune/AstraZeneca, Novartis and Sanofi/Regeneron and consults for Regeneron/Sanofi, LEO Pharma, MedImmune/AstraZeneca, Novartis, Incyte, Janssen and Pfizer.

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What's already known about this topic?

- Dupilumab has been shown to be an efficacious treatment for atopic dermatitis in several clinical trials.
- However, it is known that there may be considerable differences in patient characteristics and treatment responses between clinical trials and daily practice.

What does this study add?

- This study presents the first experience with dupilumab treatment in 95 patients with atopic dermatitis in daily practice in two Dutch university hospitals.

- Less stringent inclusion and exclusion criteria and follow-up schedules, in contrast to those used in clinical trials, might better represent daily practice.
- Dupilumab treatment shows a clinically relevant improvement of physician- and patient-reported outcome measures; besides patient-reported eye symptoms (in 59 of 95 patients; 62%) and an apparent increase in orofacial (nonocular) herpes simplex virus reactivation (eight of 95 patients; 8%), there were no other safety concerns during follow-up up to 16 weeks of dupilumab treatment.

Atopic dermatitis (AD) is a complex and heterogeneous chronic inflammatory skin disease. AD is characterized by severe itch and recurrent eczematous lesions. Up to 20% of the worldwide paediatric population and approximately 2–10% of all adults have AD.[1,2] AD can have a profound negative effect on quality of life as it is the skin disease with the highest non-fatal health burden.[1]

In addition to being advised to avoid triggers and use moisturizers, patients with AD are mostly treated with topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs). Around 15% of patients with AD are considered to have moderate-to-severe disease requiring phototherapy or systemic immunosuppressive therapy.[3,4] The use of systemic glucocorticosteroids, phototherapy and conventional systemic immunosuppressive agents, including ciclosporin A, azathioprine, mycophenolic acid, mycophenolate mofetil and methotrexate, can be effective and is well tolerated in many patients but may have limitations such as side-effects and an unfavourable risk–benefit ratio.[5–7] In addition, most of these treatments are used off-label and there are limited long-term treatment data available.[5,8–10]

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

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

Patients and methods

Study design and patients

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

All patients were aged ≥ 18 years and fulfilled the criteria for dupilumab treatment set forth by the Dutch Society of Dermatology and Venereology (Appendix S1; see Supporting Information).[15] Patients visited the outpatient clinic at baseline, week 4 and after either 12 (Amsterdam University Medical Center) or 16 (Erasmus University Medical Center) weeks of treatment. In one of the centres, data were collected according to the harmonized dataset of the TREAT Registry Taskforce.[16–18]

Treatment

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

Outcome measures

Patient characteristics and previous and current AD treatment were assessed at baseline. Clinical examinations were conducted by a maximum of seven trained and proficient raters at each visit. Physician-reported severity was reported using the Eczema Area and Severity Index (EASI; 0–72) and the

Investigator's Global Assessment for AD (IGA; 0–4).[20,21] In addition, patient-reported outcome measures (PROMs) were assessed at every visit; these included a numeric rating scale (NRS) to assess pruritus for the 7 days or 24 h prior to the visit (referred to hereafter as NRS peak pruritus past 7 days and NRS peak pruritus past 24 h, respectively; 0–10),[22] the Dermatology Life Quality Index (DLQI; 0–30) and the Patient-Oriented Eczema Measure (POEM; 0–28).[23,24] These outcome measures are in line with the core outcome set defined by the global Harmonising Outcome Measures for Eczema (HOME) initiative.[25,26] Furthermore, we calculated the number of days until the minimal clinically important difference (MCID) was reached, as well as the proportion of patients who reached the MCID at follow-up (12–16 weeks).[27,28] Patients with a baseline score lower than the MCID were excluded from this analysis. Collection of blood samples (liver, renal and haematological tests) and additional safety assessments (i.e. blood pressure measurement and urinalysis) in patients with concomitant use of systemic immunosuppressants were conducted to monitor safety. Furthermore, potential drug-related adverse events were recorded.

Evaluation of effectiveness

Treatment effect was evaluated using the estimated mean change in EASI scores over time in the first 16 weeks of dupilumab treatment, and IGA scores recorded at baseline and follow-up (12–16 weeks). Furthermore, the estimated mean changes in PROMs (NRS peak pruritus past 7 days/24 h, POEM and DLQI) over time in the first 16 weeks of treatment were analysed. These estimated mean scores were based on our linear mixed-effects (LME) model.

Data analysis

Studying data on patients treated in a real-world setting comes with several challenges, due to variation resulting from the use of inclusion and exclusion criteria and follow-up schedules that are less stringent than those used in clinical trials. To evaluate the effectiveness of dupilumab, we used LME models to describe and present changes in the repeatedly measured, continuous scores of interest in time (days since start of treatment). The use of these models allows for the analysis of unbalanced repeated measurements, that is, measurements that are not taken at exactly the same points in time for all patients. The use of this model is more efficient than cross-sectional analyses that only consider a subset of measurements taken at a particular point in time. The use of random effects makes it possible to take into account the fact that measurements originating from the same patients are not independent. We analysed measurements performed at visits from the start up to and including 17 weeks (16 weeks, visit window of +7 days) of treatment. The use of square-root transformations to normalize the residuals and improve the model fit was confirmed by evaluating histograms of the data and using the Akaike Information Criterion (Appendix S2; see Supporting Information).

Predicted values of the (continuous) score of interest, which are shown in the figures, are based on the LME models and transformed back to the original scale. Confidence intervals (CIs) for the predicted values were determined using the bootstrap method. We used natural cubic splines to model the nonlinear association between outcomes and follow-up time. This nonlinear association was confirmed and the appropriate number of degrees of freedom was chosen based on the Akaike Information Criterion.[29,30] Visual evaluation of the trajectories estimated by the spline showed that they could not be approximated by a piecewise linear fit, which would have the advantage of directly interpretable parameter estimates. Sex, age and concomitant immunosuppressive treatment were included as covariates in our model. We allowed the estimated trajectories over time to differ between treatment groups by including interaction terms. However, as the likelihood ratio test showed that there was no evidence for these interactions, we did not include them in the final model, in the interest of the interpretability of the parameter.

Analyses were performed using SPSS 24·0 (IBM, Armonk, NY, U.S.A.) and R version 3·4·1 (R Foundation for Statistical Computing, Vienna, Austria).

Ethical approval

Our study was exempted from evaluation by the local medical research ethics committees (MEC-2017-1123; W18_097#18·123). The study conduct was in accordance with the STROBE recommendations.[31]

Results

Population

Table 1 presents the baseline characteristics of the 95 patients (Erasmus University Medical Center: n = 60; Amsterdam University Medical Center: n = 35) included in our analyses. Sixty-two per cent (59 of 95) of the patients were male, with a median age of 42 years (interquartile range 27–52 years). Onset of AD was before the age of 2 years in 72% (68 of 95) of the patients. Asthma (65%), allergic contact dermatitis (45%), and allergic (rhino)conjunctivitis and/or atopic (kerato)conjunctivitis (72%) were reported. All of the patients had been treated with systemic immunosuppressants prior to the start of dupilumab treatment, and 72% had used at least two different conventional systemic immunosuppressants, mostly ciclosporin A (88%) and methotrexate (58%) (Table 1).

The median IGA score at baseline was 3·0 (interquartile range 2·0–3·0). Based on the LME model, at baseline, patients had an estimated mean EASI score of 18·6 (95% CI 16·0–21·4), an estimated mean POEM score of 21·4 (95% CI 19·7–23·3), an estimated mean score for NRS peak pruritus past 7 days of 7·4 (95% CI 6·1–8·6), an estimated mean score for NRS peak pruritus past 24 h of 7·5 (95% CI 6·1–8·9) and an estimated mean DLQI score of 12·5 (95% CI 10·4–14·6).

Table 1 Demographic and clinical characteristics of the patients at baseline (n = 95)[a]

Characteristic	
Age at the start of dupilumab treatment (years), median (IQR)	42 (27–52)
Male, n (%)	59 (62)
Race, n (%)	
White	73 (77)
Black	9 (9)
Asian	11 (12)
Other[b]	2 (2)
Age of onset, n (%)	
0 to < 2 years	68 (72)
2 to < 6 years	11 (12)
6 to < 18 years	8 (8)
≥ 18 years	7 (7)
Age of onset (years), median (IQR)	0 (0·0–2·0)[c]
Disease duration until start of dupilumab (years), mean ± SD	35·5 ± 16·5[c]
Previous use of conventional systemic immunosuppressants, n (%)[e,f]	
Ciclosporin A	84 (88)
Methotrexate	55 (58)
Azathioprine	29 (31)
Mycophenolic acid/mycophenolate mofetil	36 (38)
Number of previous used conventional systemic immunosuppressants, n (%)[e]	
1	27 (28)
2	36 (38)
3	23 (24)
4	9 (9)
Atopic/allergic conditions, n (%)[g]	
Asthma	62 (65)
Allergic (rhino)conjunctivitis/atopic (kerato)conjuncitvitis[h]	68 (72)
Allergic contact dermatitis[i]	43 (45)
Body mass index, median (IQR)	25·0 (22·3–28·3)[d]

IQR, interquartile range. [a]Diagnosis of atopic dermatitis based on the U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis: n = 35; [b]Chinese-Creole (n = 1), Dutch-Indonesian (n = 1); [c]missing data: n = 1 (1%); [d]missing data: n = 3 (3%); [e]previous use of systemic glucocorticoids is not reported because of anamnestic inconsistency in short- and long-term use; [f]besides conventional systemic immunosuppressants, the following systemic therapies were used: dupilumab, study (n = 2); apremilast (n = 2); ustekinumab (n = 1); omalizumab (n = 1); alitretinoin (n = 2); lebrikizumab, study (n = 2); fevipiprant, study (n = 1); and upadacitinib, study (n = 1); [g]patient reported (n = 60), physician diagnosed (n = 30); [h]merged as one category because of the differences in definition and registration in the two university hospitals; [i]positive patch tests in history; the other 55% is 'tested negative', 'never tested' or 'unknown'.

Effectiveness of dupilumab treatment

Figure 1 shows the changes in the outcome measures over time, up to 12 weeks (NRS peak pruritus past 24 h) and 16 weeks (EASI, POEM, NRS peak pruritus past 7 days) of treatment. The IGA scores, measured at baseline and follow-up, and the change in the estimated mean DLQI scores are shown in Figures S1 and S2 (see Supporting Information). The estimated mean EASI scores and PROMs at baseline and after 12 or 16 weeks of treatment, based on our LME model, are shown in Table 2. The percentage change from baseline to 16 weeks of treatment was −61% (95% CI −71%, −46%) for EASI, −53% (95% CI −63%, −44%) for POEM and −41% (95% CI −53%, −30%) for NRS peak pruritus past 7 days; the percentage change for NRS peak pruritus past 24 h from baseline to 12 weeks of treatment was −57% (95% CI −99%, −23%). IGA 0 or 1 (clear or almost clear) was reached in 38% of the patients. Table 3 shows that the MCID for all outcome measures is estimated to be reached within 5 weeks of treatment. At 12–16 weeks of follow-up, the MCIDs for EASI, POEM, DLQI, the NRS peak pruritus past 7 days and the NRS peak pruritus past 24 h were reached in 66%, 86%, 65%, 65% and 70% of the patients, respectively.[27,28]

In our cohort, 62 patients (65%) were using systemic immunosuppressants, including systemic glucocorticosteroids, at the start of dupilumab treatment. Systemic immunosuppressive treatment was continued during dupilumab treatment in 43 patients (43 of 95, 45%; Table 4). Table 4 shows that concomitant immunosuppressants were successfully tapered off and stopped in 34 patients (29 of 43, 67%) in the first 16 weeks of treatment. In five patients with flares or insufficient response to dupilumab treatment, systemic glucocorticosteroids were started for a period of 2–8 weeks. Three patients were treated with systemic antibiotics.

Side-effects

In our cohort, 59 patients (59 of 95, 62%) reported eye symptoms, including redness, itching, stinging, burning, tearing, scaling, crusting and foreign body sensation. Sixteen patients consulted an ophthalmologist; of these, 13 patients were diagnosed with (allergic) (kerato)conjunctivitis (n = 9), blepharitis (n = 2) or sicca (n = 2). Most patients were treated with artificial tears, antihistamine eyedrops, fluorometholone 0·1% eyedrops or tacrolimus 0·03% eye ointment. The prevalence of pre-existing ocular comorbidities in our cohort is unknown. In addition, 12 episodes of orofacial herpes simplex virus (HSV) reactivation were reported in eight patients (eight of 95, 8%), with recurrent infections during follow-up in three patients (Table S1; see Supporting Information). None of these patients had HSV infections around the eyes. In addition, none of these patients experienced eye pain, chemosis or blurred vision, which makes the possibility of their having HSV eye infections highly unlikely.[32] There were no clinically significant changes in laboratory parameters or additional safety assessments (i.e. blood pressure measurement and urinalysis) in those patients with concomitant use of systemic immunosuppressants.

Discontinuation of dupilumab treatment

Five patients discontinued dupilumab treatment. One of these discontinued dupilumab treatment because of a monoarthritis

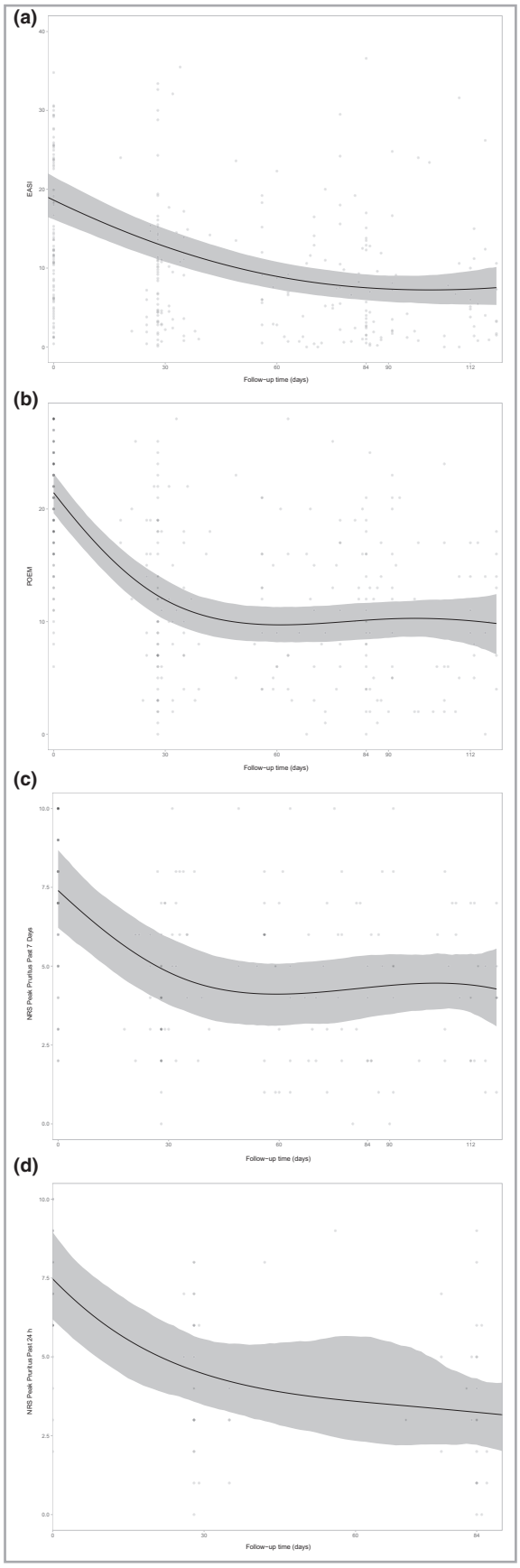

Fig 1. Estimated mean change in Eczema Area and Severity Index (EASI), Patient-Oriented Eczema Measure (POEM) and numeric rating scale (NRS) scores for peak pruritus for the past 7 days or 24 h (NRS peak pruritus past 7 days and NRS peak pruritus past 24 h, respectively) in patients with atopic dermatitis (n = 95). A linear mixed-effects model was used to model changes over time. Higher scores indicate a worsened state. The grey area represents the 95% confidence interval (CI). (a) The estimated mean EASI score (0–72) decreased from 18·6 (95% CI 16·0–21·4) at baseline to 7·3 (95% CI 5·4–10·0) at 16 weeks of dupilumab treatment. An outlier presenting with an EASI score of 72 at baseline is not shown in this figure but is included in the model. (b) The estimated mean POEM score (0–28) decreased from 21·4 (95% CI 19·7–23·3) at baseline to 10·1 (95% CI 7·9–12·2) at 16 weeks of dupilumab treatment. (c, d) Pruritus was evaluated differently in the two university hospitals: the Erasmus University Medical Center used the NRS peak pruritus score for the 7 days prior to the visit, while the Amsterdam University Medical Center used the NRS peak pruritus score for the 24 h prior to the visit. (c) The estimated mean NRS peak pruritus past 7 days score (0–10) decreased from 7·4 (95% CI 6·2–8·6) at baseline to 4·4 (95% CI 3·6–5·5) at 16 weeks of treatment; these data are derived from the observation of 60 patients during 16 weeks of follow-up. (d) The estimated mean NRS peak pruritus past 24 h score (0–10) decreased from 7·5 (95% CI 6·1–8·9) at baseline to 3·2 (95% CI 2·2–4·3) at 12 weeks of treatment; these data are derived from the observation of 35 patients during 12 weeks of follow-up.

in the right ankle, which started a few days after the first dupilumab administration. The other four patients discontinued because of a lack of clinical response after 9, 15, 17 and 18 weeks, respectively. No evident common phenotypical characteristics, laboratory markers or other predictors of failure could be detected in these patients.

Discussion

In this observational study, dupilumab treatment was evaluated in a daily practice cohort of 95 patients who had AD and whose eczema could not be adequately controlled with TCSs, TCIs or conventional systemic immunosuppressants. Dupilumab treatment resulted in a rapid decrease in EASI, IGA, POEM, DLQI and NRS peak pruritus past 7 days/24 h scores in the first 16 weeks of treatment (Fig. 1 and Table 2; see also Fig. S1, Fig. S2 and Table S2; see Supporting Information). Overall, dupilumab was well tolerated in most patients, although 62% of the patients reported eye symptoms (Table S1; see Supporting Information). In contrast to the case in previous clinical trials and the limited daily practice literature, in this study, dupilumab treatment was combined with concomitant systemic immunosuppressants in 45% (43 of 95) of the patients.[11,33] Continuation of conventional systemic immunosuppressants in the first weeks of dupilumab treatment seems to be an effective and safe way to transition to monotherapy with dupilumab but this needs to be studied in larger numbers of patients. This emphasizes the importance of the introduction of registries such as the national registries of the TREatment of ATopic eczema

Table 2 Effectiveness of dupilumab in daily practice

Outcome measure (range)	Estimated mean score at baseline (95% CI)	Estimated mean score at the end of follow-up (95% CI)	Change in score from baseline to the end of follow-up (%) (95% CI)
EASI (0–72)	18·6 (16·0–21·4)	7·3 (5·4–10·0)	−61 (−71, −46)
POEM (0–28)	21·4 (19·7–23·3)	10·1 (7·9–12·2)	−53 (−63, −44)
NRS peak pruritus past 7 days (0–10)[a]	7·4 (6·2–8·6)	4·4 (3·6–5·5)	−41 (−53, −30)
NRS peak pruritus past 24 h (0–10)[b]	7·5 (6·1–8·9)	3·2 (2·2–4·3)	−57 (−99, −23)
DLQI (0–30)	12·5 (10·5–14·5)	4·3 (2·8–5·9)	−66 (−75, −47)

EASI, Eczema Area and Severity Index; CI, confidence interval; POEM, Patient-Oriented Eczema Measure; NRS, numeric rating scale; DLQI, Dermatology Life Quality Index; the estimated mean scores in our cohort were derived via the use of a linear mixed-effects model; confidence intervals for the predicted values were determined using the bootstrap method; the percentage change in our cohort was based on the estimated mean baseline score and the estimated mean score at 16 weeks of treatment; [a]data derived from the observation of 60 patients during 16 weeks of follow-up; [b]data derived from the observation of 35 patients during 12 weeks of follow-up.

Table 3 Minimal clinically important differences (MCIDs)

	EASI	POEM	DLQI	NRS peak pruritus past 7 days[a]	NRS peak pruritus past 24 h[b]
MCID	6·6	3·4	4	2·7	2·7
Time until MCID is reached (days)[c]	29	9	11	29	21
Percentage of patients reaching MCID after 12–16 weeks of treatment (%)	66	86	65	65	70
Number of patients with a baseline score < MCID[d]	20	0	7	2	1

EASI, Eczema Area and Severity Index; POEM, Patient-Oriented Eczema Measure; DLQI, Dermatology Life Quality Index; NRS, numeric rating scale; [a]data derived from the observation of 60 patients during 16 weeks of follow-up; [b]data derived from the observation of 35 patients during 12 weeks of follow-up; [c]estimation derived using a linear mixed-effects model; [d]patients with a baseline score < MCID were excluded from the MCID analyses.

(TREAT) Registry Taskforce for monitoring systemic treatments in daily practice.[18]

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

Overall, patients in the current study had lower baseline EASI scores than patients in previous dupilumab studies and trials (Table S2; see Supporting Information).[11] In our study, patients were not asked to discontinue topical steroids or systemic immunosuppressants before the start of dupilumab treatment, resulting in lower baseline EASI scores than those from clinical trials that required a minimum washout period of 2 and 4 weeks, respectively. Currently available daily practice studies with relatively high EASI scores did not report the presence of systemic treatment at baseline.[34,35] From clinical experience, we know that discontinuation of systemic immunosuppressants in patients with AD often results in the exacerbation of their disease.[38] Therefore, the use of conventional systemic immunosuppressants during dupilumab treatment was continued initially in a subset of patients, in a tapering schedule guided by PROMs. Although it would be interesting to study whether using dupilumab together with one of the systemic immunosuppressants used in our patient population would be of particular benefit, we did not perform inter- and intragroup comparisons between patients on different concomitant systemic immunosuppressants because this would have led to nonrobust conclusions, due to the relatively small subsets of patients (Table 4).

Interestingly, baseline PROMs in daily practice, including NRS peak pruritus past 7 days/24 h, POEM and DLQI, were comparable with those from patients' clinical trials (Table S2; see Supporting Information).[11] Even though 65% (62 of 95) of patients in this study were still being treated with a systemic immunosuppressant at baseline, they had relatively poor PROMs at the start of dupilumab treatment. This might be the result of a long history of severe disease in most patients in our cohort, in contrast to the case with patients in previous clinical trials. Although Dutch regulations do not require patients to have a minimum severity score to warrant dupilumab treatment, they do require patients to have failed treatment with at least one systemic immunosuppressant in a sufficient dose for at least 4 months with intensive guidance and instructions (Appendix S1; see Supporting Information). The majority of patients in our study (72%), and a similar proportion of patients in the daily practice studies available, had been treated with at least two different conventional systemic

Table 4 Concomitant systemic immunosuppressive treatment in patients undergoing dupilumab treatment (total n = 95)

Category	Patients (%)
Discontinued systemic immunosuppressive treatment prior to or at the start of dupilumab treatment[a]	52 (55)
Discontinued systemic immunosuppressive treatment in the first 16 weeks of dupilumab treatment[b]	29 (31)
Discontinued CsA	8 (8)
Discontinued AZA	3 (3)
Discontinued MTX	1 (1)
Discontinued MPA/MMF	2 (2)
Discontinued prednisone	15 (16)
Underwent systemic immunosuppressive treatment for > 16 weeks of dupilumab treatment	9 (9)
Treated with CsA	3 (3)
Treated with AZA	0 (0)
Treated with MTX	1 (1)
Treated with MPA/MMF	2 (2)
Treated with prednisone	3 (3)
Treated with multiple systemic immunosuppressants[c]	5 (5)

CsA, ciclosporin A; AZA, azathioprine; MTX, methotrexate; MPA, mycophenolic acid; MMF, mycophenolate mofetil; [a]nineteen of the patients in this group (19 of 95; 20%) discontinued systemic immunosuppressive treatment at the start of or one day before starting dupilumab treatment; of these, four patients (four of 95; 4%) were being treated with CsA, three patients (three of 95; 3%) were being treated with AZA, 11 patients (11 of 95; 12%) were being treated with MTX, and one (one of 95; 1%) was being treated with prednisone; [b]median number of weeks systemic immunosuppressive treatments was continued: CsA, 6 weeks; AZA, 7 weeks; MTX, 4 weeks; MPA/MMF, 10 weeks; prednisone, 4 weeks; [c]in one patient, prednisone was continued for 4 weeks but MPA was discontinued at the start of dupilumab treatment; in one patient, AZA was continued for 4 weeks and prednisone was continued for 16 weeks; in one patient, prednisone was continued for 16 weeks but apremilast was discontinued at start of dupilumab treatment; in one patient, AZA was continued for 7 weeks but prednisone was discontinued at the start of dupilumab treatment; and, in one patient, MPA was continued for 16 weeks but CsA was discontinued at the start of dupilumab treatment.

immunosuppressants, in contrast to a minority (26–28%) who used at least one systemic immunosuppressant in the SOLO trials.[11,33–37] This suggests that patients in daily practice are at the end of the 'severity spectrum'. Because a long-term severity measure is not available, surrogate markers such as previous treatment with systemic immunosuppressants may be used.

Interestingly, a comparable relative reduction in both physician-reported severity and PROMs is achieved after at least 12 weeks of treatment (Figure 1 and Table 2; also see Figure S1 and Table S2; see Supporting Information), although direct comparison of these scores is complicated due to the different study designs used in this study, other daily practice studies and SOLO trials.[11,33–37] The percentage of patients reaching IGA 0/1 in our patient population (38%) is equal to the percentage of patients reaching the primary end point in the SOLO1/2 trials (38%; Fig. S2; see Supporting Information). However, in addition to IGA 0/1, an improvement of ≥ 2 on IGA was required in the SOLO trials.

We observed that the MCIDs for the PROMs (POEM, DLQI, NRS peak pruritus past 7 days/24 h) were reached prior to that for the physician-reported severity score (EASI), which suggests that patients' symptoms improve prior to clinical severity. This corresponds to our clinical observation that, in dupilumab-treated patients, the itch improves before the eczema disappears.

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

We found an incidence of 8% (eight of 95) of orofacial HSV reactivation in our cohort. The absence of typical HSV-infection-related eye complaints makes HSV eye involvement in these infections highly unlikely. A recent meta-analysis showed a slightly lower incidence of 6·1% reported in dupilumab clinical trials.[42] This incidence was not significantly different in patients in the placebo groups (5·2%). Possibly, concomitant systemic immunosuppressants, which were used in four of eight patients, may have contributed to the higher incidence found in our cohort. Moreover, in the previously mentioned clinical trials, it was found that there was a higher incidence of severe and clinically important herpes infections, including herpes zoster and eczema herpeticum, in the placebo groups.[43] In our cohort, there were no cases of severe, clinically important herpes infections.

Daily practice data were prospectively collected at two university medical hospitals in the Netherlands. Although the centres used slightly different follow-up schedules (12 weeks vs. 16 weeks), different outcome measures (NRS peak pruritus past 24 h vs. NRS peak pruritus past 7 days) and different assessments of baseline characteristics (allergic comorbidities vs. the U.K. Workings Party's Diagnostic Criteria for Atopic Dermatitis), we were able to analyse the data by using an LME model. However, as a result, we could not retrieve a standard deviation for the outcomes as advised by the reporting guidelines for clinical trials of the HOME initiative.[44]

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

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

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 Patient-reported side-effects.

Table S2 Baseline and follow-up scores in our daily practice cohort, limited daily practice literature and clinical trials (dupilumab every 2-week treatment).

Fig S1. Estimated mean change in Dermatology Life Quality Index scores in patients with atopic dermatitis, from the start of dupilumab treatment to 16 weeks of treatment (n = 95).

Fig S2. Investigator's Global Assessment scores at baseline and follow-up (between 12 and 16 weeks).

Appendix S1 Criteria for dupilumab treatment, set forth by the Dutch Society of Dermatology.

Appendix S2 Histograms, Akaike Information Criterion of original and square-root-transformed scale.