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# Long-term effectiveness and safety of treatment with dupilumab in patients with atopic dermatitis: results of the TREAT NL (TREatment of ATopic eczema, the Netherlands) registry

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**Capsule summary**

- There is a lack of evidence on dupilumab treatment for atopic dermatitis from observational studies, in particular on long-term treatment in daily practice.
- Dupilumab treatment of up to 84 weeks, in combination with topical treatment and initial concomitant systemic treatment, can be considered effective and is generally well-tolerated.

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Novartis, Incyte, Janssen, Pfizer; PS: consultancies in the past for Sanofi 111017 and AbbVie 041217 (unpaid), independent research grants in the past > 5 years ago, contract support: involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of e.g. psoriasis and atopic dermatitis for which we get financial compensation paid to the hospital.

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**Abstract**

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

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

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

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

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

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

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94 **Body of manuscript**

95 **Introduction**

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

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

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

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## Methods

*Study design and patient population*

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

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

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

*Study outcomes*

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

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

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

*Statistical analyses*

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

We analyzed a predefined population of all patients while receiving dupilumab injections every two weeks with a follow-up duration of up to 84 weeks. For each patient, multiple measurements of the outcomes were obtained during follow-up. To deal with the correlation between measurements from the same patient, mixed effect models were fitted. More specifically, we used linear mixed-effects

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models to analyze EASI, POEM, and DLQI and ordinal logistic mixed-effects models to analyze IGA and NRS pruritus. In all models, follow-up time, gender, age, body mass index (BMI), (Fitzpatrick) skin type and concomitant systemic therapy were added as additive fixed effects. The effect of follow-up time was described by a natural spline function to allow non-linear effects. The knots of the natural spline function were placed at the appropriate percentiles of the data. Optimal degrees of freedom for the natural spline function were chosen based on the Bayesian Information Criterion. All other variables were assumed to have a linear effect on the outcome. To capture correlation between measurements from the same patient, a random intercept was added to all models. All observations with missing values were excluded from the analyses.

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

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## Results

*Patient characteristics*

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

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

*Treatment effectiveness*

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

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

*Safety of treatment*

Seventy-nine severe AEs were registered in 69 patients (n=69/221, 31.2%) (table III). Sixty-one of these AEs were considered probably and possibly linked to dupilumab. Eye complaints were most frequently reported: 46 events in 46 patients (n=46/221, 20.8%). Forty-five were possibly or probably and 1 doubtfully linked to dupilumab. On average, the ocular severe AEs occurred after 36 days (range: 0-280 days). Of the patients experiencing ocular severe AEs 39 patients (n=39/46, 84.8%) had more than one allergic comorbidity. In addition, two-thirds of these patients had an IGA 3 or 4 at baseline (n=28/42, 66.7%) and the mean EASI was 14.6 (SD 10.5), which did not significantly differ from patients without

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ocular severe AEs (p=0.143 and p=0.853 respectively). Thirty-three patients had eye complaints not classified as severe. Other severe AEs, mainly considered not related or doubtfully related to dupilumab, are described in table III. The AEs described as peri-oral dermatitis, depressed mood, eczema exacerbation, arthritis, joint/muscle strain complaints, herpes zoster, herpes simplex, hair loss and paradoxical facial erythema were possibly or probably linked to dupilumab. Eleven severe AEs (n=11/79, 13.9%) were accounted as serious AEs. Four of these were considered not and 7 doubtfully related to dupilumab.

*Treatment schedule adjustments*

In 21 patients (n=21/221, 9.5%) the dupilumab dosing was adjusted, either by prolonging or shortening the injection interval. Nine patients (n=9/221, 4.1%) prolonged. Seven of these patients increased the injection interval to once every 3 weeks and 2 patients to once every 4 weeks. Eight out of these 9 patients prolonged due to severe adverse events: eye complaints in 6 patients and depressed mood in 2 patients. Both patients reporting depressed mood had prior history of these symptoms and reported improvement after prolonging. One patient prolonged due to achieving complete disease control. In 2 patients the interval was shortened secondarily (from 4 to 3 weeks after 168 days and from 3 to 2 weeks after 105 days of a prolonged interval, respectively) due to disease flares. In 12 patients (n=12/221, 5.4%) the interval was shortened due to ineffectiveness. Of these patients, 4 were shortened to a 10-day and 8 to a weekly interval. One of these patients eventually discontinued treatment due to persisting ineffectiveness. In 6 patients there was clinical improvement. One patient did not improve. Follow-up time was not sufficient for this assessment in the other patients.

*Treatment discontinuation*

Fourteen patients (n=14/221, 6.3%) discontinued dupilumab. In 7 patients treatment was discontinued due to ineffectiveness after 66, 111, 123, 126, 166, 204, 336 days. One patient switched to a weekly

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interval prior to discontinuation. One patient discontinued as a result of non-adherence and three patients due to severe AEs: mono-arthritis of the ankle days after the first dupilumab injection,[14] paradoxical facial erythema[15] and panniculitis. These complaints resolved after discontinuation. Three patients discontinued based on physician recommendation because of anticipated pregnancy.

**Discussion**

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

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

In the models of our effectiveness analyses we included patients only while receiving the on-label dose of 300mg dupilumab every 2 weeks without a minimum treatment duration. Patients that discontinued treatment or continued in an alternative dosing schedule due to ineffectiveness or substantial side-

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effects were not included thereafter. Gender, age, BMI, skin type and concomitant systemic therapy were added as additive fixed effects in our models and the same effect size over time during treatment was assumed for these variables. We found significantly lower scores of EASI and IGA for females and for concomitant immunomodulating therapy, whereas patients with skin type IV had significantly higher scores of EASI, DLQI and IGA. The effectiveness of dupilumab in different racial subgroups has been confirmed in a pooled analyses of three phase 3 trials, although the sample size of Black/African American patients was relatively small.[24]

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

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

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

*Conclusion*

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

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320 **Abbreviations and acronyms**

321 AD: atopic dermatitis; AE: adverse event; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and
322 Severity Index; IGA: Investigator Global Assessment; IQR: interquartile range; NRS: Numerical Rating
323 Scale; POEM: Patient-Oriented Eczema Measure; PROM: Patient Reported Outcome Measure; SD:
324 standard deviation; SE: standard error; TREAT NL: TREatment of ATopic eczema, the Netherlands.

325

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**Figure legends**

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

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

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

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

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456 **Tables**

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457 Table I. Patient characteristics at baseline

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| Patient characteristics | TREAT NL cohort (n=221)[a] |
|---|---|
| **Sex – no. (%)** | |
| Male | 127 (57.5) |
| Female | 94 (42.5) |
| **Age at start dupilumab, median (IQR) – years** | 41 (27-52) |
| **Age of onset AD – years** | |
| Median age (IQR) | 0 (0-4)[1] |
| <2 years – no. (%) | 153 (69.2) |
| ≥2-<6 years | 19 (8.6) |
| ≥6-<12 years | 11 (5.0) |
| ≥12-<18 years | 9 (4.1) |
| ≥18 years | 28 (12.7) |
| **Ethnicity – no. (%)** | |
| White | 178 (80.5) |
| Black | 19 (8.6) |
| Asian | 22 (10.0) |
| Other[b] | 2 (0.9) |
| **Fitzpatrick skin type – no. (%)** | |
| I | 9 (4.1) |
| II | 126 (57.0) |
| III | 41 (18.6) |
| IV | 19 (8.6) |
| V | 22 (10.0) |
| VI | 4 (1.8) |
| **BMI – median (IQR)** | 24.7 (22.1-27.5)[2] |
| **Atopic/allergic conditions (patient-reported/physician-diagnosed) – no. (%)** | |
| Asthma | 143 (64.7)[c] |
| Allergic (rhino)conjunctivitis and/or atopic (kerato)conjunctivitis | 179 (81.0)[c] |
| Eosinophilic esophagitis | 0 (0.0)[d,m] |
| Food allergies | 121 (54.8)[e,3]/30 (40.0)[d] |
| Allergic contact dermatitis | 113 (51.1)[f,4] |
| **Family history of atopic diseases[g] - no. (%)** | 160 (72.4)[5] |
| **Previous use of systemic therapies for AD – no. (%)** | |
| Ciclosporin | 197 (89.1) |
| Azathioprine | 46 (20.8) |
| Methotrexate | 103 (46.6) |
| Mycophenolic acid/mycophenolate mofetil | 75 (33.9) |
| Systemic corticosteroids[h] | 136 (61.5) |
| Other medication[i] | 24 (10.9) |
| Investigational medication[j] | 9 (4.1) |
| **Number of previous used systemic immunomodulating therapies[k] – no. (%)** | |
| 0 | 3 (1.4)[l] |
| 1 | 68 (30.8) |
| 2 | 90 (40.7) |
| 3 | 42 (19.0) |
| ≥ 4 | 18 (8.1) |
| **Previous use of phototherapy – no. (%)** | |
| Yes | 166 (75.1) |
| No | 33 (14.9) |
| Unknown | 22 (10.0) |
| **Type of previous used phototherapy[m] – no. (%)** | |
| NB-UVB[m] | 10 (13.3) |
| BB-UVB[m] | 2 (2.7) |
| UVB-unspecified[m] | 33 (44.0) |
| UVA[m] | 3 (4.0) |
| UVA1[m] | 2 (2.7) |
| UVAB[m] | 0 (0.0) |
| PUVA[m] | 11 (14.7) |

| | |
|---|---|
| Unknown[m] | 15 (20.0) |
| Other[m] | 1 (1.3) |
| **Number of previous used phototherapies[m] – no. (%)** | |
| 0 | 12 (16.0) |
| 1 | 52 (69.3) |
| 2 | 10 (13.3) |
| 3 | 1 (1.3) |
| **Immunomodulating therapy at start dupilumab – no. (%)** | |
| None | 118 (53.4) |
| Ciclosporin | 37 (16.7) |
| Azathioprine | 8 (3.6) |
| Methotrexate | 10 (4.5) |
| Mycophenolic acid/mycophenolate mofetil | 11 (5.0) |
| Systemic corticosteroids | 36 (16.3) |
| Omalizumab | 0 (0.0) |
| Other medication[n] | 1 (0.5) |
| Investigational medication | 0 (0.0) |
| **Treatment at outpatient daycare treatment unit in the past year[m] – no. (%)** | 13 (17.3) |
| **Hospitalization for AD in the past year[m] – no. (%)** | 7 (9.3) |

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

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

Table II. Effectiveness of dupilumab, estimated scores over time

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

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

| | |
|---|---|
| **Total number of severe adverse events – no.** | 79 |
| **Action on severe adverse event – no.** | |
| Treatment discontinuation | 3 |
| Adjustment of treatment schedule | 6 |
| None | 70 |
| **Course of severe adverse event – no.** | |
| Recovered/resolved | 10 |
| Recovered/resolved with sequelae | 1 |
| Recovering/resolving | 6 |
| Not recovered/resolved | 17 |
| Fatal | 0 |
| Unknown | 45 |
| **Relatedness to dupilumab treatment – no.** | |
| Not related | 6 |
| Doubtful | 12 |
| Possible | 19 |
| Probable | 42 |
| Very likely | 0 |
| Definite | 0 |
| **Type of severe adverse event[a] – no.** | |
| Eye disorders | |
| Eye complaints | 46 |
| - (Kerato)conjunctivitis | 24 |
| - Sicca complaints | 4 |
| - Blepharitis | 2 |
| - Epiphora | 1 |
| - Combined diagnoses[b] | 15 |
| Musculoskeletal and connective tissue disorders | |
| - Joint/muscle strain complaints | 6 |
| - Arthritis | 2 |
| Cardiac disorders | |
| - Angina pectoris | 3 |
| - Acute coronary syndrome | 1 |
| - Chest pain, unknown cause | 1 |
| Injury, poisoning and procedural complications | |
| - Bone fracture (not spontaneous) | 2 |
| Endocrine disorders | |
| - Adrenal insufficiency[c] | 2 |
| Skin and subcutaneous tissue disorders | |
| - Hair loss | 2 |
| - Perioral dermatitis | 1 |
| - Panniculitis, unknown cause | 1 |
| - Exacerbation of eczema | 1 |
| - (Paradoxical) facial erythema | 1 |
| Blood and lymphatic system disorders[d] | |
| - (Increase of) neutropenia | 1 |
| - Liver function abnormalities | 1 |
| Nervous system disorders | |
| - Bell's palsy | 1 |
| Psychiatric disorders | |
| - Depressed mood | 2 |
| Renal and urinary disorders | |
| - Pyelonephritis | 1 |
| Neoplasms benign, malignant and unspecified | |
| - Bladder carcinoma[e] | 1 |
| Infections and infestations | |

| | |
|---|---|
| - Herpes zoster | 1 |
| - Herpes simplex | 1 |
| Surgical and medical procedures | |
| - Allergenic desensitisation procedure | 1 |
| **Serious adverse events[f] – no.** | 11 |

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

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**Supplementary figures and tables**

Supplementary table I. Concomitant immunomodulating therapy

Mendeley link: https://data.mendeley.com/datasets/rs3t44yj4f/draft?a=04dbe36a-5452-4d87-947f-12f13900eda7

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

Mendeley link: https://data.mendeley.com/datasets/nmmz5rrmd9/draft?a=bff89a19-49cc-498f-ad90-6d3385256fa5

Supplementary table III. Effectiveness of dupilumab, regression coefficients

Mendeley link: https://data.mendeley.com/datasets/fzbswj43rg/draft?a=d2a5fbc4-8a4b-4c2b-971e-6cdafa75353d

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**Supplementary figure legend**

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

The follow-up duration of the participants ranged from 0 to 85.6 weeks. The daily practice setting resulted in different follow-up durations for each outcome measure due to the fact that not all outcomes were collected on the same day.

Mendeley link: https://data.mendeley.com/datasets/sdvwjpydnm/draft?a=23fefc19-ca16-4183-8853-4abd00f1fd3d

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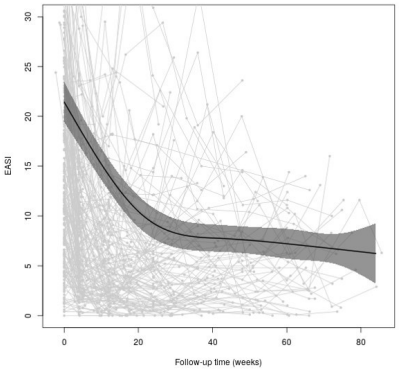
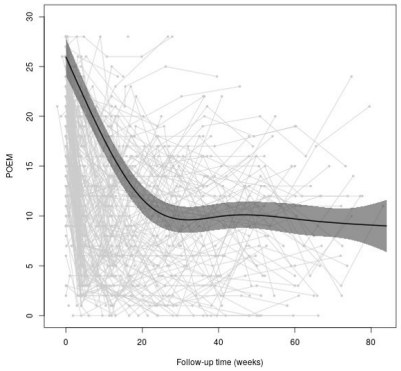
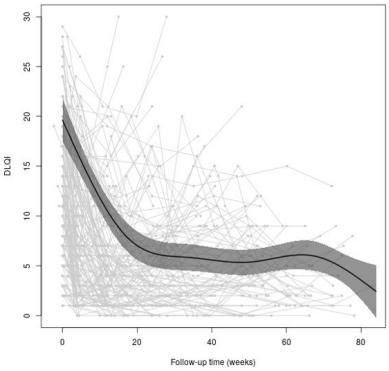



EASI




POEM




DLQI

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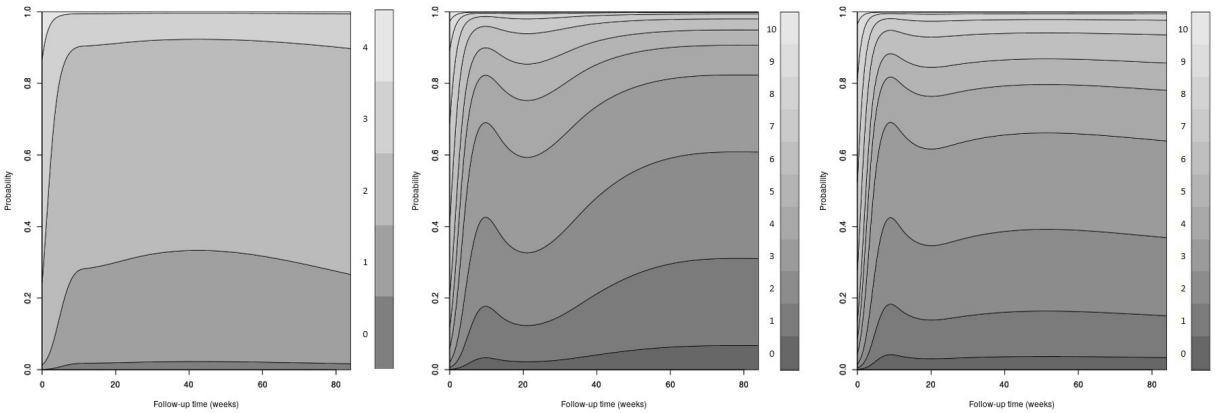


IGA NRS mean pruritus 7d NRS peak pruritus 24h

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