ORIGINAL ARTICLE

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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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 of patients with atopic dermatitis 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 the Eczema Area and Severity Index, −16.9 (SE, 1.4) for the Patient-Oriented Eczema Measure, and −17.2 (SE, 1.6) for the Dermatology Life Quality Index. We found a trend for improvement over time for the Investigator Global Assessment and Numerical Rating Scale for pruritus. 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, and 14 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 of 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. (J Am Acad Dermatol https://doi.org/10.1016/j.jaad.2020.05.128.)

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Conflicts of interest: Dr Middelkamp-Hup is a consultant for Sanofi and Pfizer. Dr Hijnen is an investigator for LEO Pharma, MedImmune/AstraZeneca, Novartis, and Sanofi/Regeneron and is a consultant for Regeneron/Sanofi, LEO Pharma, MedImmune/AstraZeneca, Novartis, Incyte, Janssen, and Pfizer. Dr Spuls has been a consultant in the past for Sanofi 111017 and AbbVie 041217 (unpaid), received independent research grants >5 years ago, and is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic dermatitis for which financial compensation is paid to the hospital. Drs Bosma, de Wijs, van Nieuwenhuizen, and Gerbens have no conflicts of interest to declare.

IRB approval status: Our study was exempted from evaluation by the local Medical Research Ethics Committees (MEC-2017-1123; W18_097#18.123).

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

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

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

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.

METHODS

Study design and patient population

We conducted a registry-embedded observational prospective cohort study. Patients with physician-diagnosed AD who started treatment with dupilumab in the 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 health care professionals and aspired to be scheduled at baseline, at 4 weeks and 12 to 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 were 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] Dupilumab was prescribed off-label in 2 patients because they were 17 years old at the time. All patients started treatment with 300-mg dupilumab injections every 2 weeks after an initial loading dose of 600 mg. Patients were allowed to concomitantly continue using conventional systemic immunomodulating treatment in a tapering schedule and were allowed to use topical treatments (eg, 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.

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

Effectiveness was analyzed by using investigator-reported and patient-reported outcome measures. Investigator-reported outcome measurements consisted of the Eczema Area and Severity Index (EASI, 0-72)[8] and the Validated Investigator Global Assessment scale for Atopic Dermatitis (IGA, 0-4).[9] Patients completed the following patient-reported outcome measures: 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 the 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. Serious AEs were those that resulted in death, were life-threatening, required (prolonging of) hospitalization, or resulted in persistent or significant disability or in congenital anomaly or birth defect.[13]

Abbreviations used:

AD:	atopic dermatitis
AE:	adverse event
DLQI:	Dermatology Life Quality Index
EASI:	Eczema Area and Severity Index
EMC:	Erasmus MC University Medical Center
IGA:	Investigator Global Assessment
NRS:	Numerical Rating Scale
POEM:	Patient-Oriented Eczema Measure
TREAT NL:	TREatment of ATopic eczema, the Netherlands
UMC:	University Medical Centers

Statistical analyses

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

We analyzed a predefined population of all patients while receiving dupilumab injections every 2 weeks with a follow-up duration of up to 84 weeks. For each patient, multiple measurements of the outcomes were obtained during follow-up. To deal with the correlation between measurements from the same patient, mixed-effect models were fitted. More specifically, we used linear mixed-effects models to analyze EASI, POEM, and DLQI and used ordinal logistic mixed-effects models to analyze IGA and NRS pruritus. In all models, follow-up time, sex, age, body mass index, 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 nonlinear 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) and R 3.4.1 (Foundation for Statistical Computing, Vienna, Austria) software. In all analyses, effects were considered statistically significant if $P < .05$.

RESULTS

Patient characteristics

The study included 221 patients (Amsterdam UMC, n = 75; EMC, n = 146), and their baseline characteristics are summarized in Table I. Of the 221 patients included, most were men (127 [57.5%]), white (178 [80.5%]), and had skin type II (126 [57.0%]). AD occurred before the age of 2 in 153 patients (69.2%), and the median age at start of dupilumab was 41 years (interquartile range, 27-52 years).

Unless contraindicated, all patients were previously treated with other systemic immunomodulating therapies. After starting dupilumab, 103 of the 221 patients (46.6%) continued their conventional systemic therapy because it was deemed undesirable to discontinue. Most of these patients used cyclosporin (37 [16.7%]) or systemic corticosteroids (36 [16.3%]). Eighty-three patients discontinued this concomitant therapy after a median of 50 days (Supplemental Table I, available via Mendeley at https://doi.org/10.17632/rs3t44yj4f.1). One patient had a pre-existent type 4 allergy for polysorbate 80 (ie, 1 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.

According to our model, a "median" patient, being a 41-year-old man with a body mass index of 25 kg/m^2 and skin type II without use of concomitant systemic immunomodulating therapy, had an estimated EASI of 21.4 (SE, 1.0), POEM of 25.9 (SE, 1.0), and DLQI of 19.6 (SE, 1.1) at baseline (Table II).

Treatment effectiveness

The course until 84 weeks of treatment for the 6 outcome measurements is shown in Figs 1 and 2. An improvement of all outcome measurements was observed, in particular in the first 12 weeks of treatment. The estimated change in score from baseline until 84 weeks was −15.2 (SE, 1.7) for EASI, −16.9 (SE, 1.4) for POEM, and −17.2 (SE, 1.6) for DLQI (Table II). We found a trend for improvement of the scores for IGA and NRS pruritus (Supplemental Table II, available via Mendeley at https://doi.org/10.17632/nmmz5rrmd9.1). The daily practice setting resulted in different follow-up durations for each outcome measure (Supplemental Fig 1, available via Mendeley at https://doi.org/10.17632/sdvwjpydnm.1). The mean follow-up duration for the outcome measurements varied from 28.9 to 31.4 weeks (SD, 22.8-23.9 weeks; range, 0-85.6 weeks).

In our model we found that women had significantly lower scores of EASI (−3.04 [SE, 0.75], P = 9.24E-13) and IGA (−1.20 [SE, 0.32], P = .0002) compared with men as a fixed effect over time during treatment, whereas the patients with skin type IV (n = 19) had higher scores for EASI (+2.90 [SE, 1.27], P = .0241), DLQI (+2.56 [SE. 1.26], P = .0439), and

Table I. Patient characteristics at baseline

Patient characteristics	TREAT NL cohort (N = 221)* No. (%) or median (IQR)
Sex	
Male	127 (57.5)
Female	94 (42.5)
Age at start of dupilumab, y	41 (27-52)
Age of onset AD, y	
Age, y	0 (0-4)†
<2 y	153 (69.2)
≥2 to <6 y	19 (8.6)
≥6 to <12 y	11 (5.0)
≥12 to <18 y	9 (4.1)
≥18 y	28 (12.7)
Race/ethnicity	
White	178 (80.5)
Black	19 (8.6)
Asian	22 (10.0)
Other‡	2 (0.9)
Fitzpatrick skin type	
I	9 (4.1)
II	126 (57.0)
III	41 (18.6)
IV	19 (8.6)
V	22 (10.0)
VI	4 (1.8)
Body mass index, kg/m^2	24.7 (22.1-27.5)§
Atopic/allergic conditions (patient reported/physician diagnosed)	
Asthma	143 (64.7)‖
Allergic (rhino)conjunctivitis and/or atopic (kerato)conjunctivitis	179 (81.0)‖
Eosinophilic esophagitis	0 (0.0)¶,#
Food allergies	121 (54.8)**,†† /30 (40.0)¶
Allergic contact dermatitis	113 (51.1)‡‡,§§
Family history of atopic diseases‖‖	160 (72.4)¶¶
Previous use of systemic therapies for AD	
Cyclosporin	197 (89.1)
Azathioprine	46 (20.8)
Methotrexate	103 (46.6)
Mycophenolic acid/mycophenolate mofetil	75 (33.9)
Systemic corticosteroids##	136 (61.5)
Other medication***	24 (10.9)
Investigational medication†††	9 (4.1)
No. of previous used systemic immunomodulating therapies‡‡‡	
0	3 (1.4)§§§
1	68 (30.8)
2	90 (40.7)
3	42 (19.0)
≥4	18 (8.1)
Previous use of phototherapy	
Yes	166 (75.1)
No	33 (14.9)
Unknown	22 (10.0)
Type of previously used phototherapy#	
Narrowband ultraviolet B	10 (13.3)
Broadband ultraviolet B	2 (2.7)
Ultraviolet B-unspecified	33 (44.0)
Ultraviolet A	3 (4.0)

Continued

Table I. Cont'd

Patient characteristics	TREAT NL cohort (N = 221)* No. (%) or median (IQR)
Ultraviolet A1	2 (2.7)
Ultraviolet AB	0 (0.0)
Psoralen plus ultraviolet A	11 (14.7)
Unknown	15 (20.0)
Other	1 (1.3)
No. of previously used phototherapies[#]	
0	12 (16.0)
1	52 (69.3)
2	10 (13.3)
3	1 (1.3)
Immunomodulating therapy at the start of dupilumab	
None	118 (53.4)
Cyclosporin	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)
Alitretinoin	1 (0.5)
Investigational medication	0 (0.0)
Treatment at outpatient daycare treatment unit in the past year[#]	13 (17.3)
Hospitalization for AD in the past year[#]	7 (9.3)

AD, Atopic dermatitis; *EMC*, Erasmus University Medical Center; *IQR*, interquartile range; *TREAT NL*, TREatment of ATopic eczema, the Netherlands; *UMC*, University Medical Centers.
*Diagnosis of AD based on U.K. Working Party's Diagnostic Criteria for Atopic Eczema: n = 75 (Amsterdam UMC patients).
†Missing data: n = 1 (0.5%).
‡Mixed (n = 2).
§Missing data: n = 13 (5.9%).
‖Patient-reported at EMC and physician-diagnosed in Amsterdam UMC.
¶Physician-diagnosed in n = 75 Amsterdam UMC patients.
#Data for only available for n = 75 Amsterdam UMC patients.
**Patient-reported: n = 79 at EMC and n = 42 at Amsterdam UMC.
††Missing data: n = 14 (9.6%).
‡‡Positive patch test: remaining 48.4% were never tested, unknown, or tested negative
§§Missing data: n = 1 (0.5%)
‖‖First-degree family member with at least 1 of the following atopic diseases: AD, asthma, or allergic (rhino)conjunctivitis.
¶¶Missing data: n = 16 (7.2%).
##Systemic corticosteroids: use unknown, 49 (22.2%); no use, 36 (16.3%).
***Other medication: apremilast (n = 2), dupilumab (n = 1), omalizumab (n = 1), ustekinumab (n = 1), dapsone (n = 1), alitretinoin (n = 7), acitretin (n = 5), fumaric acid (n = 5), dimethyl fumarate (n = 1).
†††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).
‡‡‡Not including the use of systemic corticosteroids because of anamnestic inconsistency.
§§§Three patients did not receive any past systemic therapies because of contraindications: 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).

IGA (+1.57 [SE, 0.55], P = .0042) compared with 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 = .0001), IGA (−0.73 [SE, 0.26], P = .0046), and NRS mean pruritus past 7 days (−0.77 [SE, 0.34], P = .0231) compared with absence of concomitant therapy (Supplemental Table III, available via Mendeley at https://doi.org/10.17632/fzbswj43rg.1).

Safety of treatment

There were 79 severe AEs registered in 69 of the 221 patients (31.2%) (Table III), and 61 of these AEs were considered probably and possibly linked to dupilumab. Eye complaints were most frequently reported: 46 events in 46 patients (20.8%), and 45 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 46 patients experiencing ocular severe AEs, 39

Table II. Effectiveness of dupilumab, estimated scores over time*

	Outcomes											
	EASI (0-72)				POEM (0-28)				DLQI (0-30)			
Time	Est score	SE†	Est change in score from baseline, (%)	SE‡	Est score	SE†	Est change in score from baseline, (%)	SE‡	Est score	SE†	Est change in score from baseline, (%)	SE‡
Baseline	21.4	1.0			25.9	1.0			19.6	1.1		
4 wk	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 wk	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 wk	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 wk	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 wk	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 wk	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 wk	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 wk	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

DLQI, Dermatology Life Quality Index; *EASI*, Eczema Area and Severity Index; *Est*, estimated; *POEM*, Patient-Oriented Eczema Measure.
*Scores are displayed for the "median" patient: male, 41 years old, body mass index of 25 kg/m^2, Fitzpatrick skin type II, no use of concomitant medication. The estimated scores and changes in score are based on our linear mixed-effects models.
†SE for estimated score.
‡SE for estimated change in score.

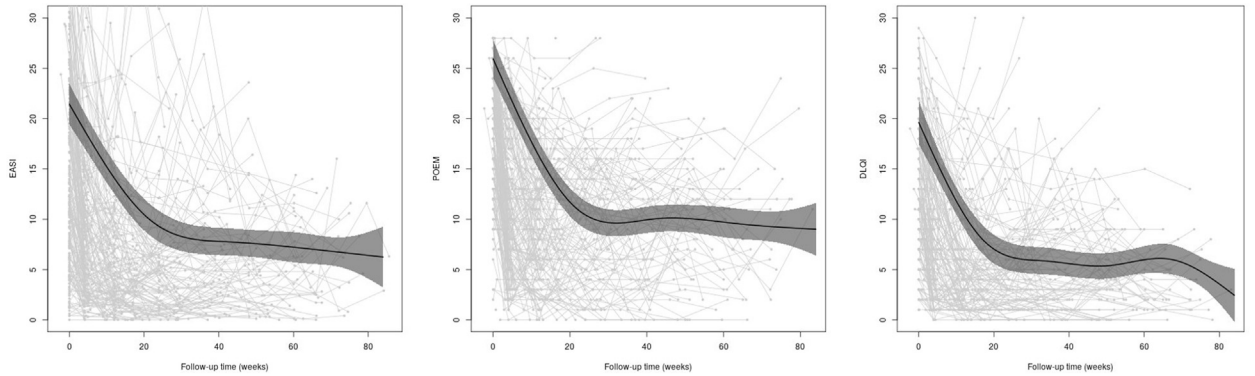

Fig 1. Outcome measures assessed over time until 84 weeks of treatment by the Eczema Area and Severity Index (*EASI*), the Patient-Oriented Eczema Measure (*POEM*), and the Dermatology Life Quality Index (*DLQI*). Results are based on our linear mixed-effects models. Higher scores indicate higher disease activity or burden. The *dark grey area* surrounding the black line represents the SE. Estimated scores are based on our "median" patient, a 41-year-old man with a body mass index of 25 kg/m^2 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.

patients (84.8%) had more than 1 allergic comorbidity. In addition, 28 of 42 of these patients (66.7%) had an IGA of 3 or 4 at baseline (IGA missing: n = 4), and the mean EASI was 14.6 (SD, 10.5), which did not significantly differ from patients without ocular severe AEs (P = .143 and P = .853, respectively). Eye complaints in 33 patients were 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 perioral 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. Of 79 severe AEs, 11 (13.9%) accounted as serious AEs, with 4 considered not related and 7 doubtfully related to dupilumab.

Treatment schedule adjustments

The dupilumab dosing in 21 of 221 patients (9.5%) was adjusted by prolonging or shortening the injection interval. Nine patients (4.1%) prolonged: 7

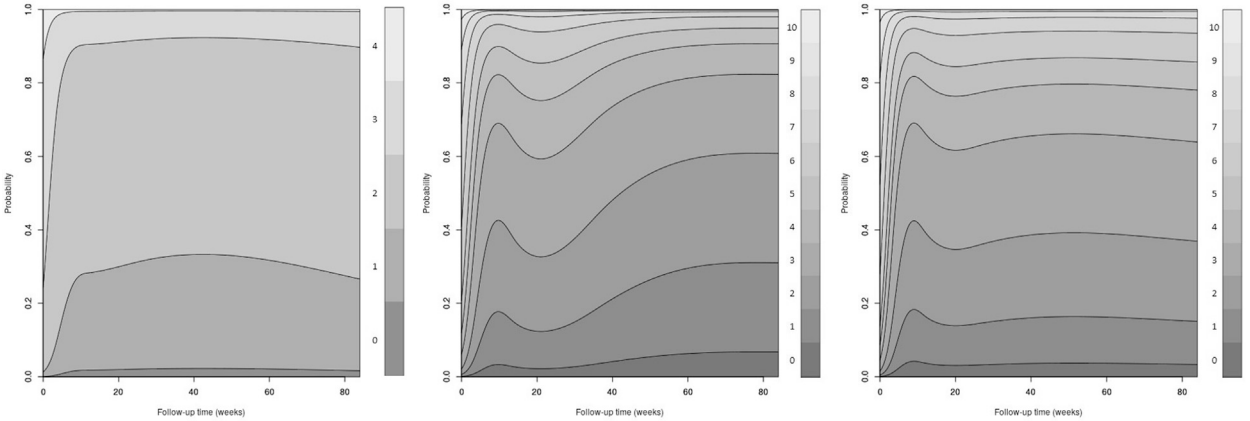

Fig 2. Outcome measures over time until 84 weeks of treatment by the Investigator Global Assessment (*IGA*) for atopic eczema and the Numerical Rating Scale (*NRS*) mean pruritus past 7 days and NRS peak pruritus past 24 hours. Estimated probability in a range from 0 to 1 for the answer categories based 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 or burden. Estimated scores are based on our "median" patient, a 41-year-old man with a body mass index of 25 kg/m^2 and Fitzpatrick skin type II who does not use concomitant systemic therapy. Over time there was an increase in probability for IGA 1 and IGA 2 and a decrease for IGA 3 and IGA 4. For the NRS measures, there was an increase in lower scores over time at the expense of higher scores. NRS peak pruritus past 24 hours was registered in the Amsterdam University Medical Centers only.

patients increased the injection interval to once every 3 weeks and 2 patients to once every 4 weeks. Eight of these 9 patients prolonged due to severe AE: eye complaints in 6 patients and depressed mood in 2. 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. The interval in 2 patients 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 of 221 patients (5.4%) the interval was shortened due to ineffectiveness: 4 were shortened to a 10-day interval 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

Of the 221 patients, 14 (6.3%) discontinued dupilumab. Treatment in 7 patients was discontinued due to ineffectiveness after 66, 111, 123, 126, 166, 204, and 336 days. One patient switched to a weekly interval before discontinuation. One patient discontinued as a result of nonadherence, and 3 patients discontinued due to severe AEs: monoarthritis 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, and 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 (Figs 1 and 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 300 mg/wk was used, instead of every 2 weeks according to the label. Moreover, there are differences between clinical trials and daily practice. The psoriasis literature has shown that approximately 30% of patients who are included into registries

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

Variable	No.
Total number of severe adverse events	79
Action on severe adverse event	
Treatment discontinuation	3
Adjustment of treatment schedule	6
None	70
Course of severe adverse event	
Recovered/resolved	10
Recovered/resolved with sequelae	1
Recovering/resolving	6
Not recovered/resolved	17
Fatal	0
Unknown	45
Relatedness to dupilumab treatment	
Not related	6
Doubtful	12
Possible	19
Probable	42
Very likely	0
Definite	0
Type of severe adverse event*	
Eye disorders/complaints	46
(Kerato)conjunctivitis	24
Sicca complaints	4
Blepharitis	2
Epiphora	1
Combined diagnoses†	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‡	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§	
(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‖	1
Infections and infestations	
Herpes zoster	1
Herpes simplex	1
Surgical and medical procedures	
Allergenic desensitization procedure	1
Serious adverse events¶	11

*Subdivided into Medical Dictionary for Regulatory Activities terminology categories.
†Combined diagnoses: (kerato)conjunctivitis and blepharitis (n = 5), (kerato)conjunctivitis and sicca complaints (n = 3), (kerato)conjunctivitis, sicca complaints, and blepharitis (n = 2), sicca complaints and blepharitis (n = 2), conjunctivitis and (increase of) ectropion (n = 2), and epiphora and ectropion (n = 1).
‡Adrenal insufficiency occurred in 2 patients, due to discontinuation of long-term treatment with systemic corticosteroids.
§No significant laboratory abnormalities were found aside from worsening of a pre-existing neutropenia in 1 patient and liver function abnormalities due to alcohol abuse in 1 patient.
‖The bladder carcinoma occurred after treatment discontinuation.
¶Four serious adverse events were considered not related to the dupilumab treatment, and the relatedness to dupilumab of the other 7 events was considered doubtful.

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 or concomitant therapy was not allowed, or both. Interestingly, our baseline scores for POEM and DLQI were comparable or higher. After 12 to 24 weeks of treatment, we found similar scores of both investigator-reported as well as patient-reported outcomes.

In the models of our effectiveness analyses, we included patients only while receiving the on-label dose of 300 mg of dupilumab every 2 weeks, without a minimum treatment duration. Patients who discontinued treatment or continued in an alternative dosing schedule due to ineffectiveness or substantial side effects were not included thereafter. Sex, age, body mass index, 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 women 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 was confirmed in a pooled analysis of 3 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 the 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 most of the patients with eye complaints had allergic comorbidities (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 due to a 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, because most patients received treatment at home. Also, bias may have been induced by the nonblinded observational nature of the study. Further, for feasibility reasons, only severe AEs are registered as part of the TREAT core dataset.[7] In the EMC, AEs were registered by inquiring about side effects. This insinuates a level of relatedness and may have led to unrelated AEs not being registered.

Further investigation of the safety of dupilumab treatment, 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 or side effects, or both.

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-reported 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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