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ORIGINAL ARTICLE

Atopic Dermatitis, Urticaria and Skin Disease

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

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Abstract

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

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

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

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

Abbreviations: AD, atopic dermatitis; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; Generic five-dimension five-level EQ-5D-5L, EuroQoL scale; HrQoL, health-related quality of life; IL, interleukin; IQR, interquartile range; MCID, minimal clinically important difference; METC, Medical Research Ethics Committee; NRS, Numeric Rating Scale; PARC, pulmonary and activation-regulated chemokine; PMD, pellucid marginal degeneration; POEM, Patient-Oriented Eczema Measure; TARC, thymus- and activation-regulated chemokine; TCS, topical corticosteroids; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

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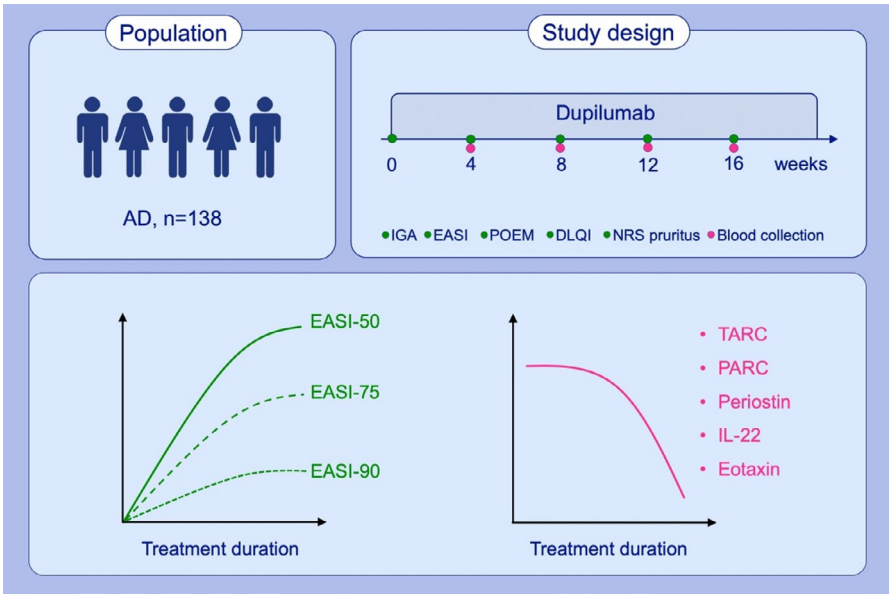
treatment, disease severity-related serum biomarkers (TARC, PARC, periostin, and IL-22), eotaxin-1, and eotaxin-3 significantly decreased.

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

KEYWORDS

atopic dermatitis, biomarkers, daily practice, disease severity, dupilumab



GRAPHICAL ABSTRACT

This study evaluated the clinical effectiveness and safety of 16-weeks of dupilumab treatment in adults with AD. Dupilumab treatment significantly suppressed disease severity-related serum biomarkers and eosinophil chemokines. By the end of the treatment, the EASI-50 and EASI-75 was achieved by 86% and 62% of patients, respectively.

Abbreviations: AD, Atopic dermatitis; DLQI, Dermatology life quality index; EASI, Eczema area and severity index; IGA, Investigators global assessment; NRS, Numeric rating scale; PARC, Pulmonary and activation-regulated chemokine; POEM, Patient-oriented eczema measure; TARC, Thymus- and activation-regulated chemokine

1 | INTRODUCTION

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

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

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

2 | METHODS

2.1 | Study design

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

2.2 | Patients and outcome measures

All 138 patients were assed prior to initiation and for 16 weeks during dupilumab treatment. At baseline, all patients received a loading dose of dupilumab 600 mg subcutaneously administered by a clinician, followed by subcutaneous dupilumab 300 mg every other week (mostly self-administered). Systemic immunosuppressive treatment was discontinued before starting dupilumab treatment in most patients, or a shared decision on continuation of systemic immunosuppressive treatment during dupilumab treatment was made. Concomitant treatment with TCS was allowed. At baseline, and after 4, 8, 12, and 16 weeks of treatment, disease severity was assessed by the Eczema Area and Severity Index (EASI). Additionally, patient-reported outcomes including the Patient-Oriented Eczema Measure (POEM), weekly average Numeric Rating Scale (NRS) pruritus, Dermatology Life Quality Index (DLQI), and generic five-dimension five-level EuroQoL scale (EQ-5D-5L) were collected. Clinical endpoints (all at weeks 4, 8, 12, and 16, unless otherwise indicated) included the mean percent change from baseline in EASI, NRS pruritus, DLQI (at week 16), and POEM, proportions of patients with ≥50%, ≥75%, or ≥90% improvement from baseline in EASI score (EASI-50, EASI-75 or EASI-90), achieving ≥4-point reduction in weekly average NRS pruritus, reporting "no problem" on the EQ-5D-5L pain/discomfort and anxiety/depression subscales (week 16), achieving ≥4-point improvement in DLQI score (minimal clinically important difference (MCID) at week 16), and achieving ≥4-point improvement in POEM score (MCID) and change over time for number of days with itch because of eczema (POEM item 1) and number of nights that sleep was disturbed in the past week (POEM item 2). In addition, the proportion of patients using systemic immunosuppressive drugs during dupilumab treatment was monitored.

2.3 | Clinically relevant response

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

2.4 | Safety

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

2.5 | Serum biomarkers

Patients using oral immunosuppressive drugs at one of the five time points and patients using oral immunosuppressive drugs within 2 (fast-acting drugs) or 4 (slow-acting drugs) weeks before screening were excluded. Twenty-one biomarkers associated with different disease pathways were measured: severity-associated markers (IL-22, thymus- and activation-regulated chemokine [TARC], pulmonary and activation-regulated chemokine [PARC], and periostin), Th2-associated markers (IL-4, IL-13, and thymic stromal lymphopoietin [TSLP]), Th17-associated markers (IL-6, IL-17, IL-21, IL-22, IL-23, and IL-26), Th22-associated markers (IL-20, IL-22, IL-26), a Th1-related marker (IL-12), an inflammation-related marker (tumor necrosis factor [TNF] alpha), a pruritus-related marker (IL-31), eosinophil markers (IL-5, eotaxin-1, eotaxin-3), and neutrophil markers (elastase, IL-8) (Table S1). Biomarkers were measured before initiation of dupilumab treatment (screening) and after 4, 8, 12, and 16 weeks of treatment using multiplex immunoassays as previously described.[6]

2.6 | Super-responders and development of conjunctivitis at week 16

Patients were stratified by the achievement of a clinically relevant improvement in all of the three key domains at week 16 (super-responders) and the development of conjunctivitis. Clinical characteristics were compared in the total group between patients who did or did not achieve a clinically relevant improvement at week 16 and

TABLE 1 Baseline characteristics

	Total group (n = 138)	Biomarker subgroup (n = 35)	*P*-value
Age (y), mean (SD)	43.4 (15.4)	39.8 (13.1)	.12[a]
Men, n (%)	86 (62.3)	25 (71.4)	.20[b]
Atopic/allergic diseases at baseline, n (%)			
Allergic rhinitis	100 (72.5)	27 (77.1)	.47[b]
Asthma	90 (65.2)	24 (68.6)	.63[b]
Food allergy	70 (50.7)	21 (60.0)	.20[b]
Allergic conjunctivitis	89 (64.5)	27 (77.1)	.18[b]
Previous use of systemic immunosuppressants for atopic dermatitis, n (%)	136 (98.6)	35 (100.0)	.68[b]
History of ≥2 oral immunosuppressive treatments, n (%)	84 (60.9)	22 (62.9)	.78[b]
Previous use of cyclosporin A, n (%)	131 (94.9)	34 (97.1)	.49[b]
Previous use of methotrexate, n (%)	55 (39.9)	11 (31.4)	.24[b]
Previous use of azathioprine, n (%)	46 (33.3)	13 (37.1)	.58[b]
Previous use of mycophenolate mofetil/ enteric-coated mycophenolate sodium, n (%)	40 (39.0)	11 (31.4)	.71[b]
EASI score, median (IQR)	19.9 (13.6-28.3)	24.4 (16.8-31.9)	.19[c]
Missing, n (%)	3 (2.2)	2 (5.7)	–
Weekly average pruritus NRS, median (IQR)	7 (6.0-8.0)	7 (5.0-8.0)	.57[c]
POEM score, median (IQR)	20 (16.0-23.0)	20 (16.0-25.0)	.86[c]
Missing, n (%)	3 (2.2)	1 (2.9)	–
DLQI score, median (IQR)	12.5 (8.0-19.0)	10 (7.5-19.0)	.52[c]
Missing, n (%)	2 (1.4)	2 (5.7)	–
EQ-5D-5L dimension, n (%)			
Missing, n (%)	2 (2.2)	1 (2.9)	–
Mobility			
No problems	106 (77.9)	27 (79.4)	.81[b]
Problems	30 (22.1)	7 (20.6)	
Self-care			
No problems	114 (84.4)	28 (82.4)	.70[b]
Problems	21 (15.6)	6 (17.6)	
Usual activity			
No problems	48 (35.3)	15 (44.1)	.21[b]
Problems	88 (64.7)	19 (55.9)	
Pain/discomfort			
No problems	20 (14.7)	5 (14.7)	1.00[b]
Problems	116 (85.3)	29 (85.3)	
Anxiety/depression			
No problems	58 (42.6)	15 (44.1)	.84[b]
Problems	78 (57.4)	19 (55.9)	

[a]Independent sample *t* test.

[b]chi-square test.

[c]Mann-Whitney U test.

patients with and without conjunctivitis at week 16. Baseline and changes over time in serum biomarkers were compared between patients included in the biomarker subgroup who did or did not achieve a clinically relevant improvement at week 16 and patients with and without conjunctivitis at week 16.

2.7 | Statistical analysis

Data were analyzed at baseline and 4, 8, 12, and 16 weeks after initiation of dupilumab treatment, except for patients with discontinuation of dupilumab treatment, which are described separately.

TABLE 2 Effectiveness outcomes during dupilumab treatment in 138 patients

	Baseline (n = 138)	Week 4 (n = 138)	Week 8 (n = 138)	Week 12 (n = 138)	Week 16 (n = 136)
Concomitant use of systemic prednisone, n (%)	37 (26.8)	23 (16.8)	14 (10.2)	11 (8.0)	9 (6.6)
Accumulated dose of systemic prednisone (mg), median (IQR)	12.5 (7.5-25.0)	10.0 (5.0-11.3)*	5.0 (3.5-10.0)*	5.0 (3.5-10.0)*	2.5 (2.0-10.0)*
EASI score, median (IQR)	19.9 (13.6-28.3)	7.8 (5.6-13.5)*	6.2 (3.1-9.1)*	4.5 (2.2-8.5)*	4.0 (2.0-7.6)*
Missing, n (%)	3 (2.2)	1 (0.7)	4 (2.9)	2 (1.4)	0 (0)
ΔEASI from baseline, mean (SD)	–	−12.1 (9.9)	−15.0 (10.6)	−15.7 (10.7)	−16.3 (10.9)
ΔEASI % from baseline, mean (SD)	–	−51.1 (31.4)	−64.8 (32.2)	−68.4 (35.5)	−73.1 (26.5)
EASI-50, n (%)	–	84 (62.7)	107 (81.7)	110 (82.7)	114 (85.7)
EASI-75, n (%)	–	27 (20.1)	58 (44.3)	74 (55.6)	82 (61.7)
EASI-90, n (%)	–	4 (3.0)	17 (13.0)	31 (23.3)	32 (24.1)
EASI ≤ 7, n (%)	8 (5.9)	57 (41.6)	78 (58.2)	94 (69.1)	96 (70.6)
Weekly average pruritus NRS, median (IQR)	7.0 (6.0-8.0)	4.0 (2.0-6.0)*	3.0 (2.0-5.0)*	3.0 (1.0-5.0)*	3.0 (1.0-5.0)*
Missing, n (%)	1 (0.7)	1 (0.7)	2 (1.4)	1 (0.7)	0 (0)
ΔWeekly average pruritus NRS % from baseline, mean (SD)	–	−38.3 (41.3)	−45.3 (46.2)	−48.8 (48.0)	−53.5 (35.0)
Weekly average pruritus NRS, proportion of patients who achieved improvement (reduction) ≥4 points from baseline, n (%)	–	52 (37.7)	67 (48.6)	75 (54.3)	79 (57.2)
DLQI score, median (IQR)	12.5 (8.0-19.0)	–	–	–	3.0 (2.0-6.0)*
Missing, n (%)	2 (1.4)	–	–	–	1 (0.7)
ΔDLQI from baseline, mean (SD)	–	–	–	–	−9.2 (6.3)
Proportion of patients with ≥ 4-point improvement in DLQI score, n (%)	–	–	–	–	102 (77.9)
POEM score, median (IQR)	20.0 (16.0-23.0)	10.0 (5.0-15.5)*	8.0 (4.0-13.0)*	7.0 (3.0-12.5)*	7.0 (3.0-12.0)*
Missing, n (%)	3 (2.2)	9 (6.5)	4 (2.9)	5 (3.6)	0 (0)
ΔPOEM from baseline, mean (SD)	–	−8.9 (6.0)	−11.0 (7.0)	−11.6 (7.0)	−12.0 (6.6)
Proportion of patients with ≥4-point improvement in POEM score, n (%)	–	102 (83.6)	117 (92.9)	116 (93.5)	119 (93.0)
ΔPOEM item 1 (itch) from baseline, mean (SD)	–	−1.4 (1.4)	−1.7 (1.5)	−1.8 (1.5)	−1.9 (1.5)
ΔPOEM item 2 (sleep) from baseline, mean (SD)	–	−1.5 (1.5)	−1.7 (1.5)	−1.8 (1.5)	−1.8 (1.6)
EQ-5D item 4 (pain/discomfort): proportion of patients reporting "no problem", n (%)	20 (14.7)	–	–	–	63 (48.1
Missing, n (%)	2 (1.4)	–	–	–	5 (3.7)
EQ-5D item 5 (anxiety/depression): proportion of patients reporting "no problem", n (%)	58 (42.6)	–	–	–	92 (70.2)
Missing, n (%)	2 (1.4)	–	–	–	5 (3.7)

Note: Data were analyzed by using a Wilcoxon matched-pairs signed-rank test.

*Statistically significant ($P < .05$) compared to baseline.

Clinical outcome measures at each follow-up time point were compared using the Wilcoxon signed-rank test. Serum biomarker levels were normalized by a log-transformation. Differences in biomarker levels between T0 (baseline) and T1 (4 weeks), and between T1 (4 weeks) and T4 (16 weeks) were compared using the Wilcoxon signed-rank test. *P*-values <.05 were considered statistically

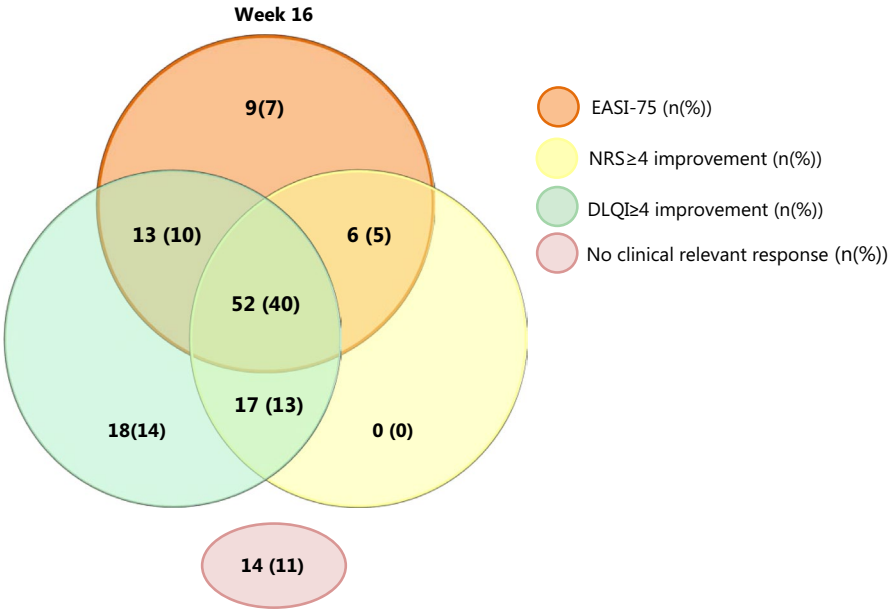


FIGURE 1 Characterization of the patients with a clinical relevant response: proportion of patients achieving EASI-75 or NRS ≥4-point improvement or DLQI ≥4-point improvement after 16 weeks of dupilumab treatment (outcomes available in 129 patients) [Color figure can be viewed at wileyonlinelibrary.com]

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

significant. Differences in baseline characteristics and serum biomarkers between subgroups stratified by treatment response and development of conjunctivitis at week 16 were analyzed by using a *t* test for normally distributed data, Mann-Whitney U test for variables with a non-normal distribution, and chi-square test for categorical variables. All statistical analyses were conducted using SPSS (for Windows, version 25.0, SPSS Inc) and Prism (version 7.4; GraphPad).

3 | RESULTS

3.1 | Patients and baseline characteristics

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

3.2 | Effectiveness

After 16 weeks of treatment, the mean percent change in EASI score was −73%. At week 16, the EASI-50, EASI-75, and EASI-90 were achieved by 114 (86%), 82 (62%), and 32 (24%) patients, respectively (Figure S1). The proportion of patients achieving EASI ≤7 (clear-mild AD) at week 16 was 71% (Table 2). The weekly average NRS pruritus significantly decreased from baseline (NRS pruritus mean = 6.9, SD = 2.1) to week 16 (NRS pruritus mean = 3.1, SD = 2.2; $P < .001$) (Figure S1). At week 16, 79 patients (57%) achieved ≥4 points improvement (reduction) in weekly average pruritus NRS. Treatment with dupilumab also improved other patient-reported outcomes including the health-related quality of life, symptoms of AD, pain/discomfort, sleep and symptoms of anxiety and depression (Table 2). The DLQI score significantly decreased from baseline (mean = 13.4, SD = 7.2) to week 16 (mean = 4.3, SD = 4.2; $P < .001$) with 78% of the patients achieving a ≥4-point improvement in DLQI score after 16 weeks of treatment. The POEM score significantly decreased from baseline (mean = 19.7, SD = 5.5) to week 16 (mean = 7.7, SD = 5.9; $P < .001$). The proportion of patients reporting "no problems" on the EQ-5D-5L pain/discomfort and anxiety/depression subscale increased from baseline (15% and 43%) to week 16 (48% and 70%).

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

TABLE 3 Side effects during dupilumab treatment in 138 patients

Number of patients with, n (%)	
Conjunctivitis (total)	47 (34.1)
Mild conjunctivitis	20 (14.5)
Moderate-severe conjunctivitis (ophthalmologist-confirmed, anti-inflammatory eye drops/ointment)	27 (19.6)
Blood eosinophilia (≥0.45 × 10 × 9/L)	
Screening	45 (32.6)
4 wk	67 (48.6)
8 wk	78 (56.5)
12 wk	76 (55.1)
16 wk	78 (56.5)
Eye irritation	34 (24.6)
Headache	14 (10.1)
Injection site reaction	7 (5.1)
Gastro-intestinal complaints	7 (5.1)
Fatigue	6 (4.3)
Hair loss	5 (3.6)
Herpes Simplex	4 (2.9)
Blepharitis	4 (2.9)
Flu like symptoms	3 (2.2)

3.3 | Safety

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

The most reported side effects during dupilumab treatment were eye irritation in 34 patients (25%) (including symptoms of dry eyes, itch, and tearing) and conjunctivitis in 47 patients (34%) (symptoms and signs including hyperemia of the conjunctiva) (Table 3). Patients were diagnosed with mild conjunctivitis when signs and symptoms could be controlled with artificial tears, antihistamine eye drops, or topical treatment with anti-inflammatory ointment on the eyelids. Patients who needed treatment with ocular anti-inflammatory eyedrops or ointment were diagnosed with a moderate to severe conjunctivitis by an ophthalmologist. Out of the 47 patients developing conjunctivitis during treatment with dupilumab, 20 patients (15%) had mild conjunctivitis, and 27 patients (20%) had moderate to severe conjunctivitis. Treatment characteristics are described in Table 4.

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

The proportion of patients with a blood eosinophilia (≥0.45 × 10 × 9/L) increased from screening (45 patients [33%]) to week 16 (78 patients [57%]). Increased blood eosinophil levels were not associated with symptoms and did not result in dose adjustment or treatment discontinuation of dupilumab. No other laboratory abnormalities were observed during treatment with dupilumab in this study.

3.4 | Biomarkers

For the biomarker analysis, twenty-one biomarkers (Table S1) were measured in a subgroup of 35 patients without concomitant use of oral immunosuppressive drugs at 5 different time points (screening, after 4, 8, 12, and 16 weeks of treatment with dupilumab). Baseline characteristics were not significantly different between the patients included for the biomarker analysis and the total group of patients (Table 1).

Dupilumab treatment significantly reduced severity-related serum biomarkers TARC, PARC, periostin, and IL-22 from screening through week 4. TARC and periostin further decreased from week 4 through week 16 (Figure 2). IL-4 showed a significant increase from screening (median 0.27 pg/mL, IQR 0.27-0.27) through week 4 (median 1.44 pg/mL, IQR 0.90-1.88) ($P < .0001$). IL-13 was stable from screening to week 4, but then increased significantly from week 4 (median 7.16 pg/mL, IQR 3.00-15.61) through week 16 (median 9.13 pg/mL, IQR 3.02-19.18) ($P = .037$). Dupilumab treatment significantly decreased serum levels of eotaxin-1 and eotaxin-3 from screening through week 4 (from median 103.33 pg/mL [IQR 78.33-130.01] to 83.52 pg/mL [IQR 63.57-133.55] at week 4 $P = .038$, and from median 5.51 pg/mL [IQR 3.54-8.89] to 1.91 pg/mL [IQR 1.70-2.52], $P < .0001$, respectively).

No significant changes were found in the levels IL-5, IL-6, IL-8, IL-12, IL-17, IL-20, IL-21, IL-23, IL-26, IL-31, TNF-a, TSLP, and elastase during dupilumab treatment (Figure S2).

3.5 | Super-responders and development of conjunctivitis at week 16

The baseline EASI score was significantly higher among patients who achieved a clinically relevant improvement in all of the 3 key domains of the clinically relevant response compared to patients who did not achieve a clinically relevant improvement in all of the three domains (median EASI [IQR] 23.5 [16.5-31.8] vs 18.3 [12.6-26.5], $P = .024$). Other baseline characteristics (total group and biomarker subgroup and baseline serum biomarkers (biomarker subgroup)) did not significantly differ between patients who did or did not achieve a clinically relevant improvement in all of the three key domains of the clinically relevant response and patients with or without conjunctivitis (Tables S2-S6). Changes over time in EASI

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

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

[a]Multiple treatments per patient.

and serum biomarkers did also not significantly differ between patients with or without conjunctivitis at week 16 (Table S6).

4 | DISCUSSION

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

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

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

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

The proportion of patients developing new onset or worsening of conjunctivitis (34%) was higher compared to previous phase 3 clinical trials (9%-28%).[1,2,7] This might be explained by an increased awareness of conjunctivitis. In the study by Faiz et al, conjunctivitis was also the most reported side effect in 38.2% of the patients which

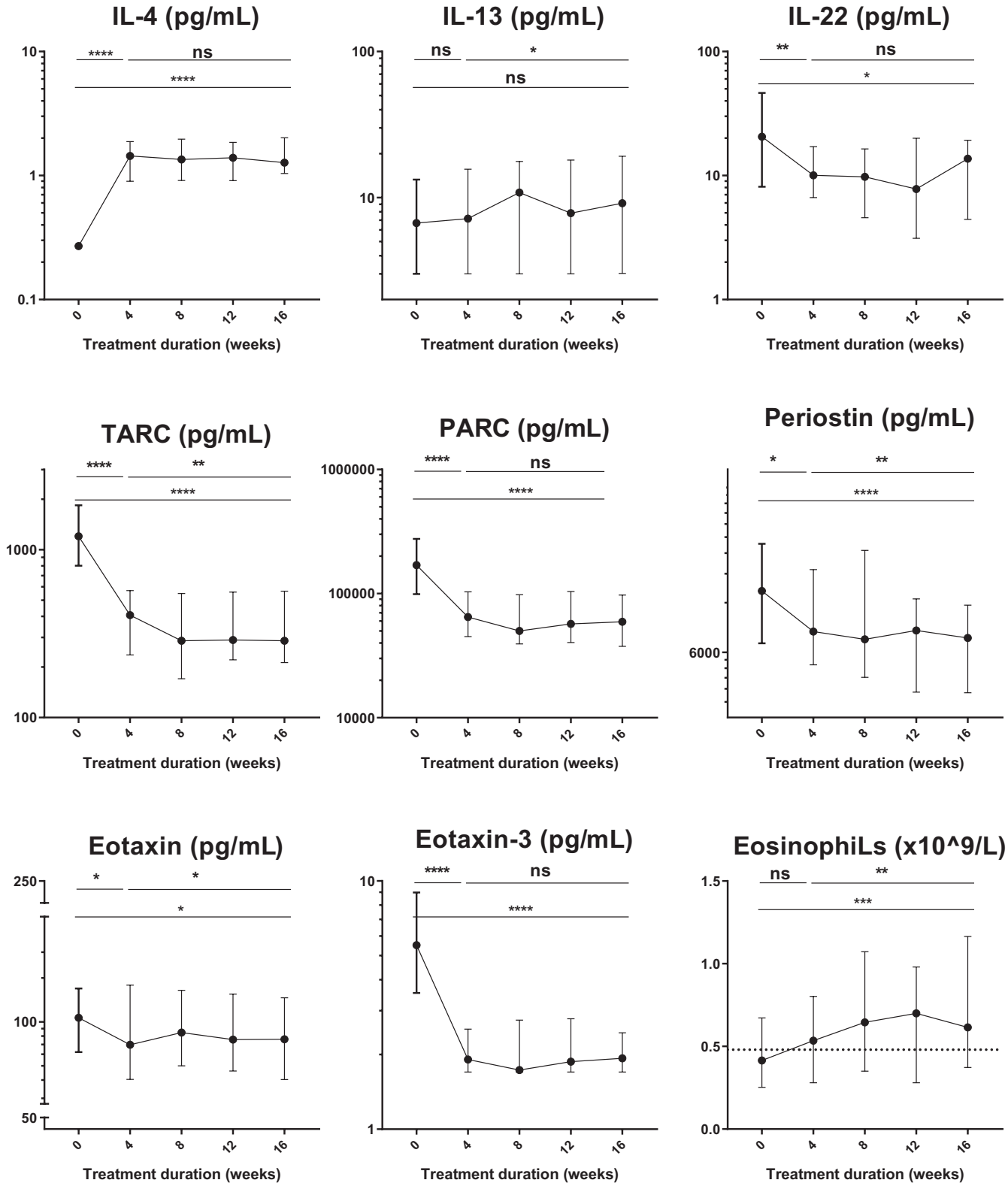


FIGURE 2 Serum biomarkers and blood eosinophil levels showing significant change over time during treatment with dupilumab

is comparable with the conjunctivitis rates in this study. The proportion of patients who discontinued dupilumab treatment due to ophthalmological events was higher in the study by Faiz et al (10 patients [4.2%] compared to our study [2 patients 1.4%]).[8] Moderate-severe conjunctivitis needing treatment with anti-inflammatory eyedrops/ointment was observed in 27 patients (20% of total patient group) of whom the majority had a history of preexisting conjunctivitis (83%). However, in all patients, signs and symptoms significantly worsened and anti-inflammatory treatment was initiated during dupilumab treatment. In this cohort, patient-reported history of conjunctivitis

and severity of AD at baseline were not predictors for the development of conjunctivitis during dupilumab treatment. In a previous study, we described the clinical characteristics of 13 moderate to severe dupilumab-treated AD patients developing conjunctivitis with inflammation of the conjunctiva and hyperemia of the limbus as prominent features.[9] Nodular swelling of the limbus was present in the most severe cases. In addition, we described a remarkable scarcity of conjunctival goblet cells accompanied by an inflammatory T-cell and eosinophilic infiltrate in six dupilumab-treated patients with an ophthalmologist-confirmed conjunctivitis requiring anti-inflammatory treatment.[10] We hypothesized that the IL-13 blocking effect of dupilumab might lead to reduction of goblet cells and mucin production in a subpopulation of patients with AD, which may potentially result in irritative conjunctivitis. Given the high proportion of patients developing new onset or worsening of conjunctivitis during dupilumab in daily practice, potentially leading to serious ocular complications, optimal treatment and risk management is necessary. Remarkably, increased incidence of conjunctivitis was not observed in asthma and sinusitis trials with dupilumab, suggesting a disease-specific predisposition in a subpopulation of AD patients.[11-13] A prospective study on ocular co-morbidity in moderate to severe AD patients before and during dupilumab treatment is already initiated in our center.

We observed elevated eosinophil levels in the peripheral blood during treatment with dupilumab. The proportion of patients with observed elevated eosinophil levels in our study was comparable with the patients included in the study by Faiz et al However, in our study none of the patients discontinued dupilumab treatment due to eosinophilia compared to 5 patients (2.1%) in the study by Faiz et al.[8] Transient eosinophilia was also observed in clinical trials including patients treated with dupilumab for asthma, AD and chronic sinusitis and nasal polyposis.[7,11-14] This supports the hypothesis that dupilumab inhibits the migration of eosinophils into the tissues by suppressing the IL-4- and IL-13-stimulated production of eotaxins without influencing the production or migration from the bone marrow. Eotaxins are released from endothelial cells that have been stimulated with IL-4 and IL-13 and attract eosinophils and other inflammatory cells. Eosinophils stimulate the production of Th2-associated cytokines by T-lymphocytes which in turn prolong the survival and mediate the activation and migration of eosinophils.[15] Previous studies have shown that dupilumab decreased eotaxin-2 and eotaxin-3 levels locally in nasal polyp tissue, nasal secretion, and serum from chronic rhinosinusitis patients.[11,16] In this study, we show that serum concentrations of eotaxin-1 and eotaxin-3 chemokines decreased during dupilumab treatment. These data suggest that dupilumab suppresses eosinophil chemokines both systemically and locally.

Dupilumab has shown to normalize the RNA expression of Th2-related inflammatory molecules and reverse skin barrier abnormalities in biopsies from 18 AD patients treated with dupilumab in phase 1 studies.[17] A recent study including 54 patients treated with dupilumab in a clinical trial showed a significant decrease of Th2-related serum biomarkers TARC, PARC, and periostin after 16 weeks of treatment.[18] Both studies included a subgroup of patients from clinical trials, and there are no data available on biomarkers in dupilumab-treated AD patients in daily practice. Moreover, only a selective group of biomarkers reflecting Th2 activation was studied, while it is known that besides Th2 signaling, activation of Th22, Th17, and Th1 is also observed in patients with AD.[19] In this study, we showed that treatment with dupilumab significantly decreased serum biomarkers that have been implicated as biomarkers of AD severity and treatment response, including TARC, PARC, periostin, and IL-22. An interesting finding of this study was the increase of Th2 cytokines IL-4 and IL-13 during treatment with dupilumab, although levels were still relatively low. Since other Th2-related biomarkers (TARC, PARC, and periostin) did decrease, we hypothesize that IL-4 receptor alpha blockade with dupilumab might result in an increase of unbound circulating IL-4 and IL-13 levels. The increase of IL-4 and IL-13 might be a temporary phenomenon, since it is likely that long-term suppression of IL-4Rα will lead to a decreased production of IL-4 and IL-13 by T cells. Dupilumab treatment significantly decreased serum IL-22 levels. No effect on Th17 related biomarkers was observed. Nevertheless, it is questionable whether the Th17 pathway plays a role in our population of European AD patients, since Th17 activation has been strongly associated with mainly Asian and pediatric AD subtypes, and in European-American populations with only the intrinsic AD subtype.[20] The Th22 pathway is commonly activated in all major subtypes of AD.[20]

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

CONFLICTS OF INTEREST

Marjolein de Bruin-Weller is a principal investigator and advisory board member for AbbVie and Regeneron Pharmaceuticals, Inc; is a principal investigator, advisory board member, and consultant for Sanofi Genzyme; is a advisory board member for Eli Lilly; is a advisory board member for UCB; and is a principal investigator and advisory board member for Pfizer. Marie-Louise Schuttelaar: Sanofi Genzyme – advisory board member, consulting fees. The other authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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