Received: 19 August 2022 | Revised: 7 October 2022 | Accepted: 2 November 2022

DOI: 10.1111/pai.13887

ORIGINAL ARTICLE

WILEY

Dupilumab in daily practice for the treatment of pediatric atopic dermatitis: 28-week clinical and biomarker results from the BioDay registry

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Funding information
AbbVie; Eli Lilly and Company; LEO Pharma Research Foundation; Pfizer; Sanofi

Editor: Marina Atanaskovic-Markovic

Abstract

Background: Dupilumab has proven to be an effective and safe treatment for atopic dermatitis (AD) in pediatric patients in clinical trials. However, few daily practice studies are available. The aim of this study is to evaluate the effect of 28 weeks dupilumab treatment on effectiveness, safety, and serum biomarkers in pediatric patients with moderate-to-severe AD in daily practice.

Methods: Patients visited the outpatient clinic at baseline, 4, 16, and 28 weeks of treatment. Disease severity was assessed by the Eczema Area and Severity Index (EASI), Investigator Global Assessment (IGA), Numeric Rating Scale (NRS)-pruritus and -pain, and the Patient-Oriented Eczema Measure (POEM). Side effects were evaluated. Nineteen severity-associated serum biomarkers were measured. Predicted-EASI (p-EASI) was calculated.

Results: Sixty-one patients were included. Respectively 75.4%, 49.2%, and 24.6% reached EASI-50, EASI-75, and EASI-90 and 36.1% achieved an IGA-score (almost) clear. Improvement of ≥4 points on POEM, NRS-pruritus, and NRS-pain was reached by 84.7%, 45.3%, and 77.4%, respectively. Most reported side effects were conjunctivitis ($n = 10$) and headache ($n = 4$). Biomarkers TARC, PARC, periostin, sIL-2Ra, and eotaxin-3 significantly decreased during treatment. The p-EASI showed a significant correlation with disease severity.

Conclusion: Dupilumab treatment significantly improved disease severity and disease-associated symptoms and decreased severity-associated serum biomarkers in pediatric AD patients in daily practice.

KEYWORDS
atopic dermatitis, biomarkers, dupilumab, p-EASI, pediatric

E. Kamphuis and C.M. Boesjes share first authorship. M. de Graaf and M.L.A. Schuttelaar share last authorship.

1 | INTRODUCTION

Atopic dermatitis (AD) is a common inflammatory skin disease characterized by recurrent eczematous lesions and intense itch. A recent international, cross-sectional survey in the general pediatric population showed a self-reported, 1-year prevalence of AD up to 20.1%, of which <15% had severe AD.[1] Since AD is associated with a high impact on quality of life (QoL) for both children with AD and their caregivers, adequate maintenance therapy to achieve long-term control of the disease is important.[2]

Currently, dupilumab, an interleukin (IL)-4 receptor-α monoclonal antibody inhibiting IL-4 and IL-13 signaling, is approved for the treatment of patients aged 6–17 years with moderate-to-severe AD in Europe and the United States.[3] Results of three phase III clinical trials with children and adolescents showed that dupilumab significantly improves AD symptoms and QoL, with an acceptable safety profile.[4–7]

To evaluate AD severity and treatment response, serum biomarkers can be used as an objective outcome measurement.[3,8,9] In adults with AD, serum biomarkers significantly decreased during dupilumab treatment.[3,8] When combining specific severity-associated serum biomarkers, AD severity can be predicted by calculating the predicted-Eczema Area and Severity Index (EASI) score (p-EASI).[10–12]

A limited number of clinical daily practice studies on the effect of dupilumab in pediatric AD patients are currently available, and data regarding the effect of treatment on serum biomarkers in this population is lacking. Therefore, the aim of this study is to evaluate the 28-week clinical effectiveness and safety of dupilumab for the treatment of pediatric AD in daily practice. Furthermore, the effect of dupilumab treatment on serum biomarkers and the correlation with disease severity are evaluated.

Key Message

Dupilumab significantly improved disease severity in pediatric patients with moderate-to-severe atopic dermatitis (AD) after 28 weeks of treatment in daily practice. This is the first study showing that the severity-associated serum biomarkers significantly decreased in pediatric AD patients during dupilumab treatment.

2 | METHODS

2.1 | Study design and population

This prospective multicenter observational cohort study included children (aged ≥6 to <12 years) and adolescents (aged ≥12 to <18 years) with moderate-to-severe AD treated with dupilumab. The study was conducted at the department of Dermatology of the University Medical Center Groningen, the National Expertise Center for Atopic Dermatitis from the University Medical Center Utrecht (UMCU), and the department of Dermatology of the Radboud University Medical Center. All patients were registered in the BioDay registry, a multicenter registry that includes patients with moderate-to-severe AD treated with biologics or small molecules. The study was approved by the local Medical Research Ethics Committee as a noninterventional study and performed according to the declaration of Helsinki. All patients and/or parents gave written informed consent.

2.2 | Treatment

Adolescents with a body weight < 60 kg were treated with subcutaneous dupilumab 200 mg every 2 weeks (Q2W), after a loading dose of 400 mg. In case of a body weight ≥ 60 kg, patients received a loading dose of 600 mg, followed by 300 mg Q2W. Children weighing 15–60 kg received 300 mg at baseline and after 2 weeks, and thereafter 300 mg dupilumab every 4 weeks. All patients visited the outpatient clinic at baseline and after 4,16, and 28 weeks of dupilumab treatment. Concomitant treatment with TCS was allowed. If possible, systemic immunosuppressive treatment was discontinued before dupilumab initiation.

2.3 | Outcome measures

Disease severity was assessed by the EASI (range 0–72)[13] and the 6-point Investigator's Global Assessment (IGA) (range: clear—almost clear—mild—moderate—severe—very severe). The EASI and IGA were rated by trained physicians. In addition, patient-reported outcomes measures (PROMs) included the Patient-Oriented Eczema Measure (POEM) (range 0–28),[14] the Numeric Rating Scale (NRS) (range 0–10) of the average pruritus[15] and pain[16] of the past week, and sleep deprivation (yes or no). Endpoints were also evaluated as a proportion of patients who achieved ≥50%, ≥75%, or ≥90% improvement in EASI score (EASI-50, EASI-75, and EASI-9, respectively), (almost) clear on the IGA score, ≥4 points reduction in NRS-pruritus and -pain score, and ≥4 points improvement in POEM score at week 4,16, and 28 compared to baseline. Furthermore, the proportion of patients achieving absolute cutoff scores indicating controlled disease (EASI ≤ 7, NRS-pruritus score ≤ 4 or POEM ≤ 7)[17] at week 28 were analyzed. Side effects were reported, and laboratory parameters were monitored.

2.4 | Serum biomarkers

For a subgroup of pediatric patients, 19 biomarkers were measured at baseline, week 4 and 16: severity-associated markers (thymus- and activation-regulated chemokine (TARC), pulmonary and activation-regulated chemokine (PARC), periostin, and soluble

IL-2-receptor alpha (sIL-2Ra)), T helper (Th)2-associated markers (IL-4, IL-5, and IL-13), Th17-/Th22-associated markers (IL-6, IL-17, IL-22, and IL-23), Th1-associated markers (IL-12 and interferon-gamma-induced protein (IP)-10), inflammatory markers (IL-1b, granulocyte colony-stimulating factor (GCSF), and monocyte chemoattractant protein (MCP)-1), regulatory cytokines (IL-10), and eosinophil markers (eotaxin-1, and eotaxin-3).[8,10–12] Acquisition of data was performed using a FlexMAP3D system (Bio-Rad) using xPonent 4.1 software (Luminex). Data analysis was performed using Bioplex manager 6.1.1 (Bio-Rad). All assays were performed at the laboratory of translational immunology of the UMCU.[18] Patients were selected based on the availability of serum at all timepoints. Selected biomarkers were used to calculate the p-EASI score using a validated formula.[10–12]

2.5 | Statistical analysis

Multiple imputation ($n = 15$) (MI), with predictive mean matching for continuous variables (EASI, IGA, POEM, NRS-pruritus and -pain, and sleep deprivation), was applied for missing values in outcomes (14.9%) to avoid bias and loss of statistical power.[19] Variables age, gender, concomitant immunosuppressive therapy at baseline, and the presence of active asthma were used as predictors for MI and in a second step as covariates in the generalized estimating equations (GEE). GEE was used to analyze clinical outcomes.[20] The autoregressive working correlation structure was included in the analyses to correct for multiple measurements of outcomes over time. Results for continuous outcomes were presented as the change in the mean (compared to baseline) with 95% confidence intervals (CI) and *p*-Values. For dichotomous outcomes, regression coefficients were transformed to odds ratios (OR). Distribution of biomarkers was reported in box plots. The Wilcoxon rank test was used to analyze the differences in biomarker levels between different timepoints. Correlation between the EASI and p-EASI was assessed by the Pearson Rho. *p*-Values < .05 were considered as statistically significant. Statistical analyses were performed with IBM SPSS Statistics for Windows (version 28.0). GraphPad Prism (version 8.3) was used to construct figures.

3 | RESULTS

3.1 | Patient and baseline characteristics

A total of 61 patients, 16 children and 45 adolescents, with moderate-to-severe AD were treated with dupilumab between March 2020 and July 2022. The majority of patients had two or more atopic comorbidities (68.9%). Forty-one patients (67.2%) had been treated with systemic immunosuppressive treatment for their AD in the past. At baseline, 20 patients (32.8%) were using immunosuppressive therapy for their AD (washout of <2 weeks for short-acting drugs and <4 weeks for long-acting drugs). Baseline characteristics are shown in Table 1.

3.2 | Effectiveness

All effectiveness outcomes showed a significant improvement during 28 weeks of dupilumab treatment. Mean EASI score significantly changed from 20.2 (SD 10.8) to 6.4 (SD 7.3) ($p < .001$). The proportion of patients who reached EASI-50, EASI-75, and EASI-90 were 75.4% ($n = 46$), 49.2% ($n = 30$), and 24.6% ($n = 15$), respectively (Figure 1). Twenty-two patients (36.1%) scored (almost) clear on the IGA. Mean NRS-pruritus and POEM significantly changed from 6.4 (SD 2.4) to 3.5 (SD 2.1) ($p < .001$) and from 19.5 (SD 7.0) to 9.6 (SD 5.1) ($p < .001$), respectively. Improvement of ≥4 points on the NRS-pruritus, NRS-pain, and POEM was reached by 45.3%, 77.4%, and 84.7%, respectively. The proportion of patients achieving at least one absolute cutoff score indicating controlled disease after 28 weeks of dupilumab treatment was 86.9% ($n = 53$) (Figure 2). The proportion of patients with sleep deprivation decreased significantly (by 50.8%) between baseline and week 28 (OR = 0.1, $p < .001$). There was no significant difference between week 16 and week 28 for all outcome measures. It was possible to discontinue oral immunosuppressive therapy in 75% (15/20) of the patients before their week-4 visit, and in all patients before their week-16 visit. All effectiveness outcomes are presented in Figure 1 and Table 2.

3.3 | Safety

A total of 27 patients (44.3%) experienced at least one side effect. Most frequently reported side effects were conjunctivitis ($n = 10$ (16.4%)) and headache ($n = 4$ (6.6%)) (Table 3). At week 28, five patients discontinued dupilumab treatment, two patients due to fear of needles, two patients due to an side effect (conjunctivitis and conjunctivitis/limbitis), and one patient due to ineffectiveness.

3.4 | Serum biomarkers

A subgroup of 17 patients was included for biomarker analysis. Dupilumab treatment significantly reduced severity-associated markers sIL-2Ra, periostin, TARC, and PARC from baseline to week 4 (Figure 3A). TARC and PARC significantly further decreased between week 4 and week 16. IL-4 significantly increased between baseline (median 0.30 pg/ml (interquartile range (IQR) 0.30–0.30)) and week 4 (median 1.73 (IQR 0.30–2.28), $p < .01$) and slightly decreased between week 4 and week 16 (median 0.83 (IQR 0.49–1.81), $p = .15$). Eosinophil attraction marker eotaxin-3 significantly decreased from baseline (median 5.16 (IQR 0.46–13.52)) to week 4 (median 0.46 (IQR

TABLE 1 Baseline characteristics

Patient characteristics	Total group	Biomarker subgroup	Non-biomarker subgroup
N	61	17	44
Male, *n* (%)	30 (49.2)	8 (47.1)	22 (40.0)
Age (years), mean (SD)	14 (3.2)	13 (3.7)	14 (3.1)
Atopic comorbidities, *n* (%)			
Allergic asthma	30 (49.2)	6 (35.3)	24 (54.5)
Use of inhalation corticosteroids	13 (21.3)	3 (17.6)	10 (22.7)
Allergic rhinitis	43 (70.5)	12 (70.6)	31 (70.5)
Allergic conjunctivitis	31 (50.8)	10 (58.5)	21 (47.7)
Food allergy	29 (47.5)	9 (52.9)	20 (45.5)
≥2 atopic comorbidities	42 (68.9)	12 (70.6)	30 (68.2)
Past treatment, *n* (%)			
UVB phototherapy	21 (34.4)	5 (29.4)	16 (36.4)
Systemic treatment	41 (67.2)	13 (76.5)	28 (63.6)
Methotrexate	8 (13.1)	2 (11.8)	6 (13.6)
Cyclosporin A	36 (59.0)	13 (76.5)	23 (52.3)
Azathioprine	1 (1.6)	0 (0.0)	1 (2.3)
Mycophenolate mofetil	2 (3.3)	0 (0.0)	2 (4.5)
Tralokinumab	2 (3.3)	0 (0.0)	2 (4.5)
Upadacitinib	1 (1.6)	0 (0.0)	1 (2.3)
Abrocitinib	1 (1.6)	1 (5.9)	0 (0.0)
≥2 systemic treatments	9 (14.8)	2 (11.8)	7 (15.9)
Immunosuppressives at baseline or in wash-out	20 (32.8)	9 (52.9)	11 (25.0)
Cyclosporin A	13 (21.3)	6 (35.3)	7 (15.9)
Prednisolone	4 (6.5)	1 (5.9)	3 (6.8)
Methotrexate	3 (4.9)	2 (11.8)	1 (2.3)
Disease specific			
EASI, mean (SD)	20.2 (10.8)	19.5 (7.5)	20.5 (11.9)
NRS-pruritus, mean (SD)	6.4 (2.4)	6.6 (2.8)	6.3 (2.3)
NRS-pain, mean (SD)	3.6 (3.6)	4.4 (3.8)	3.4 (3.5)
POEM, mean (SD)	19.5 (7.0)	19.2 (6.7)	19.4 (7.2)
IGA, *n* (%)			
Mild	2 (3.3)	0 (0.0)	2 (4.5)
Moderate	29 (47.5)	8 (47.1)	21 (47.7)
Severe	22 (36.1)	9 (52.9)	13 29.5)
Very severe	8 (13.1)	0 (0.0)	8 (18.2)
Sleep deprivation, *n* (%)			
Yes	44 (72.1)	13 (76.5)	31 (70.5)
Laboratory parameters			
Blood eosinophilia[a] at baseline, *n* (%)	34 (55.7)	12 (70.6)	22 (50.0)
Missing, *n* (%)	4 (6.6)	0 (0.0)	4 (9.1)

Note: Data after multiple imputation. Standard deviation (SD) was calculated as the standard error of the mean (SEM) multiplied by $\sqrt{n}$.

Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; *N*, number; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure; UVB, ultra violet B.

[a]Blood eosinophils ≥ 0.6 × 109/L for children aged < 12 years and ≥0.4 × 109/L for children aged ≥ 12 years.

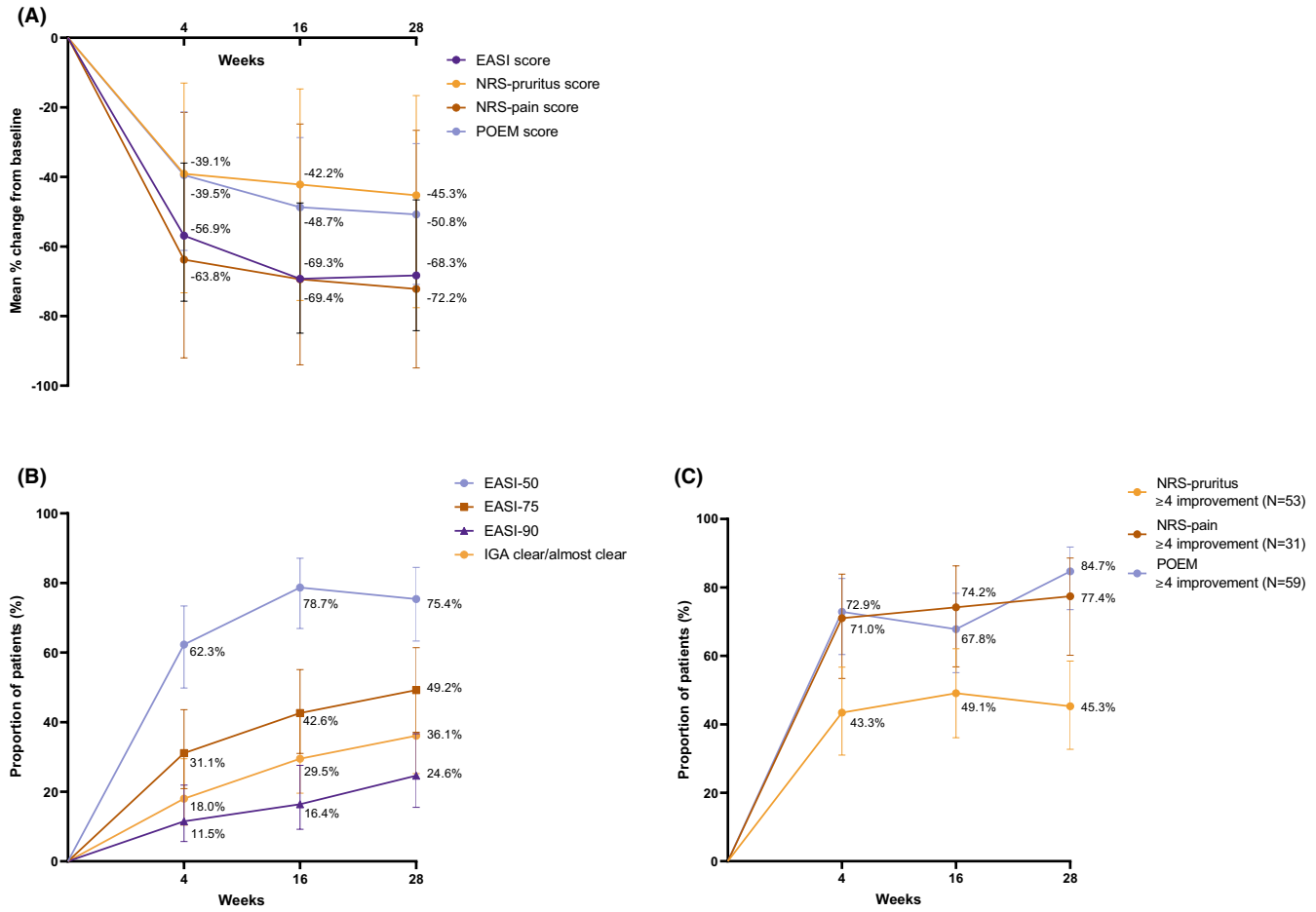

FIGURE 1 Clinician- and patient-reported outcomes on the effect of 28 weeks dupilumab treatment. Data after multiple imputation. (A) Mean percentage change from baseline for EASI, NRS-pruritus, POEM and NRS-pain score; (B) Proportion of patients who achieved EASI-50, EASI-75 or EASI-90 or an IGA-score of (almost) clear; (C) Proportion of patients who achieved ≥4 points improvement in NRS-pruritus score, NRS-pain score or POEM score. Patients with a score of ≤3 at baseline were excluded. 95% confidence interval of the proportions is shown with error bars. EASI, Eczema Area and Severity Index; GEE, generalized estimating equations; IGA, Investigator's Global Assessment; *N*, number; NRS, Numeric Rating Scale; POEM, Patient-Oriented Eczema Measure

0.46–2.96), $p < .05$) and was further stabilized at week 16. Median blood eosinophil levels increased from 0.64×10^9/L (IQR 0.38–1.09) to 0.83×10^9/L (IQR 0.36–1.43) at week 16 (Figure 3B). All other biomarkers remained low and did not show a significant change during treatment (Figure S1). Furthermore, the calculated p-EASI scores showed a significantly high correlation with the clinical EASI scores (Pearson Rho $r = .64$, $p < .001$) (Figure 3C).

4 | DISCUSSION

In the current study, disease severity based on both clinical and patient-reported outcomes, significantly improved in pediatric patients with moderate-to-severe AD treated with dupilumab in daily practice.

When comparing the results of this study to phase III clinical trials, only week 16 data can be compared. In the current study, 42.6% of the patients achieved EASI-75 after 16 weeks of treatment. In clinical trials, this proportion in pediatric AD patients varied between 38.1% and 73.3%, with most percentages closer to 73.3%.[4–7] This difference might be explained by the fact that in clinical trials, patients with immunosuppressive drugs and/or a low EASI score at baseline were excluded. In this daily practice study, 32.8% of the patients were in the wash-out of or were concomitantly treated with immunosuppressive treatments at dupilumab initiation, indicating more severe AD in these patients. In addition, 67.2% of the patients had received immunosuppressive therapy for AD in the past, which is quite high compared with clinical trials (13.1–24.4%), also indicating a more severe AD in this cohort.[4–7] For patients with severe AD, it is more difficult to achieve endpoints. Also, patients with concomitant immunosuppressive treatment at baseline already had a relatively lower EASI score at baseline, which made it more difficult to achieve 75% improvement in EASI score at week 16. Use of immunosuppressive treatment at baseline may therefore cause a possible underestimation of the effect of dupilumab treatment in this study.

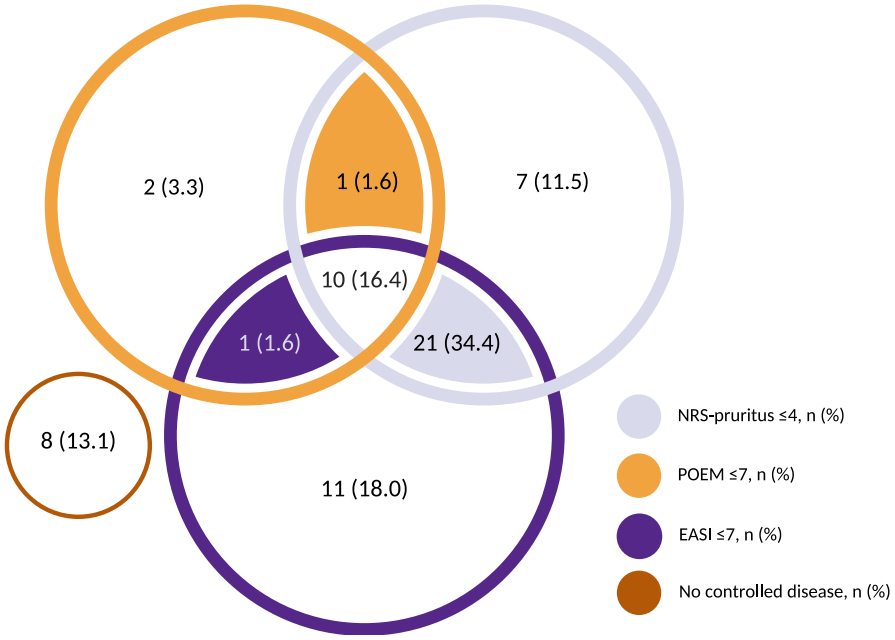

FIGURE 2 Patients with controlled disease at week 28 in the domains defined by Treat-to-Target in Atopic Dermatitis: NRS-pruritus ≤ 4, POEM ≤ 7 or EASI ≤ 7. Data after multiple imputation. EASI, Eczema Area and Severity Index; *N*: number; NRS: Numeric Rating Scale; POEM: Patient-Oriented Eczema Measure

A few daily practice studies of dupilumab for pediatric AD have been published previously. All of these studies found a significant improvement of AD severity during dupilumab treatment.[21–27] After 16–24 weeks of treatment, EASI-50 was achieved by 67.0%–99.3% of the patients.[21,23,24] EASI-75 was achieved by 42.0%–66.7% of the patients.[21–24] In the current study, the proportions of patients that achieved EASI-50 and EASI-75 after 16–28 weeks were 75.4%–78.7% and 42.6%–49.2%, respectively, which were within the range of the other daily practice studies. Other clinical outcomes used in the published daily practice studies differ from our study, making them difficult to compare.

Daily practice data from the same BioDay registry on effectiveness and safety of dupilumab treatment in 138 adult AD patients showed achievement of EASI-75 by 61.7% at week 16.[8] This is higher compared to the results in this pediatric population and could be explained by the fact that systemic immunosuppressive treatment was discontinued before dupilumab initiation in most adult patients. In the study by Ariëns et al, 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) was 89.0% at week 16.[8] According to other cutoff scores (EASI ≤ 7, NRS-pruritus score ≤ 4 or POEM ≤ 7), defined by Treat-to-Target, 86.9% of the patients in the current study achieved controlled disease in at least one domain at week 28.[17] These scores, indicating controlled disease, can be used for shared decision-making on dupilumab continuation, modification, or discontinuation in daily practice.

Regarding safety analysis, side effects reported in clinical trials and previous daily practice studies were in line with our study (e.g., conjunctivitis, headache, head neck dermatitis, joint pain, and site-injection reaction).[4–7,21–27] The prevalence of reported conjunctivitis was 6.7%–14.8% in clinical trials and 5.6%–17.0% in other daily practice studies, which is quite similar to our results (16.4%).[4–7,21–27] Ariëns et al. found that 34.1% of the adult patients developed conjunctivitis. Based on this study, conjunctivitis seems more common in adults than in children treated with dupilumab for AD in daily practice.[8]

Furthermore, to the best of our knowledge, this is the first study demonstrating serum biomarkers in pediatric AD patients treated with dupilumab. Serum levels of biomarkers related to AD severity and treatment response (TARC, PARC, periostin, and sIL-2Ra)[3,8–12] significantly decreased in this pediatric population. This is consistent with findings of Guttman-Yassky et al. and Ariëns et al.[3,8], which showed a decrease in these biomarkers in adult AD patients during dupilumab treatment. In both the adult and this pediatric population from the BioDay registry, it was found that IL-4 levels significantly increased and then slightly decreased during dupilumab treatment.[8] Despite the nonsignificant, though similar pattern of IL-13, our hypothesis of IL-4Rα blocking by dupilumab resulting in more unbound circulating IL-4 and IL-13, is strengthened. Long-term suppression of IL-4Rα might lead to a decrease of IL-4 and IL-13 production by T-cells, resulting in slightly lower IL-4 and IL-13 levels at week 16.[8] Eotaxin-3, an eosinophil marker that normally attracts eosinophils into the skin, was also significantly decreased.[8] This could explain why an increase in blood eosinophils is seen in AD patients treated with dupilumab, without influencing production and migration of eosinophils from the bone marrow.[28] No changes were observed in Th-cell-related and proinflammatory cytokines which indicates that there is no overt systemic immune skewing or activation upon 16 weeks of dupilumab treatment. However, consistently higher levels of the Th2-related marker periostin were found compared to adult patients.[8] Previous studies suggested that Th2-related markers are more highly expressed in younger children, and that these markers are associated with allergic comorbidities.[29] Since 70.6% of this cohort was diagnosed with two or more atopic diseases, this might explain the high overall levels of periostin over time. In addition, this study showed a good correlation between the p-EASI and

TABLE 2 Effectiveness outcomes during the first 28 weeks of dupilumab treatment

Effectiveness of clinical outcomes				Baseline –week 16		Baseline –week 28		Week 16–Week 28	
Continuous outcomes	Baseline	Week 16	Week 28	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value	β (95% CI)	*p*-Value
EASI, mean (SD)	20.2 (10.8)	6.2 (5.7)	6.4 (7.3)	−14.0 (−16.4 to 11.7)	<.001	−13.8 (−16.5 to 11.2)	<.001	−0.2 (−1.6 to 2.0)	.811
POEM, mean (SD)	19.5 (7.0)	10.0 (12.7)	9.6 (5.1)	−9.4 (−12.7 to 6.2)	<.001	−9.9 (−11.8 to 7.9)	<.001	−0.4 (−3.8 to 2.9)	.798
NRS-pruritus, mean (SD)	6.4 (2.4)	3.7 (2.0)	3.5 (2.1)	−2.8 (−3.5 to 2.0)	<.001	−2.9 (−3.6 to 2.3)	<.001	−0.2 (−0.8 to 0.4)	.551
NRS-pain, mean (SD)	3.6 (3.6)	1.1 (1.9)	1.0 (1.5)	−2.5 (−3.5 to 1.6)	<.001	−2.6 (−3.5 to 1.8)	<.001	−0.1 (−0.7 to 0.5)	.786
Dichotomous outcomes	Baseline	Week 16	Week 28	OR	*p*-Value	OR	*p*-Value	OR	*p*-Value
EASI ≤ 7, *n* (%)	4 (6.6)	37 (60.7)	42 (68.9)	27.7	<.001	42.6	<.001	1.5	.327
POEM ≤ 7, *n* (%)	3 (4.9)	28 (45.9)	15 (24.6)	16.6	<.001	5.7	.018	0.3	.063
NRS-pruritus ≤ 4, *n* (%)	15 (24.6)	40 (65.6)	39 (63.9)	7.1	<.001	6.6	<.001	0.9	.855
Sleep deprivation, yes, *n* (%)	44 (72.1)	11 (18.0)	13 (21.3)	0.1	<.001	0.1	<.001	1.3	.597

Note: Data after multiple imputation. Standard deviation (SD) was calculated as standard error of the mean (SEM) multiplied by $\sqrt{n}$. Odds ratio (OR) was calculated as exp (β).

Abbreviations: CI, Confidence Interval; EASI, Eczema Area and Severity Index; *N*, number; NRS, Numeric Rating Scale; OR, odds ratio; POEM, Patient-Oriented Eczema Measure; SD, standard deviation.

TABLE 3 Side effects during 28 weeks of dupilumab treatment

Side effects	*N* (%)
Number of patients	61
Number of side effects	43
Number of patients with side effect	27 (44.3)
Ocular:	
Conjunctivitis	10 (16.4)
Limbitis	1 (1.6)
Dry eyes	3 (4.9)
Thick eyelids	1 (1.6)
Unspecified eye complaints	1 (1.6)
Teary eyes	1 (1.6)
Skin related:	
Hair loss	3 (4.9)
Head neck dermatitis	2 (3.3)
Psoriasis	2 (3.3)
Injection site reaction	1 (1.6)
Itch after injection	1 (1.6)
Gastro-intestinal:	
Nausea	2 (3.3)
Diarrhea	1 (1.6)
Constipation	1 (1.6)
Abdominal pain	1 (1.6)
Other:	
Headache	4 (6.6)
Fatigue	3 (4.9)
Vertigo	1 (1.6)
Joint pain	1 (1.6)
Muscle pain	1 (1.6)
Paresthesia	1 (1.6)
Food intolerance	1 (1.6)

Abbreviation: *N*, number.

AD severity scores. The p-EASI could therefore be of use in monitoring AD disease severity in pediatric AD patients.

Strengths of this study are the multicenter, prospective, and observational design alongside the use of validated assessments and severity-associated serum biomarkers. A limitation of this study is the relatively small sample size. Furthermore, the concomitant use (or washout period) of immunosuppressive therapy at the time of dupilumab initiation could have influenced the results. Additionally, the entire study period took place under COVID-19 restrictions that contributed to the amount of missing data. However, this was covered by multiple imputations and the use of GEE.

5 | CONCLUSION

Dupilumab treatment significantly improved disease severity and disease-associated symptoms and decreased severity-associated

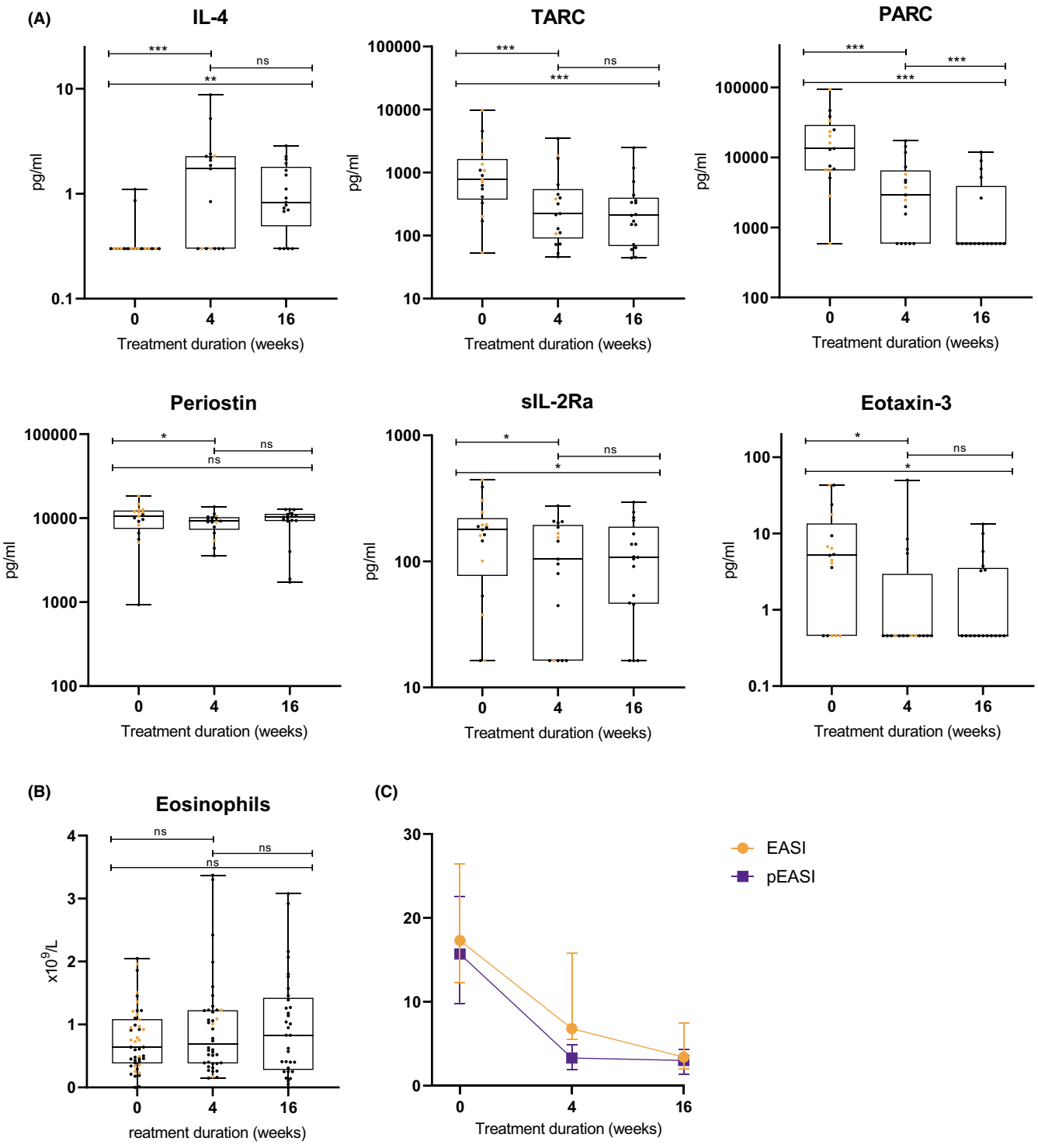

FIGURE 3 Serum biomarkers, blood eosinophil levels, and EASI and p-EASI scores during dupilumab treatment. (A) Serum biomarkers with significant change over time during dupilumab treatment. Biomarker levels were log-transformed. (B) Blood eosinophils during dupilumab treatment; (C) Median EASI and p-EASI during dupilumab treatment. *$p < .05$; **$p < .01$; ***$p < .005$. Orange dots correspond with concomitant use of immunosuppressive therapy at that time point. EASI, Eczema Area and Severity Index; IL, interleukin; ns, non-significant; PARC, pulmonary and activation-regulated chemokine; p-EASI, predicted EASI; sIL-2Ra, soluble interleukin-2-receptor alpha; TARC, thymus- and activation-regulated chemokine

serum biomarkers in pediatric patients with moderate-to-severe AD in daily practice after 28 weeks. Overall, dupilumab was well tolerated. In the future, long-term daily practice data is necessary to evaluate both long-term safety and effectiveness of dupilumab and changes in serum biomarkers by dupilumab treatment in pediatric AD.

ACKNOWLEDGMENTS

None.

FUNDING INFORMATION

The BioDay registry is sponsored by Sanofi/Regeneron, Abbvie, Leo Pharma, Pfizer and Eli Lilly. They have no influence on the collection, analysis and interpretation of the data.

CONFLICT OF INTEREST

C.M. Boesjes is a speaker for Abbvie and Eli Lilly. D.S. Bakker is a speaker for Sanofi Genzyme and Leo Pharma. F. van Wijk is a speaker and/or consultant for Janssen, Johnson&Johnson, and Takeda and has received grants from Regeneron, Leo Pharma, Sanofi Genzyme, BMS, Galapagos, and Takeda. M.S. de Bruin-Weller is a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Aslan, Arena, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi Genzyme. M. de Graaf is a consultant, advisory board member, and/or speaker for Sanofi Genzyme and Regeneron and Leo Pharma, and is an advisory board member for Eli Lilly. M.L.A. Schuttelaar is a consultant, advisory board member, and/or speaker for AbbVie, Pfizer, Leo Pharma, Sanofi Genzyme, Eli Lilly and Galderma. All other authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Kamphuis E, Boesjes CM, Loman L, et al. Dupilumab in daily practice for the treatment of pediatric atopic dermatitis: 28-week clinical and biomarker results from the BioDay registry. *Pediatr Allergy Immunol*. 2022;33:e13887. doi: 10.1111/pai.13887