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Patient-centered dupilumab dosing regimen leads to successful dose reduction in persistently controlled atopic dermatitis

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Abstract

Background: At present, no real-world studies are available on different dupilumab dosing regimens in controlled atopic dermatitis (AD). The aim of this study was to clinically evaluate a patient-centered dupilumab dosing regimen in patients with controlled AD and to relate this to serum drug levels and serum biomarkers.

Methods: Ninety adult AD patients from the prospective BioDay registry were included based on their dupilumab administration interval according to a predefined patient-centered dosing regimen. Group A ($n = 30$) did not fulfill the criteria for interval prolongation and continued using the standard dupilumab dosage (300 mg/2 weeks), group B ($n = 30$) prolonged dupilumab interval with 50% (300 mg/4 weeks), and group C ($n = 30$) prolonged dupilumab interval with 66%–75% (300 mg/6–8 weeks). AD severity score, patient-reported outcomes, serum dupilumab levels, and serum biomarkers were analyzed over time.

Results: Disease severity scores did not significantly change over time during the tapering period in any of the groups. In groups B and C, the Numeric Rating Scale (NRS)-pruritus temporarily significantly increased after interval prolongation but remained low (median NRS-pruritus ≤4). Median dupilumab levels remained stable in group A (standard dosage), but significantly decreased in groups B and C (24.1 mg/L (IQR = 17.1–45.6); 12.5 mg/L (IQR = 1.7–22.3)) compared with the levels during the standard dosage (88.2 mg/L [IQR = 67.1–123.0, $p < .001$]). Disease severity biomarker levels (CCL17/CCL18) remained low in all study groups during the whole observation period.

Conclusions: This study showed that dose reduction was successful in a subgroup of patients with controlled AD by using a patient-centered dosing regimen. These patients showed stable low disease activity and low severity biomarkers over time.

KEYWORDS
atopic dermatitis, daily practice, dose reduction, dupilumab, patient-centered dosing regimen
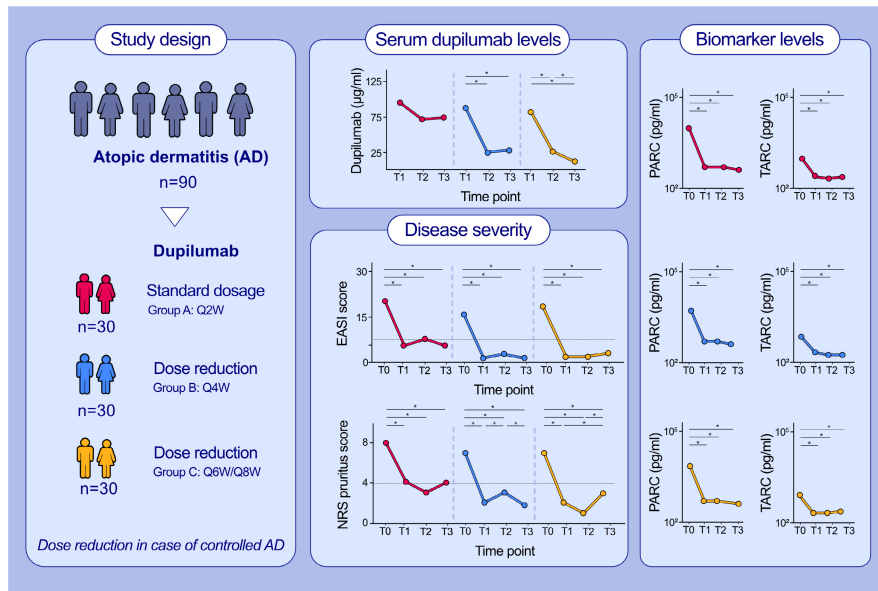
GRAPHICAL ABSTRACT

Dose reduction was successful in a subgroup of controlled AD patients by using a patient-centered dupilumab dosing regimen. Despite significantly lower dupilumab levels, the EASI-score and disease severity biomarkers (TARC/CCL17 and PARC/CCL18) in groups B (Q4W) and C (Q6W/Q8W) remained low and stable. These findings are the first step toward personalized dupilumab treatment for controlled AD patients in clinical practice.

Abbreviations: AD, atopic dermatitis; EASI, eczema area and severity index; PARC (CCL18), pulmonary and activation-regulated chemokine; PROMs, patient-reported outcome measures; Q2W, every two weeks; Q4W, every four weeks; Q6W, every six weeks; Q8W, every eight weeks; TARC (CCL17), thymus and activation-regulated chemokine

1 | INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic and relapsing inflammatory skin diseases worldwide.[1] Better understanding of the underlying immune pathogenesis of AD has led to the development of new, more targeted therapies.[2]

Dupilumab, a fully human monoclonal antibody targeting the interleukin-4 receptor alpha (IL-4Rα), thereby blocking the IL-4 and IL-13 pathway, is the first antibody based treatment that became commercially available for the treatment of AD.[3] The registered dose of dupilumab for adult patients is a loading dose of 600 mg subcutaneously, followed by 300 mg every other week (Q2W). Results from dupilumab treatment in clinical trials[2,4,5] and daily practice[6,7] show a clinically relevant improvement in physician-reported outcome measures and patient-reported outcome measures (PROMs). During long-term treatment with the standard dosage of dupilumab (Q2W), most of the patients AD remained controlled.[8]

Continuing the standard dosage in patients with persistently controlled AD might lead to overtreatment and an increase in adverse events (e.g. injection side reactions, conjunctivitis).[9] Previous literature has shown a positive effect of interval prolongation in case of conjunctivitis.[10] The question arises whether interval prolongation in the case of stable disease can reduce costs and the risk of side effects, while maintaining clinical effectiveness. At present, no literature is available for different dupilumab dosing regimens in the case of persistently controlled AD. Only one daily practice study is published regarding the effectiveness of starting dupilumab Q4W, in this study the decision for dupilumab Q4W was based on economic capacity of patients instead of controlled disease.[11] Most of the current evidence on different biologic dosing regimens in case of controlled disease in daily practice includes biologic tapering in rheumatologic diseases and psoriasis. The European recommendations for rheumatoid arthritis (RA) already described tapering strategies for biologic treatments in RA patients with persistent remission.[12] In a recent tapering study with biologics in psoriasis, tight dose reduction did not lead to persistent flares or safety issues.[13] Based on these findings, a pragmatic daily practice patient-centered dupilumab dosing regimen

was developed for patients with controlled AD during dupilumab treatment.

The primary aim of this study was to clinically evaluate a patient-centered dupilumab dosing regimen in patients with controlled AD in daily practice and to relate this to serum drug levels. Our secondary aim was to provide insight into the course of biomarkers in the context of individual dosing of dupilumab.

2 | METHODS

2.1 | Study design

This observational cohort study was performed at the department of Dermatology of the University Medical Center Utrecht and University Medical Center Groningen, the Netherlands. Ninety adult AD patients treated with dupilumab, who followed the patient-centered dosing regimen, were selected based on their dupilumab administration interval. All included patients participated in the prospective BioDay registry, which contains daily practice data on the effectiveness and safety of dupilumab for the treatment of AD, including both patient-reported outcomes (PRO's) as well as clinical parameters.

This study was approved by the local Medical Research Ethics Committee as a non-interventional study (METC 18/239) and was performed according to the declaration of Helsinki. All patients provided written informed consent.

2.2 | Patients and patient-centered dosing regimen

All patients received a loading dose of dupilumab 600 mg subcutaneously administered by a clinician (treatment baseline, T0), followed by a standard maintenance dose of dupilumab 300 mg Q2W subcutaneously administered during the first year of treatment. All patients were seen once every 3 months. A patient-centered dosing regimen for the treatment of dupilumab was developed and introduced from the beginning of 2019. This regimen was based upon tapering protocols of biological treatment in other diseases (e.g. psoriasis, RA)[13-15] and clinical experience. The injection intervals were stepwise prolonged guided by the Eczema Area and Severity Index (EASI) score. Patients were eligible for dose reduction after 52 weeks of dupilumab treatment (tapering baseline, T1) when the disease activity was controlled: EASI ≤ 7, indicating mild disease activity or less,[16] for at least 6 months. The actual decision for dose reduction of dupilumab was based on shared-decision making between patient and physician. First, the dosage was reduced to 66% of the standard dosage, by prolonging the interval to every three weeks (Q3W). If patients remained in a state of controlled disease (EASI score ≤7), the dosage was further reduced to 50% of the standard dosage, by doubling the original interval to every four weeks (Q4W). Subsequently, in case of persistently controlled disease, the dose was further reduced by gradually extending the

interval to every six weeks (Q6W) (33% of the standard dosage) followed by every eight weeks (Q8W) (25% of the standard dosage). The interval was shortened in case of increased pruritus scores reported by the patient, or increased physician-reported disease severity scores.

Patients were divided after 52 weeks of treatment (based on their dupilumab administration interval) into three groups, A, B, and C (Figure 1). Group A did not fulfill the criteria for dose reduction (e.g. uncontrolled disease or patients wish to continue standard dosage) and therefore continued standard dupilumab dosage (Q2W) throughout the whole observation period. Group B was able to prolong dupilumab interval with 50% (Q4W), and group C was able to prolong dupilumab interval with 66%–75% (Q6W/Q8W) of the standard dosage. Due to the small number of patients who were able to taper to Q6W or Q8W, these two dosing groups were combined. Time point 2 (T2) and time point 3 (T3) differ individually due to the pragmatic approach of the patient-centered dosing regimen and daily practice setting with differences in treatment duration. However, the time of dose adjustment was at least 3 months prior to the measurements of disease severity, dupilumab serum levels, and serum biomarkers.

2.3 | Outcome measures

In order to investigate the proportion of patients with persistently controlled disease despite dose reduction of dupilumab treatment, EASI score and weekly average Numeric Rating Scale (NRS)-pruritus were measured during every visit. Controlled AD in this study was defined as an EASI score ≤ 7[16]; NRS pruritus ≤4 was considered as a second treatment goal.[17]

2.4 | Serum dupilumab levels

Serum dupilumab levels were measured at T1, T2, and T3 using an enzyme-linked immunosorbent assay (ELISA). Maxisorp microtiter plates were coated overnight at room temperature (RT) with 1 μg/ml monoclonal anti-dupilumab (clone 1G11). This is a chimeric antibody of rabbit origin, with a mouse IgG2b Fc, recombinantly expressed as described before.[18] After five times washing with PBS/0.02% Tween (PT), plates were incubated for 1 h at room temperature with patient serum samples, diluted 100-fold and 2000-fold in high performance ELISA buffer (HPE, Sanquin). Subsequently, the plates were washed with PT and incubated for 1 h with 0.5 μg/ml mouse monoclonal antihuman IgG4 (clone MH164.4, Sanquin). After washing, the ELISA was developed with 1-step ultra TMB-ELISA Substrate Solution (thermoFischer) diluted with MilliQ water (ratio 3:1). The reaction was stopped with 0.2 M HCl. Delta of the absorption at 450 and 540 nm was determined and compared with a titration curve of dupilumab in each plate. Lower Limit of Quantification is 0.3 μg/mL; accuracy and precision ranged from 87% to 102% and 4.4% CV to 12.2% CV.
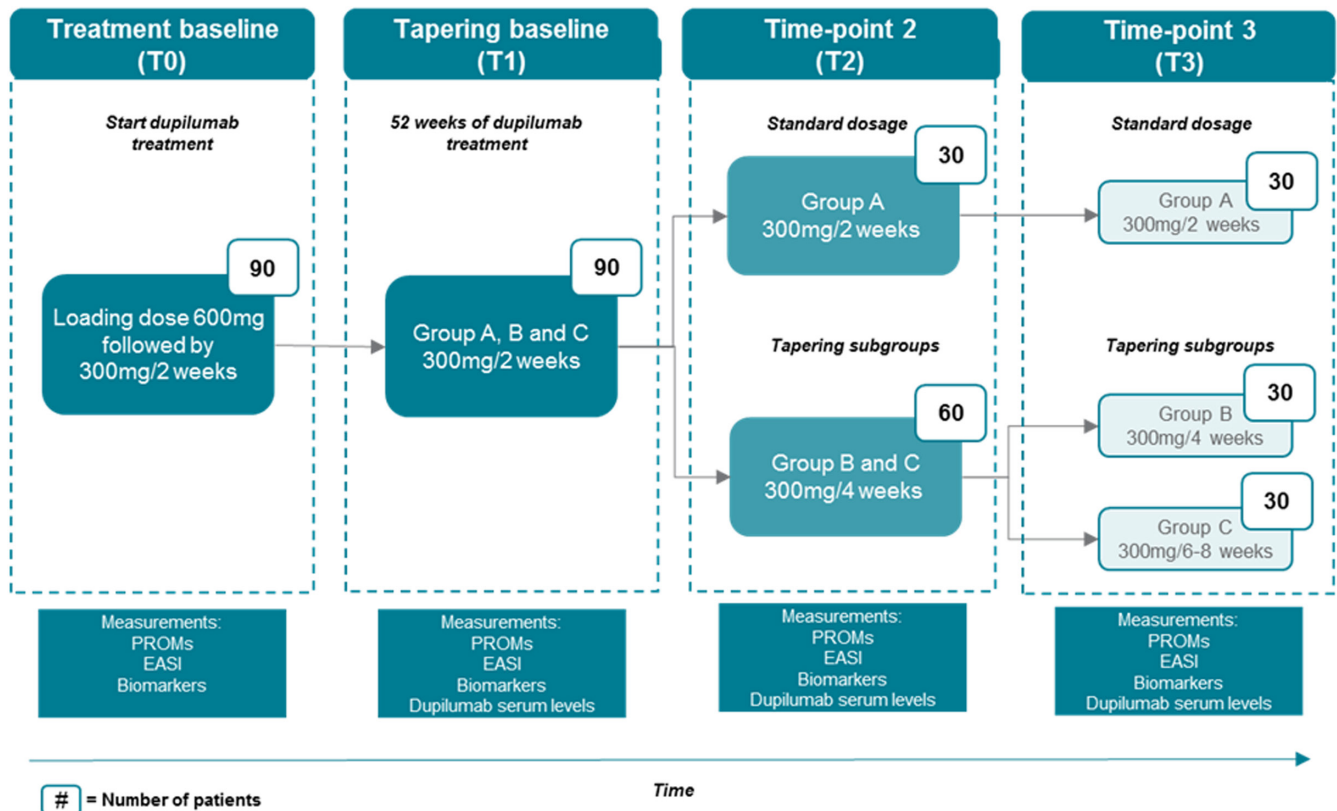
FIGURE 1 Study design with patient-centered dupilumab dosing regimen. At T2 and T3, the dupilumab dose adjustment was at least 3 months prior to the measurements. Abbreviations: EASI, Eczema Area and Severity Index; PROMs, patient reported outcome measurements

2.5 | Serum biomarkers

Serum biomarkers were measured at T0, T1, T2, and T3 using multiplex immunoassays as previously described.[19] Nineteen biomarkers associated with different disease pathways were measured: disease severity-associated markers (IL-22, pulmonary and activation-regulated chemokine (PARC/CCL18), thymus- and activation-regulated chemokine (TARC/ CCL17), periostin (OSF-2), and soluble interleukin-2 receptor alpha (sIL-2Rα)), Th2-associated markers (IL-4, IL-5, and IL-13), Th17-associated markers (IL-6, IL-17, IL-22, and IL-23), Th22-associated marker (IL-22), Th1-associated markers (IL-12 and IP-10), inflammatory markers (IL-1b, IL-10, GCSF, and MCP1), and eosinophil markers (IL-5, eotaxin-1, and eotaxin-3).

2.6 | Statistical analysis

Data were analyzed for each study group at initiation of dupilumab treatment (T0), after 52 weeks of treatment (T1), and at the two time points (T2 and T3) after implementing the patient-centered dosing regimen. Differences in clinical outcome measures and biomarker levels between treatment baseline (T0) and tapering baseline (T1), and between tapering baseline (T1) and subsequent time points T2 and T3 were compared for each group separately using the paired Wilcoxon signed-rank test. Additionally, serum dupilumab levels

at T2 and T3 were compared with tapering baseline (T1) using the paired Wilcoxon signed-rank test for the groups separately.

Serum dupilumab levels from group A (Q2W) were used as reference category for groups B and C to assess the effect of dose reduction on serum dupilumab levels. Differences in serum dupilumab levels were compared between the subgroups B and C vs. standard dosage group A at T1, T2, and T3 using the Mann Whitney test. Serum biomarker levels were compared between the subgroups A, B, and C at each time point using the Wilcoxon signed-rank test. Serum biomarker levels were normalized by a log-transformation for the radar plots.

False discovery rate was used to correct for multiple testing. p-values <.05 were considered statistically significant. All statistical analyses were conducted using SPSS (for Windows, version 25.0, SPSS Inc.), Prism (version 7.4; GraphPad), and R (Version 1.3.1093).

3 | RESULTS

3.1 | Patient population and implementation of the patient-centered dosing regimen

A total of 90 adult AD patients with a follow-up of at least 91 weeks were included based on their dupilumab administration intervals. At dupilumab treatment initiation, the mean age was 42.4 (SD 16.4) and

the majority of patients were male (65.6%, n = 59) (Table 1). A total of 23 patients (25.6%) used immunosuppressive drugs at the start of dupilumab treatment (Table 2). The median EASI score at start of dupilumab (T0) was 17.9 (IQR = 12.4–25.3) with no significant differences between the three subgroups (p = .29). At T0, patients reported a median NRS pruritus score of 7.0 (IQR = 5.0–8.0) with no significant differences between the three subgroups (p = .15).

3.2 | Clinical outcome measures

3.2.1 | Differences in EASI score within study groups over time

Dupilumab treatment led to a significant decrease of disease severity during the first year of treatment (p < .001) with a median EASI score of 17.9 (IQR = 12.4–25.3) at treatment baseline (T0) compared with a median EASI score of 2.7 (IQR = 1.0–5.4) after one year of treatment (T1) in the total cohort. In group A (not fulfilling dose reduction criteria and continued standard dosage), disease severity was stable over time, with no significant differences observed in EASI scores comparing T1 with T2 and T3 (p = .27 and p = .87). At T1, T2, and T3, a total of 50.0%, 40.0%, and 50.0% of the patients in group A had controlled AD (EASI ≤ 7), respectively. The most frequently reported reasons for continuation of standard dosage despite controlled disease were severe asthma and patient's wish (e.g. high pruritus score or fear for reoccurrence of symptoms). Additionally, the proportion of patients in whom AD remained controlled (EASI ≤ 7) despite dose reduction of dupilumab treatment was analyzed. At T2 (dosage Q4W for at least 3 months), 83.3% (n = 25) of the patients in group B, and 86.7% (n = 26) of the patients in group C had controlled AD. No

significant differences in EASI score were observed between T1 and T2 in both subgroups (p = .17 and p = .79). At T3, an extended dosing interval of Q6W/Q8W had been applied in group C of which 28 patients (93.3%) had controlled AD, and no significant difference in EASI score was observed compared with T1 (p = .19) (see Table 2 and Figure 2).

3.2.2 | Differences in NRS pruritus within study groups over time

Dupilumab treatment significantly decreased NRS pruritus during the first year of treatment (p < .001) with a median score of 7.0 (IQR = 5.0–8.0) at treatment baseline (T0) compared with a median score of 2.0 (IQR = 1.0–4.0) after one year of treatment (T1) in the total cohort. At T1, T2, and T3, a total of 65.4%, 70.0%, and 68.8% of the patients in group A had NRS pruritus ≤4, respectively. In group A, NRS pruritus was stable over time, and no significant differences were observed in NRS pruritus comparing T1 with T2 and T3 (p = .88 and p = .47). At T2 (dosage Q4W for at least 3 months), 79.2% of the patients in group B, and 88.0% of the patients in group C had NRS pruritus ≤4. In the dose tapering group B, the median NRS pruritus score at T2 (median 3.0; IQR = 2.0–4.0) was significantly higher compared with T1 (median 2.0; IQR = 1.0–3.0; p = .03). No significant difference for group B was found between T1 (median 1.7; IQR = 0.8–3.6) and T3 (median 1.5; IQR = 0.6–3.9) (p = .92). At T3 (dosage Q6W/Q8W for at least 3 months), 66.7% of the patients in group C had NRS pruritus ≤4. In group C, the median NRS pruritus score at T3 was significantly higher (median 3.0; IQR = 1.0–5.0) compared with T1 and T2, respectively, 2.0 (IQR = 1.0–3.0), p = .01 and 1.0 (IQR = 0.0–3.5), p = .03 (Table 2 and Figure 2).

TABLE 1 Patient characteristics per study group

	Total	Group A Q2W	Group B Q4W	Group C Q6W/Q8W	Adjusted p-value
N	90 (100)	30 (100)	30 (100)	30 (100)	
Gender (male), n (%)	59 (65.6)	18 (60.0)	23 (76.7)	18 (60.0)	.38
Age, mean (SD)	42.4 (16.4)	36.2 (15.9)	47.6 (17.2)	43.3 (14.3)	.29
BMI, mean (SD)	26.1 (5.4)	28.3 (6.1)	25.7 (6.2)	24.8 (3.2)	.29
Missing	26 (28.9)	11 (36.7)	8 (26.7)	7 (23.3)	
Age at AD onset[a], n (%)					
Childhood	80 (88.9)	28 (93.3)	26 (86.7)	26 (86.7)	.66
Adolescence	3 (3.3)	1 (3.3)	1 (3.3)	1 (3.3)	
Adulthood	7 (7.8)	1 (3.3)	3 (10.0)	3 (10.0)	
Atopic comorbidity[a], n (%)					
Allergic asthma	54 (60.0)	19 (63.3)	21 (70.0)	14 (46.7)	.29
Allergic rhinitis	66 (73.3)	22 (73.3)	25 (83.3)	19 (36.3)	.31
Allergic conjunctivitis	56 (62.2)	20 (66.7)	21 (70.0)	15 (50.0)	.31
Food allergy	46 (51.1)	19 (63.3)	11 (36.7)	16 (53.3)	.29

Abbreviations: BMI, body mass index; SD, Standard deviation.

[a]No missings were found for age at AD onset and atopic comorbidities.

TABLE 2 Treatment characteristics per study group for each time point

	Treatment baseline (T0)	Tapering baseline (T1)	Time point 2 (T2)	Time point 3 (T3)
Total cohort, *n*	90	90	90	90
Group A				
Dupilumab Q2W, *n*	30	30	30	30
Mean treatment duration (weeks)	0 (0)	52.4 (3.7)	84.5 (8.6)	115.3 (15.7)
Use of immunosuppressive drugs, *n* (%)	8 (26.7)	2 (6.7)	2 (6.7)	2 (6.7)
Missing	1 (3.3)	9 (30.0)	11 (36.7)	7 (23.3)
EASI score, median (IQR)	20.9 (12.5–30.3)	6.4 (3.1–8.6)	7.5 (3.7–9.5)	5.4 (2.2–9.7)
Missing	0 (0)	1 (3.3)	4 (13.3)	1 (3.3)
Weekly average pruritus NRS, median (IQR)	8.0 (6.0–9.0)	4.0 (2.0–5.0)	3.0 (1.3–5.0)	4.0 (3.0–5.0)
Missing	5 (16.7)	4 (13.3)	10 (33.3)	14 (46.7)
Serum TARC levels, median (IQR)	2890.0 (1085.5–8039.5)	418.0 (315.3–951.0)	370.5 (180.3–684.5)	556.0 (298.0–817.0)
Missing	0 (0)	2 (6.7)	4 (13.3)	5 (16.7)
Serum dupilumab levels, median (IQR)	n.a.	95.4 (40.6–108.8)	71.4 (44.2–101.2)	73.6 (38.0–118.0)
Missing	n.a.	0 (0)	4 (13.3)	0 (0)
Group B				
Dupilumab Q4W, *n*	30	30	30	30
Mean treatment duration (weeks)	0 (0)	52.1 (4.0)	115.5 (22.6)	141.0 (22.5)
Use of immunosuppressive drugs, *n* (%)	6 (20.0)	2 (6.7)	1 (3.3)	1 (3.3)
Missing	0 (0)	10 (33.3)	7 (23.3)	3 (10.0)
EASI score, median (IQR)	15.8 (11.8–19.7)	1.7 (0.75–3.6)	2.5 (1.2–3.8)	1.5 (0.6–3.9)
Missing	0 (0)	1 (3.3)	0 (0)	0 (0)
Weekly average pruritus NRS, median (IQR)	7.0 (4.0–8.0)	2.0 (1.0–3.0)	3.0 (2.0–4.0)	2.0 (1.0–3.0)
Missing	1 (3.3)	1 (3.3)	6 (20.0)	7 (23.3)
Serum TARC levels, median (IQR)	1413.5 (899.5–2948.5)	291.0 (211.0–438.3)	301.0 (210.8–427.3)	291.0 (202.5–407.3)
Missing	0 (0)	2 (6.7)	0 (0)	2 (6.7)
Serum dupilumab levels, median (IQR)	n.a.	88.9 (65.3–127.0)	24.1 (17.1–45.6)	28.6 (11.7–47.9)
Missing	n.a.	1 (3.3)	0 (0)	0 (0)
Group C				
Dupilumab Q6W/Q8W, *n*	30	30	30	30
Mean treatment duration (weeks)	0 (0)	52.7 (3.4)	95.7 (20.2)	139.6 (22.1)
Use of immunosuppressive drugs, *n* (%)	9 (30.0)	0 (0)	2 (6.7)	1 (3.3)
Missing	0 (0)	10 (33.3)	13 (43.3)	7 (23.3)
EASI score, median (IQR)	18.4 (12.2–26.8)	2.3 (0.6–3.1)	2.0 (0.6–3.6)	2.9 (0.7–5.2)
Missing	0 (0)	0 (0)	3 (10.0)	0 (0)
Weekly average pruritus NRS, median (IQR)	7.0 (4.3–8.0)	2.0 (1.0–3.0)	1.0 (0.0–3.5)	3.0 (1.0–5.0)
Missing	2 (6.7)	2 (6.7)	5 (16.7)	3 (10.0)
Serum TARC levels, median (IQR)	2948.0 (1186.3–6945.0)	364.0 (204.0–476.0)	281.0 (213.0–578.0)	295.5 (185.0–569.8)
Missing	0 (0)	1 (3.3)	3 (10.0)	2 (6.7)
Serum dupilumab levels, median (IQR)	n.a.	82.0 (66.8–101.0)	25.8 (20.3–48.8)	12.5 (1.7–22.3)
Missing	n.a.	0 (0)	3 (10.0)	0 (0)

Abbreviations: EASI, Eczema Area and Severity Index; IQR, interquartile range; n.a., non-applicable; NRS, numerical rating scale; TARC, thymus- and activation-regulated chemokine.
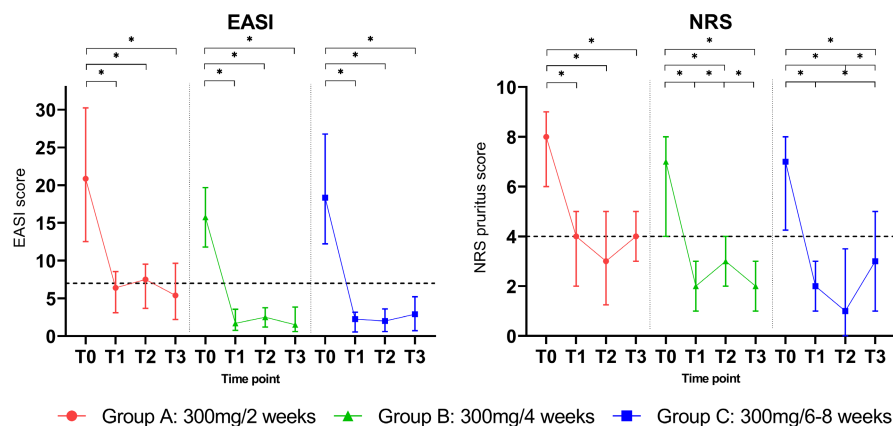
Clinical outcome measures

FIGURE 2 EASI and NRS scores per study group per time point. Cut-off value EASI score of ≤7 indicating controlled AD; NRS-pruritus score of ≤4 is considered as a treatment goal. *p-value < .05. Symbols represent medians with interquartile range (vertical lines).

3.3 | Serum dupilumab levels

In the standard dosage group A, serum dupilumab levels remained stable over time. The median dupilumab levels in the individual dosing groups B and C decreased significantly from a median of 88.9 mg/L (IQR = 65.3–127), and 82.0 mg/L (IQR = 66.8–101.0) at T1 to 24.1 mg/L (IQR = 17.1–45.6), and 25.8 mg/L (IQR = 20.3–48.8) at T2 ($p < .001$, $p < .001$). In patients tapering dupilumab to Q6W/Q8W (group C), serum dupilumab levels further decreased to 12.5 mg/L (IQR = 1.7–22.3) at T3 ($p < .001$) (Figure 3).

As expected, significantly higher serum dupilumab levels were observed in the standard dosage group (A) compared with the study groups B and C at T2 and T3 ($p < .001$ and $p < .001$).
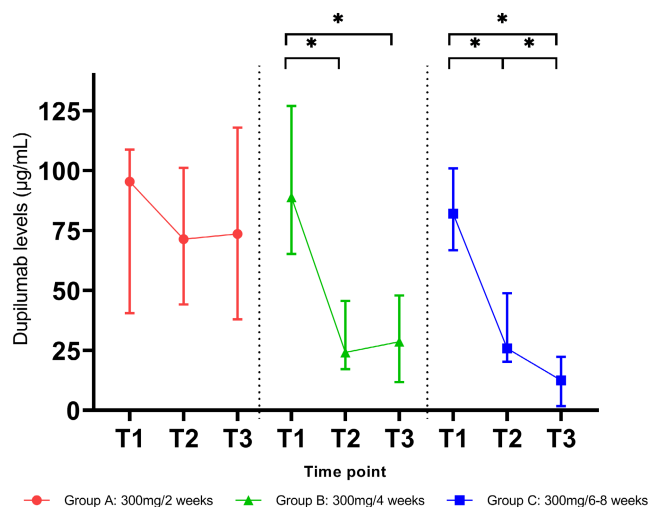
3.4 | Serum biomarker levels

A total of 19 serum biomarkers were measured via multiplex immunoassays. Extreme outliers ($n = 4$ patients) were excluded due to possible detection errors.

In all subgroups, severity-related serum biomarkers PARC/CCL18 ($p = .001$) and TARC/CCL17 ($p = .001$) significantly decreased during the first year of dupilumab treatment (all patients using Q2W) (Figure 4). During the tapering period, PARC/CCL18 and TARC/CCL17 remained low in all groups at all time points (T1, T2, and T3). Looking at the effect of tapering on the other serum biomarkers levels, no relevant significant differences were found for other severity-associated biomarkers and Th1, Th2, Th17-related markers in groups A (only MCP1 had a significant difference at T3 compared with T1), B, and C at T2 and T3 compared with T1 (Figure S1). Radar plots were used to visualize differences in biomarker levels between groups A, B, and C for each time point (Figure S2). The biomarker profiles of the different dupilumab dosing groups were largely overlapping at each time point with no significant differences between the study groups. This indicates that the biological markers were stably low during tapering of dupilumab in AD with no effect of interval prolongation on biological activity regarding the selected biomarkers.

FIGURE 3 Serum dupilumab levels per study group at each time point. *p-value < .05. Symbols represent medians with interquartile range (vertical lines).

4 | DISCUSSION

In this study, dose reduction was successful in a subgroup of patients with controlled AD by using a patient-centered dupilumab dosing regimen. Disease activity and severity biomarkers remained low and stable over time. Although, NRS scores temporarily increased after interval prolongation, the changes in NRS scores were small and NRS scores remained low (median NRS pruritus scores ≤4).

To our knowledge, only one study (SOLO-continue) has investigated the effect of different dupilumab dosing regimens on disease activity.[20] This randomized controlled trial was a continuation of the SOLO study, in which patients continued dupilumab treatment in different dose regimens. High-responding dupilumab-treated patients at week 16 (reaching EASI-75 or IGA 0–1) in the SOLO-continue study were re-randomized 2:1:1:1 to continue their original regimen of dupilumab (Q1W or Q2W) or to receive dupilumab Q4W or Q8W or a placebo for 36 weeks. In contrary to our study, the authors in the SOLO-continue study concluded

FIGURE 4 Significant differences over time in serum levels of disease severity biomarker TARC and PARC within study groups. *p-value < .05. In the clustered graphs, symbols represent medians with interquartile range (vertical lines). PARC/CCL18, pulmonary and activation-regulated chemokine; TARC/CCL17, thymus- and activation-regulated chemokine.
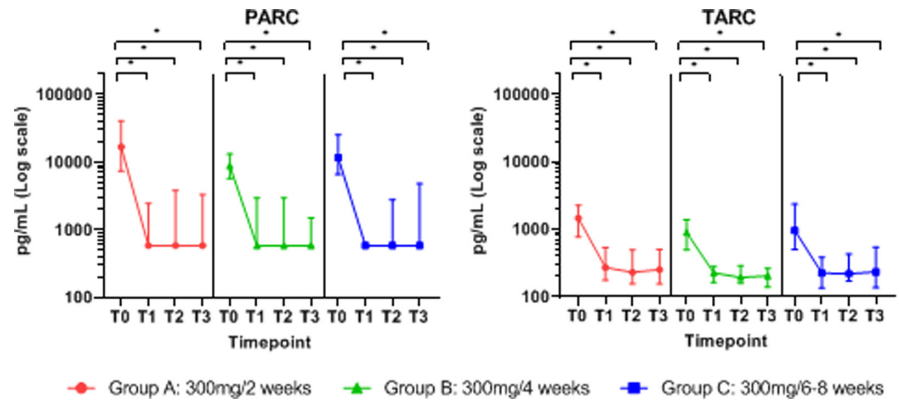
that dose reduction resulted in a diminution of response for all endpoints (including EASI and NRS pruritus) and therefore recommended the approved regimen of dupilumab Q2W for long-term treatment.[20] Dose reduction was applied based on IGA or relative delta EASI at an early point in the treatment (16 weeks) without the possibility of tapering slowly over time. In our study, a patient-centered dosing regimen was used based on absolute EASI score (mild disease) for at least 6 months and shared-decision making, and started after a much longer treatment period of 52 weeks. In addition, the dosing interval was gradually prolonged and every dose adjustment lasted at least 3 months before initiating the next dose adjustment. Since our study was a daily practice study, all cases were evaluated individually at all time points. The shared-decision making and tapering after persistent controlled disease might explain why prolonging the dupilumab dosing interval was more successful in our study compared with the SOLO-continue study. Additionally, Lee et al. analyzed clinical practice data on the clinical effectiveness of dupilumab Q4W and concluded that monthly dupilumab therapy was clinically effective and safe in adult patients with moderate-to-severe AD.[11] The dosing of dupilumab Q4W was not decided by disease activity or patient characteristics but by the patients themselves and mainly based on their economic capacity (due to lack of reimbursement of dupilumab in their country). Additionally, 70.2% (40/57) of the AD patients who received dupilumab Q4W had concomitant treatment with weekly methotrexate. Lee et al. showed EASI-50 and EASI-75 responses in 84.2% and 47.4% of the AD patients using dupilumab Q4W at week 16[11] compared with EASI-50 (85.7%–98.1%) and EASI-75 (60.6%–81.5%) response rates for patients using dupilumab Q2W at week 16 in other recently published real-world studies.[21–24] These results indicate that starting dupilumab treatment with a prolonged dosing interval may result in an overall less favorable treatment outcome, which was not the case in our individual dose reduction protocol based on disease activity.

Although AD remained controlled in the majority of patients in groups B and C (EASI ≤ 7), NRS scores temporarily increased after dose reduction. The clinical relevance of these differences are questionable as the changes in NRS scores were small and inconsistent and median NRS scores remained ≤4, which is also considered as a treatment target.[17]

In our study, serum dupilumab levels (Q2W) were comparable with levels described in clinical trials.[25–27] While serum dupilumab levels decreased significantly over time in the dose reduction groups (groups B and C), the EASI score remained remarkably stable and low in these study groups. Although the precise mechanism of action of dupilumab has not been completely elucidated,[28] binding of dupilumab to (skin homing) T- and B-cells seems to be able to reduce Th2-related cytokines and IgE production.[29–32] Sufficient clinical response despite dose reduction might be explained by persistent IL-4Rα saturation by dupilumab due to a relatively high concentration of dupilumab in sera or inter-patient variability in the target receptor (IL-4Rα) availability. Perhaps IL-4Rα saturation by dupilumab can also be achieved with lower serum dupilumab levels, and full IL-4Rα saturation might not even be needed to achieve maximum clinical effectiveness. Therefore, more research is necessary to determine inter-patient variability and the pharmacokinetics of dupilumab in different dosing regimens[33] and to determine how drug levels are related to IL-4Rα saturation and clinical effectiveness.

The biomarker profiles of the different dupilumab dosage groups were largely comparable over time. Additionally, the severity markers PARC/CCL18 and TARC/CCL17 remained significantly lower at every time point for all subgroups compared with severity marker levels at the time of start of dupilumab treatment. Previous studies observed significantly suppressed type-2 inflammatory biomarkers in serum, including TARC/CCL17 and PARC/CCL18, after 16 weeks of dupilumab treatment.[24,30] After 52 weeks of dupilumab treatment, Bakker et al. found that dupilumab treatment completely blocked IL-4Rα expression, accompanied by a decrease in serum TARC/CCL17 levels, and a rapid decrease of Th2 and Th22 cytokine production.[29] In our study, disease severity markers also remained low during a follow-up of at least 91 weeks, despite dose reduction of dupilumab. Other biomarkers also did not change while tapering dupilumab in persistently controlled AD compared with standard dosage (dupilumab Q2W) suggesting stable disease over time despite dose tapering.

4.1 | Limitations

This study has some limitations. First, the included patients were divided into three study groups based on their dupilumab

administration interval. As a result, this study subscribes the ability of dose reduction on an individual level but more research is needed to determine the percentage of successful (and unsuccessful) dose reduction in daily practice as patients who shortened interval after dose reduction were not included. Second, the patient-centered dosing regimen was based on controlled AD. Patients in group A, who were not eligible for or did not agree with dose tapering, showed higher disease severity scores compared with the groups B and C. Therefore, a direct comparison between standard dosing and dose reduction was not feasible in this study design.

5 | CONCLUSION

This study showed that patient-centered dose reduction after 52 weeks of dupilumab was successful in a subgroup of patients with persistently controlled AD. Despite significantly lower dupilumab levels, the EASI score and disease severity biomarkers (TARC/CCL17 and PARC/CCL18) in groups B (Q4W) and C (Q6W/Q8W) remained low and stable. These findings are the first step toward personalized dupilumab treatment for controlled AD patients in clinical practice.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to conception and design of this study and have been involved in drafting or revising the manuscript. All authors have given final approval of the version to be published an agreed to be accountable for all aspects of the work.

CONFLICT OF INTEREST

L. Spekhorst is a speaker for Abbvie. D. Bakker is a speaker for Sanofi Genzyme and LEO Pharma. J. Drylewicz has nothing to disclose. T. Rispens has nothing to disclose. F. Loeff has nothing to disclose. C. Boesjes is a speaker for Abbvie and Eli Lilly. J. Thijs is a speaker for Sanofi Genzyme and LEO Pharma. G. Romeijn has nothing to disclose. L. Loman has nothing to disclose. M. Schuttelaar is an advisor, consultant, speaker and/or investigator for AbbVie, Pfizer, LEO Pharma, Regeneron, Sanofi Genzyme, Eli Lilly and Galderma. She has received grants from Regeneron, Sanofi Genzyme, Novartis and Pfizer. F. van Wijk is a consultant, advisory board member, and/or speaker for Janssen, Johnson&Johnson, and Takeda, and received research funding from Pfizer, Takeda, BMS, Leo Pharma, and Regeneron (non-related the submitted work). M. de Graaf is an advisor, consultant, speaker or investigator for Sanofi-Genzyme, Regeneron Pharmaceuticals, LEO Pharma and Eli Lilly. M. de Bruin-Weller has been a consultant, advisory board member, and/or speaker for AbbVie, Almirall, Arena, Aslan, Eli Lilly, Galderma, Janssen, Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzyme.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

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