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Successful tapering of dupilumab in patients with atopic dermatitis with low disease activity: a large pragmatic daily practice study from the BioDay registry

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Abstract

Background Limited data are available regarding patient-centred dosing of dupilumab for atopic dermatitis (AD) in daily practice.

Objectives To evaluate our patient-centred dupilumab dosing regimen in daily practice, to assess prognostic factors for successful tapering and to estimate medication-related cost savings.

Methods This prospective multicentre study included adult patients with AD, participating in the BioDay registry, treated with dupilumab for ≥ 1.3 years. Interval prolongation was considered in the case of dupilumab standard dose for ≥ 1 year and persistent controlled AD [Eczema Area and Severity Index (EASI) ≤ 7; ≥ 6 months]. Primary endpoints were the mean EASI and Numeric Rating Scale (NRS)-pruritus after the start of tapering. Prognostic factors for successful tapering were analysed with logistic regression and a cost-savings analysis was performed.

Results A total of 595 patients were included, of whom 401 patients [mean EASI 2.5 (SD 2.3); NRS-pruritus of 2.4 (SD 1.9) at the start of tapering] prolonged their dupilumab interval. In 83.3% of these patients tapering was successful; most patients used dupilumab every 3 or 4 weeks (Q3W/Q4W). A significant small increase was observed for EASI (highest mean 3.5) and NRS-pruritus (highest mean 3.2) ($P < 0.001$); however, scores remained low. Predicting successful tapering showed nonsignificant odds ratios for all incorporated variables. The estimated cost savings was €3 977 033.98 for 401 patients between January 2019 and June 2022.

Conclusions This study showed successful tapering of dupilumab in 83.3% of patients with AD who attempted tapering, while maintaining controlled disease and with the majority using Q3W/Q4W. Interval prolongation can be beneficial both for the patient and from a socio-economic perspective.

What is already known about this topic?

- Recently we have shown that dupilumab dose reduction was successful and safe in a subgroup of patients with controlled atopic dermatitis (AD) by using a patient-centred dosing regimen.

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What does this study add?

- This study showed successful tapering of dupilumab in 83.3% of patients with AD who attempted tapering, while maintaining controlled disease and with the majority using dupilumab every 3 or 4 weeks.
- Interval prolongation can be beneficial both for the patient and from a socio-economic perspective.

Atopic dermatitis (AD) is a complex and heterogeneous skin disorder characterized by a disrupted epidermal barrier function, skin inflammation and chronic pruritus. Knowledge of the immunological pathogenesis of AD has expanded in the past decade leading to the development of new advanced targeted treatments. One of these treatments is dupilumab, a fully human monoclonal antibody that targets the interleukin (IL)-4 receptor α (IL-4Rα), thereby inhibiting the IL-4 and IL-13 cytokine pathways. Based on clinical trials, the label recommends for adult patients a loading dose of dupilumab 600 mg subcutaneously followed by a maintenance dose of 300 mg every other week (Q2W).[1] Dupilumab treatment showed a clinically relevant improvement on physician- and patient-reported outcome measures and the majority of patients maintained controlled AD over the long term using the standard dosage of 300 mg Q2W.[2]

Despite dupilumab's effectiveness, antibody-based treatment can have some disadvantages such as adverse events (AEs) and high costs.[3] Dose reduction of dupilumab while maintaining clinical effectiveness enables individual dosing, which will benefit the patient as well as lowering the budget impact. We recently investigated the safety and effectiveness of a patient-centred dupilumab dosing regimen on an individual patient level.[4] This study showed that dose reduction was successful and safe in a subgroup of patients with controlled AD, as supported by other daily practice studies.[5,6] However, more research is needed to determine the percentage of successful dose reduction in daily practice and to identify prognostic factors for successful tapering.

Therefore, the aim of this study was to evaluate our patient-centred dupilumab dosing regimen in a large daily practice cohort. Our secondary aim was to identify clinical characteristics for successful tapering and to estimate medication-related cost savings.

Patients and methods

Study design and patient population

This study was part of the Dutch BioDay registry,[7] a prospective, observational and multicentre cohort study that consecutively includes all patients with AD who start dupilumab treatment. Adult patients with AD were selected with a dupilumab treatment duration of ≥ 1 year based on our patient-centred dosing regimen (Figure S1; see Supporting Information). Patients with controlled disease [Eczema Area and Severity Index (EASI) ≤ 7[8]], who tapered dupilumab before 1 year of dupilumab treatment (e.g. due to patient's wish or AEs), were also included ($n=34$). In the case of multiple treatment episodes, the longest treatment episode was included in the analyses. The data lock was in June 2022.

In patients with AD with comorbid asthma, interval prolongation might lead to an asthma exacerbation. Therefore, patients with severe comorbid asthma (e.g. systemic prednisone use or yearly hospital admission) were advised to continue the recommended dose of dupilumab 300 mg Q2W ($n=5$). Patients who tapered dupilumab before 52 weeks due to AEs and did not have controlled disease ($n=7$) or used 300 mg every week ($n=13$) were excluded as they did not fulfil the criteria for the patient-centred dosing regimen.

The BioDay registry was considered noninterventional by the local medical ethics committee (METC 18/239) and the study was performed according to the Helsinki Declaration. All patients provided written informed consent.

Patient-centred dosing regimen

At baseline, all patients received a loading dose of dupilumab 600 mg subcutaneously, followed by dupilumab 300 mg Q2W in the first year. A standardized patient-centred dosing regimen for dupilumab treatment was developed and has been applied within the BioDay registry since 2019. Dupilumab interval prolongation was considered in the case of dupilumab treatment Q2W for at least 1 year and controlled AD (EASI ≤ 7) for ≥ 6 months (Figure S1).[4] The decision for actual interval prolongation was based on shared decision-making. Patients continued with the longest possible dosing interval while maintaining controlled AD. In cases of disease flares and inadequate response to intensifying topical treatment, patients returned to the previous effective dose interval. During each visit the amount of the most frequently used topical steroids per week was recorded with the following categories: 0, 0–10, 10–30 or >30 grams.

Outcome measures

The primary outcome measures were assessed at every visit using the EASI[8] and the Numeric Rating Scale (NRS) (range 0–10)[9] of the average weekly pruritus. Secondary endpoints were the proportions of patients achieving EASI ≤ 7 (indicating controlled disease[8]), Investigator Global Assessment (IGA) ≤ 2 (indicating mild disease[10]) and NRS-pruritus ≤ 4 (considered as treat-to-target[11]).

(Un)successful tapering

Patients in whom the dosing interval was shortened to Q2W after initial tapering, and who continued Q2W $\geq 50\%$ of the follow-up time, were defined as 'tapering failures'. Patients who shortened the interval but maintained a prolonged interval [e.g. every 4 weeks (Q4W) to every 3 weeks (Q3W)] or did another tapering attempt and succeeded (i.e. $\geq 50\%$ of the follow-up time prolonged interval) were not considered to be 'tapering failures'. Every patient with a dose reduction

(prolonged interval ≥ Q3W) who did not fit the definition of 'tapering failure' was considered to be successful.

Cost-savings analysis

Cumulative reduced dupilumab doses and costs were compared with the standard dose during the whole observation period (January 2019–June 2022). The cumulative dose after tapering baseline was calculated for each patient and corrected for treatment duration per dose interval. Indirect costs, such as other medical costs or visit costs, were not included. Dupilumab costs were based on actual Dutch prices during the study.

Statistical analyses

The start of tapering was defined as the tapering baseline. Due to the pragmatic daily practice approach of this study, the timing of the tapering baseline differed per patient. The percentage of patients per dosing interval after 1 year was determined by examining the distribution of different dosing intervals at every visit. The effect of the tapering protocol on the primary outcomes EASI and NRS over time was analysed with a linear regression model. We included a residual covariance (i.e. generalized estimating equations type) matrix in the model to correct for multiple measurements over time within patients. This model is robust for missing at random as there are fewer follow-up outcomes due to patients not reaching a particular time point. Results were reported as means with 95% confidence intervals (CIs). We calculated one overall *P*-value for time with a likelihood ratio test.[12]

Additionally, we explored prognostic factors for successful tapering with logistic regression. We defined the following possible prognostic factors for successful dose tapering: sex, age, body mass index, time of onset of AD, presence of atopic comorbidities, referral hospital and, additionally, EASI, IGA, NRS-pruritus and eosinophils at the start of dupilumab treatment and the tapering baseline. For continuous prognostic factors, the assumption of linearity was assessed with restrictive cubic splines.[13] When applicable, patients with a second successful tapering attempt were included in the analysis only once; any correction for multiple measurements was therefore redundant. Estimation of the logistic regression models was performed with Firth's correction, as we included a relatively high number of prognostic factors in the analysis.[14] Results were presented as odds ratios with 95% CI and *P*-values. Prior to the analysis, we noted missing values on multiple prognostic factors. As a complete case analysis may introduce bias and loss of statistical power, we applied multiple imputation (MI) for logistic regression. MI was performed with predictive mean matching for continuous variables and logistic regression for categorical variables. All the pre-specified prognostic factors and outcomes were included in the imputation. Based on the amount of missing data, data were imputed 50 times;[15] the analysis was performed on each imputed dataset. Results were subsequently pooled with Rubin's rule.

All data were analysed using IBM SPSS Statistics 26.0.0.1 (IBM, Armonk, NY, USA) and SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline and treatment characteristics for the total cohort

A total of 595 BioDay patients (mean age 42.0 years, SD 15.4) from four academic and seven nonacademic Dutch hospitals were included; 356 patients (59.8%) were male. The mean EASI and NRS-pruritus before the start of dupilumab treatment was 18.2 (SD 11.8) and 6.8 (SD 2.3), respectively (Table 1).

Primary and secondary endpoints after implementing the patient-centred dupilumab dosing regimen

Over time, 401 of 595 (67.4%) patients prolonged their dupilumab interval; the mean treatment duration at the start of tapering (tapering baseline) was 65.5 (SD 25.3) weeks, with a mean EASI of 2.5 (SD 2.3) and NRS-pruritus of 2.4 (SD 1.9) (Tables 1 and 2). An overview of the dupilumab dosing intervals per visit and a flowchart of patients is shown in Figure 1 and Figures S2 and S3 (see Supporting Information). Both mean EASI and NRS-pruritus in the tapering cohort ($n=401$) changed significantly over time ($P<0.001$) [mean follow-up time of 68.5 weeks (SD 48.2)], with an increase to 3.1 (95% CI 2.7–3.4) and 3.0 (95% CI 2.8–3.3) after 3 months of tapering, respectively (Figure 2). After 6 months of tapering this was 3.0 (95% CI 2.6–3.4) and 2.8 (95% CI 2.5–3.1), respectively, for EASI and NRS-pruritus. The mean EASI score remained low, with the highest estimated mean of 3.5 (95% CI 2.7–4.2) after 18 months of tapering. Similarly, NRS-pruritus remained low, with the highest estimated mean of 3.2 (95% CI 2.8–3.6) after 12 months of start tapering (Figure 2). Notably, the upper limits of all CIs remained for EASI below 7 and for NRS-pruritus below 4, the cut-off points for mild disease. The percentages of patients with EASI ≤ 7 and NRS-pruritus ≤ 4 during tapering are shown in Table 2.

At the tapering baseline ($n=401$), at which every patient used dupilumab 300 mg Q2W, 32.9% of the patients ($n=107$) used no topical steroids, 27.4% ($n=89$) used 0–10 g weekly, 35.1% ($n=114$) used 10–30 g weekly and 4.6% ($n=15$) used > 30 g weekly ($n=76$ missing). At all tapering doses, the amount of the most frequently used topical steroids was slightly higher compared with the tapering baseline (Q2W). During tapering, fewer patients used no topical steroids, while using 0–10 g weekly became the largest group in every dose group (Figure S4; see Supporting Information). Follow-up measurements of 194 patients, not able ($n=80$) or willing to taper ($n=114$), are shown in Table S1 (see Supporting Information).

(Un)successful tapering

In total, 83.3% (334 of 401) of the patients who attempted interval prolongation successfully continued dupilumab treatment with a prolonged interval (Table 2 and Figures S2 and S3). In the tapering cohort ($n=401$), shortening of the interval to the standard dose of 300 mg Q2W after prolongation was needed in 21.2% (85 of 401) of the patients after a mean time of 30.5 weeks (SD 30.6). At the time of

Table 1 Patient and baseline characteristics for the total cohort and tapering cohort

	Total cohort (start of treatment)	Tapering cohort (start of tapering)
Cohort, *n* (%)	595 (100)	401 (100)
Male, *n* (%)	356 (59.8)	253 (63.1)
Age, mean (SD)	42.0 (15.4)	43.1 (15.3)
Missing	0	0
BMI, mean (SD)	25.5 (4.6)	–
Missing	158	
Age at AD onset, *n* (%)		
Childhood	488 (84.4)	327 (83.4)
Adolescence	33 (5.7)	24 (6.1)
Adulthood	57 (9.9)	41 (10.5)
Missing	17	9
Use of immunosuppressive therapy	145 (24.8)	9 (2.2)[a]
Missing	11	66
Atopic comorbidity		
Allergic asthma, *n* (%)	330 (56.6)	222 (56.5)
Missing	12	8
Allergic rhinitis, *n* (%)	389 (66.6)	267 (67.8)
Missing	11	7
Allergic conjunctivitis, *n* (%)	338 (58.6)	236 (60.4)
Missing	18	10
Food allergy, *n* (%)	264 (45.8)	178 (45.6)
Missing	18	11
EASI score, mean (SD)	18.2 (11.8)	2.5 (2.3)
Missing	13	34
IGA score, median (IQR)	3.0 (3.0–4.0)	1.0 (1.0–2.0)
Missing	19	32
Weekly average NRS-pruritus score, mean (SD)	6.8 (2.3)	2.4 (1.9)
Missing	102	71
Eosinophils levels, median (IQR), ($\times 10^9$ L^{-1})	0.3 (0.2–0.5)	0.3 (0.2–0.5)
Missing	41	83

[a]Not indicated for AD. Patients were recorded as using immunosuppressive therapy when prednisone or ciclosporin had been used within 1 week before assessment of the outcome measurements; in the case of methotrexate, 4 weeks was taken into account. AD, atopic dermatitis; BMI, body mass index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment scale; IQR, interquartile range; NRS, Numerical Rating Scale.

interval shortening the mean EASI was 6.0 (SD 4.4) and significantly improved to 3.8 (SD 3.3) after 3 months of using Q2W ($P < 0.05$); the mean NRS-pruritus was 4.4 (SD 2.3) and significantly improved to 3.2 (SD 2.3) ($P < 0.05$). A second tapering attempt was successful in 18 of 401 (4.5%) patients with mean duration of 39.4 weeks (SD 18.4) between the first and second attempt. These patients remained on a prolonged interval for $\geq 50\%$ of the follow-up time [mean 53.1 weeks (SD 30.5)] and were defined as 'successful tapering'. Sixty-seven of 401 (16.7%) patients who attempted tapering but shortened the interval to standard dose and continued Q2W $\geq 50\%$ of the whole observation period were defined as 'tapering failures'.

Prediction of successful tapering

The prognostic factors for successful dose reduction from univariable analysis were allergic asthma and a high NRS-pruritus at the start of dupilumab treatment; both variables were associated with a lower chance of tapering dupilumab successfully (Table S2; see Supporting Information). Multivariable analysis showed nonsignificant odds ratios for all incorporated variables (Figure 3, Table S2). The C-statistic was 0.71, which indicates a moderate ability of the model to discriminate between successful and unsuccessful tapering.

Cost savings of tapering dupilumab

The price of dupilumab treatment was stable throughout the study period; 1 year of dupilumab treatment in the Netherlands costs €16 350.88.[16] In total, 401 patients tapered dupilumab with a mean cost savings of €9917.79 per patient; the total cost savings for these 401 patients was estimated at €3 977 033.98 between January 2019 and June 2022 (3.5 years). The estimated annual cost savings was €1 136 295.42 during this study.

Discussion

In this prospective cohort study investigating our patient-centred dosing regimen, a total of 401 patients with AD prolonged their dupilumab dose interval. Tapering was successful in 83.3% (334 of 401) of these patients while maintaining controlled disease, with the majority using dupilumab Q3W or Q4W. A significant small increase after the start of tapering was observed for EASI and NRS-pruritus (highest estimated mean 3.5 and 3.2, respectively) but both remained low. The total estimated cost savings due to the implementation of our patient-centred dosing regimen was €3 977 033.98 between January 2019 and June 2022.

Only a few studies have been published on different dosing regimens of dupilumab in AD.[1,4,5,17] Interestingly, while daily practice studies concluded that lower dosages were feasible in a substantial group of patients, the SOLO-continue study recommended the approved regimen of dupilumab 300 mg Q2W for long-term treatment.[1] The methodology (e.g. inclusion criteria, shared decision-making) and outcomes (e.g. definition of successful dose reduction) differ substantially between the daily practice studies

Table 2 Treatment characteristics per dose interval for 401 patients who attempted tapering

	BL tapering (*n* = 401)	+ 3 m (*n* = 355)	+ 6 m (*n* = 300)	+ 9 m (*n* = 237)	+ 1 y (*n* = 194)	+ 1 y 6 m (*n* = 119)	+ 2 y (*n* = 67)	+ 2 y 6 m (*n* = 48)
Patients who discontinued treatment (cumulative *n*)	0	13	15	21	25	33	36	39
Patients who did not reach the follow-up time point (cumulative *n*)	–	11	45	96	154	222	289	314
Patients with missing visit	–	22	41	47	28	27	9	0
Dupilumab Q2W, *n*	401	3	36	31	28	15	9	12
EASI score, mean (SD)	2.5 (2.3)	0.9 (1.2)	3.4 (3.1)	3.4 (3.8)	4.0 (5.1)	5.7 (4.7)	4.9 (3.3)	3.4 (3.0)
EASI score ≤ 7, *n* (%)	352 (95.9)	2 (100.0)	26 (89.7)	21 (91.3)	20 (90.9)	8 (66.7)	5 (71.4)	11 (91.7)
Missing	34	1	7	8	6	3	2	0
IGA ≤ 2, *n* (%)	353 (95.7)	2 (100.0)	27 (90.0)	21 (91.3)	19 (86.4)	9 (75.0)	6 (85.7)	11 (91.7)
Missing	32	1	6	8	6	3	2	0
NRS-pruritus, mean (SD)	2.4 (1.9)	1.5 (0.7)	2.8 (1.7)	2.3 (2.2)	3.1 (2.6)	3.7 (2.3)	3.4 (2.3)	4.1 (2.3)
NRS-pruritus ≤ 4, *n* (%)	277 (83.9)	2 (100)	19 (76.0)	19 (86.4)	18 (75.0)	8 (66.7)	6 (75.0)	7 (58.3)
Missing	71	1	11	9	4	3	1	0
Dupilumab Q3W/Q4W, *n*	0	351	262	185	130	69	39	17
EASI score, mean (SD)	–	2.9 (2.9)	3.0 (3.0)	2.7 (2.5)	2.9 (2.7)	3.2 (3.2)	2.9 (2.6)	2.4 (2.0)
EASI score ≤ 7, *n* (%)	–	269 (92.1)	190 (89.6)	121 (93.8)	87 (88.8)	52 (89.7)	35 (92.1)	15 (100)
Missing	NA	59	50	56	32	11	1	2
IGA ≤ 2, *n* (%)	–	267 (92.1)	194 (91.1)	122 (95.3)	91 (91.9)	53 (93.0)	33 (86.8)	15 (100)
Missing	NA	61	49	57	31	12	1	2
NRS-pruritus, mean (SD)	–	3.0 (2.2)	2.9 (2.2)	2.8 (2.2)	3.1 (2.3)	2.5 (2.2)	3.0 (2.2)	2.4 (2.0)
NRS-pruritus ≤ 4, *n* (%)	–	221 (74.7)	161 (75.9)	118 (77.6)	74 (77.1)	42 (82.4)	27 (73.0)	13 (81.3)
Missing	NA	55	50	33	34	18	2	1
Dupilumab Q5W/Q6W, *n*	0	1	2	20	30	25	14	14
EASI score, mean (SD)	–	3.6 (0)	3.9 (3.4)	2.3 (2.3)	1.9 (1.7)	2.1 (2.3)	1.7 (1.8)	2.0 (2.1)
EASI score ≤ 7, *n* (%)	–	1 (100)	2 (100)	14 (93.3)	22 (100)	18 (94.7)	13 (100)	12 (92.3)
Missing	NA	0	0	5	8	6	1	1
IGA ≤ 2, *n* (%)	–	1 (100)	2 (100)	15 (100)	22 (100)	18 (94.7)	12 (92.3)	9 (81.8)
Missing	NA	0	0	5	8	6	1	3
NRS-pruritus, mean (SD)	–	3.0 (NA)	6.5 (0.7)	4.1 (2.9)	2.8 (2.1)	2.7 (2.2)	2.8 (1.9)	2.8 (2.0)
NRS-pruritus ≤ 4, *n* (%)	–	1 (100)	0 (0)	8 (50.0)	20 (76.9)	18 (85.7)	11 (78.6)	11 (84.6)
Missing	NA	0	0	4	4	4	0	1
Dupilumab Q7W/Q8W, *n*	0	0	0	1	6	10	5	5
EASI score, mean (SD)	–	–	–	0 (0)	1.8 (2.3)	3.4 (3.5)	2.0 (1.8)	0.7 (0.8)
EASI score ≤ 7, *n* (%)	–	–	–	1 (100)	4 (100)	4 (100)	3 (100)	4 (100)
Missing	NA	NA	NA	0	2	6	2	1
IGA ≤ 2, *n* (%)	–	–	–	1 (100)	4 (100)	4 (100)	3 (100)	4 (100)
Missing	NA	NA	NA	0	2	6	2	1
NRS-pruritus, mean (SD)	–	–	–	0 (0)	1.0 (0.8)	2.1 (2.3)	2.0 (1.4)	3.7 (3.1)
NRS-pruritus ≤ 4, *n* (%)	–	–	–	1 (100)	4 (100)	6 (85.7)	4 (100)	2 (66.7)
Missing	NA	NA	NA	0	2	3	1	2

BL, baseline; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment scale; NA, not applicable; NRS, Numerical Rating Scale; Q2W, every other week; Q3W, every 3 weeks; Q4W, every 4 weeks; Q5W, every 5 weeks; Q6W, every 6 weeks; Q7W, every 7 weeks; Q8W, every 8 weeks; m, month; y, year.

and the clinical trial SOLO-continue. This probably explains the differences in outcomes and conclusions. Furthermore, it might be that prolonging the interval at 16 weeks of treatment is too early, as Bangert *et al.* showed that specific immune-cell populations in the skin persisted for up to 1 year after clinical response while using dupilumab, which were absent in healthy controls.[18]

The effects of implementing our patient-centred dupilumab dosing regimen in daily practice on disease activity were measured by EASI and NRS-pruritus. We chose to include all patients from the tapering cohort, independently of interval shortening, to assess the direct effect of our patient-centred dosing regimen. We observed an increase in EASI and NRS-pruritus scores shortly after tapering dupilumab, with a significant effect over time. These results may suggest a negative impact of dose reduction. We nevertheless observed that the mean EASI and NRS-pruritus scores, and their CIs remained below the clinically accepted cutoff points of 7 and 4, respectively. This significant effect over time was most likely caused by a relatively large number of patients combined with a large number of measurements, thus leading to high statistical power. Moreover, as the changes in EASI and NRS-pruritus scores were very small, they did not reach the minimal clinically important difference.[19,20] Therefore, the clinical relevance of these significant changes over time is questionable.

The use of topical corticosteroids parallel to the treatment with dupilumab is an important strategy in the treatment of AD.[21] In clinical trials higher efficacy was observed after 16 weeks of dupilumab treatment combined with topical steroids (delta EASI of –81.2% and 61.8% of the patients with ≥ 3 points reduction in NRS)[22] compared with dupilumab monotherapy (delta EASI of –71.4% and 50.3% of the patients with ≥ 3 points reduction in NRS).[23] A small

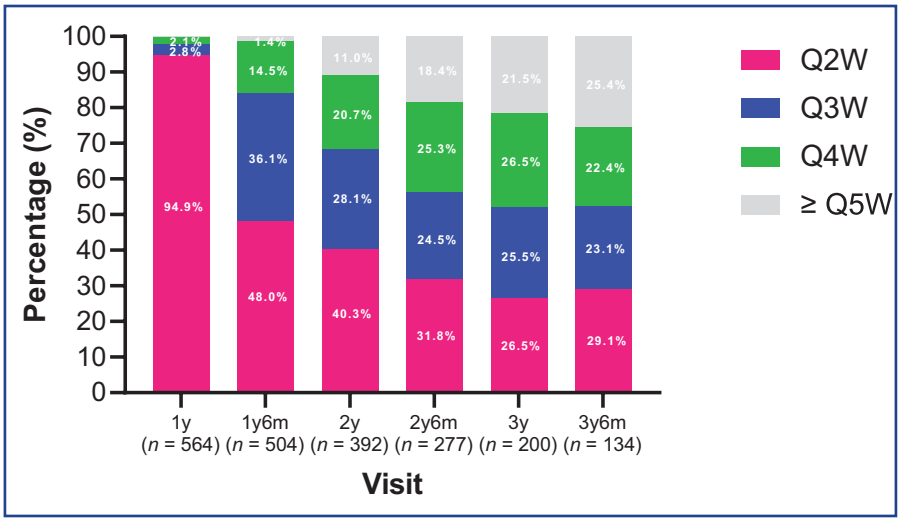

Figure 1 Overview of dupilumab dosage per visit. Q2W, every other week; Q3W, every 3 weeks; Q4W, every 4 weeks; Q5W, every 5 weeks; m, month; y, year.

increase in the amount of the most frequently used topical steroids was observed in the tapering groups compared with tapering baseline and might have contributed to the maintenance of controlled disease during tapering. As the majority of the patients used less than 10 g weekly, the use of topical steroids remained low and safe despite reducing the dupilumab dose.

Due to the absence of a dose-reduction protocol in the literature our patient-centred dosing regimen was based on tapering protocols of biologic treatment in other diseases (e.g. psoriasis[24,25] and rheumatoid arthritis[26,27]) and clinical experience. The current strategy was based on standardized treatment goals, defined as low disease activity based on EASI $\leq$ 7.[8] However, patients who shortened the interval again to the standard dose of 300 mg Q2W had a mean EASI of 6.0 with a mean NRS-pruritus of 3.7, which was not completely in line with our protocol, as shortening of the interval should be considered in the case of EASI $>$ 7. In our study, it seems that in clinical practice an EASI $\leq$ 4 and/or NRS-pruritus of 3 was considered to be controlled disease by the patient and physician.

Clinical and biologic (tapering) baseline variables were analysed for their predictive value for successful tapering. However, it was not possible to find any significant prognostic factor in the multivariable analysis and to our knowledge no other prediction studies are available yet in the literature. Further evaluation of these and other predictors is needed to assess the predictive value of these prognostic factors.

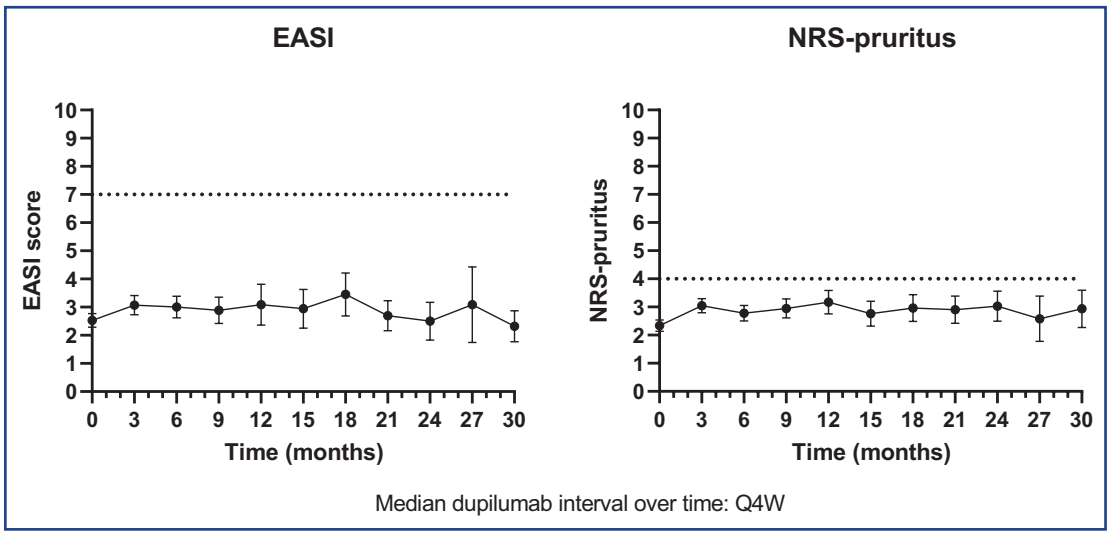

Figure 2 The course of estimated mean EASI and NRS-pruritus with 95% CI in the tapering cohort (n=401). Time point 0 is the tapering baseline for each patient. Time points and follow-up duration differed between patients. To analyse the effect of implementation of the protocol, patients who shortened dupilumab to Q2W after prolonging the interval are included. A significant effect is observed for both EASI and NRS-pruritus over time (P-value $<$ 0.001). However, the changes are small and the outcome measures remained low. The cutoff value of the EASI score at $\leq$ 7 indicates controlled AD; an NRS-pruritus score of $\leq$ 4 is considered to be a treatment goal. Symbols represent estimated means with 95% CIs (vertical lines). AD, atopic dermatitis; CI, confidence interval; EASI, Eczema Area and Severity Index; NRS, Numerical Rating Scale; Q2W, every 2 weeks; Q4W, every 4 weeks.

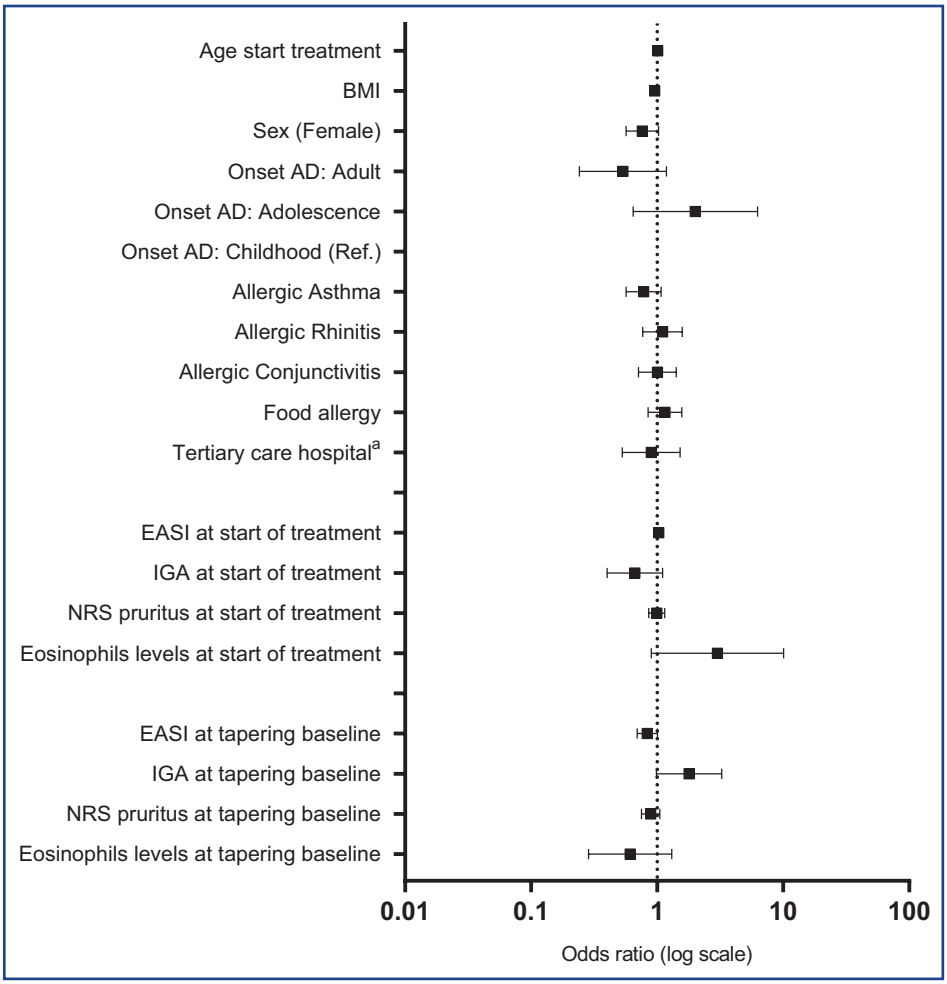

Figure 3 Nonsignificant prognostic factors for successful tapering (odds ratios) determined by multivariable logistic regression analysis ($n=401$). [a]Tertiary care hospital compared with secondary care hospitals. AD, atopic dermatitis; BMI, body mass index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment scale; NRS, Numerical Rating Scale.

Successful dose reduction may be dependent on patient motivation and/or, perhaps, physician-related factors (e.g. management with regard to expectations, ability to motivate patients to taper and/or temporarily increase their use of topical steroids). Clinical practice showed us that for successful dose reduction it was important to sufficiently inform the patient about the possibility of (marginal) flaring and the importance of timely use of topical steroids. Furthermore, 21.2% (18 of 85) of the patients successfully prolonged their interval in a second attempt, indicating that a second attempt to taper is worth trying.

Prolonging the dupilumab dosing interval, while maintaining controlled AD, will benefit the patient as the frequency of dupilumab injections decreases as well as the risk for developing AEs. Considering the high costs of dupilumab (around €16 000 per patient per year in the Netherlands) adequate and effective use of the drug is of great importance to reduce the budget impact. This study showed considerable cost savings, with an estimated cost savings of €3 977 033.98 for 401 patients between January 2019 and June 2022, which is an important finding from the socioeconomic perspective.

There are limitations. As our study was designed as a pragmatic daily practice study, patients fulfilling the criteria of controlled disease (EASI ≤ 7 for 6 months) were not randomized into a dose-reduction group and a standard-dose group. Therefore, noninferiority could not be investigated for our patient-centred dosing regimen and consequently, the results of this study are limited to a within-patient comparison. Additionally, lack of a control group also limits the interpretation of the cost-effectiveness analysis: these results should be interpreted as an indication rather than an accurate estimation of cost savings. Another limitation is the absence of validated flare criteria for AD. Therefore, our flare criteria comprised a definition based on patient and physician opinion combined with EASI and/or NRS-pruritus.

In conclusion, this study showed successful tapering of dupilumab in 83.3% of patients with AD who attempted tapering, while maintaining controlled disease, with the majority using Q3W or Q4W. Interval prolongation can be beneficial both for the patient and from a socioeconomic perspective. Future studies are needed to evaluate whether tapering of dupilumab before 52 weeks of treatment will show the same results.

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Conflicts of interest

L.S.S. is a speaker for AbbVie. C.M.B. is a speaker for AbbVie and Eli Lilly. D.S.B. is a speaker for Janssen, LEO Pharma, Novartis and Sanofi. I.M.H. is a consultant, advisory board member and/or speaker for AbbVie, Eli Lilly, Janssen, LEO Pharma, Regeneron Pharmaceuticals and Sanofi. R.A.T. is an advisory board member of Eli Lilly, LEO Pharma and Novartis. F.M.G. was an advisory board member and/or speaker for AbbVie, LEO Pharma, Novartis and Sanofi. W.R.H.T. is an advisor, consultant and/ot speaker for AbbVie, LEO Pharma, Novartis and Sanofi. M.S.d.B.-W. is a consultant, advisory board member and/or speaker for AbbVie, Almirall, Arena, Aslan, Eli Lilly, Galderma, Janssen, LEO Pharma, Pfizer, Regeneron and Sanofi. M.-L.A.S. is an advisor, consultant, speaker and/or investigator for AbbVie, Eli Lilly, Galderma, LEO Pharma, Pfizer, Regeneron and Sanofi. She has received grants from Novartis, Pfizer, Regeneron and Sanofi. M.d.G. is a consultant, advisory board member and/or speaker for AbbVie, Eli Lilly, LEO Pharma, Novartis, Pfizer and Sanofi. The authors not listed here declare no conflicts of interest.

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

The BioDay registry was considered noninterventional by the local medical ethics committee (METC 18/239) and was performed according to the Helsinki Declaration. All patients provided written informed consent.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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