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ORIGINAL ARTICLE

Adjusted dose regimens in dupilumab treatment for atopic dermatitis: Daily practice experiences

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Abstract

Background: Clinical trials with dupilumab in atopic dermatitis (AD) patients showed a trend towards better effectiveness with a weekly or biweekly dosing interval, compared with extended dosing intervals. However, literature about adjusted dose regimens in daily practice is lacking.

Objectives: To evaluate adjusted dosing intervals of dupilumab for AD in daily practice.

Methods: An observational, longitudinal cohort study was conducted in AD patients who started dupilumab treatment in daily practice. Dosing intervals were adjusted upon shared decision making between physicians and patients in daily practice, without strict criteria. Disease courses of patients with shortened or extended dosing intervals were illustrated using spaghetti plots. In addition, data of patients who were treated with standard or extended dosing intervals were analysed using linear mixed effect (LME) models to determine the estimated effectiveness of extended dosing regimens.

Results: In total, 180 AD consecutive patients treated with dupilumab in daily practice were included in our study. Patients with an extended dosing interval ($n = 28$) had relatively low Eczema Area and Severity Index (EASI) scores at the time of interval adjustment (range: 0–7) and the majority of patients showed continuous effectiveness after adjustment. In patients with a shortened dosing interval ($n = 26$), the scores at the time of adjustment were more widespread (range: 0–34) and follow-up showed variable disease courses. Based on the LME model, we found an overall continuous improvement of EASI scores in time, in patients with a regular and extended interval.

Conclusions: Patients with extended dosing intervals showed sustained effectiveness, similar to patients with standard dosing intervals. The effects of

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Jill I. Olydam and Linde E. M. de Wijs are equally contributed to this study.

shortened intervals on disease severity could not be adequately analysed due to methodological limitations in this retrospective study.

KEYWORDS
atopic dermatitis, daily practice, dose regimens, dupilumab, registry

INTRODUCTION

Atopic dermatitis (AD) is a common, inflammatory skin disease which can have a large impact on quality of life. It is characterised by chronic recurrent eczematous lesions, itch and sleep loss.[1,2]

Dupilumab was the first biologic that was approved for AD treatment and inhibits interleukin (IL)4 and IL-13 signalling by targeting the interleukin IL4 receptor subunit α.[3] The 16-week and 1-year efficacy and safety of weekly and biweekly dosing intervals for 300 mg dupilumab in comparison to placebo were confirmed in phase II and III clinical trials.[4–6] No statistically significant or clinically relevant differences were found between both dose regimens. A dose-finding study showed that dupilumab 300 mg every week or every other week had better outcomes compared with 300 mg dupilumab every 4 weeks, although it is arguable whether the differences are clinically relevant.[7] However, European Medicines Agency and Food and Drug Administration approved dupilumab treatment in a regimen of 300 mg every 2 weeks for treatment of moderate-to-severe AD.[8,9]

In daily practice, long-term treatment with dupilumab, without adjustments of dose regimens is therefore considered common practice. However, several reasons in favour of extended dosing intervals exist. First, an increasing number of side effects including allergic conjunctivitis, facial redness, alopecia and joint complaints are reported in literature.[10–15] In some patients, a longer dosing interval (every three weeks, every four weeks [Q3W, Q4W]) resulted in reduction of side effects.[16]

Second, the relatively high costs of dupilumab treatment in daily practice (approximately €17,000/year excl. additional healthcare costs in the Netherlands), might advocate for attempting to extend dosing intervals. On the other hand, a large proportion of patients do not experience the intended effectiveness (e.g., Investigator Global Assessment 0/1) of dupilumab in daily practice. On the other hand, several patients in our out-patient clinic reported to experience disease flares in the second week of their 2-week interval which might promote shortened intervals.

Until now, literature on shortened or extended dupilumab dose intervals in daily practice is lacking. Therefore, we aimed to evaluate adjusted dose regimens of dupilumab treatment for AD in daily practice.

METHODS

Study design and patient population

We conducted an observational, longitudinal cohort study using data that was prospectively collected in daily practice at the Department of Dermatology at the Erasmus Medical Center (MC) University Medical Centre in the context of the Erasmus MC Immune-Mediated Inflammatory Disorders Registry, from October 2017 until October 2020. All adolescent and adult AD patients who started dupilumab treatment were informed about the collection of data. Data of patients who were treated for at least 12 weeks at the time of data-analysis and who gave consent to publish pseudonymized information relating to them were consecutively included. Also, patients who were treated in an adjusted dose regimen should have been treated in this interval for 12 weeks to be eligible for inclusion in this study. Visits were conducted by trained healthcare professionals (e.g., residents and dermatologists).

Dupilumab 300 mg treatment was started biweekly (Q2W) in all patients, according to the product label. Dupilumab dose regimens were adjusted in daily practice through shared decision making between patient and physician, without uniform dose adjustment criteria. Extended dose intervals represent a 3 weekly dupilumab injection and shortened intervals represent a weekly dupilumab injection. Reasons for extending the interval could be presence of side effects or sustained disease control. Reasons for shortening the interval included insufficient effectiveness or increased disease activity (e.g., itch) in the days before dupilumab injections in the Q2W interval. Adjustments in dupilumab dose regimens and use of concomitant systemic immunosuppressants were recorded. The use of topical therapy including moisturisers, topical corticosteroids and calcineurin inhibitors was encouraged.

Study outcomes

Data collected at every visit until a second adjusted dupilumab dose regimen, or end of study (October 15, 2020), whichever occurred earlier, were included in our analyses. Data collected after a second dose adjustment were censored. At baseline, patient characteristics, therapeutic history, and current AD treatment were recorded. We collected Eczema Area and Severity Index (EASI: 0−72) scores at every visit to assess disease severity in time. As EASI-scores can only be collected during a live consultation and not all dose regimens were adjusted during live consultations due to the corona pandemic, this resulted in missing of EASI scores at the time of dose adjustment. In patients with missing EASI scores at dose adjustment, the last EASI score before adjustment was used.

Data analysis

To compare characteristics between patients treated with different dose regimens, we used a χ^2 test ($E < 5$: Fisher's exact) for comparison of proportions and Mann−Whitney U or Kruskal−Wallis tests for comparison of distributions across different dose regimens. Disease severity in time was plotted for every individual patient using spaghetti plots. Because data was collected in daily practice, follow-up schemes show variation in the timing of visits. We used linear mixed effects (LME) models to evaluate the effectiveness of extended, shortened and normal dupilumab dose regimens. The dependent variable was the repeatedly measured EASI-scores, and the independent variables were group (extended, shortened or normal regimen), time since start of dupilumab treatment, gender, age at start of treatment (in years) and body mass index (BMI). In addition, an interaction effect between group (using normal as reference category) and the time since change in interval was included in the model to describe the direct effect of a change interval on subsequently measured EASI-scores. This analysis thus accounts for an effect of a change of interval on subsequent EASI-scores that builds up linearly over time. The effect of the time since start of dupilumab treatment was modelled using natural cubic splines, to account for nonlinear association between scores and time since start of treatment. The number of degrees of freedom of the splines (which determines the complexity/smoothness of the nonlinear association) was chosen using the Akaike Information Criterion. To account for the within-patient correlations of the repeatedly measured EASI-scores, a random intercept and a random slope of time since start of treatment were included in the model. The variables age and BMI were omitted from the final analysis due to nonsignificance. The results of the linear mixed models for the predicted EASI-scores were shown graphically, as a function of the treatment group, time since start of treatment and time since change in interval. 95% confidence intervals for the predicted values were determined. Analyses were performed using SPSS 24.0 (IBM) and R version 3.4.1 (Foundation for Statistical Computing) (R packages: splines and lme4).

Due to the retrospective design of this study, details on the timing of EASI scoring within the dupilumab interval were lacking. Timing of EASI scoring within the 2 weeks between injections might of particular relevance for patients whose intervals were shortened due to flaring at the end of the second week. For this reason, data of patients treated in a shortened dose regimen were only used for showing individual disease courses, but were not included in the analysis of the estimated effectiveness using LME models.

RESULTS

Patient characteristics

In total, 180 AD patients were consecutively included in our study (Table 1). Patients were treated in the standard Q2W interval ($n = 126$), a shortened QW interval ($n = 26$), or an extended interval ($n = 28$). In general, gender was equally distributed in all groups, and the age at start of dupilumab was not significantly different between groups ($p = 0.362$). The majority of patients were Caucasian, while the proportions of races within the different groups were not statistically different. Although BMI was highest in the shortened interval group and lowest in the extended interval group, differences in BMI were not statistically significant. As discussed in the methods section, some patients lacked an EASI score determined at the exact time of date adjustment (shortened $n = 17/26$; extended $n = 17/28$).

Sustained disease control was the reason for extending the interval in 20 patients ($n = 20/28$) (Table 1). In eight patients the interval was extended due to side effects, resulting in less side effects in three patients. Six patients reported ocular side effects, one patient reported headache and one patient experienced recurrent episodes of Herpes Simplex Virus.

Insufficient effectiveness and/or increased disease severity in the second week after injection were the reasons for shortening the dosing interval in all 26 patients. Patients were treated for a median of 39 weeks (interquartile range [IQR] 27−65) when the

TABLE 1 Patient characteristics

	Normal interval (q2w) ($n = 126$)	Shortened interval ($n = 26$)	Extended interval ($n = 28$)	Sign.
Female sex—no. (%)	57 (45)	11 (42)	15 (54)	0.665[a]
Age—median (IQR)	36 (26-51)	27 (22–48)	35 (28–58)	0.362[b]
Race—no. (%)				0.123[a]
Caucasian	104 (83)	20 (77)	25 (89)	
Black	7 (6)	5 (20)	1 (3)	
Asian	10 (8)	1 (4)	1 (3)	
Other	2 (2)	0 (-)	1 (3)	
Missing	3 (2)	0 (-)	0 (-)	
BMI—median (IQR)	24.6 (22.0–27.4)[1]	26.0 (23.0—28.9)[2]	24.0 (21.8—25.9)[3]	0.208[b]
Age at onset AD	0 (0-10)[4]	0 (0-7)	0 (0-16)	0.768[b]
Atopic/allergic conditions—no. (%)				0.992[a]
Asthma	85 (68)	17 (68)	19 (66)	
Allergic (rhino)conjunctivitis	101 (80)	20 (77)	23 (82)	
Allergic contact dermatitis	55 (44)[5]	13 (50)[6]	13 (46)	
Therapeutic history AD—no. (%)				0.582[a]
Cyclosporine A	109 (87)	25 (100)	28 (97)	
Methotrexate	44 (35)	12 (48)	15 (52)	
Azathioprine	22 (18)	2 (8)	9 (31)	
Mycophenolic acid	46 (37)	8 (32)	10 (35)	
Immunomodulating therapy at the start of dupilumab—no. (%)				0.399[a]
None	48 (38)	9 (35)	16 (57)	
Cyclosporine	35 (28)	8 (30)	3 (11)	
Azathioprine	6 (5)	0	2 (7)	
Methotrexate	9 (7)	1 (4)	2 (7)	
Mycophenolic acid	9 (7)	3 (12)	2 (7)	
Systemic corticosteroids	17 (14)	5 (19)	3 (11)	
Alitretinoin	2 (1)	0	0	
Weeks of dupilumab treatment at the time of interval adjustment—median, (IQR)	-	39 (27–65)	62 (47–83)	0.014[c]
Reason for interval switch—no. (%)	-			0.000[d]
Sustained disease control		0 (-)	20 (71)	
Side effects		0 (-)	8 (29)	
Insufficient effectiveness, flares during Q2W interval		26 (100)	0 (-)	
Patients with a second dose adjustment	-			
Number of patients—no. (%)		8 (31)	8 (29)	0.860[a]
Number of weeks after first adjustment—median (IQR)		30 (18–43)	18 (13–26)	0.619[c]

TABLE 1 (Continued)

	Normal interval (q2w) ($n = 126$)	Shortened interval ($n = 26$)	Extended interval ($n = 28$)	Sign.
Reasons for second dose adjustment—no. (%)	-			0.077[d]
Insufficient disease control		4 (50)	8 (100)	
Side effects		2 (25)	0 (-)	
Sustained disease control		2 (25)	0 (-)	

Note: Missing values: [1]$n = 3$, [2]$n = 16$, [3]$n = 5$, [4]$n = 6$, [5]$n = 29$, [6]$n = 7$.

Abbreviations: BMI, body mass index; IQR, interquartile range.

[a]χ^2;

[b]Kruskal–Wallis Test;

[c]Mann–Whitney *U* test;

[d]Fisher's exact.

interval was shortened, and 62 weeks (IQR 47–83) at the time of interval extension. Twenty of the patients with an extended interval persisted until end of study, while eight patients switched again to the Q2W interval before the end of study due insufficient disease control with extended intervals. A second interval switch was applied in eight of the patients treated in a shortened interval (8/26). This was due to insufficient disease control ($n = 4$), side effects ($n = 2$), or sustained disease control ($n = 2$).

Six patients were unable to discontinue their systemic concomitant treatment during dupilumab treatment (two patients with extended dosing interval and four patients with shortened dosing interval). One patient with extended dosing interval continued using a low dose methotrexate and the other patient used a low dose of systemic corticosteroid due to adrenal insufficiency. The four patients with shortened dosing intervals were able to discontinue the systemic concomitant treatment after dosing interval alteration.

Effectiveness of adjusted dose regimens

Individual disease courses of patients treated with different dose regimens are shown in Figure 1. Patients with an extended interval had relatively low EASI scores at the time of adjustment (range: 0–7) and the majority of patients showed continuous effectiveness after adjustment. Patients with extended intervals due to side effects (red lines), showed worse EASI scores after interval extension compared to patients with extended intervals due to sustained disease control (blue lines). In patients with shortened intervals, the severity scores at the time of adjustment were more widespread ranging from 0 to 34, and follow-up showed a more variable disease course compared to patients with an extended interval. This might be the result of variance in timing of EASI scoring within the 2-week treatment interval.

Based on the LME model, we found an overall continuous improvement of EASI scores in time, regardless of the applied dose interval (Supporting Information: Table S1). Our analyses showed a minor, nonsignificant negative effect on disease severity (i.e., worse disease) in patients with an extended interval. However, patients still improved according to EASI scores due to the overall improvement in time, resulting in sustained disease control (Figure 2).

DISCUSSION

To our knowledge this is the first study investigating the effect of adjusted dose regimens on disease severity in AD patients treated with dupilumab in daily practice. In this study, dose regimens were adjusted through shared decision making between physician and patients due to reasons such as sustained effectiveness, side effects, insufficient effectiveness or disease flares in the second week of the standard interval. Our analyses showed that patients who were treated in an extended interval showed sustained effectiveness, similar to patients with a standard interval. The effect of shortened intervals on disease severity could not be adequately analysed due to methodological limitations resulting from the retrospective design of this study.

Differences in effectiveness of several dose regimens were investigated in phase II and III trials, but results are remain debatable.[4–7] Phase 2b dose-ranging trials showed that 300 mg QW and 300 mg Q2W dose regimens had better outcomes, but this study was not powered to directly compare different dose regimens.[7] In the LIBERTY AD SOLO-CONTINUE trial (phase III), high-responding patients

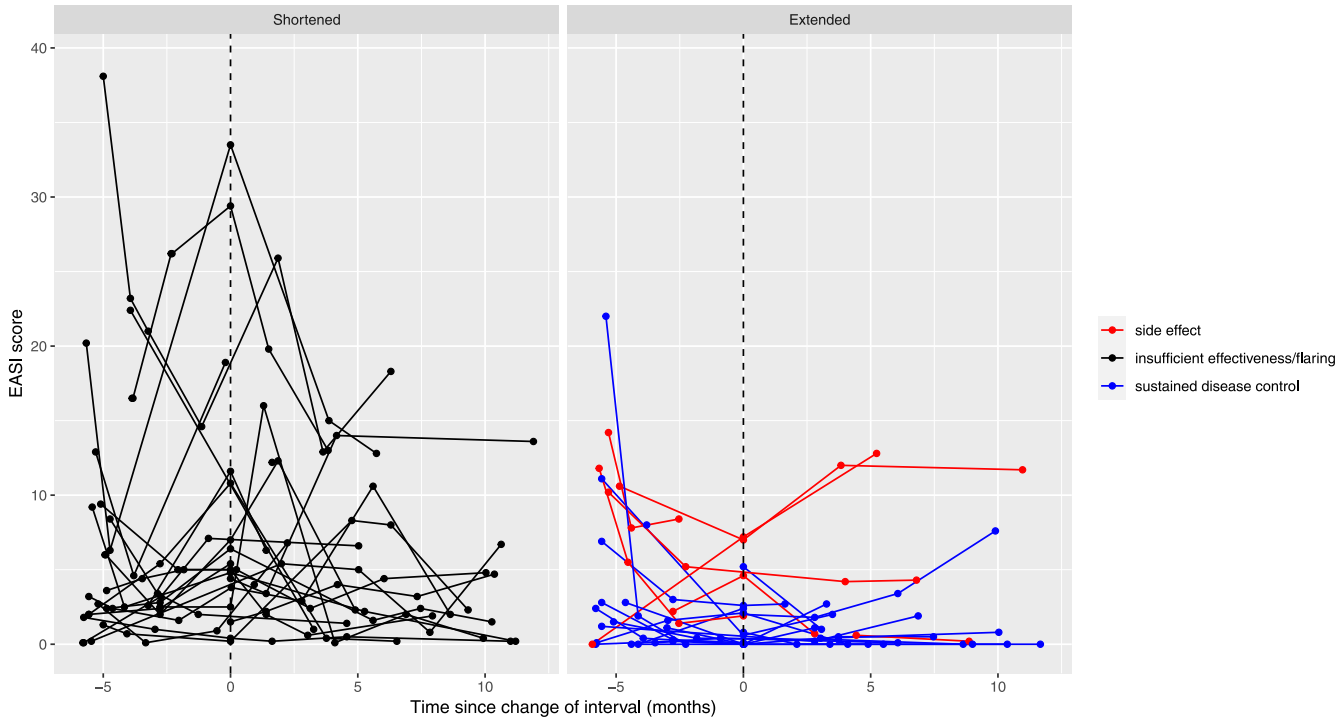

FIGURE 1 Disease severity of individual patients treated in adjusted dupilumab dose regimens in time. Individual disease courses of patients with a shortened interval (black), and extended interval due to sustained disease control (blue) or experienced side effects (red) were illustrated using spaghetti plots. Disease severity scores (Eczema Area and Severity Index) were shown in time, expressed as time since adjusted dose regimen.

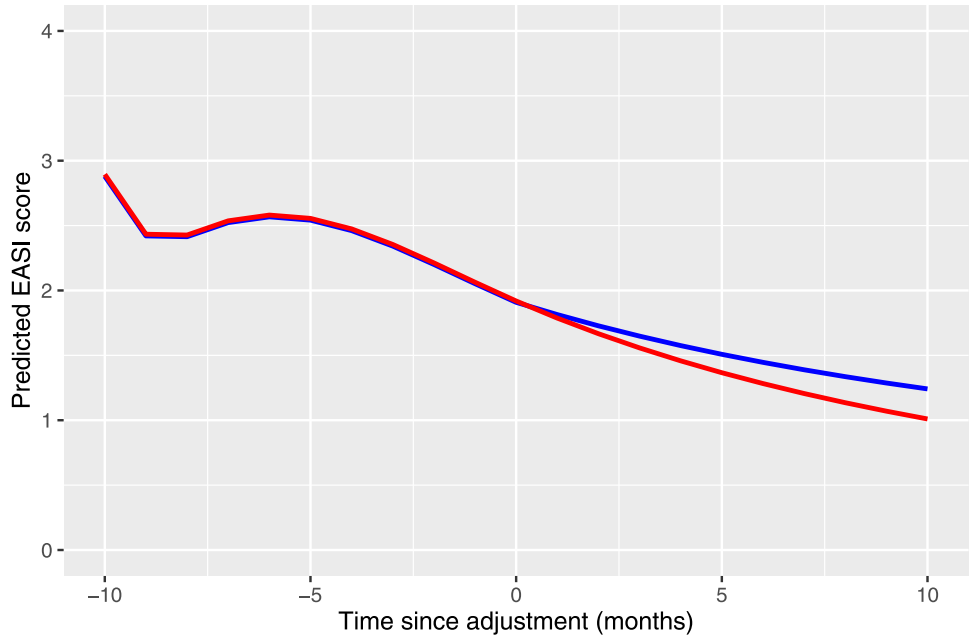

FIGURE 2 Disease severity of patients treated in a standard or extended dupilumab dose regimen. The estimated severity scores of patients treated in a standard (Q2W) interval (red) or an extended interval (blue) are shown, illustrated as cubic splines. Scores are based on our LME models. LME, linear mixed effect.

who were treated with dupilumab in the (LIBERTY AD) SOLO 1 and 2 clinical trials, were rerandomized.[17] Patients were rerandomized (2:1:1:1) to continue in their original regimen of 300 mg dupilumab every 1 or 2 weeks, or to cross-over to a longer dosing interval of 4, or 8 weeks for a total duration of 36 weeks. This study revealed a maintained response over time which was approximately similar in the weekly and biweekly interval. This response was numerically, but overall not statistically significant, better than the longer dosing intervals. As a result, the approved regimen of dupilumab 300 mg every 2 weeks was recommended for long-term treatment.[17] In this study, an extended interval of dupilumab administration every three weeks was not investigated.

However, possibilities for any dose tapering in case of sustained disease control would be of great relevance due to the high costs associated with innovative therapies (e.g., drug costs dupilumab Q2W are approximately €15.000 per patient per year in The Netherlands). Most of the current evidence on biologic tapering results from studies evaluating the effect of adjusted dose regimens in other diseases including psoriasis vulgaris (PSO). Tapering of biologics in patients with PSO who showed stable and low disease activity or clinical remission seemed to be safe and effective, although the optimal dose tapering strategy still needs to be determined and implemented in daily practice.[18–24]

At present, there are several research gaps that need further exploration to adequately taper drugs in inflammatory diseases such as PSO and AD. This includes the evaluation of the long-term impact of tapering on disease activity, quality of life, and safety. This might require the use of (clinical) criteria for dose tapering. However, determining strict criteria for dose tapering might be complicated in a highly heterogeneous and multifactorial disease such as AD. To take this heterogeneity of the population and disease into account, criteria should at least include more specific outcome domains (e.g., EASI, Patient-Oriented Eczema Measure), which is comparable to the treat-to-target approach as recently published. In patients in this study, dupilumab was tapered based on a shared decision making process between the healthcare provider and patient. In case of agreement on achievement of sustained disease control, the dose regimen could be extended. Shortened intervals were applied in case of insufficient disease control or a patient experiencing disease flares in the second week of their 2-week dosing interval. Supportive tools which indicate disease control, such as the AD Control Tool could be used. Because of the highly fluctuating nature of AD and subjectiveness of the currently used measures in AD, (biologic) predictors for successful dose-adjustment would be highly valuable. Currently, there are no data available on predictors for successful dose tapering during dupilumab treatment. In studies investigating predictors for successful dose tapering in PSO, it was found that lower BMI and early treatment effect turned out to be a possible predictors for successful dose tapering.[25] In our study, patients who were switched to an extended interval showed a lower BMI compared with patients in the standard or shortened interval, although this was not statistically significant. However, the nonrandomized design of this study does not allow for analysing predictive factors of the effect of random adjustment of the dose regimen. Still, we found that when patient and physician agreed on achieving disease control, dose adjustment was successful in the majority of patients, resulting in sustained disease control (Figure 2).

There are several limitations in this study arising from the retrospective and observational design. These include the lack of standardised dose-adjustment strategies and limited observation period. Due to the observational nature of the data, it is difficult to disentangle the direct causal effect of the dose regime (e.g., a shortening of the interval would be hypothesised to lead to lower subsequent EASI-scores) from the reverse causal effect that patients with more severe disease severity and thus higher EASI-scores are usually not assigned extended dupilumab intervals. To account for this issue, we used LME models incorporating both fixed and random effects. The independent variable group (e.g., gender, time since start treatment and dose regimen adjustment) served to model the statistical association due to the aforementioned reverse causal effect of EASI-scores on treatment interval. Another limitation due to the retrospective design of this study was the inability to model the effect of a shortened interval in time. Since information about the timing within the treatment interval at the time of EASI scoring was lacking, this could have limited the validity in illustrating the estimated effect on EASI scores in time from the moment of dose adjustment.

In conclusion, our study demonstrated that extended dupilumab dose intervals, based on a shared decision making process between patients and physicians, seems to be effective in daily practice. Unfortunately, the effect of shortened intervals could not be determined due to methodological limitations of this study. Future studies in daily practice are warranted to determine the optimal dose-adjustment eligibility criteria, dose regimens, and definitions of successful dose adjustment.

CONFLICT OF INTEREST

D. H.: investigator for Abbvie, LEO pharma, Galderma, MedImmune/Astrazeneca, Novartis, Sanofi/Regeneron;

consultancies for Regeneron/Sanofi, LEO pharma, MedImmune/AstraZeneca, Novartis, Incyte, Janssen, Pfizer, Lilly. The remaining authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to publication of their case details.

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SUPPORTING INFORMATION

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

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