

ORIGINAL ARTICLE

Treatment of atopic dermatitis with dupilumab: experience from a tertiary referral centre

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Abstract

Background Management of moderate-to-severe atopic dermatitis (AD) frequently requires treatment with systemic therapies. Dupilumab is the first biological agent approved for treatment of moderate-to-severe AD. Although promising results have appeared in clinical trials, real-life data on efficacy and safety are lacking.

Objectives To assess effectiveness and safety of treatment with dupilumab in the real-life clinical setting at a Danish tertiary referral centre.

Methods All patients with AD treated with dupilumab from October 2017 to October 2018 at Bispebjerg Hospital, Denmark, were included in the study. Patients were evaluated three times: at treatment initiation and at 1 and 3 months after first dupilumab injection. At each visit, disease activity was assessed by severity score (Eczema Area and Severity Index, EASI), patient-reported outcomes (Dermatology Life Quality Index, DLQI, pruritus and sleep score) and serological markers [immunoglobulin (Ig)E, eosinophil count and lactate dehydrogenase (LDH)].

Results A total of 43 patients were included in the study. The mean reduction in EASI score from baseline was 19.6 points (72.4%) at 1-month and 22.6 points (76.7%) at 3-month follow-up. EASI, DLQI, pruritus score, sleep score, IgE and LDH were all statistically significantly reduced between baseline and 1- and 3-month follow-up. Mean reductions in EASI score and LDH at 3-month follow-up were significantly correlated ($P = 0.003$). One patient (2.3%) discontinued treatment due to side-effects, and seven patients (18.4%) developed conjunctivitis during the study period.

Conclusion The effectiveness and safety of dupilumab treatment in a real-life clinical setting are comparable to that of phase 3 clinical trials. LDH is suggested as a potential serological marker predictive of treatment response.

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Conflicts of interest

CMO, JGH, LBN and JVS: none declared; SFT: has served on advisory boards, been a paid speaker and received research grants from Sanofi; TA: has provided teaching at meetings sponsored by Sanofi, has received unrestricted grant and has participated in advisory boards for Sanofi.

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease affecting approximately 20% of children and 7–10% of adults in western countries.¹ AD is characterized by dry skin and recurrent flares of pruritic, eczematous skin lesions with great variability in the clinical presentation.² Treatment with emollients and topical anti-inflammatory agents comprises the cornerstone in the management of mild AD, while systemic treatment with immunosuppressive drugs (i.e. methotrexate, ciclosporin and azathioprine) is frequently required to ensure adequate disease control in patients with moderate-to-severe AD, although these drugs are not always effective and associated with frequent side-effects.³

Accordingly, the management of recalcitrant AD poses a challenge to dermatologists. The increasing understanding of the immunopathology underlying AD has formed the basis for development of biological agents specifically targeting key inflammatory mediators involved in the pathophysiology of AD.^{4,5} Dupilumab, a fully human monoclonal antibody targeting interleukin (IL)-4 and IL-13, is the first biological agent approved by the FDA and EMA for treatment of moderate-to-severe AD.^{6,7} With the recent approval of dupilumab in Europe (2018), reports on real-life clinical experiences with dupilumab are scarce. In this study, we present real-life data from consecutive AD patients treated with dupilumab at a Danish tertiary referral centre.

Materials and methods

Study population and data collection

All patients starting treatment with Dupixent (Sanofi Genzyme, dupilumab) at Bispebjerg Hospital, Denmark, from October 2017 to October 2018 were included in the study. Patients were evaluated three times: at initiation of dupilumab treatment and 1 and 3 months after treatment initiation (scheduled appointments for all patients in dupilumab treatment). Patients filled in an extensive questionnaire, exploring demographics and disease characteristics including personal and family history of AD, age at onset of AD, comorbidities including allergic symptoms from eyes and nose (allergic rhinoconjunctivitis) and airways (asthma). Questions were adopted from the ISAAC (The International Study of Asthma and Allergies in Childhood) and ECRHS (European Community Respiratory Health Survey) studies.^{8,9}

At each visit, disease severity was assessed by the physician using the Eczema Area and Severity Index (EASI)-,¹⁰ and quality of life (QoL) was assessed using the Danish version of the Dermatology Life Quality Index (DLQI) questionnaire.¹¹ In addition, a visual analogue scale (VAS) of 0–10 points was used to assess itch intensity and impact on sleep from AD. All patients had moderate-to-severe AD. To be considered for dupilumab treatment, patients had to meet the following criteria: age ≥ 18 years, EASI score > 16 , DLQI > 10 and failure on previous treatment with two or more traditional systemic immunosuppressive therapies. Patients transferred to dupilumab directly from another systemic immunosuppressive therapy could receive dupilumab despite EASI < 16 and DLQI < 10 .

Blood samples were taken at each visit, comprising total serum immunoglobulin E (IgE) ($\times 10^3$ IU/L), serum lactate dehydrogenase (LDH) (U/L) and eosinophil count (count $\times 10^9$ /L). Genomic DNA from whole blood was genotyped for the three most common loss-of-function mutations/deletion in the flaggrin gene (*FLG*): R2447X, R501X and 2282del4.¹² Additional information was extracted from the patients' files.

Statistical analyses

Wilcoxon matched-pairs signed rank test was used to test differences in EASI score, DLQI score, VAS itch, VAS sleep, total serum IgE, LDH and eosinophil count between baseline and follow-ups. When calculating the difference in EASI score between baseline and follow-ups, patients with an EASI score < 16 were included (comprise patients transferred directly from a traditional systemic immunosuppressive treatment), although only a minor reduction in EASI score was expected for these patients. Spearman's r correlation was used to measure the association between baseline EASI score, baseline serum LDH and baseline total serum IgE, respectively, and to assess the associations between the reduction in EASI score and the reductions in serum LDH and total serum IgE from baseline to 3-month follow-up.

Information on age, EASI score, total serum IgE and serum LDH was used to characterize patients at baseline. For each of these variables, patients were dichotomized into two groups: patients above and patients below the median. Fisher's exact test was used to test for difference in treatment response (assessed by EASI-75, equivalent to patients experiencing at least at 75% reduction in mean EASI score) at 1- and 3-month follow-up in relation to age, sex, *FLG* mutation status, asthma, hay fever, body mass index (BMI) baseline EASI score, baseline total serum IgE and baseline serum LDH.

All statistical analyses were performed using IBM SPSS statistics 22 (SPSS, Inc., Chicago, IL, USA).

Ethical considerations

Data for this study were primarily obtained from a clinical database of patients with AD, which have been approved by the local ethics committee and the Danish Data Protection Agency. All patients received oral information, and written consent to extract relevant data from patient records was obtained.

Results

A total of 43 patients with AD, 15 women and 28 men, initiated treatment with dupilumab and were included in the study (Table 1). Four patients had participated in a phase 3 clinical trial of dupilumab and continued treatment after the trial (post-trial access). These patients were included in the study with respect to adverse events and treatment continuation; however, data on severity, self-reported outcomes and serological markers from these four patients were not obtained. Another three patients had initiated treatment in the autumn 2017 in an early access programme. For these patients, consecutive data on severity, self-reported outcomes and serological markers were obtained at baseline and both follow-ups and included in the study. A total of 41 patients were treated with 300 mg dupilumab every second week following a loading dose of 600 mg at treatment initiation (label use). Two patients received reduced dose of dupilumab (300 mg every third week), one due to

Table 1 Characteristics of 43 patients with AD initiating treatment with dupilumab

Age at onset of AD, years, median (min–max)	1.25 (0.0–40.0)
Age at dupilumab initiation, years, median (min–max)	42 (18–78)
Women, % (n/n_{total})	35% (15/43)
BMI, median (min–max)	24.9 (16.9–36.2)
First degree relative with AD, % (n/n_{total})	59% (16/27)
<i>FLG</i> mutation carrier, % (n/n_{total})	33% (8/24)
History of asthma, % (n/n_{total})	65% (21/32)
History hay fever, % (n/n_{total})	77% (23/30)
History of conjunctivitis, % (n/n_{total})	29% (11/38)

Age at onset of AD, $n = 18$; age at dupilumab initiation, $n = 43$; BMI, $n = 21$. AD, atopic dermatitis; BMI, body mass index (weight in kg/height in metres squared); *FLG*, flaggrin gene.

bodyweight <50 kg, and one patient was reduced in dosage from week 5 to week 10 due to development of tics. Full dose was resumed when tics disappeared.

All patients had a history of treatment with at least two traditional systemic immunosuppressive therapies which were discontinued due to insufficient disease control or side-effects. Most patients had received treatment with methotrexate and azathioprine, and a few patients had been treated with ciclosporin prior to the dupilumab treatment. Two patients received overlapping systemic immunosuppressive therapy during the study period: One patient continued treatment with azathioprine during the first month of dupilumab treatment, and another patient received prednisolone for 2 weeks during the study period. All patients used concomitant moisturizers, and as all the patients had severe chronic disease, they self-administered topical corticosteroids at start-up and in the study period during flares.

Data on EASI score, DLQI, VAS itch, VAS sleep, total serum IgE, serum LDH and eosinophil count at baseline and at 1- and 3-month follow-up are presented in Table 2. At baseline, the median EASI score was 24.5 points, and the mean reduction in EASI score was 19.6 points (72.4%) at 1-month and 22.6 points (76.7%) at 3-month follow-up (Fig. 1). At 1-month follow-up, a total of 82.4% of the patients had experienced at least a 50% reduction in EASI score from baseline (EASI-50), whereas at 3-month follow-up 90.0% of the patients had achieved EASI-50. At 1-month follow-up, 58.8% of the patients had achieved EASI-75, and at 3-month follow-up, 63.3% of the patients had achieved EASI-75.

There was a significant reduction in EASI score, DLQI, VAS itch, VAS sleep, total serum IgE and serum LDH between baseline and 1-month follow-up, and baseline and 3-month follow-up. The decrease was most pronounced from baseline to

Table 2 Patient characteristics at baseline and follow-up after 1 and 3 months[†]

	Baseline	One-month follow-up	<i>P</i> -value*	Three-month follow-up	<i>P</i> -value**	<i>P</i> -value***
Days from baseline, median (min–max)	–	31 (15–90)	–	96 (55–171)	–	–
EASI score	(<i>n</i> = 38)	(<i>n</i> = 34)	<0.001	(<i>n</i> = 30)	<0.001	0.112
Median (min–max)	24.5 (6.4–71.4)	4.2 (0–25.6)		4.1 (0–19.7)		
Mean (SD)	27.3 (13.9)	7.7 (7.6)		5.9 (5.7)		
Change in EASI score from baseline, mean (SD)	–	19.6 (13.0)	–	22.6 (15.4)	–	–
Percentage change in EASI score from baseline, % (SD)	–	72.4 (22.4)	–	76.7 (21.8)	–	–
EASI-50, % (<i>n</i> / <i>n</i> _{total})	–	82.4 (28/34)	–	90.0 (27/30)	–	–
EASI-75, % (<i>n</i> / <i>n</i> _{total})	–	58.8 (20/34)	–	63.3 (19/30)	–	–
EASI-90, % (<i>n</i> / <i>n</i> _{total})	–	23.5 (8/34)	–	33.3 (10/30)	–	–
Itch (VAS)	(<i>n</i> = 35)	(<i>n</i> = 30)	<0.001	(<i>n</i> = 26)	<0.001	0.836
Median (min–max)	8.0 (2–10)	2.0 (0–7)		2.0 (0–9)		
Mean (SD)	7.3 (2.3)	2.4 (2.3)		2.4 (2.5)		
Sleep (VAS)	(<i>n</i> = 35)	(<i>n</i> = 30)	<0.001	(<i>n</i> = 25)	<0.001	0.606
Median (min–max)	7.0 (0–10)	0 (0–7)		0 (0–7)		
Mean (SD)	5.7 (3.2)	1.2 (2.0)		1.2 (2.2)		
DLQI	(<i>n</i> = 18)	(<i>n</i> = 19)	<0.001	(<i>n</i> = 13)	<0.001	0.385
Median (min–max)	11.5 (2–21)	4 (0–23)		9 (0–22)		
Mean (SD)	12.9 (5.0)	5.5 (6.0)		8.8 (8.3)		
Serum total IgE	(<i>n</i> = 33)	(<i>n</i> = 20)	0.044	(<i>n</i> = 24)	<0.001	0.001
Median (min–max)	2320 (17–35 800)	2295 (37–16 700)		2295 (13–28 200)		
Mean (SD)	5798 (7746)	3959 (4324)		4588 (6437)		
Serum total IgE Percentage change from baseline, % (SD)	–	11.06 (22.37)	–	34.69 (16.62)	–	–
Eosinophil count	(<i>n</i> = 38)	(<i>n</i> = 25)	0.157	(<i>n</i> = 27)	0.131	0.525
Median (min–max)	0.43 (0.08–1.50)	0.46 (0.05–6.10)		0.42 (0–2)		
Mean (SD)	0.55 (0.37)	0.91 (1.3)		0.59 (0.53)		
Serum LDH	(<i>n</i> = 27)	(<i>n</i> = 19)	<0.001	(<i>n</i> = 21)	<0.002	0.507
Median (min–max)	235 (129–340)	187 (59–239)		183 (2–239)		
Mean (SD)	226.5 (49.8)	177.6 (40.7)		174.5 (48.2)		

Significant *P*-values are shown in bold.

*One-month follow-up compared with baseline, **three-month follow-up compared with baseline, ***three-month follow-up compared with 1-month follow-up, conjunctivitis: diagnosed by doctor, AD, atopic dermatitis; BMI, body mass index (weight in kg/height in metres squared); EASI, Eczema Area and Severity Index; EASI-50/75/90, percentage reduction from baseline EASI score; VAS, visual analogue scale (0–10 with 10 being most severe); DLQI, Dermatology Life Quality Index; IgE, immunoglobulin E; LDH, lactate dehydrogenase.

[†]Missing data were excluded for each analysis.

1 month, and no significant difference between 1-month and 3-month follow-up was present for any of the variables, except for serum IgE which continued to decrease significantly between 1- and 3-month follow-up.

The mean percentage reduction in VAS itch from baseline was 70.3% at 1-month follow-up and 67.5% at 3-month follow-up. For VAS sleep, the mean percentage reduction from baseline was 71.2% at 1-month follow-up and 66.6% at 3-month follow-up.

Eosinophil count did not change significantly between baseline and follow-ups. For seven patients, there was an increase in eosinophil count at 1-month follow-up (to values $>1.0 \times 10^9/L$), and for two patients, eosinophil count was further increased (to values $\geq 1.5 \times 10^9/L$) at 3-month follow-up.

A total of six patients had a baseline total serum IgE below $300 \times 10^3 IU/L$. These patients experienced a decrease in serum IgE at both 1- and 3-month follow-up. Also, five out of six of these patients achieved EASI-75 at 1-month follow-up, and the

mean percentage reduction in EASI score at 3-month follow-up was 89.7%.

At baseline, we found a positive correlation between EASI score and serum LDH ($P = 0.026$; Fig. 2), and at 3-month follow-up, we found a positive correlation between reduction in EASI score and reduction in serum LDH ($P = 0.003$; Fig. 3). No significant correlations were present between EASI score and total serum IgE at baseline ($P = 0.08$) and between reduction in EASI score and reduction in total serum IgE ($P = 0.34$) at 3-month follow-up.

Compared to men, women were significantly more likely to achieve EASI-75 at 1-month as well as 3-month follow-up (Table 3). Younger patients were significantly more likely to achieve EASI-75 compared to older patients at 1-month follow-up. Patients with high baseline EASI score were significantly less likely to achieve EASI-75 compared to patients with low baseline EASI at 1-month follow-up. Also, patients with a high baseline IgE were significantly less likely to obtain EASI-75 at 1-month follow-up compared to patients with a low baseline total serum IgE. Age, baseline EASI score and baseline total serum IgE were not significantly related to treatment response (assessed by EASI-75) at 3-month follow-up.

FLG mutation status (available in 24 patients), asthma, hay fever, BMI and serum LDH were not related to response to treatment, assessed by EASI-75, at 1-month follow-up. No multivariate statistical model for calculating adjusted associations between the variables and EASI-75 could be made due to small number of patients in each group.

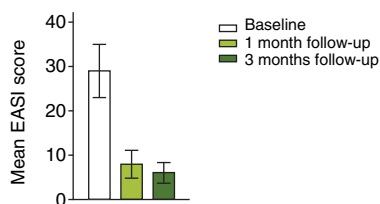


Figure 1 Bar graph showing mean Eczema Area and Severity Index (EASI) score (SD as error bars) at baseline and at 1- and 3-month follow-up.

Side-effects

A total of seven patients (18.4%) developed conjunctivitis during the 3-month follow-up period. Of these, three patients had a

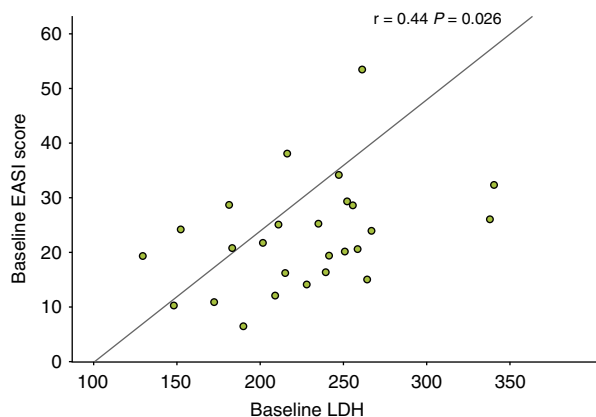


Figure 2 Correlation between baseline Eczema Area and Severity Index (EASI) score and baseline serum lactate dehydrogenase (LDH). $r = 0.44$, $P = 0.026$.

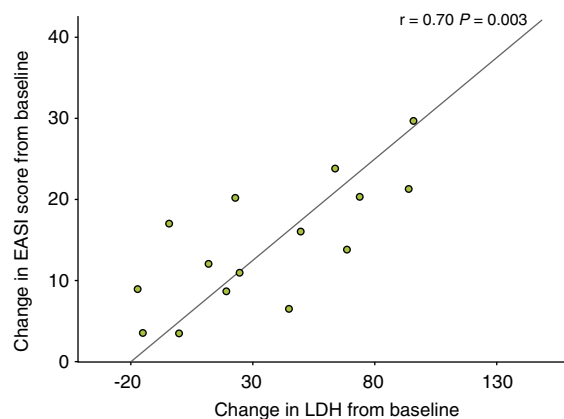


Figure 3 Correlation between change in Eczema Area and Severity Index (EASI) score and change in serum lactate dehydrogenase (LDH) from baseline to 3-month follow-up. $r = 0.70$, $P = 0.003$.

Table 3 Association between baseline characteristics and change in disease activity (EASI75)

	One-month follow-up, n (%)	Achieved EASI75, n (%)	P-value	Three-month follow-up, n (%)	Achieved EASI75, n (%)	P-value
Sex						
Women	12 (35.3)	11 (91.7)	–	11 (36.7)	10 (90.9)	–
Men	22 (64.7)	9 (40.9)	0.009	19 (63.3)	9 (47.4)	0.02
Age						
>42 years	16 (47.0)	6 (37.5)	–	13 (43.3)	7 (53.9)	–
≤42 years	18 (53.0)	14 (77.8)	0.035	17 (56.7)	12 (70.6)	0.45
BMI						
>24.9	10	7 (70.0)	–	8 (47.1)	6 (75.0)	–
≤24.9	9	3 (33.3)	0.19	9 (52.9)	4 (44.4)	0.33
Asthma						
Yes	17 (65.4)	8 (47.1)	–	14 (60.9)	7 (50.0)	–
No	9 (34.6)	6 (66.7)	0.43	9 (39.1)	7 (77.8)	0.23
Hay fever						
Yes	17 (70.8)	8 (47.1)	–	16 (72.7)	9 (56.3)	–
No	7 (29.2)	5 (71.4)	0.39	6 (27.3)	5 (83.3)	0.35
FLG mutation carrier						
Yes	5 (31.2)	1 (20.0)	–	4 (26.6)	2 (50.0)	–
No	11 (68.8)	6 (54.6)	0.31	11 (73.3)	6 (54.6)	1.0
Baseline EASI score						
>24.5	16 (47.0)	6 (37.5)	–	15 (50.0)	8 (53.3)	–
≤24.5	18 (53.0)	14 (77.8)	0.035	15 (50.0)	11 (73.3)	0.44
Baseline total serum IgE						
>2320 × 10 ³ IU/L	13 (46.4)	5 (38.4)	–	13 (52.0)	8 (61.5)	–
≤2320 × 10 ³ IU/L	15 (53.6)	12 (80.0)	0.031	12 (48.0)	9 (75.0)	0.67
Baseline serum LDH						
>235 U/L	9 (39.1)	7 (77.8)	–	8 (42.1)	6 (75.0)	–
≤235 U/L	14 (60.9)	7 (50.0)	0.22	11 (57.1)	6 (54.6)	0.63

Significant *P*-values are shown in bold.

BMI, body mass index (weight in kg/height in metres squared); EASI, Eczema Area and Severity Index; EASI-75, at least 75% reduction from baseline EASI score; FLG, filaggrin gene; IgE, immunoglobulin E; LDH, lactate dehydrogenase.

history of conjunctivitis before treatment with dupilumab. No case of conjunctivitis resulted in discontinuation of treatment within the study period. Two patients (4.7%) discontinued treatment with dupilumab, one due to pregnancy, and one due to development of acute onset of fever without any infectious focus, interpreted as serum sickness, within the first weeks of treatment.

Discussion

Dupilumab is the first biological agent approved for treatment of moderate-to-severe AD and offers a new therapeutic approach by specifically targeting key inflammatory pathways in the pathophysiology underlying AD. Here we present real-life data from the first 43 AD patients treated with dupilumab at a Danish tertiary referral centre.

Overall, treatment with dupilumab improved signs and symptoms of AD with statistically significant reduction in EASI, DLQI, pruritus and sleep score from baseline at 1- and 3-month follow-up. No further significant differences in EASI, DLQI,

pruritus and sleep score were present between 1- and 3-month follow-up, indicating that the main achievement takes place within the first month of treatment, although a less dramatic improvement continues. At 3-month follow-up, the overall percentage reduction in EASI score for all patients was 76.7% (EASI-50: 90.0% and EASI-75: 63.3%). Although these results also include some patients transferred from other systemic treatments with initial EASI score values below 16, the results are in accordance with the previously reported results on efficacy of dupilumab in phase 3 clinical trials (SOLO 1, SOLO 2, CHRONOS and CAFÉ).^{13–15} In the present study, the effectiveness of dupilumab evaluated by percentage reduction in EASI score, EASI-50 and EASI-75 at week 12 was similar to results obtained from clinical trials of dupilumab in combination with topical corticosteroids (CAFÉ, EASI-75: 62% and CHRONOS, EASI-75: 69%)^{14,15} and was slightly higher than the efficacy in trials with dupilumab as monotherapy (SOLO 1, EASI-75: 51.3% and SOLO 2, EASI-75: 44.2%).¹³ This was expected, as concomitant treatment with topical anti-inflammatory agents is

common practice in the clinical setting and to a major degree self-administered in this group of chronic patients.

Pruritus, scratching and disturbed sleep are known to have major impact on QoL in patients with AD.¹⁶ Hence, assessment of these symptoms is important when evaluating treatment response in the clinical setting. The finding that the median pruritus score was reduced from 8 at baseline to 2 at 1- and 3-month follow-up, and that median sleep score was reduced from 7 at baseline to 0 at 1- and 3-month follow-up, emphasizes how treatment with dupilumab markedly improves key symptoms of AD and positively influences patients' daily living.

The improvement in signs and symptoms was accompanied by changes in serological parameters. At baseline, median total serum IgE and LDH were above the normal reference ranges. Both total serum IgE and LDH decreased significantly. Reduction in total serum IgE following dupilumab treatment has been reported before¹⁷ and is to be expected considering the mechanism of action of dupilumab as IL-4 and IL-13 cause increased production of IgE.¹⁸ LDH is an enzyme expressed in almost all tissue, and during tissue damage, LDH is released to the blood stream. Elevated serum LDH has been reported to be associated with increased severity of AD reflecting increased cell turnover in eczematous lesions.¹⁹ This is in accordance with our results showing a significant correlation between baseline EASI score and baseline serum LDH level. The finding that the reduction in serum LDH significantly correlated with reduction in EASI score suggests LDH as a possible serological marker for assessing treatment response; however, results from larger cohorts are needed to confirm this correlation.

High EASI and high serum IgE at baseline were predictors for not achieving at least 75% reduction in EASI score at 1-month follow-up but not at 3-month follow-up, suggesting that longer duration of treatment may be required for the full effect of dupilumab to occur in patients with more severe AD. Patients with low IgE at baseline ($<300 \times 10^3$ IU/L), representing patients with intrinsic AD,²⁰ responded remarkably well, indicating that both intrinsic and extrinsic types of AD are candidates for dupilumab therapy. The finding that women were significantly more likely to achieve EASI-75 at both one- and 3-month follow-up compared to men has not previously been reported. However, due to missing data and the relatively small size of the cohort, bias cannot be excluded, and these tendencies must be investigated in larger cohorts before any conclusion can be drawn.

The finding that 18.4% of the patients developed conjunctivitis during the first 3 months of treatment is in accordance with data from clinical trials demonstrating conjunctivitis to be one of the most frequent adverse events related to dupilumab treatment (combined incidence 8% in phase 2B and 3 clinical trials).²¹ In addition, the proportion of patients who discontinued treatment with dupilumab due to side-effects was comparable with findings in phase 3 clinical trials (2% vs. 1–2%).⁴

We conclude that real-life data on treatment with dupilumab show an effectiveness and tolerability profile comparable to phase 3 clinical trials. Patients with high EASI score and high IgE at baseline required a longer duration of treatment for the full effect of dupilumab to occur. We found LDH to be a potential biomarker for disease severity and response to treatment.

References

- Weidinger S, Beck LA, Bieber T, Kabashima K, Irvine AD. Atopic dermatitis. *Nat Rev Dis Primers* 2018; **4**: 1.
- Guttman-Yassky E, Waldman A, Ahluwalia J, Ong PY, Eichenfield LF. Atopic dermatitis: pathogenesis. *Semin Cutan Med Surg* 2017; **36**: 100–103.
- Snast I, Reiter O, Hodak E, Friedland R, Mimouni D, Leshem YA. Are biologics efficacious in atopic dermatitis? A systematic review and meta-analysis. *Am J Clin Dermatol* 2018; **19**: 145–165.
- Frampton JE, Blair HA. Dupilumab: a review in moderate-to-severe atopic dermatitis. *Am J Clin Dermatol* 2018; **19**: 617–624.
- Ariens LFM, Bakker DS, van der Schaft J, Garritsen FM, Thijs JL, de Bruin-Weller MS. Dupilumab in atopic dermatitis: rationale, latest evidence and place in therapy. *Ther Adv Chronic Dis* 2018; **9**: 159–170.
- Fabbrocini G, Napolitano M, Megna M, Balato N, Patruno C. Treatment of atopic dermatitis with biologic drugs. *Dermatol Ther* 2018; **8**: 527–538.
- Beck LA, Thaci D, Hamilton JD *et al.* Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014; **371**: 130–139.
- Asher MI, Keil U, Anderson HR *et al.* International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995; **8**: 483–491.
- Burney PG, Luczynska C, Chinn S, Jarvis D. The European Community Respiratory Health Survey. *Eur Respir J* 1994; **7**: 954–960.
- Hanifin JM, Thurston M, Omoto M, Cherill R, Tofte SJ, Graeber M. The eczema area and severity index (EASI): assessment of reliability in atopic dermatitis. EASI Evaluator Group. *Exp Dermatol* 2001; **10**: 11–18.
- Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI)—a simple practical measure for routine clinical use. *Clin Exp Dermatol* 1994; **19**: 210–216.
- Palmer CN, Irvine AD, Terron-Kwiatkowski A *et al.* Common loss-of-function variants of the epidermal barrier protein flaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet* 2006; **38**: 441–446.
- Simpson EL, Bieber T, Guttman-Yassky E *et al.* Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 2016; **375**: 2335–2348.
- Blauvelt A, de Bruin-Weller M, Gooderham M *et al.* Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet* 2017; **389**: 2287–2303.
- de Bruin-Weller M, Thaci D, Smith CH *et al.* Dupilumab with concomitant topical corticosteroid treatment in adults with atopic dermatitis with an inadequate response or intolerance to ciclosporin A or when this treatment is medically inadvisable: a placebo-controlled, randomized phase III clinical trial (LIBERTY AD CAFE). *Br J Dermatol* 2018; **178**: 1083–1101.
- Jeon C, Yan D, Nakamura M *et al.* Frequency and management of sleep disturbance in adults with atopic dermatitis: a systematic review. *Dermatol Ther* 2017; **7**: 349–364.
- Guttman-Yassky E, Bissonnette R, Ungar B *et al.* Dupilumab progressively improves systemic and cutaneous abnormalities in patients with atopic dermatitis. *J Allergy Clin Immunol* 2018; **143**: 155–172.

- 18 Osinka K, Dumycz K, Kwiek B, Feleszko W. Novel therapeutic approaches to atopic dermatitis. *Arch Immunol Ther Exp (Warsz)* 2018; **66**: 171–181.
- 19 Thijs J, Krastev T, Weidinger S *et al.* Biomarkers for atopic dermatitis: a systematic review and meta-analysis. *Curr Opin Allergy Clin Immunol* 2015; **15**: 453–460.
- 20 Karimkhani C, Silverberg II, Dellavalle RP. Defining intrinsic vs. extrinsic atopic dermatitis. *Dermatol Online J* 2015; **21**: 13030/qt14p8p404.
- 21 Treister AD, Kraff-Cooper C, Lio PA. Risk factors for dupilumab-associated conjunctivitis in patients with atopic dermatitis. *JAMA Dermatol* 2018; **154**: 1208–1211.