ORIGINAL ARTICLE

Effect of dupilumab on hand eczema in patients with atopic dermatitis: An observational study

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ABSTRACT

Systemic treatment options for chronic hand eczema are limited. Dupilumab is used in atopic dermatitis (AD) but is not licensed for (isolated) hand eczema. In this observational prospective study we aimed to determine the response of hand eczema to dupilumab in patients with AD. Adult patients with hand eczema and AD received dupilumab s.c. at a 600 mg loading dose, followed by 300 mg every 2 weeks. Primary outcome was a minimum improvement of 75% on the Hand Eczema Severity Index after 16 weeks (HECSI-75). Secondary outcomes were severity, measured using the Photographic guide; quality of life improvement as patient-reported outcome, measured using the Dermatology Life Quality Index (DLQI); and AD severity, measured using the Eczema Area and Severity Index (EASI). Forty-seven patients were included (32 males; mean age, 45 years). HECSI-75 was achieved by 28 (60%). Mean HECSI score reduction was 49.2 points (range, 0–164; 95% within-subject confidence interval, 46.4–52.0), which was already significantly decreased after 4 weeks ($P < 0.001$). DLQI score mean improvement was 8.8 points (standard deviation [SD], 6.0) or 70.0% decrease (SD, 26.4) ($P < 0.001$). Eighteen patients (38%) were classified as responders on the Photographic guide. There was no difference in response between chronic fissured and recurrent vesicular clinical subtypes. Similar percentages of patients achieving EASI-75 and HECSI-75 were seen after 16 weeks. In conclusion, this study shows a favorable response of hand eczema to dupilumab in patients with AD. This raises the question whether a response will also be seen in isolated hand eczema.

Key words: atopic dermatitis, biological, dupilumab, hand eczema, treatment.

INTRODUCTION

Systemic treatment options are limited for chronic hand eczema patients. Currently, alitretinoin is the only approved systemic treatment option for all clinical subtypes of severe chronic hand eczema. The European guidelines recommend alitretinoin as a secondary treatment option for severe chronic hand eczema in patients with inadequate response to topical corticosteroids,[1] but the drug shows variable efficacy. Alitretinoin is primarily effective in the clinical subtype of hyperkeratotic hand eczema; in other subtypes, its effect is less profound.[2] For patients who are unresponsive to or intolerant of alitretinoin, remaining treatment options are scarce. Dupilumab is a monoclonal antibody inhibiting interleukin (IL)-4 and IL-13 signaling.[3] Having shown its efficacy and safety in several large trials,[4] this biologic has now become widely available for the treatment of atopic dermatitis (AD). So far, only three case studies have been published on the effect of dupilumab on (isolated) hand eczema.[5–7] Hand eczema is common in patients with AD[8] and various hand eczema classification

systems exist which include the etiological subtype atopic hand eczema.[9,10] This subtype is characterized as a hand eczema seen in patients with AD (previous or current) according to the UK Working Party criteria.[11] In this study, we aimed to evaluate the effect of dupilumab on hand eczema in a cohort of patients treated for AD.

METHODS

Study population

This was a prospective observational study carried out at the Department of Dermatology of the University Medical Center Groningen. Between October 2017 and September 2018, we consecutively included patients aged 18 years or older with AD and concomitant atopic hand eczema. These patients started treatment with dupilumab at a loading dose of 600 mg s.c., followed by 300 mg every 2 weeks over the course of 16 weeks. The diagnosis of hand eczema was made by the treating dermatologist according to current guidelines.[1,9] Patients with a minimum hand eczema severity of moderate on the

Photographic guide by Coenraads *et al.*[12] at baseline were considered for analysis. Patients using systemic immunosuppressive/immunomodulating drugs at baseline or during the 16-week study period were excluded. A minimum washout period of 2 weeks was applied before baseline for cyclosporin, and a minimum washout of 4 weeks was applied for azathioprine and methotrexate. In five cases the use of oral prednisolone was permitted to be stopped during the week before baseline. The use of other concomitant medication (including topical corticosteroids/calcineurin inhibitors, and inhaled, nasal and ocular corticosteroids used respectively for asthma, rhinitis and conjunctivitis) was permitted during the study period. No further exclusion criteria were applied.

All procedures performed in this study were in accordance with the ethical standards of the institutional research committee (Medical Ethical Review Board of the University Medical Center Groningen, reference: METc 2018/344) and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The Medical Ethical Review Board confirmed that the current study did not fall under the scope of the Medical Research Involving Human Subjects Act.

Informed consent was obtained from all individual participants included in this study. Additional informed consent was obtained from all individual participants for whom identifying information (photographs) is included in this article.

Outcome measures

The primary outcome measure was a minimum improvement of 75% on the Hand Eczema Severity Index after 16 weeks (HECSI-75).[13] The HECSI was measured at baseline, and weeks 4, 8, 12 and 16 by a trained research nurse. This instrument includes erythema, fissures, vesicles, scaling, edema, induration/papules, and measurement of the affected area to grade the severity of hand eczema. The score ranges 0–360, with higher scores representing more severe disease. The percentage of patients with a minimum HECSI improvement of 50% (HECSI-50) and 90% (HECSI-90) was determined as the secondary outcome, as well as mean change and percentage change between baseline and week 16. Another secondary outcome was response to treatment after 16 weeks, defined as an improvement of two steps or more on the Photographic guide compared with baseline. This physician-rated instrument covers five degrees of severity (clear, almost clear, moderate, severe, very severe) and takes into account the intensity and percentage of hand surface involved.[12] The Dermatology Life Quality Index (DLQI) was used as a patient-reported outcome to assess improvement in quality of life between baseline and week 16.[14] A minimum improvement of 4 points was considered a clinical meaningful change.[15] The percentage of patients reaching a minimum of 75% improvement on the Eczema Area and Severity Index score for severity of AD (EASI-75) between baseline and 16 weeks was recorded to assess the concomitant effect of dupilumab on AD.[16,17]

The following variables were recorded at baseline: total duration of hand eczema in years; concomitant medication; the Investigator Global Assessment score for severity of AD (clear, almost clear, mild, moderate, severe, very severe); total immunoglobulin (Ig)E level; occupation and risk assessment for developing hand eczema in this occupation;[18] performance of wet work;[18] irritant contact dermatitis (ICD);[1] patch testing/contact allergies; clinical subtype of hand eczema;[9] smoking status (current/stopped/non-smoking) and pack years;[19] and use of previous systemic immunosuppressive/immunomodulatory medication.

Statistical analysis

Hand Eczema Severity Index values are graphically presented as the percentage of patients achieving HECSI-50, HECSI-75 and HECSI-90 at the various time points. Also, mean percentage change and 95% within-subject confidence intervals (CI) are plotted.[20] Friedman's ANOVA with post-hoc Dunn–Bonferroni test were used to compare mean HECSI change scores at various time points. DLQI mean scores at baseline and 16 weeks were compared with a paired *t*-test. The EASI score was expressed as the percentage of patients improving 75% or more (EASI-75). The χ^2-test was used to compare percentages in independent groups. For nine cases, the week 8 and week 12 visits did not take place. For these visits, the last observation carried forward method was used with the observations from week 4. There were no dropouts or cases lost to follow up during the 16-week study period. Calculations were performed with IBM SPSS Statistics for Windows, version 23.0 (IBM, Armonk, NY, USA) and GraphPad Prism version 7.02 for Windows (GraphPad Software, La Jolla, California, USA, www.graphpad.com). $P < 0.05$ was regarded as statistically significant.

RESULTS

A total of 55 patients consecutively treated with dupilumab for AD with concomitant hand eczema was considered for this study. Eight of them used systemic corticosteroids at baseline and subsequently during (a part of) the 16-week study period. These patients were excluded from analysis, leading to a total of 47 included hand eczema patients with concomitant AD. Of these, 16 (34%) reported that their hand eczema was the main complaint at baseline, although they had moderate to very severe AD. For basic characteristics, see Table 1.

Hand Eczema Severity Index score improved in 45 patients (96%). HECSI-75 was achieved by 28 patients (60%) at week 16. HECSI-50 was achieved by 41 (87%) and HECSI-90 by 15 (32%). Mean percentage change in HECSI score between baseline and 16 weeks was −74.6% (range, −100.0 to 0; 95% within-subject CI, −67.9 to −81.2; Fig. 1). The mean difference in HECSI score between baseline and 16 weeks was 49.2 points (range, 0–164; 95% within-subject CI, 46.4–52.0). Mean HECSI score was already significantly improved after 4 weeks compared with baseline ($P < 0.001$). This effect was sustained up to 16 weeks.

There was no significant difference in proportion of patients reaching HECSI-75 between patients with a clinical diagnosis of chronic fissured (18/35, 51%) and recurrent vesicular (10/12, 83%) hand eczema ($P = 0.09$), both clinically inflammatory subtypes (Fig. 2). Of the 14 patients with ICD,

Table 1. Baseline characteristics of study population (*n* = 47)

Sex, *n* (%)	
Male	32 (68.1)
Female	15 (31.9)
Age, mean (range), years	45.2 (20–69)
Duration of disease, mean (range), years	27.4 (0–68)
Baseline severity Photographic guide, *n* (%)	
Moderate	27 (57.4)
Severe	11 (23.4)
Very severe	9 (19.1)
Baseline HECSI score, mean (range)	62 (7–169)
Baseline DLQI score, mean (range)	12.6 (2–30)
Baseline severity IGA, *n* (%)	
Mild	1 (2.1)
Moderate	14 (29.8)
Severe	21 (44.7)
Very severe	11 (23.4)
Baseline EASI score, mean (range)	25.6 (5.7–71.4)
Total IgE level, *n* (%)[†]	
Normal (<116 kU/L)	6 (14.0)
Elevated (≥116 kU/L)	37 (86.0)
Clinical subtype of hand eczema, *n* (%)	
Chronic fissured	35 (74.5)
Recurrent vesicular	12 (25.5)
Etiological factors for hand eczema	
Patch testing performed, *n* (%)	32 (68.1)
At least one positive reaction to the European baseline series, *n* (% of *n* tested)[23,24]	14 (43.8)
Metals	8 (25.0)
Preservatives	5 (15.6)
Fragrances	5 (15.6)
Rubbers	3 (9.3)
Topicals	2 (6.3)
Other[‡]	2 (6.3)
Irritant contact dermatitis, *n* (%)	14 (29.8)
Working in a wet work occupation, *n* (%)	7 (14.9)[§]
Working in a high-risk occupation for hand eczema, *n* (%)	9 (19.1)[§]
No. of systemic immunosuppressive/immunomodulatory medications used, median (range)	2 (1–6)
Cyclosporin, *n* (%)	46 (97.9)
Prednisolone, *n* (%)	35 (74.5)
Methotrexate, *n* (%)	16 (34.0)
Azathioprine, *n* (%)	12 (25.5)
Alitretinoin, *n* (%)	7 (14.9)
Mycophenolic acid, *n* (%)	4 (8.5)
Mycophenolate mofetil, *n* (%)	2 (4.3)
Tacrolimus (oral), *n* (%)	2 (4.3)
Intoxications	
Current smoker, *n* (%)	17 (36.2)
Pack years (current and stopped smokers), median (range), years	14 (0–175)

[†]Missing in four patients. [‡]Colophonium/4-tert-butylphenol formaldehyde resin in one patient, and *p*-phenylenediamine/Disperse Orange 3 in the other patient. [§]Twenty-eight of 47 patients performed paid work at baseline. DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; IGA, Investigator Global Assessment (for atopic dermatitis).

10 (71%) reached HECSI-75. There was no significant difference with patients who did not have ICD (18/33, 54%; *P* = 0.34). There was no significant difference between an elevated (≥116 kU/L) or normal (<116 kU/L) total IgE at baseline regarding achieving HECSI-75 (*P* = 0.99) or EASI-75 (*P* = 0.68) at 16 weeks.

Eighteen patients (38%) could be classified as responders (two steps improvement or more) on the Photographic guide after 16 weeks of dupilumab treatment. All but three patients (44/47, 94%) improved at least one step (see Table 2). Again, there was no difference in response between patients with a clinical diagnosis of chronic fissured (11/35, 31%) and recurrent vesicular (7/12, 58%) hand eczema (*P* = 0.10).

An EASI-75 was achieved by 27 patients (57%) at week 16. The mean percentage change in EASI score between baseline and 16 weeks was −71.5% (range, −96.0 to +66.5; 95% CI, −63.1 to −79.8). The percentage of patients reaching EASI-50/75/90 and HECSI-50/75/90 was quite similar (Fig. 3) These outcomes were achieved concomitantly in 72% (for EASI/HECSI-50), 38% (for EASI/HECSI-75) and 9% (for EASI/HECSI-90) of patients. Notably, however, it was also common that only EASI-50/75/90 or HECSI-50/75/90 was achieved. For EASI-75 and HECSI-75 this occurred in 19 of 47 patients (40%; Table 3). Of note, achieving EASI-50/75/90, while not achieving HECSI-50/75/90, does not mean that these patients did not experience any effect on the hands at all; the improvement was just less profound (25–87%). Only two patients experienced no HECSI improvement at all; they did, however, achieve EASI-75.

Dermatology Life Quality Index scores improved with a mean of 8.8 points (standard deviation [SD], 6.0) or a 70.0% decrease from baseline (SD, 26.4) (*P* < 0.001). Of the 28 patients reaching HECSI-75, 25 (89%) improved 4 points or more on the DLQI. For patients reaching EASI-75, this number was 26 of 27 (96%). This difference was not statistically significant (*P* = 0.81). Mean change in DLQI score did not significantly differ between the chronic fissured (8.1 points; SD, 5.3) and recurrent vesicular (10.8 points; SD, 7.5) clinical subtypes (*P* = 0.18).

Topical medication (corticosteroids/calcineurin inhibitors) use for the whole body could be decreased in quantity and/or potency in 36 patients (77%) between baseline and 16 weeks. Of the 11 remaining patients, one did not use any topical medication during the study, eight remained at the same quantity and potency, one switched to a stronger potency but used a lower quantity, and one had to intensify topical therapy. Of the 40 patients that used between 10 and 200 g or more of topical medication per week at baseline, 26 (65%) were able to taper their topical medication use to less than 10 g/week during the 16 weeks (see Appendix S1 for an overview of concomitant medication use).

DISCUSSION

This study shows a marked improvement of hand eczema in patients treated with dupilumab for AD. The large majority of patients showed improvement on the HECSI, the Photographic
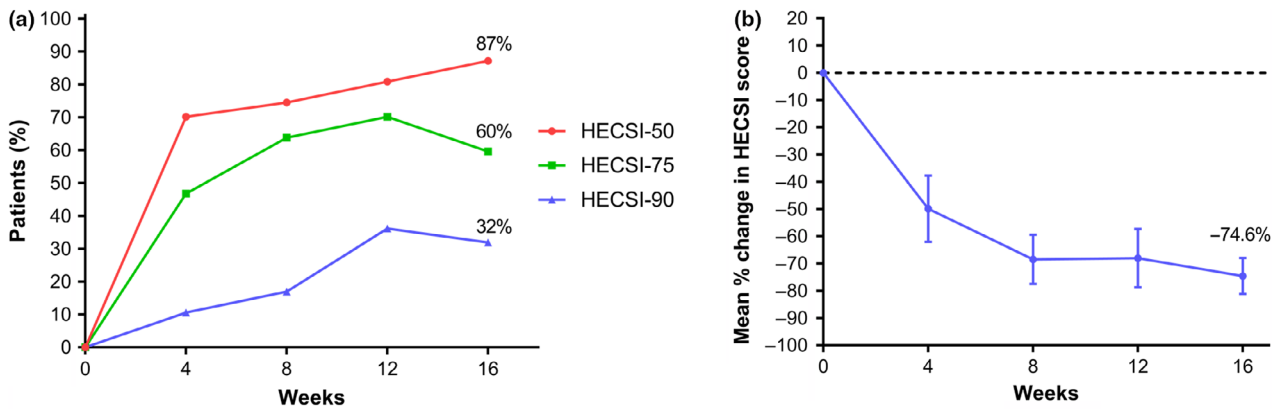
Figure 1. Hand Eczema Severity Index (HESCI) score development during dupilumab treatment (*n* = 47). (a) Percentages of patients achieving 50%, 75% and 90% reduction in HECSI score (HECSI-50, HECSI-75 and HECSI-90) at weeks 4, 8, 12 and 16. (b) Mean percentage change in HECSI score from baseline up to 16 weeks; negative values indicate improvement. Error bars reflect 95% within-subject confidence intervals[20] and the dashed line indicates baseline.

Figure 2. Clinical improvement of patients after 16 weeks of dupilumab treatment. (a) A patient with very severe chronic fissured hand eczema improving from a Hand Eczema Severity Index (HECSI) score of 129 to 9. (b) A patient with very severe recurrent vesicular hand eczema improving from a HECSI score of 168 to 4.

Figure 3. Percentage of patients achieving 50%, 75% and 90% improvement on the Hand Eczema Severity Index (HECSI-50, HECSI-75 and HECSI-90) and on the Eczema Area and Severity Index (EASI-50, EASI-75 and EASI-90) after 16 weeks of dupilumab therapy.

guide, and the DLQI for both clinically inflammatory subtypes of hand eczema seen in this study.

Although minimally important change of the HECSI has not yet been studied, we chose HECSI-75 as the primary cut-off point, analogous to the EASI-75 which is currently often reported. Our experience with hand eczema patients is that a 75% improvement in HECSI score is very often regarded as clinically meaningful, by physicians as well as patients.

This study included not only patients with a hand eczema Photographic severity rating of severe, but also moderate. Alitretinoin is licensed only for use in severe hand eczema, which is why future studies into dupilumab for isolated hand eczema
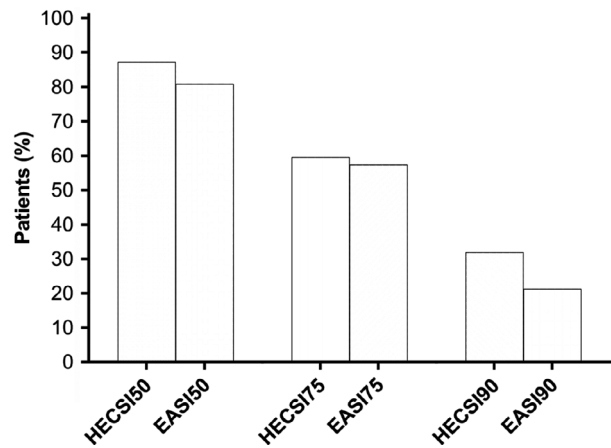
should also focus on patients with this severity. In this regard, it should be noted that previously performed trials with alitretinoin versus placebo used a five-scale Physician Global Assessment instrument (clear/almost clear/mild/moderate/severe, including the subjective patient items pruritus and pain)[2] which differs from the Photographic guide for severity used in the current study (clear/almost clear/moderate/severe/very severe).[12]

The current study shows that the Photographic guide in combination with our definition of responder (two steps improvement or more) may not be suitable as the outcome measure for severity when including moderate hand eczema. Only a minority of patients could be classified as responders, largely because a status of clear on the Photographic guide is hard to achieve. Even with very few symptoms (often

Table 2. Comparison of hand eczema severity on the Photographic guide between baseline and 16 weeks, and percentage responders at week 16 for each baseline severity and in total

	Severity on the Photographic guide at 16 weeks (*n*)					Total	Responders at week 16 (%)
	Clear	Almost clear	Moderate	Severe	Very severe		
Severity on the Photographic guide at baseline (*n*)							
Moderate	5	20	2	0	0	27	19
Severe	2	3	5	1	0	11	46
Very severe	0	6	2	1	0	9	89
Total	7	29	9	2	0	47	38

Table 3. Number of patients achieving 50%, 75% and 90% improvement on the Hand Eczema Severity Index (HECSI-50, HECSI-75 and HECSI-90) versus patients achieving 50%, 75% and 90% improvement on the Eczema Area and Severity Index (EASI-50, EASI-75 and EASI-90) after 16 weeks of dupilumab therapy

	EASI-50 after 16 weeks		
	No	Yes	Total
HECSI-50 after 16 weeks			
No	2	4	6
Yes	7	34	41
Total	9	38	47

	EASI-75 after 16 weeks		
	No	Yes	Total
HECSI-75 after 16 weeks			
No	10	9	19
Yes	10	18	28
Total	20	27	47

	EASI-90 after 16 weeks		
	No	Yes	Total
HECSI-90 after 16 weeks			
No	26	6	32
Yes	11	4	15
Total	37	10	47

corresponding with a very low HECSI score) it feels intuitive to choose almost clear as severity measure. Because of this, it is hard to achieve the responder status for patient with a baseline moderate hand eczema. This is reflected in the high number of patients with a status of almost clear after 16 weeks in the baseline moderate group.

It was interesting that there were some discrepancies between patients achieving HECSI-50/75/90 and those achieving EASI-50/75/90. Possible reasons for these discrepancies could be that there are various mechanisms underlying pathophysiology, or differences in pharmacokinetics between subjects, responsible for a varying response to dupilumab. The two patients not improving on the HECSI at all might have had a different type of hand eczema than the rest of the population, although this was not apparent from their clinical presentation or from other measured variables.

The main limitations of this study are the lack of a control group and its limited follow-up time. The intention of performing this study was to explore the possible usefulness of larger (preferably randomized controlled) studies into this subject. Sixteen weeks was chosen as end-point because at this time point a maximum and durable effect of dupilumab is shown to be reached in AD.[17] Longer follow-up durations are needed to establish whether this is also the case in hand eczema. Another limitation is that the use of concomitant topical corticosteroids was permitted. Potentially, this could distort the observed effect of dupilumab on hand eczema. Furthermore, irritating and allergic factors might have had an influence on the severity score, with 15% of all patients performing wet work and 19% working in a high-risk occupation for hand eczema. Several patients (*n* = 15) had not been tested for contact allergies using patch tests because of their AD severity. Patch tests results are difficult to interpret in these patients.[21] Although this is a limitation of the study, it probably does not greatly influence the observed improvement of patients because they most likely did not alter their exposure during the study. Finally, the skin-specific DLQI was used as the patient-reported outcome in this study. However, quality of life impairments and improvement concerning the hands might have been concealed by the (improvement in) concomitant AD on the rest of the body. The Quality Of Life in Hand Eczema Questionnaire[22] would have been a more appropriate instrument, but a validation study of the Dutch version is still ongoing.

In conclusion, this study shows that AD patients with hand eczema can expect an improvement of their hand eczema severity when treated with dupilumab. The observation that hand eczema of both clinically inflammatory subtypes responded favorably to dupilumab may hold promise for patients with isolated hand eczema, mainly in cases in which a clear irritant or allergic etiology has been identified and avoided without substantial improvement of the hand eczema. This should be investigated in future studies.

arranging education from Sanofi-Genzyme. Dr De Bruin-Weller is a member of advisory boards of AbbVie, UCB, Eli-Lilly, Pfizer, Sanofi-Genzyme and Regeneron, and received consultancy fees from Sanofi/Genzyme/Regeneron and AbbVie. No other conflicts are reported.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Concomitant medication during dupilumab treatment.