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ORIGINAL ARTICLE

Experiences from daily practice of upadacitinib treatment on atopic dermatitis with a focus on hand eczema: Results from the BioDay registry

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Abstract

Background: Real-world data on the effectiveness of upadacitinib on atopic dermatitis (AD), hand eczema (HE) and HE in the context of AD are limited.

Objectives: To evaluate the effectiveness and safety of upadacitinib on AD and on HE in patients with AD.

Methods: This prospective observational cohort study includes clinical outcomes: Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), Hand Eczema Severity Index (HECSI), Photographic guide; and PROMs: average pruritus and pain Numeric Rating Scale (NRS) score of the past week, Patient-Oriented Eczema Measure (POEM), Patient-Oriented Eczema, Dermatology Life Quality Index (DLQI), Atopic Dermatitis Control Tool (ADCT), Patient Global Assessment of Disease (PGAD), Quality Of Life Hand Eczema Questionnaire (QOLHEQ) at baseline, Week 4, and Week 16 of upadacitinib-treated patients. Adverse events were monitored during each visit.

Results: Thirty-eight patients were included, of which 32 patients had HE. At Week 16, EASI-75 was achieved by 50.0%. Absolute cutoff score NRS-pruritus ≤4 was reached by 62.5%, POEM ≤7 by 37.5%, DLQI ≤5 by 59.4%, ADCT <7 by 68.8%, and PGAD rating of at least 'good' by 53.1%. HECSI-75 was achieved by 59.3% and (almost) clear on the Photographic guide by 74.1%. The minimally important change in QOLHEQ was achieved by 57.9%. Sub-analysis in patients with concomitant irritant contact dermatitis showed no differences. Safety analysis showed no new findings compared to clinical trials.

Conclusions: Upadacitinib can be an effective treatment for patients with AD and concomitant HE in daily practice. Future studies should focus on the effectiveness of upadacitinib on chronic HE, especially on the different etiological subtypes of HE, including HE in non-atopic individuals.

1 | INTRODUCTION

Both atopic dermatitis (AD) and hand eczema (HE) are prevalent inflammatory skin disorders; with over 50% of AD patients also presenting with hand involvement in the clinical population.[1–4] AD patients also have a fourfold increased lifetime prevalence of HE compared to individuals without AD.[5] Approximately one third of the general adult population (including patients with HE) reports (a history of) AD.[2] One method of classifying HE is based on its aetiology.[6] The pathogenesis of HE is often multifactorial, with more than one underlying aetiology. Both exogenous and endogenous factors may influence the pathogenesis of HE, with AD being the most recognized endogenous factor.[7] Aside from atopic HE, other etiological HE subtypes are irritant contact dermatitis (ICD), allergic contact dermatitis (ACD) and protein contact dermatitis (PCD).[7]

Despite high HE prevalence, functional impairment, and decreased quality of life; treatment options for HE patients, refractory to topical corticosteroids, are limited.[2,3,8] Recently, several new AD treatments have been developed; some of which have also shown potential in (atopic) HE patients. For example, dupilumab, an IL-4 and IL-13 inhibiting interleukin (IL)-4 receptor-α antibody, proved effective for treating HE in AD patients.[9] Other recently available systemic treatments for AD include Janus Kinase (JAK)-inhibitors, which target several cytokine pathways beyond the Th2 pathway. Therefore, it is plausible that JAK inhibitors could effectively treat HE irrespective of the (etiological) subtype. Daily practice data of upadacitinib effectiveness in AD is promising, but scarce. Only three clinical daily practice studies and a few case series/reports have been published.[10–23] Moreover, daily practice data of the effectiveness of upadacitinib on HE in AD patients has not been published. Therefore, the aim of this prospective BioDay registry study is to evaluate the 16-week effectiveness and safety of upadacitinib on AD and HE in AD patients in daily practice.

2 | MATERIALS AND METHODS

2.1 | Study design

This study included Dutch BioDay registry patients from the dermatology departments of the University Medical Center Groningen (UMCG) and the Medical Center Leeuwarden (MCL). The BioDay registry is a prospective multicentre observational cohort study that includes daily practice AD patients treated with biologics or small molecules. The study was approved by the local Medical Research Ethics Committee as a non-interventional study (METC 18-239). This study adheres to the declaration of Helsinki; written informed consent was obtained from all patients.

2.2 | Study population, dosage and concomitant medication

All AD patients who received upadacitinib, during September 2021 and June 2022, were included. All patients met the criteria for upadacitinib treatment established by the Dutch Society of Dermatology and Venereology (see Appendix S1 in Supporting Information).[24] Each patient received 15 mg of upadacitinib once daily at baseline. However, patients with a severe clinical presentation and an extensive disease history received 30 mg of upadacitinib at baseline. The upadacitinib dosage was altered from 15 to 30 mg and vice versa if deemed appropriate due to ineffectiveness and/or adverse events (AEs). Implementation of a strict washout (12 weeks for dupilumab and 4 weeks for conventional systemic therapies [cyclosporin A, methotrexate, azathioprine, prednisolone and mycophenolate mofetil] or JAK inhibitors [baricitinib and abrocitinib]) was neither feasible nor required for this daily practice study. All systemic medication was discontinued at/prior to baseline. Concomitant usage of topical corticosteroids alongside upadacitinib was permitted. Patients were assessed at baseline, after 4 weeks, between 8 and 12 weeks, and after 16 weeks of upadacitinib treatment.

2.3 | Outcome measures

2.3.1 | AD outcome measures

Disease severity was determined using the Eczema Area and Severity Index (EASI) (range: 0–72)[25] and the 6-point Investigator's Global Assessment (IGA) (clear–almost clear–mild–moderate–severe–very severe); rating was performed by trained physicians. Endpoints of the physician-reported outcomes were defined as the proportion of patients who achieved an EASI score improvement of ≥50%, ≥75% or ≥90% (EASI-50, EASI-75, EASI-90, respectively) compared to baseline. Absolute cutoff scores were an EASI ≤7[26] and an IGA of (almost) clear. Furthermore, patient-reported outcomes measures (PROMs) included the average pruritus[27] and pain[28] Numeric Rating Scale (NRS) score of the past week (range: 0–10), the Patient-Oriented Eczema Measure (POEM) (range: 0–28),[29] the Dermatology Life Quality Index (DLQI) (range: 0–30),[30] the Atopic Dermatitis Control Tool (ADCT) (range: 0–24),[31] and the Patient Global Assessment of Disease (PGAD) (poor–fair–good–very good–excellent).[32] The ADCT was developed to evaluate patient-perceived disease control of AD and consists of six questions. The PGAD is a single question: 'Considering all the ways in which your eczema affects you, indicate how well you are doing'. Absolute PROMs cutoff scores were the proportion of patients who achieved a NRS-pruritus ≤4,[26] NRS-pain ≤4, POEM ≤7,[26] DLQI ≤5,[26] ADCT <7,[31] or PGAD of at least 'good'.[32]

2.3.2 | HE outcome measures

HE disease severity was determined using the Hand Eczema Severity Index (HECSI)[33] (range: 0–360) and the Photographic guide (clear–almost clear–moderate–severe–very severe)[34]; rating was performed by trained physicians. Endpoints were the proportion of patients who achieved a HECSI score improvement of ≥50%, ≥75% or ≥90% (HECSI-50, HECSI-75, HECSI-90, respectively) compared to baseline. An absolute cutoff score was (almost) clear on the Photographic guide. Health-related quality of life in HE patients was assessed with the Quality Of Life Hand Eczema Questionnaire (QOLHEQ) (range: 0–120).[35] The QOLHEQ consists of four domains: symptoms, emotions, functioning and treatment/prevention. Endpoints of the QOLHEQ were the proportion of patients who achieved the minimally important change (MIC), requiring a total score improvement of 22 points.[36] For the subscales, the smallest detectable change (SDC) was regarded as the MIC, as the Dutch version of the QOLHEQ was not able to detect changes as small as the MIC that was found in the interpretability study.[36] The MIC for the subdomains were: symptoms 6 points, emotions 7 points, functioning 8 points and treatment/prevention 5 points.[36]

2.3.3 | Classification of HE and atopic comorbidities

Patients were interviewed using a questionnaire to identify possible contributing etiological factors of HE and atopic comorbidities (see Appendix S1 in Supporting Information). ICD was established when relevant occupational or non-occupational exposure to irritants (wet work[37,38] and friction) was confirmed. ACD was verified through positive patch test results to allergens with relevant exposure. PCD was diagnosed in the context of relevant exposure to proteins and a history of immediate skin reaction. Data of allergic asthma were collected according to the Global Initiative for Asthma guideline[39] and allergic rhinitis using the Allergic Rhinitis and its Impact on Asthma guideline.[40]

2.4 | Adverse events

AEs and laboratory parameters were monitored during each patient visit. AE severity was rated in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0).[41]

2.5 | Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 28). Figures were made using GraphPad Prism (version 8). The analyses included the clinical outcomes and PROMs from baseline, Week 4 and Week 16; except for the ADCT, which was only filled in at baseline and Week 16. Multiple imputation was applied on clinical outcomes and PROMs to prevent bias and loss of statistical power. The data were imputed 30 times, based on the percentage of missing data of these variables (26.7%).[42,43] The variables age, sex, concomitant oral immunosuppressive therapy at baseline, the number of dropouts and the motivation for dropping out (lack of efficacy and AEs) were used as predictors. Outcomes were analysed with generalized estimating equations (GEE). To correct for multiple measurements of outcomes, the autoregressive working correlation structure was implemented in all analyses models. Age, sex, concomitant oral immunosuppressive therapy at baseline, the number of dropouts and the motivation for dropping out were included as covariates. Sub-analyses on the usage of topical corticosteroids (yes/no) were performed using GEE and if patients numbers were sufficient, sub-analyses on etiological subtypes of HE were performed. Results for continuous outcomes were presented as change in mean score with 95% confidence intervals (CI) and p-values. Regression coefficients were transformed to odds ratios (OR) for dichotomous outcomes. A p-value of <0.05 was deemed statistically significant.

3 | RESULTS

3.1 | Patient and baseline characteristics

This study included 38 AD patients. Baseline characteristics are displayed in Table 1 (details of individual patients are shown in Table S2). Thirty-two patients presented with HE (84.2%). In addition to atopic HE, two patients had ACD and 12 patients had ICD as a contributing etiological subtype. At baseline, 33 (86.8%) patients may have still been experiencing therapeutic effects of their previous AD treatments (including dupilumab, baricitinib, cyclosporine A and prednisolone) as no wash-out period was implemented. Thirty-five (92.1%) patients had previously received two or more systemic AD treatments (the majority had been treated with cyclosporin A [n = 35] and/or dupilumab [n = 33]). At baseline, the mean EASI score was 17.2 (standard deviation [SD] 12.3) and 32 (84.2%) patients had an IGA score of moderate-to-very-severe. The mean baseline HECSI score was 45.2 (SD 50.4) and 21 (65.6%) patients had a moderate-to-very-severe Photographic guide score.

3.2 | Upadacitinib dosage

All patients were administered 15 mg upadacitinib once daily at baseline, with the exception of one patient, who received 30 mg. Five patients switched to 30 mg of upadacinitib during the study period; two patients at Week 8, two patients during Week 12 and one patient in Week 16. In total, six (15.8%) patients were being treated with 30 mg of upadacitinib at Week 16. Patients requiring 30 mg never switched to 15 mg.

TABLE 1 Baseline characteristics

Baseline characteristics	Total cohort	Subgroup with HE
N	38	32
Upadacitinib dosage, n (%)		
15 mg	37 (97.4)	31 (96.9)
30 mg	1 (2.6)	1 (3.1)
Age, mean (SD)[a], years	34.2 (12.6)	34.6 (12.7)
Sex, n (%)		
Male	24 (63.2)	19 (59.4)
Female	14 (36.8)	13 (40.6)
BMI, mean (SD)	26.6 (6.4)	26.4 (6.8)
Smoking		
Current smoker, n (%)	12 (31.6)	12 (37.5)
Pack years,[54] mean (SD), years	3.6 (6.8)	4.0 (7.2)
History of HE?		
Yes, n (%)	34 (89.5)	32 (100.0)
HE age of onset, mean (SD), years	-	10.7 (17.3)
HE duration, mean (SD), years	-	23.9 (14.1)
Etiological classification, n (%)		
Irritant contact dermatitis	12 (31.6)	12 (37.5)
Allergic contact dermatitis	2 (5.3)	2 (6.3)
Protein contact dermatitis	0 (0.0)	0 (0.0)
Contributing etiological factors HE, n (%)		
Patch testing performed, n (%)	22 (57.9)	17 (53.1)
At least one positive patch test reaction to an allergen from the allergen groups,[55] n (%)	12 (31.6)	10 (31.3)
Metals	6 (15.8)	5 (15.6)
Preservatives	3 (7.9)	3 (9.4)
Fragrances	5 (13.2)	4 (12.5)
Rubbers	1 (2.6)	1 (3.1)
Dyes/colours	1 (2.6)	1 (3.1)
Topicals	3 (7.9)	3 (9.4)
Corticosteroids	1 (2.6)	0 (0.0)
Other	4 (10.5)	3 (9.4)
Performing wet work,[37,38] n (%)	7 (18.4)	7 (21.9)
High-risk occupation for HE,[56] n (%)	7 (18.4)	7 (21.9)
Baseline HECSI score, mean (SD)	-	45.2 (50.4)
Baseline HE severity based on the Photographic guide, n (%)		
Almost clear	-	11 (34.4)
Moderate	-	9 (28.1)
Severe	-	9 (28.1)
Very severe	-	3 (9.4)
Baseline QOLHEQ score, mean (SD)	-	38.7 (26.2)
Atopic comorbidities, n (%)		
Allergic asthma	23 (60.5)	19 (59.4)
Allergic rhinitis	29 (76.3)	24 (75.0)
Allergic conjunctivitis	26 (68.4)	21 (65.6)
Food allergy	10 (26.3)	10 (31.3)
AD age of onset, n (%)		
Childhood (≤12 years)	33 (86.8)	28 (87.5)

TABLE 1 (Continued)

Baseline characteristics	Total cohort	Subgroup with HE
Adolescence (12 to <18 years)	2 (5.2)	1 (3.1)
Adult (≥18 years)	3 (7.9)	3 (9.4)
Baseline EASI, mean (SD)	17.2 (12.3)	18.2 (12.8)
Baseline IGA, n (%)		
Almost clear	3 (7.9)	2 (6.3)
Mild	3 (7.9)	1 (3.1)
Moderate	13 34.2)	11 (34.4)
Severe	17 (44.7)	16 (50.0)
Very severe	2 (5.3)	2 (6.3)
NRS-pruritus, mean (SD)	6.1 (2.5)	6.3 (2.4)
NRS-pain, mean (SD)	4.3 (3.8)	4.7 (3.2)
DLQI score, mean (SD)	12.0 (7.2)	12.5 (7.5)
POEM score, mean (SD)	17.5 (6.2)	18.3 (5.4)
ADCT score, mean (SD)	12.2 (6.1)	12.3 (5.9)
PGAD score, n (%)		
Poor	10 (26.3)	9 (28.1)
Fair	17 (44.7)	15 (46.9)
Good	8 (21.1)	6 (18.8)
Very good	3 (7.9)	2 (6.3)
Excellent	0 (0.0)	0 (0.0)
Systemic medication history, n (%)	38 (100.0)	32 (100.0)
Cyclosporine A	35 (92.1)	29 (90.6)
Methotrexate	15 (39.5)	13 (40.6)
Alitretinoin	1 (2.6)	1 (3.1)
Azathioprine	5 (13.2)	4 (12.5)
Dupilumab	33 (86.8)	28 (87.5)
Tralokinumab	1 (2.6)	1 (3.1)
Baricitinib	11 (28.9)	10 (31.3)
Prednisolone	29 (76.3)	24 (75.0)
MMF/MPA	1 (2.6)	1 (3.1)
History of ≥2 immunosuppressives	35 (92.1)	30 (93.8)
In wash-out of immunosuppressive therapy at baseline, n (%)	33 (86.8)	27 (84.4)
Dupilumab	20 (52.6)	15 (46.9)
Baricitinib	10 (26.3)	10 (31.3)
Prednisolone	2 (5.2)	2 (6.3)
Cyclosporin A	1 (2.6)	0 (0.0)
Suspension of systemic therapy prior to baseline, mean (SD), weeks		
Dupilumab	3.4 (1.5)	3.6 (1.5)
Baricitinib	0.9 (0.7)	0.9 (0.8)
Prednisolone	0.5 (0.7)	0.5 (0.7)
Cyclosporin A	0.0 (0.0)	-

Note: Data after multiple imputation.

Abbreviations: AD, atopic dermatitis; ADCT, Atopic Dermatitis Control Tool; BMI, body mass index; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HE, hand eczema; HECSI, Hand Eczema Severity Index; IGA, Investigator's Global Assessment; MMF, mycophenolate mofetil; MPA, mycophenolic acid; N, number; NRS, Numeric Rating Scale; PGAD, Patient Global Assessment of Disease; POEM, Patient-Oriented Eczema Measure; QOLHEQ, Quality of Life Hand Eczema Questionnaire; SD, standard deviation.

[a]SD was calculated as the standard error of the mean (SEM) multiplied by √n.

[b]See Table S1 for an overview of the allergen groups.

TABLE 2 Effectiveness outcomes

Continuous outcomes	Baseline	Week 4	Week 16	Baseline–Week 4 β (95% CI)	p-value	Baseline–Week 16 β (95% CI)	p-value	Week 4–Week 16 β (95% CI)	p-value
EASI, mean (SD)[a]	17.2 (SD 12.3)	8.5 (SD 11.4)	4.8 (SD 4.5)	−8.6 (−12.3 to −4.9)	<0.001	−12.1 (−16.2 to −8.1)	<0.001	−3.5 (−7.4 to 0.3)	0.070
NRS-pruritus, mean (SD)	6.0 (SD 2.6)	3.1 (SD 2.2)	3.6 (SD 3.2)	−3.1 (−4.1 to −2.0)	<0.001	−2.5 (−3.7 to −1.2)	<0.001	0.6 (−0.8 to 2.0)	0.412
NRS-pain, mean (SD)	4.2 (SD 3.3)	1.5 (SD 2.6)	2.1 (SD 3.1)	−2.7 (−3.8 to −1.6)	<0.001	−2.3 (−3.7 to −0.8)	0.002	0.4 (−1.0 to 1.8)	0.565
POEM, mean (SD)	17.5 (SD 6.2)	8.3 (SD 5.6)	9.9 (SD 6.2)	−9.4 (−11.8 to −7.1)	<0.001	−7.7 (−10.2 to −5.3)	<0.001	1.7 (−0.4 to 3.8)	0.109
DLQI, mean (SD)	12.0 (SD 7.2)	4.9 (SD 5.9)	4.6 (SD 4.1)	−7.1 (−9.2 to −4.9)	<0.001	−7.5 (−9.9 to −5.0)	<0.001	−0.4 (−2.5 to 1.7)	0.728
ADCT, mean (SD)	12.2 (SD 6.1)	-	5.7 (SD 4.7)	-	-	−6.6 (−8.7 to −4.6)	<0.001	-	-
HECSI, mean (SD)	45.2 (SD 50.4)	8.4 (SD 15.4)	10.3 (SD 14.0)	−33.9 (−50.6 to −17.2)	<0.001	−31.5 (−49.2 to −13.8)	<0.001	2.4 (−3.3 to 8.0)	0.406
QOLHEQ, mean (SD)	38.7 (SD 26.2)	18.1 (SD 18.3)	20.9 (SD 20.8)	−21.3 (−30.2 to −12.5)	<0.001	−19.8 (−27.9 to −11.7)	<0.001	1.6 (−5.2 to 8.3)	0.650
Dichotomous outcomes	**Baseline**	**Week 4**	**Week 16**	**OR[b]**	**p-value**	**OR**	**p-value**	**OR**	**p-value**
EASI ≤7, n (%)	8 (21.1)	23 (65.7)	24 (75.0)	9.9	<0.001	18.0	<0.001	2.1	0.162
NRS-pruritus ≤4, n (%)	10 (26.3)	29 (82.9)	20 (62.5)	14.7	<0.001	5.0	0.009	0.3	0.118
NRS-pain ≤4, n (%)	22 (57.9)	29 (82.9)	25 (78.1)	7.1	<0.001	1.3	0.618	0.2	0.031
POEM ≤7, n (%)	3 (7.9)	18 (51.4)	12 (37.5)	11.6	<0.001	5.4	0.008	0.5	0.127
DLQI ≤5, n (%)	7 (18.4)	23 (65.7)	19 (59.4)	9.3	<0.001	7.0	<0.001	0.8	0.677
ADCT <7, n (%)	6 (15.8)	-	22 (68.8)	-	-	9.6	<0.001	-	-
PGAD of at least 'good', n (%)	11 (28.9)	26 (74.3)	17 (53.1)	6.7	0.001	2.7	0.071	0.4	0.203

Note: Data after multiple imputation.

Abbreviations: ADCT, Atopic Dermatitis Control Tool; CI, confidence interval; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; HECSI, Hand Eczema Severity Index; N, number; NRS, Numeric Rating Scale; OR, odds ratio; PGAD, Patient Global Assessment of Disease; POEM, Patient-Oriented Eczema Measure; QOLHEQ, Quality of Life Hand Eczema Questionnaire; SD, standard deviation.

[a]SD was calculated as the standard error of the mean (SEM) multiplied by $\sqrt{n}$.

[b]OR was calculated as exp(β).

## 3.3 | Effectiveness

3.3.1 | Atopic dermatitis

All AD outcomes are presented in Table 2 and Figures 1 and 2. Change in EASI scores at Week 4 and Week 16 of individual patients are shown in Figure S1. The mean EASI score significantly reduced from 17.2 (SD 12.3) at baseline to 8.5 (SD 11.4) at Week 4 (p < 0.001) and to 4.8 (SD 4.5) at Week 16 (p < 0.001) (Table 2). The proportion of patients who reached EASI-50, EASI-75 and EASI-90 at Week 16 were 75.0% (n = 24), 50.0% (n = 16) and 25.0% (n = 8), respectively (Figure 1A). The proportion of patients with EASI ≤7 increased significantly between baseline and Week 16 (OR = 18.0, p < 0.001) (Table 2). After 16 weeks, 40.6% (n = 13) of the patients achieved an IGA score of (almost) clear (Figure 1A). Comparing Week 16 to baseline, the proportion of patients who achieved an NRS-pruritus ≤4 (OR = 5.0, p = 0.009), POEM ≤7 (OR = 5.4, p = 0.008), DLQI ≤5

(OR = 7.0, p < 0.001) or ADCT<7 (OR = 9.6, p < 0.001) increased significantly (Table 2). Between baseline and Week 4, there was a significant increase in proportion of patients reaching an NRS-pain ≤4 (OR = 7.1, p < 0.001) or PGAD rating of at least 'good' (OR = 6.7, p = 0.001) (Table 2); the differences between baseline and Week 16 were not statistically significant.

When adjusting for the usage of topical corticosteroids, no differences in significant p-values in all AD outcome measures were found (Table S3).

3.3.2 | HE outcome measures

All HE effectiveness outcomes are displayed in Table 2 and Figures 1 and 3. Change in HECSI scores at Week 4 and Week 16 of individual patients are shown in Figure S2. The mean HECSI score diminished significantly from 45.2 (SD 50.4) at baseline to 8.4 (SD 15.4,
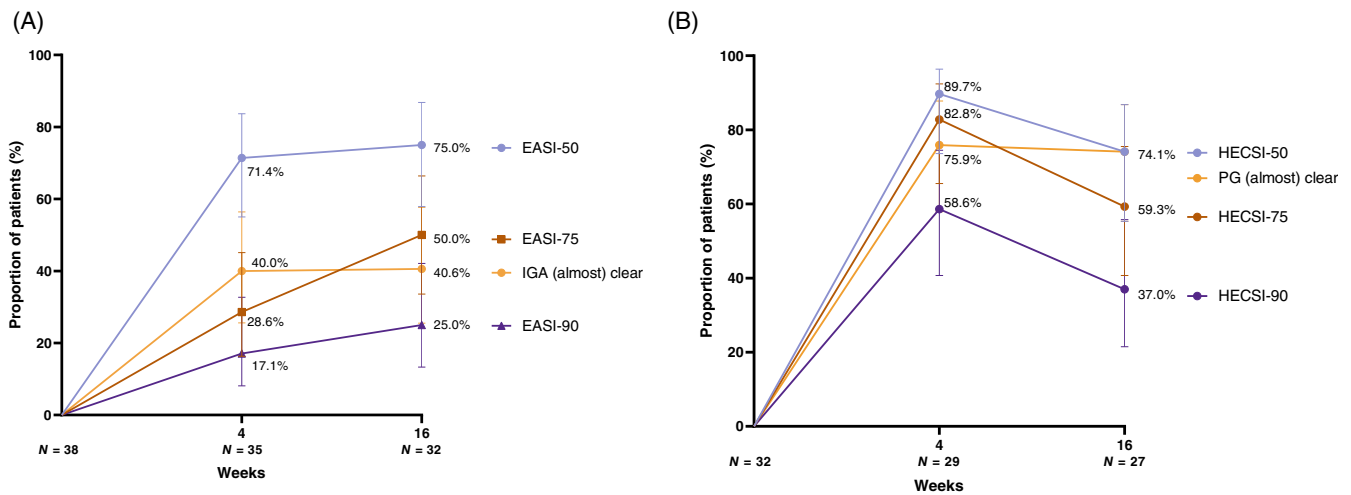
FIGURE 1 Proportion of patients who reached clinical endpoints at Week 4 and Week 16 of upadacitinib treatment. Data after multiple imputation. 95% confidence interval of the proportions is shown with error bars. (A) Proportion of patients who reached EASI-50, EASI-75 or EASI-90 or an IGA-score of (almost) clear. (B) Proportion of patients who reached HECSI-50, HECSI-75, HECSI-90 or an Photographic guide score of (almost) clear. EASI, Eczema Area and Severity Index; HECSI, Hand Eczema Severity Index; IGA, Investigator's Global Assessment; N, number; PG, Photographic guide

FIGURE 2 Proportion of patients who reached the cutoff scores at Week 4 and Week 16 of upadacitinib treatment. Data after multiple imputation. Proportion of patients who achieved an EASI ≤7, NRS-pruritus ≤4, NRS-pain ≤4, POEM ≤7, DLQI ≤5, ADCT <7 or PGAD of at least 'good'. ADCT, Atopic Dermatitis Control Tool; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; PGAD, Patient Global Assessment of Disease; POEM, Patient-Oriented Eczema Measure
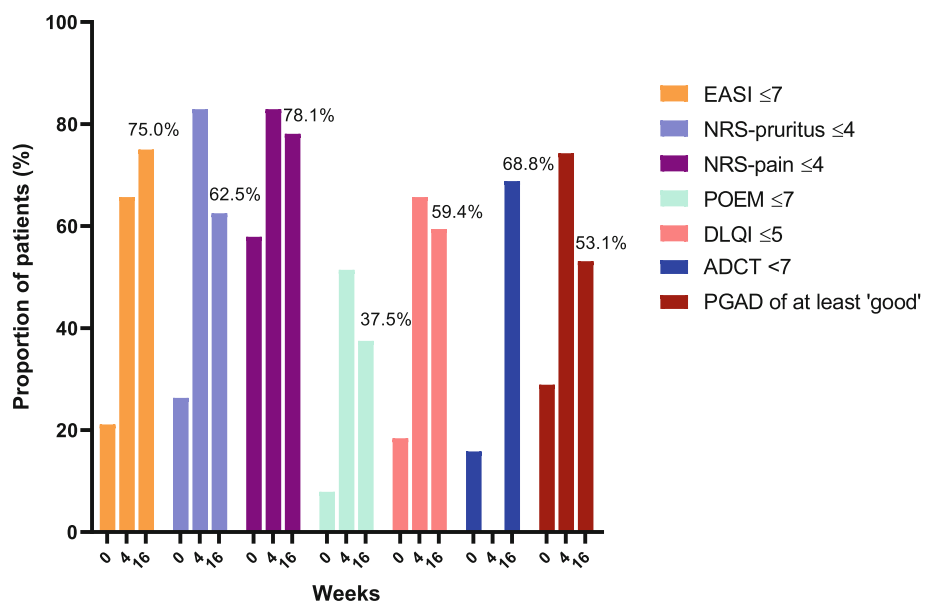

$p < 0.001$) at Week 4, and 10.3 (SD 14.0, $p < 0.001$) at Week 16 (Table 2). The proportions of patients who reached HECSI-50, HECSI-75 and HECSI-90 at Week 16 were 74.1% ($n = 20$), 59.3% ($n = 16$) and 37.0% ($n = 10$), respectively (Figure 1B). A score of (almost) clear on the Photographic guide was achieved by 74.1% ($n = 20$) of the patients at Week 16 (Figure 1B). The mean QOLHEQ score was reduced significantly from 38.7 (SD 26.2) at baseline to 20.9 (SD 20.8, $p < 0.001$) after 16 weeks (Table 2). The MIC of 22 points was achieved by 57.9% (11/19) of the patients at Week 16 (Figure 3). At Week 16, the MIC of the subdomains symptoms, emotions, functioning, and treatment and prevention were reached by 60.0% (12/20), 55.6% (10/18), 64.7% (11/17) and 55.6% (10/18) respectively (Figure 3).

When adjusting for the usage of topical corticosteroids, no differences in significant p-values in all HE outcome measures were found (Table S3). In patients with ICD ($n = 12$) and patients without ICD ($n = 20$), no significant differences were observed regarding the HECSI ($p = 0.501$), Photographic guide ($p = 0.111$) and QOLHEQ ($p = 0.318$) (Table S4). Sub-analyses on ACD ($n = 2$) were not performed due to the small sample size (Table 1).

3.4 | Safety

All AEs are listed in Table 3. Twenty-six (68.4%) patients experienced at least one AE, with AEs generally being mild (83.3%). The most
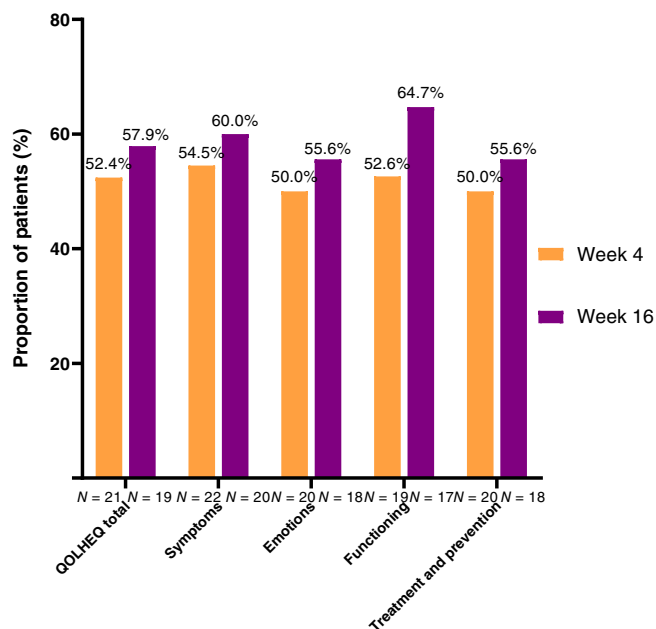
FIGURE 3 Proportion of patients who reached the minimally important change in QOLHEQ score at Week 4 and Week 16 of upadacitinib treatment. Data after multiple imputation. Proportion of patients who achieved the MIC in total QOLHEQ score (22 points), subdomain 'symptoms' (6 points), subdomain 'emotions' (7 points), subdomain 'functioning' (8 points) or subdomain 'treatment and prevention' (5 points). Patients with a total QOLHEQ score of ≤21 ($n = 8$), subdomain 'symptoms' score ≤5 ($n = 7$), subdomain 'emotions' score ≤6 ($n = 9$), subdomain 'functioning' score ≤7 ($n = 10$), and subdomain score 'treatment and prevention' ≤4 ($n = 9$) at baseline were excluded. MIC, minimally important change; N, number; QOLHEQ, Quality of Life Hand Eczema Questionnaire

prevalent AEs were acneiform eruptions ($n = 6$), fatigue ($n = 4$), herpes simplex infection ($n = 4$) and an elevated creatinine phosphokinase (CPK) ($n = 4$).

3.5 | Drop-out

A total of six patients discontinued upadacitinib during the 16-week treatment period. Two patients discontinued treatment due to lack of efficacy (one patient at Week 9 and one patient at Week 14). Four patients discontinued upadacitinib treatment due to AEs: fatigue (at Week 2), acneiform eruption (at Week 2), fatigue and nausea (at Week 3), and abdominal pain (at Week 9).

4 | DISCUSSION

This study evaluated the 16-week effectiveness and safety of upadacitinib on AD, and HE in AD patients. Clinical outcomes and PROMs of both AD and HE improved significantly after 16 weeks of upadacitinib treatment. Sub-analysis in patients with and without ICD of the

TABLE 3 Adverse events

Adverse events	N (%)
Total AEs	48
Mild AEs	40 (83.3)
Patients with AE	26 (68.4)
Gastrointestinal	
Abdominal pain	3 (7.9)
Diarrhoea	1 (2.6)
Nausea	2 (5.3)
General	
Coughing	1 (2.6)
Common cold	1 (2.6)
Xerostomia	1 (2.6)
Fatigue	4 (10.5)
Abnormal hair growth	1 (2.6)
Weight gain	1 (2.6)
Infections	
Dermatomycosis	1 (2.6)
Herpes simplex[a]	4 (10.5)
Herpes zoster	1 (2.6)
Onychomycosis	1 (2.6)
Upper airway infection	1 (2.6)
Laboratory abnormalities	
Anaemia[b]	2 (5.3)
Elevated CPK[c]	4 (10.5)
Hypertriglyceridemia[d]	3 (7.9)
Neutropenia[e]	2 (5.3)
Musculoskeletal	
Myalgia	1 (2.6)
Nervous system	
Headaches	3 (7.9)
Ocular	
Blepharitis	1 (2.6)
Conjunctivitis	1 (2.6)
Dry eyes	1 (2.6)
Other unspecified eye complaints	1 (2.6)
Skin-related	
Acneiform eruption	6 (15.8)

Abbreviations: AE, adverse event; CPK, creatinine phosphokinase; N, number.
[a]No cases of eczema herpeticum occurred.
[b]Haemoglobin <8.5 mmol/L (men) or <7.5 mmol/L (women).
[c]>3 times upper limit of normal (ULN).
[d]Triglycerides >2.0 mmol/L.
[e]Neutrophils $<1.0 \times 10^9$/L. Other reference categories: thrombocytosis $>600 \times 10^9$/L, leukopenia $<2.0 \times 10^9$/L, lymphocytopenia $<0.5 \times 10^9$/L, ALAT 3× ULN, creatinine increase of >130%, hypercholesterolemia >8.0 mmol/L.

hands showed no differences in effect of upadacitinib treatment on HE. The safety analysis showed no new findings compared to the clinical trials and the two previously published daily practice

studies.[10,21,23] Two patients discontinued treatment due to lack of efficacy and four patients due to AE(s).

In the current study, patients were treated with upadacitinib in a daily practice setting: almost all patients started with 15 mg of upadacitinib, no strict wash-out of previous systemic immunosuppressive treatment was required, and 86.6% of the patients experienced ineffectiveness or AEs while previously being treated with dupilumab. Upadacitinib showed good effectiveness in this daily practice cohort. Recently, three daily practice studies on the effectiveness and safety of upadacitinib treatment on AD have been published.[10,21,23]

Comparing the current study to the three other daily practice studies, all patients were allowed to use concomitant topical corticosteroids and baseline characteristics were comparable.[10,21,23] In the study population of Hagino et al., only 26% of patients had been previously treated with dupilumab, possibly indicating a less treatment refractory population.[23] Additionally, in the current study, atopic comorbidities were up to twice as prevalent compared to other daily practice studies.[10,21,23]

The multicentre studies conducted by Pereyra-Rodriguez et al. and Chiricozzi et al. (both $n = 43$) reported a higher proportion of patients reaching EASI-75 than the current study after 16 weeks of upadacitinib treatment (76.7% and 97.5% vs. 50.0%, respectively).[10,21] The higher proportion of patients reaching EASI-75 in these two studies may be because 60.4% and 100.0% of their patients were treated with 30 mg of upadacitinib during the 16-week treatment period, while in our study only 15.8% of the patients received 30 mg of upadacitinib. Additionally, in the study by Pereyra-Rodriguez et al., 6.9% of patients also used prednisone and 2% received phototherapy during the treatment period with upadacitinib. The permittance of these therapies in addition to topical corticosteroids could have led to an overestimation of upadacitinib effectiveness.[10] In addition, Chiricozzi et al. implemented a strict wash-out period of previous (systemic) medication (up to 12 weeks for dupilumab), such as in clinical trials.[21] In the current study, although every patient had stopped immunosuppressive therapy at/prior to baseline, the majority of patients (86.8%) were still in the wash-out of their immunosuppressive therapy at baseline. This may have caused an underestimation of the effect of upadacitinib on relative outcome measures in the current study (e.g. a lower proportion of patients reaching EASI-75) at Week 16.

Hagino et al. treated 31 patients with 15 mg upadacitinib once daily for 12 weeks.[23] This study reported a lower proportion of patients reaching EASI-75 than the current study after 4 weeks of upadacitinib treatment (51.6% vs. 71.4% respectively). Hagino et al. did not mention the implementation of a strict wash-out period. The difference in EASI-75 results may be explained by the majority of patients being in a wash-out period at Week 4 during the current study, causing an overestimation of upadacitinib at Week 4.

In the current study, upadacitinib showed also good efficacy on HE in terms of a majority of patients reaching HECSI-75, (almost) clear on the Photographic guide, and the MIC of the QOLHEQ after 16 weeks of treatment. Previous daily practice studies on the effect

of upadacitinib treatment reported no HE outcome measures.[10,21,23] In the Measure Up 1 and 2 clinical trials the effect of upadacitinib treatment on HE was analysed in terms of the HECSI score.[44] HECSI-75 was achieved by 62.0% of the patients at Week 16, which is similar compared to the current study (59.3%). Remarkably, in the current study, all HE outcomes (both clinical outcomes and PROMs) showed less improvement at Week 16 compared to Week 4. It might be hypothesized that improvement of HE at Week 4 led to an increased usage of the hands. The QOLHEQ subdomain 'functioning' results might support this theory; a higher proportion of patients achieved the MIC at Week 16 (64.7%) compared to Week 4 (52.6%). This increase in functioning may have resulted in increased exposure to the hands, which could have aggravated HE symptoms leading up to Week 16. However, hand exposure was not quantified during this study.

In this study, sub-analysis in patients with and without ICD as contributing etiological factor showed no differences in effect of upadacitinib treatment on HE in terms of HECSI, Photographic Guide and QOLHEQ score. Atopic HE is characterized by, like AD, Th2 and Th22 activation. ICD has a Th1/Th17 immune profile and ACD shows a variable immune profile depending on the allergen; ACD caused by metals has an Th1/Th17 immune profile while ACD caused by fragrance and rubber substances has an TH2/Th22 immune profile.[45] JAK inhibitors target multiple immune pathways: Th1, Th2, Th17 and Th22 and could be an effective treatment for several etiological subtypes of HE.[46] At this moment, clinical trials are evaluating the effect of JAK inhibitors on chronic HE regardless of aetiology with promising results.[47–49] It would be of added value to evaluate the effect of upadacitinib on different etiological subtypes of HE, including non-atopic HE.

All PROMs for AD (NRS-pruritus and -pain, POEM, DLQI, ADCT and PGAD) improved significantly after 16 weeks of upadacitinib treatment. In addition to the well-known PROMs, new PROMs that cover different domains of AD have been used in this study. For example, the ADCT is a brief patient self-administered instrument designed and validated to assess AD control.[31,50] This tool is still little used in other studies. A prospective, longitudinal cohort questionnaire-based study used the ADCT in patients with AD who were treated with dupilumab and found that (after imputation) 60.1%–70.8% of the patients had adequately controlled disease after 3 months of treatment.[51] This is not entirely comparable with the current study given the different timepoints of measurement; however, the proportion of patients who are adequately controlled was similar to the current study (68.8% at Week 16). Another PROM that allows a holistic assessment of eczema is the PGAD.[32] The PGAD is assessed by the single question: 'Considering all the ways in which your eczema affects you, indicate how well you are doing'. Although the PGAD is widely used in other diseases,[52] it is still little used in studies on patients with AD. A post hoc analysis from a phase 3 clinical trial (LIBERTY AD CHRONOS) by Griffiths et al. found that by Week 8, 65.2%–71.4% of the patients receiving dupilumab with concomitant topical corticosteroids rated their overall well-being in relation to their AD as 'good', 'very good', or

'excellent'.[32,53] In the current study, this proportion was already higher (74.3%) at Week 4. So, upadacitinib treatment may provide more rapid improvement in general well-being than dupilumab treatment. In addition to other PROMs, the ADCT and PGAD can contribute to a more patient-centred approach to care, allowing patients to give value to what is important to them without pre-specified scoring domains.

The strengths of this study are the multicentre, prospective and observational design alongside the use of validated assessments. Patients were treated in a third-line hospital or a second-line hospital. Additionally, new PROMs that cover different domains of eczema (ADCT and PGAD) and a validated PROM for the evaluation of HE (QOLHEQ) were used. Furthermore, the identification of etiological subtypes of HE which made it possible to analyse, however in small subgroups, the effect of upadacitinib on both atopic HE and ICD, is also a strength of this study. The small sample size and the inability to perform sub-analyses on the dosage of upadacitinib are limitations of this study.

In conclusion, upadacitinib can be an effective treatment for patients with AD. In addition, this study showed a marked improvement of HE in patients treated with upadacitinib for AD. Future studies should focus on the effect of upadacitinib on chronic HE, especially on the different etiological subtypes of HE, including HE in non-atopic individuals.

AUTHOR CONTRIBUTIONS

Esmé Kamphuis: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; project administration; data curation. **Laura Loman:** Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; formal analysis; project administration; data curation; supervision. **Henry L. Han:** Methodology; writing – review and editing. **Geertruida L. E. Romeijn:** Data curation; writing – review and editing; conceptualization. **Klaziena Politiek:** Data curation; writing – review and editing. **Marie L. A. Schuttelaar:** Conceptualization; writing – review and editing; validation; supervision; methodology; data curation.

CONFLICT OF INTEREST

Klaziena Politiek received consultancy fees for AbbVie, LEO Pharma and Sanofi Genzyme. Marie L. A. Schuttelaar is a consultant, advisory board member and/or speaker for AbbVie, Pfizer, Leo Pharma, Sanofi Genzyme, Eli Lilly and Galderma. All other authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was approved by the local Medical Research Ethics Committee as a non-interventional study (METC 18-239).

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SUPPORTING INFORMATION

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