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ORIGINAL ARTICLE

Upadacitinib treatment in a real-world difficult-to-treat atopic dermatitis patient cohort

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Abstract

Background: Upadacitinib was the first JAK-1 selective inhibitor registered for the treatment of moderate-to-severe atopic dermatitis (AD). Although efficacy and safety have been shown in clinical trials, real-world data on the use of upadacitinib in patients that have been treated with other immunosuppressants and targeted therapies is limited.

Objectives: To provide real-world evidence on the use of upadacitinib treatment in moderate-to-severe atopic dermatitis.

Methods: In this prospective observational single-centre study, all AD patients treated with upadacitinib treatment in the context of standard care were included between August 2021 and September 2022. Clinical outcome measures and adverse events (AEs) were analysed.

Results: Forty-eight patients were included. The majority ($n = 39$; 81%) had failed (ineffectiveness) on other targeted therapies, including other JAK inhibitors and biologics. Thirty-four (71%) patients were still using upadacitinib treatment at last follow up (median duration 46.5 weeks). Fourteen (29%) patients discontinued treatment due to ineffectiveness or AE. Upadacitinib treatment led to a significant decrease of disease severity during a median follow up of 37.5 weeks. Median IGA at baseline decreased from 3 (IQR 2–3) to 1.5 (IQR 1–2) at last review ($p < 0.001$). Median NRS itch decreased from 7 (IQR 5–8) at baseline to 2.25 (IQR 0.25–6.5) at last review ($p < 0.001$). Three patients discontinued treatment due to AE. Forty-eight AEs were reported, including acne-like eruptions (25%), nausea (13%) and respiratory tract infections (10%).

Conclusions: In this real-world cohort, we confirmed that upadacitinib is an effective treatment in a subset of AD patients that have failed several previous systemic immunosuppressive and biologic treatments. Overall, AE were mostly well tolerated and not a reason to discontinue treatment for most patients.

INTRODUCTION

Atopic dermatitis (AD) is a heterogeneous chronic inflammatory skin disease, characterized by intense itch and recurrent eczematous lesions.[1,2] In patients with inadequate response to first-line topical treatments, including moisturizers, topical corticosteroids and topical calcineurin inhibitors, systemic conventional immunosuppressants or targeted therapies may be needed to achieve disease control. Until recently, cyclosporine A (CsA) was the only registered systemic treatment in most European countries. In addition, methotrexate, azathioprine and mycophenolic acid were frequently used off-label. After the registration of dupilumab in 2017, another biologic and three Janus kinase

(JAK) inhibitors were registered for the treatment of moderate-to-severe AD.[3–5] Upadacitinib is a selective JAK-1 inhibitor that was registered for treatment of AD in 2021. Phase II and III clinical trials with upadacitinib have shown a significant reduction in AD symptoms after 16 weeks of treatment, and upadacitinib was generally well tolerated.[6–8] However, efficacy in a clinical trial may differ from effectiveness in daily practice. Patients can only participate in clinical trial if they meet strict in and exclusion criteria. Patients treated in daily practice often have comorbidities and concomitant medication and are excluded from clinical studies. Results from treatment in daily practice data may give a better representation of treatment effectiveness and safety in the real world.[9]

In this study, we report on the use of upadacitinib in daily practice in 48 moderate-to-severe AD patients that had already failed on systemic immunosuppressants and other targeted therapies, including biologics and JAK inhibitors.

MATERIALS AND METHODS

Population

In this prospective, observational, single-centre cohort study, all adult patients with moderate-to-severe AD who started upadacitinib in routine clinical care were included from August 2021 to June 2022 at the AD expertise centre in the Department of Dermatology in the Erasmus Medical Center (Rotterdam, the Netherlands). Our study was approved by the local Medical Research Ethics Committees (MED-2017-1123). All patients provided written informed consent. After treatment initiation, visits were scheduled after 4 weeks, 12–16 weeks and every 3 months thereafter in the context of standard care.

Upadacitinib treatment

Patients received oral upadacitinib at a dose of 15 or 30 mg daily after failure of at least one conventional systemic immunosuppressant. If AD symptoms were not controlled with 15 mg, the dose was increased to 30 mg. Patients were stimulated to continue the use of medicated topical therapy, including topical corticosteroids and topical calcineurin inhibitors.

Safety assessments

The evaluation of safety involved evaluation of adverse events (AEs) and laboratory examinations (blood count, liver enzymes and serum creatinine) at every visit. Serious AEs were defined as an event that resulted in death, was life-threatening, required (prolonging of) hospitalization or resulted in persistent or significant disability.

Outcomes

Data were collected in the 'Erasmus MC IMID Quality of Care Registry'. Patient characteristics including demographics, previous treatments and concomitant systemic treatments were recorded at baseline. In the Netherlands, to be eligible for treatment with a biologic of JAK inhibitor, adult AD patients need to have failed treatment with at least one conventional systemic immunosuppressant (e.g. cyclosporine). Both physician- and patient-reported outcome measures (PROMs) were used to analyse the effectiveness of upadacitinib treatment. The validated Investigator Global Assessment scale for atopic dermatitis (vIGA-AD: 0–4) was used to analyse the physician-reported severity. At each visit, patients were requested to fill out the numeric rating scale peak pruritus during the past 7 days (NRS itch: 0–10). The primary endpoints were evaluated by absolute cut-off scores: IGA of clear or almost clear and NRS itch ≤4.

Statistical analysis

Categorical data were evaluated as the number of patients and percentage (*n*,%). Outcomes were analysed using the Wilcoxon signed-rank test (nonparametric, numerical outcomes). To assess the effect of treatment, the median change and interquartile range (IQR) of IGA and NRS itch scores between baseline and last review were calculated. Patients who discontinued upadacitinib treatment during follow up were considered as non-responders. In the statistical analyses, *p*-values lower than 0.05 were considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics for Windows (version 28). Figures were made using GraphPad Prism (version 9).

RESULTS

Population

Forty-nine patients were included in this study. One patient was excluded from the analysis because of loss to follow up. Table 1 presents the baseline characteristics of the 48 patients included in the analyses. 44% of the patients were female ($n = 22$), with a median age of 37 years (IQR 27–49 years). 44% of the patients had asthma and 71% reported allergic (rhino) conjunctivitis. All patients were previously treated with conventional systemic immunosuppressants and/or targeted therapies. Most of these patients had used cyclosporine A ($n = 46$; 96%), and the majority ($n = 35$; 73%) also used dupilumab before starting upadacitinib treatment. Reasons for starting upadacitinib treatment were failure of previous systemic treatment ($n = 39$;81%), including baricitinib ($n = 17$; 35%), abrocitinib ($n = 2$; 4.2%), dupilumab ($n = 11$; 22.9%) and tralokinumab ($n = 2$; 4.2%). Other reasons for discontinuation were AEs of previous systemic therapy (9 [19%]). In four

TABLE 1 Baseline characteristics.

Characteristics	*n* = 48
Age at start of upadacitinib treatment (years), median (IQR)	37 (27–49)
Female, *n* (%)	22 (44)
Previous use of conventional systemic immunosuppressants[a], *n* (%)	
Cyclosporin A	46 (96)
Methotrexate	27 (56)
Azathioprine	8 (17)
Mycophenolic acid/mycophenolate mofetil	17 (35)
Dupilumab	35 (73)
Baricitinib	21 (44)
Abrocitinib	4 (8)
Tralokinumab	2 (4)
Reasons for starting upadacitinib	
Previous systemic treatment failed *n* (%)	39 (81)
Adverse events of previous therapy	9 (19)
Atopic conditions, *n* (%)	
Asthma	21 (44)
Allergic (rhino) conjunctivitis	34 (71)
Dosage at start (milligrams), (%)	
Upadacitinib 15 mg	38 (79)
Upadacitinib 30 mg	10 (21)

Abbreviations: IQR, interquartile range; n, number.

[a]Previous use of systemic corticosteroids is not reported because of inconsistency in reporting of short- and long-term use.

patients prednisone or methotrexate was slowly tapered after starting upadacitinib treatment.

Effectiveness of upadacitinib treatment

Upadacitinib treatment led to a significant decrease of disease severity during a median of 37.5 (IQR 23.5–47.5) weeks of treatment. In general, median IGA at baseline was 3 (IQR 2–3) and significantly decreased to 1.5 (IQR 1–2) at last review ($p < 0.001$). Median NRS itch significantly decreased from 7 (IQR 5–8) at baseline to 2.25 (IQR 0.25–6.5) at last review ($p < 0.001$) (Tables 2 and 3; Figure 1). 47.9% of the patients ($n = 23$) achieved an IGA score of 0 or 1 (clear or almost clear) at last review within 24 weeks of treatment. In addition, 50% patients ($n = 24$) achieved an NRS itch ≤4 at last review (Figure 2).

Thirty-four (71%) patients that were still using upadacitinib at last review (median duration of 46.5 weeks), IGA scores significantly decreased from a median of 3 (IQR 2–3) to 1 (IQR 1–2) at last review ($p < 0.001$) and the median NRS itch scores significantly decreased from a median of 6.50 (IQR 4.25–8.00) to 2 (IQR 0–3) at last review ($p < 0.001$). (Table 2, patients 1–34 n; Table 3; Figure 3). This includes thirteen patients (33%) that previously failed other JAK inhibitors and eleven patients (28%) that failed on biologics. No significant differences in the effect on IGA and NRS itch were found between patients that failed previous targeted therapies, and patients that showed a good response to targeted therapies, but that had to discontinue due to AEs.

Dosing regimens

Thirty-eight (79%) patients started upadacitinib 15 mg once daily (qd), and ten (21%) patients started 30 mg qd. In three patients (30%) that started 30 mg qd, the dose was reduced to 15 mg qd due to AEs, including decrease in Hb, pre-existing therapy resistant hypertension and persistent chest pain after recovery from COVID-19. AEs recovered in all three patients after dose reduction.

Eighteen patients maintained 15 mg qd. However, six (33%) patients discontinued therapy. One patient discontinued therapy due to acne-like eruptions. Five patients, including two patients with a temporary improvement, discontinued therapy due to ineffectiveness and the desire to discontinue therapy rather than increase the dosage to 30 mg qd.

In nineteen patients, the dosage was increased from 15 to 30 mg qd due to inadequate disease control. Thirteen (68%) patients demonstrated a favourable response after dose increase. However, two (11%) patients experienced a secondary failure after a temporary improvement and three (16%) patients still showed insufficient improvement even after a dose increase and discontinued therapy. One (5%) patient discontinued therapy due to acne-like eruptions.

Six patients started and maintained at 30 mg qd. Two (33%) patients discontinued therapy due to ineffectiveness and acne-like eruptions respectively.

Adverse events

Forty-eight AEs were registered in 27 (27 out of 48 [56%]) patients (Table 2, Table 3). The AEs reported were mostly mild, and no serious AEs occurred. The most frequently reported AEs included acne-like eruptions (12 [25%]), nausea (6 [13%]), respiratory tract infections (5 [10%] and herpes simplex virus infection (4 [8%]). Respiratory tract infections include upper respiratory tract infections,[3] pneumonia[1] and otitis.[1] Less frequently reported AEs were fatigue (3 [6%]), hair loss (3 [6%]), headache (3 [6%]), dry eyes (2 [4%]), rash (2 [4%]), anaemia (1 [2%]), brittle nails (1 [2%]), dizziness (1 [2%]), hypertension (1 [2%]) and white fingers (1 [2%]). Three patients experienced increased creatine kinase (CK) >1000 U/L, which were all associated with recent physical activity and resolved without intervention (Table 4).

Discontinuation of treatment

Fourteen patients (29%) discontinued upadacitinib treatment after a median duration of 18.5 weeks and were

TABLE 2 Patient characteristics.

Patient	Gender	Age at start	Duration (weeks)	IGA at baseline	IGA at last review	NRS itch 7d at baseline	NRS itch 7d at last review	Previous systemic medication	Dosage upa at baseline (mg)	Dosage upa at last review (mg)	Adverse events	Reason for discontinuing upa
1	M	25	53	3	0	1	0	CsA; MTX; dupi; bari	30	15	Anaemia	
2	F	40	54	2	1		3	CsA; MTX; AZA; dupi; bari	30	30		
3	F	38	48	2	1	4		CsA; dupi; bari	15	30	Hsv	
4	M	37	49	3	2			CsA; MTX; MPA; dupi; bari; abro	30	15×2		
5	M	29	50	2	3	7	2	CsA; dupi; bari	30	30	Hsv	
6	F	48	50		1		2	CsA; MTX; MPA; dupi	15	30	Brittle nails, white fingers, hair loss	
7	F	25	49	3	1	7	2	CsA; MTX; AZA; dupi; bari	30	15		
8	M	55	48	2	1	2		CsA; MTX; dupi; bari	15	15	Fatigue	
9	F	35	48	2	2	5		CsA	15	30	Acne, myalgia	
10	M	28	48	2	0	8	1	CsA; dupi	15	15		
11	M	25	48	3	1	3	3	CsA; MTX; MPA; dupi	15	15		
12	M	47	47	2	0	9	0	CsA; MPA	15	15	Fatigue	
13	F	52	47		2	7	2	CsA; MPA; AZA; dupi	15	30		
14	F	36	47	4	2	8	2	CsA; MTX; MPA; AZA; bari	15	15	Acne	
15	F	26	47	3	1	10	2	CsA; MTX; dupi	15	30	Acne, headache, nausea, CK > 1000	
16	M	54	46	3	2			CsA; MTX; MPA; dupi; bari	15	15		
17	M	41	45	3	2			CsA	15	30		
18	F	29	44	3	0	5	0	CsA; MTX; dupi	15	30	Otitis, acne	
19	M	29	38	4	2	5	4	CsA; dupi; bari	30	30	Acne, CK > 1000	
20	M	29	37	2	3	8	7	CsA; bari	15	30	CK > 1000	
21	F	42	36	2	2	5	0	CsA; MTX; MPA; AZA; dupi; bari	30	15		
22	M	22	36	2	2			CsA; dupi	15	15	Acne	
23	M	50	38		1		5	CsA; AZA	15	30		
24	M	36	41	3	2	4	0	CsA, MTX	15	15		
25	F	50	30	2	2			CsA; MTX; MPA; dupi; tralo; abro	15	30	Dry eyes, acne, hair loss	

TABLE 2 (Continued)

Patient	Gender	Age at start	Duration (weeks)	IGA at baseline	IGA at last review	NRS itch 7d at baseline	NRS itch 7d at last review	Previous systemic medication	Dosage upa at baseline (mg)	Dosage upa at last review (mg)	Adverse events	Reason for discontinuing upa
26	F	67	58	0	0	0	0	CsA; MTX; MPA; dupi	15	15	Nausea, fatigue	
27	F	28	24	2	1	7	3	CsA	15	30	Dizziness	
28	F	55	30	3	1	5	0	CsA; MTX; dupi; bari	15	15/2 days	Urti, hsv, acne, hypertension	
29	F	44	15	2	0	6	0	CsA; dupi; tralo	15	15	Hsv, hair loss	
30	F	19	47	3	1	8	8	CsA; MTX; dupi	15	30		
31	M	50	16	3	1			CsA; MTX; dupi; bari	15	15		
32	M	30	12	4	1	8	2	CsA; dupi	15	15		
33	M	62	14	4	1		0	Aza	30	30		
34	M	31	46	3	1	7	5	CsA; MPA; bari	15	30		
35	M	20	D10	2	3	7	8	CsA; MTX; MPA; AZA; dupi; bari; abro	15	30		Nci
36	M	26	D11	3	4	7		CsA; MPA; dupi; bari	15	30		Nci
37	F	57	D35	2		7		CsA; dupi; bari	15	30	Nausea	Nci
38	M	47	D13	3	2	9	0	CsA; MTX; dupi; abro	15	15	Urti, headache, rash	Tcr
39	F	20	D4	2	0	5	4	CsA; dupi; abro	30	30	UrtiI, acne	Acne
40	M	37	D4	3	3	8	7	CsA; MTX	15	15		Nci
41	F	69	D4	3	4	8	9	MTX; bari	30	30		Nci
42	M	54	D23	4	4	6	8	CsA; MTX; MPA; AZA; bari	15	30	Dry eyes	Tcr
43	M	24	D24	2	4	10	8	CsA; MTX; dupi	15	15	Nausea	Tcr
44	M	47	D37	2	0		8	CsA; MPA; dupi; bari	15	30	Acne	Acne
45	M	39	D14	2	3	8	10	CsA; MTX; AZA; dupi	15	15	Headache, nausea, rash	Nci
46	F	24	D26	3	3	7	5	CsA; dupi	15	15	Nausea, acne, pneumonia	Acne
47	F	46	D24					CsA; MTX, MPA, dupi	15	15	Acne	Nci
48	M	22	D25	4	2		4	CsA; MTX; dupi	15	30		Tcr

Abbreviations: abro, abrocitinib; AZA, azathioprine; bari, baricitinib; CK, creatinine phosphokinase; CsA, cyclosporine A; D, discontinued; dupi, dupilumab; F, female; Hsv, herpes simplex virus; IGA, Investigator Global Assessment; M, male; MPA, mycophenolic acid; MTX, methotrexate; NCI, no clinical improvement; NRS, numeric rating scale; TCR, temporary clinical response; tralo, tralokinumab; Upa, upadacitinib; Urti, upper respiratory tract infection.

TABLE 3 Effectiveness outcome measurements.

	Baseline	Last review	*p*-value
All patients			
IGA, median (IQR)	3 (2–3)	1.5 (1–2)	<0.001
NRS itch, median (IQR)	7 (5–8)	2.25 (0.25–6.5)	<0.001
Responders			
IGA, median (IQR)	3 (2–3)	1 (1–2)	<0.001
NRS itch, median (IQR)	6.5 (4.25–8)	2 (0–3)	<0.001
Non Responders			
IGA, median (IQR)	3 (2–3)	3 (2–4)	0.715
NRS itch, median (IQR)	7 (7–8)	8 (4–8)	0.765

Abbreviations: IGA, Investigator Global Assessment; NRS, numerical rating scale.

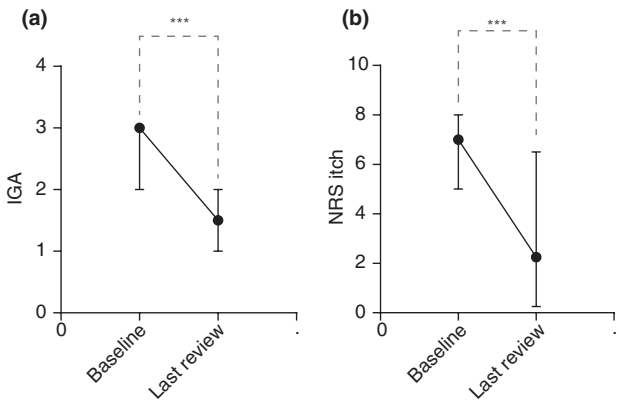

FIGURE 1 Effectiveness outcome measures in the total patient population. (a) Median decrease in Investigator Global Assessment (IGA) scale. (b) Median decrease in numeric rating scale peak pruritus during the past 7 days (NRS itch). Error bars represent the interquartile range. ***$p < 0.001$.

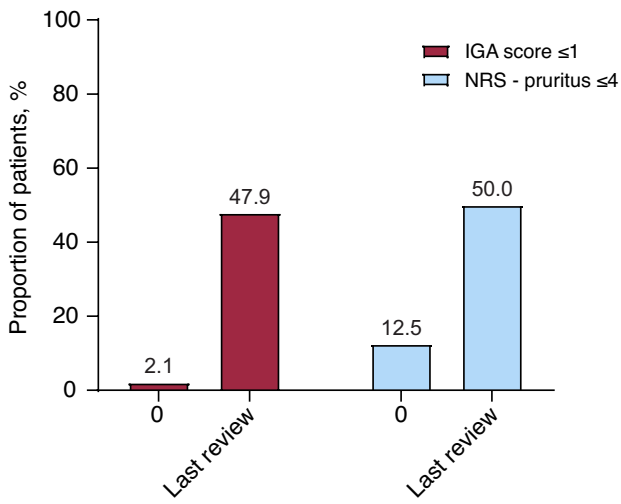

FIGURE 2 Proportion of patients who reached cut-off scores of IGA≤1 and NRS itch ≤4 at last review of upadacitinib treatment. Abbreviations: IGA, Investigator Global Assessment; NRS, numeric rating scale.

classified as non-responders. All patients had a previous use of conventional systemic immunosuppressants. Six patients (42.9%) had previously failed on JAK inhibitors and two patients (14.3%) had previously failed on biologics. Median NRS itch increased from 7 (IQR 7–8) to 8 (IQR 4–8) ($p = 0.765$). Median IGA at baseline was 3 (IQR 2–3), and median IGA at last review remained unchanged at 3 (IQR 2–4) in patients that discontinued treatment ($p = 0.715$) (Table 2, patients 35–48n; Table 3; Figure 3). Three patients (21%) discontinued treatment due to acne-like eruptions. One patient was treated with topical antibiotics for several weeks without improvement. The other two patients discontinued upadacitinib treatment because of acne-like eruptions without additional treatment. Eleven patients (79%) discontinued treatment due to ineffectiveness after median duration of 14 weeks. Four patients experienced temporary improvement but discontinued because of insufficient response after 13, 23, 24 and 24 weeks, respectively. After discontinuation of upadacitinib treatment, eight patients started abrocitinib, three patients started tralokinumab treatment and three patients started dupilumab treatment. In all patients, the choice of treatment discontinuation due to ineffectiveness was based on shared decision-making.

DISCUSSION

This is one of the first prospective daily practice cohort studies of upadacitinib treatment in adult AD patients that had been treated with other immunosuppressants and targeted therapies. Upadacitinib treatment resulted in a significant decrease of clinical outcome measures (IGA and NRS itch), and overall, upadacitinib was well tolerated in most patients. Furthermore, we found that upadacitinib treatment was successful in 33% of patients that had previously failed on other JAK inhibitors (abrocitinib and/or baricitinib). This suggests that switching within the class of JAK inhibitors can be successful in managing difficult-to-treat AD.

Even though there are major differences between daily practice and clinical trials, we tried to compare our results to

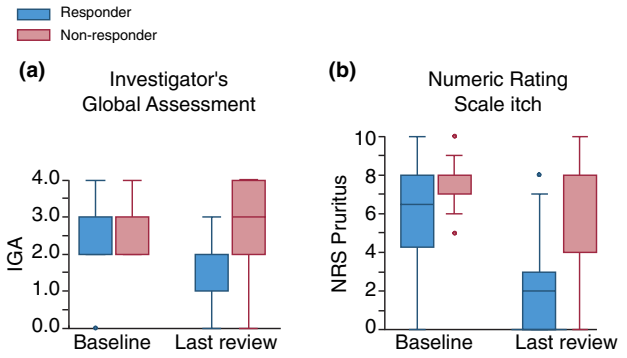

FIGURE 3 Disease severity in responders versus non-responders. (a) Investigator's Global Assessment (IGA, 0–4) (b) Numeric rating scale peak pruritus during the past 7 days (NRS itch 7d, 0–10).

TABLE 4 Adverse events in 27 patients.

Adverse event	*N* = 48	%
Acne-like eruptions	12	25
Nausea	6	12.5
Respiratory tract infections[a]	5	10.4
Herpes simplex virus infection	4	8.3
Fatigue	3	6.3
Hair loss	3	6.3
Headache	3	6.3
CK level > 1000	3	6.3
Dry eyes	2	4.2
Rash	2	4.2
Anaemia	1	2.1
Brittle nails	1	2.1
dizziness	1	2.1
Hypertension	1	2.1
White fingers	1	2.1

Abbreviations: CK, creatinine phosphokinase; N, number of adverse events.
[a]Respiratory tract infections included: otitis (*n* = 1), upper respiratory tract infections (*n* = 3) and pneumonia (*n* = 5).

previous clinical trials. Patients in the current study had lower baseline IGA scores compared to patients in clinical trials, where half of the patients had a baseline IGA score of 4. This may be the result of the required washout periods for topical and systemic treatments in clinical trials, while patients in our cohort were encouraged to continue topical steroid treatment and no washout period was used for systemic immunosuppressants.[6–8] While half of the patients in clinical trials had not been treated with any systemic immunosuppressants, all patients in our study had been treated with at least one conventional systemic immunosuppressant. In addition, the majority of patients (73%) in our cohort had previously been treated with dupilumab, while patients in the pivotal clinical trials were all naïve for biologicals and JAK inhibitors.[7] This suggests that the patients in our cohort may be at the more severe end of the disease severity spectrum and represent the most difficult-to-treat patients. In the current study, 34 patients used upadacitinib treatment at last review and showed good clinical response. Interestingly, this includes 13 patients (33%) that had previously failed on other JAK inhibitors. The differences in selectivity for JAK isoforms for the different JAK inhibitors may explain these findings.[10] Barcitinib inhibits both JAK-1 and JAK-2 tyrosine kinases, while abrocitinib and upadacitinib are more selective for JAK-1.[11–13] These different affinities for JAK-1 and JAK-2 pathways may explain why upadacitinib was effective in a subset of patients previously treated with other JAK inhibitors.[12,14] Furthermore, the effectiveness of upadacitinib treatment in patients who have failed prior therapies such as biologics or another JAK inhibitors requires further investigation.

Until now, only a few daily practice studies have been published. Five small cohort studies (with a maximum of 16 patients) showed a good clinical response in most AD patients to upadacitinib treatment,[15–19] including one study that showed adequate disease control in ten patients that failed dupilumab treatment.[15] In addition, three larger real-world studies have been published. One study (including 38 patients) showed that upadacitinib treatment can also be an effective treatment for AD patients with concomitant hand-eczema.[20] Chirricozi et al. and Gargiulo et al. showed a comparable decrease in AD outcome measurements (in 43 and 38 patients, respectively) to our study (IGA, NRS itch), however the follow up of these short-term studies were only 16 weeks, compared to a maximum of 54 weeks in our study.[21,22]

The percentage of patients reporting an AEs in our cohort was 56%, comparable to previous clinical trials that reported 53%–73% patients with at least one AE.[7] Acne-like eruptions were the most frequently reported AEs in Phase III clinical trials, with an incidence of 9.8% and 15.2% in patients receiving upadacitinib 15 mg and upadacitinib 30 mg respectively,[23] which is lower compared to the incidence reported in our cohort (12 out of 48 [25%]). The higher incidence of acne-like eruptions observed in daily practice may be caused by a reporting bias resulting from the active questioning of symptoms, compared to clinical trials in which acne-like eruptions were not of special interest. The discontinuation rate because of acne-like eruptions in our cohort was 25% (3 out of 12), which is in line with clinical trials (24%–36%).[7] This AE was found to be highly heterogeneous, ranging from folliculitis in the head/neck/trunk area to a rosacea like phenomenon. However, the pathophysiology of acne-like eruptions induced by upadacitinib treatment remains unclear. Additional research is needed to unravel the mechanisms behind these upadacitinib-induced acne-like eruptions and more specific treatments of this AE.

The second and third most reported AEs in clinical trials are upper respiratory tract infections (4%–13%) and headache (4%–7%), which show comparable incidence in our cohort, 10.4% and 6.3%, respectively. Furthermore, we observed elevated CK levels >1000 U/L with no effect on renal function in three patients (6%), that were related to increased physical activity. This finding is similar to the clinical trials,

where elevated CK levels were found in 3% up to 6% of the patients.[7] Clinical trials with baricitinib, a JAK 1–2 inhibitor, have also shown small increases in CK levels and infrequent occurrences of CK levels exceeding 1000 U/L. These elevations were related to physical activity, and CK levels returned to normal levels without interruption of therapy.[24,25] In conclusion, clinical trials and daily practice experience show that clinically relevant CK increases are uncommon and measuring CK levels does not seem to be necessary.

Strengths of this study are the prospective design, the relative large cohort when compared to previously reported daily practice studies, and the long follow up period of up to 54 weeks of treatment. Furthermore, the patients included in the current study had previously been treated with one or more conventional immunosuppressive therapies, and the majority had previously been treated with dupilumab. The patients included in this study are considered difficult-to-treat patients, that may better reflect patients treated with upadacitinib in daily practice. Limitations of this study are missing data (e.g. EASI's) partially caused by rescheduled visits, no-shows and remote visits that were more common during the pandemic.

In conclusion, our data confirm that upadacitinib treatment is effective and well tolerated in a subset of difficult to treat AD patients that have failed several previous systemic immunosuppressive and biologic treatments. As upadacitinib was not effective in 29% of patients, we want to stress it is essential to investigate predictors of clinical response.

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None.

CONFLICT OF INTEREST STATEMENT

AS: none, NB: none, JO: none, TN: none, DJH: investigator for AbbVie, Almirall, LEO pharma, AstraZeneca, Novartis, Sanofi; consultancies for Abbvie, Sanofi, LEO pharma, AstraZeneca, Novartis, Janssen, Pfizer, Lilly.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

Our study was accepted by the local Medical Research Ethics Committees (MED-2017-1123). The patients in this manuscript have given written informed consent to publication of their case details.

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