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ORIGINAL ARTICLE

Real-world effectiveness of abrocitinib treatment in patients with difficult-to-treat atopic dermatitis

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Abstract

Background: Abrocitinib is a JAK-1 selective inhibitor registered for the treatment of moderate-to-severe atopic dermatitis (AD). Although efficacy and safety have been shown in phase 3 clinical trials, data on real-world patients with a treatment history of advanced systemics are scarce.

Objectives: The objective of the study was to evaluate the effectiveness and safety of abrocitinib treatment in patients with difficult-to-treat AD in daily practice.

Methods: In this prospective observational single-centre study, all AD patients who started abrocitinib treatment in the context of standard care between April 2021 and December 2022 were included. Effectiveness was assessed using clinician- and patient-reported outcome measures. Adverse events were evaluated.

Results: Forty-one patients were included. The majority ($n = 30$; 73.2%) had failed (ineffectiveness) on other targeted therapies, including JAK inhibitors ($n = 14$, 34%) and biologics ($n = 16$, 39%). Abrocitinib treatment resulted in a significant decrease in disease severity during a median follow-up period of 25 weeks (IQR 16–34). Median EASI score at baseline decreased from 14.7 (IQR 10.4–25.4) to 4.0 (IQR 1.6–11.4) at last review ($p < 0.001$). Median NRS itch decreased from 7.0 (IQR 5–8) to 3.0 (IQR 1–2) at last review ($p < 0.001$). The most frequently reported AEs included gastrointestinal symptoms (27.6%), acne (20.7%) and respiratory tract infections (17.2%). 16 (39%) patients discontinued abrocitinib treatment due to ineffectiveness, AEs or both (41.2%, 41.2% and 11.8%, respectively).

Conclusion: Abrocitinib can be an effective treatment for patients with moderate-to-severe AD in daily practice, including non-responders to other targeted therapies.

INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases and is associated with a high disease burden.[1,2] Approximately 15% of individuals with AD are classified as moderate-to-severe patients and may require phototherapy or systemic conventional immunosuppressants or targeted therapies to achieve disease control.[3]

Currently, two biologics, dupilumab and tralokinumab, are available for the treatment of moderate-to-severe AD.[4,5] These drugs target the IL-4-receptor-alpha-chain and IL-13 cytokine, respectively. Other systemic treatments include Janus Kinase (JAK) inhibitors, which target the JAK–STAT pathway, responsible for modulating several inflammatory signalling pathways.[6–8] Since 2022 abrocitinib, a JAK-1 selective inhibitor, has been approved for the treatment of moderate-to-severe AD. Phase III clinical trials showed significant improvement in disease activity and patient-reported outcomes of moderate-to-severe AD during abrocitinib treatment.[9–12] In addition, the JADE EXTEND trial showed that abrocitinib treatment was effective and safe, regardless of prior dupilumab response.[9] However, in the latter trial dupilumab was only administered for 16 weeks, and the protocol required a 4-week washout period before initiation of abrocitinib treatment. Patients included in clinical trials may therefore not be representative for patients in daily practice.

Stringent inclusion and exclusion criteria in clinical trials lead to exclusion of patients with comorbidities and concomitant medication. Furthermore, due to the required washout periods in clinical trials, severe patients who are unable to discontinue their treatment are excluded from participation.

Data on effectiveness and safety of abrocitinib treatment in real-life patients which failed on other targeted therapies is currently missing. The aim of this study is to provide real-word data regarding the efficacy and safety of abrocitinib treatment in difficult-to-treat AD patients, including patients that previously used biologics and JAK inhibitors.

METHODS

Study design and population

In this prospective, observational, single-centre cohort study, all adult patients with moderate-to-severe AD who started abrocitinib in routine clinical care were included from April 2021 until December 2022 at the AD expertise centre in the Department of Dermatology in the Erasmus Medical Center (Rotterdam, the Netherlands). All patients met the eligibility criteria for abrocitinib treatment established by the Dutch Society of Dermatology and Venereology. This includes the criteria that patients need to have failed at least one classical systemic immunosuppressant. Data were collected in the context of the 'Erasmus MC IMID Quality of Care Registry'. The study was approved by the local Medical Research Ethics Committee as a non-interventional study (MED-2017-1123). All patients provided written informed consent.

Treatment and data collection

Patients were treated with 100 mg or 200 mg abrocitinib once daily at baseline. The dosage was altered from 100 to 200 mg and vice versa if deemed appropriate due to ineffectiveness and/or adverse events (AEs). Concomitant usage of topical corticosteroids and/or topical calcineurin inhibitors was permitted. No washout periods for systemic immunosuppressive and/or immunomodulating treatment were used. Previous systemic medication was discontinued when abrocitinib treatment was started. Patients visited the outpatient clinic at start of treatment, after 4, 12–16 weeks and every 3 months thereafter. During abrocitinib treatment AEs were evaluated and laboratory assessments (blood count, liver enzymes, serum creatinine) were performed at every visit. For safety assessment, AEs and laboratory abnormalities were ranked based on frequency and severity. Severity of AEs was based on expert opinion.

Outcome measures

Patient characteristics and previous and current AD treatment were assessed at baseline. The following patient characteristics were collected: demographics, comorbidities, past treatments, concomitant medications. Clinical examinations were performed by trained physicians at every visit. Physician-reported severity was reported using Eczema Area and Severity Index (EASI: 0–72)[13] and Investigator Global Assessment (IGA: 0–4)[14] scale for AD. In addition, Patient Reported Outcome Measures (PROMs) were assessed at every visit, namely, Numeric Rating Scale (NRS: 0–10)[15] peak pruritus during the past 7 days. Absolute cut-off scores were an EASI ≤7, IGA of clear or almost clear and NRS pruritus ≤4.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 28). Figures were made using GraphPad Prism (version 9). 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. A p-value of <0.05 was considered statistically significant.

RESULTS

Patient and baseline characteristics

A total of 41 AD patients treated with abrocitinib were included. Baseline characteristics are summarized in Table 1. 48.8% of the patients were female ($n = 20$) and most patients had skin type II ($n = 34$, 82.9%). The median age at start of abrocitinib was 29 years (IQR 23.5–40.0 years).

All patients were previously treated with conventional systemic immunosuppressants and/or targeted therapies. 18 patients (43.9%) had previously received four or more systemic AD treatments. The majority had been treated with cyclosporine ($n = 38$), dupilumab ($n = 31$) and/or methotrexate ($n = 18$). A total of 30 patients (73.2%) had failed on previous targeted therapies, including dupilumab ($n = 13$, 31.7%), tralokinumab ($n = 3$, 7.3%), baricitinib ($n = 7$, 17.1%) and upadacitinib ($n = 7$, 17.1%). 21 patients (51.2%) started with abrocitinib 100 mg QD. At baseline, the median EASI score was 14.3 (IQR 10.4–24.4) and most patients had an IGA score of moderate to severe (median 3 IQR 2–4).

Effectiveness

All physician-reported and patient-reported outcomes showed a significant improvement during abrocitinib treatment, with a median treatment duration of 28 weeks (IQR 17.5–38.0; Figure 1; Table 2). Median EASI score significantly changed from 14.3 (IQR 10.4–24.4) to 4.0 (IQR

TABLE 1 Patient characteristics at baseline.

Patient characteristics	No. (%) or median (IQR) $n=41$
Sex	
Female	20 (48.8)
Age at start abrocitinib, years	29 (23.5–40.0)
Fitzpatrick skin type	
I	1 (2.4)
II	34 (82.9)
III	3 (7.3)
IV	1 (2.4)
V	1 (2.4)
VI	1 (2.4)
Atopic/allergic conditions	
Asthma	21 (51.2)
Allergic (rhino)conjunctivitis	30 (73.2)
Allergic contact dermatitis	17 (41.5)
Previous use of systemic therapies for AD	
Cyclosporine	38 (92.7)
Azathioprine	7 (17.1)
Methotrexate	18 (43.9)
Mycophenolic acid/mycophenolate mofetil	9 (22.0)
Systemic corticosteroids	25 (61.0)
Dupilumab	31 (75.6)
Tralokinumab	6 (14.6)
Baricitinib	15 (36.6)
Upadacitinib	10 (24.4)
No. of previous used systemic therapies	
0	0
1	4 (9.8)
2	12 (29.3)
3	7 (17.1)
≥4	18 (43.9)
Previous use of phototherapy	
Yes	21 (51.2)
No	20 (48.8)
Systemic therapy at start of abrocitinib	
None	–
Conventional systemic immunosuppressants	9 (22.0)
Dupilumab	11 (26.8)
Tralokinumab	4 (9.8)
Baricitinib	7 (17.1)
Upadacitinib	10 (24.4)
Abrocitinib dosage (start of treatment) (mg)	
100	21 (51.2)
200	20 (48.8)

Abbreviations: AD, atopic dermatitis; IQR, interquartile range.

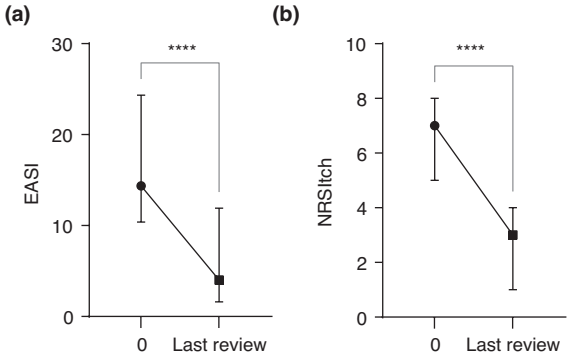

FIGURE 1 Effectiveness outcomes during abrocitinib treatment at last review. (a) Median decrease in Eczema and Area and Severity Index (EASI) score. (b) Median decrease in numerical rating scale (NRS) pruritus. Error bars represent the interquartile range. ****$p<0.0001$.

1.6–11.9) at last review ($p<0.0001$). Median IGA score significantly decreased from 3 (IQR 2–4) to 2 (IQR 1–2) at last review ($p<0.0001$). 22% of the patients achieved an IGA or score of 0 or 1 (clear or almost clear) at last review. Median NRS pruritus significantly decreased from 7.0 (IQR 5.0–8.0) to 3.0 (IQR 1.0–4.0) at last review ($p<0.0001$). 53.7% of the patients ($n=22$) achieved an EASI score of ≤7 at last review. In addition, 29 patients (70.7%) achieved an NRS-pruritus ≤4 at last review (Figure 2).

Twenty-four patients (58.5%) continued abrocitinib treatment until last review and showed a good clinical response. Including eight patients (33.3%) that previously failed other JAK inhibitors, and nine (35.5%) that failed on biologics. No significant differences in the effect on EASI, IGA and NRS pruritus were found between patients that failed previous targeted therapies and targeted therapy responders patients.

Dosing regimens

Twenty-one patients (51.2%) started with abrocitinib 100 mg QD. In six (28.6) patients that started 100 mg, the dosage was increased to 200 mg due to insufficient improvement. Five patients achieved disease improvement after increased dosage. In five patients (25%) that started 200 mg QD the dose was reduced to 100 mg due to AEs.

Safety

In total, 30 AEs were reported during abrocitinib treatment, of which 25 patients (60.9%) experienced at least 1 AE (Table 3), with AEs generally classified as mild. The most frequently reported AEs were gastrointestinal symptoms ($n=8$, 26.7%), acne ($n=6$, 20.0%) and respiratory tract infections ($n=5$, 16.7%). In four patients, laboratory abnormalities were

TABLE 2 Effectiveness outcomes.

	Baseline	Last review	*p*-value
EASI, median (IQR)	14.3 (10.4–24.4)[1]	4.0 (1.6–11.9)[2]	<0.0001
EASI median percentage change (IQR)	–	−73.5 (−98.6 to −27.5)[3]	
EASI-50, *n* (%)	–	17 (41.5)[3]	
EASI-75, *n* (%)	–	13 (31.7)[3]	
EASI-90, *n* (%)	–	8 (29.6)[3]	
IGA score	3 (2–4)[4]	2 (1–2)[5]	<0.0001
NRS pruritus, median (IQR)	7.0 (5.0–8.0)[4]	3.0 (1.0–4.0)[4]	<0.0001
EASI ≤7, *n* (%)	5 (12.2)[1]	22 (53.7)[2]	
NRS-pruritus ≤4, *n* (%)	8 (19.5)[4]	29 (70.7)[4]	
IGA score ≤1, *n* (%)	1 (2.4)[4]	9 (22.0)[5]	

Note: Missings: [1] *n* = 6, [2] *n* = 8, [3] *n* = 14, [4] *n* = 2, [5] *n* = 5.

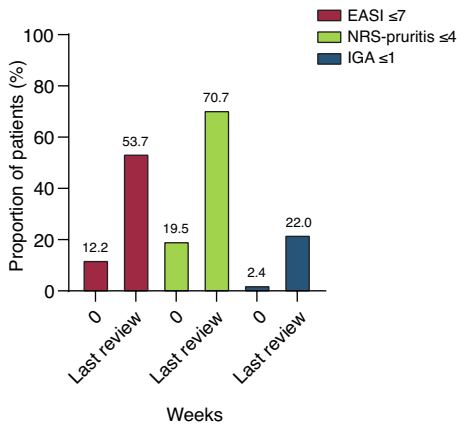

FIGURE 2 Proportion of patients who reached cut-off scores at last review of abrocitinib treatment. Proportion of patients who achieved EASI ≤7, NRS-pruritus ≤4 and IGA≤1. EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; IGA, Investigator Global Assessment.

TABLE 3 Adverse events.

Adverse events	*n* (%)
Total number of AEs	30
Number of patients with AE	25 (60.9)
Gastrointestinal symptoms	8 (26.7)
Acne	6 (20.0)
Respiratory tract infections	5 (16.7)
Fatigue	2 (6.7)
Weight gain	2 (6.7)
Herpes simplex infection	1 (3.3)
Increased liver enzymes	1 (3.3)
Headache	1 (3.3)
Hair loss	1 (3.3)
Increased creatinine	1 (3.3)
Anaemia[a]	1 (3.3)
Increased CK[b]	1 (3.3)

[a]Haemoglobin <8.5 mmol/L (men) or <7.5 mmol/L (women).
[b]CK >3 times upper limit of normal (ULN).

documented, including increased CPK levels, increased liver enzymes, increased creatinine and anaemia.

Treatment discontinuation

A total of 17 (41.5%) patients discontinued abrocitinib treatment after a median duration of 18 (IQR 11–27) weeks. 12 patients (70.6%) used a dosage of 200 mg QD before treatment discontinuation. Seven patients (41.2%) who discontinued abrocitinib treatment had previously failed on biologics and six patients (35.5%) had previously failed on JAK inhibitors. Seven patients (41.2%) discontinued treatment due to ineffectiveness. Seven patients (41.2%) discontinued due to AEs and two patients (11.8%) due to a combination of ineffectiveness and AEs. One patient (5.9%) discontinued abrocitinib treatment due to disease control. Three patients discontinued abrocitinib treatment due to laboratory abnormalities. One patient using abrocitinib 200 mg QD experienced increased symptomatic CPK levels (muscle pain, not related to extensive physical activity) that did not improve after dose reduction resulting in discontinuation of treatment. One patient developed anaemia which resulted in treatment discontinuation. One patient discontinued treatment due to increased creatinine levels, in which dose reduction was not effective. Two patients discontinued treatment due to recurrent respiratory tract infections, including pneumonia. One patient discontinued treatment due to severe nausea, which resolved after discontinuing abrocitinib. In one patient a combination of AEs (weight gain, fatigue and nausea) resulted in treatment discontinuation. After abrocitinib discontinuation 10 patients (55.6%) started upadacitinib, four patients (22.2%) started dupilumab and three patients (16.7%) tralokinumab. In all patients, the choice of treatment discontinuation due to ineffectiveness was based on shared decision-making.

DISCUSSION

This is the first study to evaluate the clinical effectiveness and safety of abrocitinib in AD patients with difficult-to-treat disease in a daily practice setting. Although clinical outcome measures showed a significant decrease during abrocitinib treatment, a substantial group of patients (41.5%) discontinued treatment due to ineffectiveness, AEs or both. The safety analysis did not reveal new findings compared to clinical trial data.[8–10] Furthermore, our findings indicated that among the abrocitinib responders 33.3% had previously failed on other JAK inhibitors (baricitinib and/or upadacitinib). This shows that switching treatment within the class of JAK inhibitors can be successful in managing difficult-to-treat AD.

To the best of our knowledge, no other daily practice studies have been published. Due to the absence of real-world data, we compared our results with the outcome measures used in clinical trials. In the JADE MONO 1 and 2 trial, a higher percentage of patients achieved an IGA of 0 or 1 compared with our study. Over 12 weeks of abrocitinib treatment 200 mg once daily, 44% and 38% of patients achieved an IGA response of 0 or 1 for JADE 1 and 2, respectively. Abrocitinib 100 mg once daily resulted in 28.4% and 24% of patients achieving an IGA response.[8–10] The percentage of patients achieving an IGA score of 0 or 1 in our study was 22% at last review.

Making comparisons with other endpoints, such as EASI-75 and improvement of ≥4 points on NRS pruritus, proved to be challenging. In clinical trials, patients are included based on strict eligibility criteria, and due to the washout period patients, who use systemic immunosuppressive treatment at baseline are excluded. However, in the current study the majority of patients still used concomitant immunosuppressive drugs at baseline. This may have resulted in an underestimation of the effect of abrocitinib on the outcome measures, due to possibly lower EASI scores at baseline. In addition, all patients were previously treated with conventional immunosuppressants and/or targeted therapies and 18 (43.9%) patients received four or more systemic AD treatments. 30 patients (73.2%) had failed on previous targeted therapies, including biologics and other JAK inhibitors. Consequently, our patient population may be classified as difficult to treat. In this study, 24 patients (58.5%) used abrocitinib treatment at last review and showed good clinical response. Interestingly, this includes nine patients (35.5%) that had previously failed on biologics. These results are in line with the results found in JADE COMPARE (phase 3) and JADE DARE (phase 3b) study. These clinical trials compared the efficacy of abrocitinib to dupilumab.[12,16] Abrocitinib treatment was also effective in dupilumab non-responders. Notably, 60% and 47% of dupilumab non-responders were able to achieve EASI-90 and IGA 0/1, respectively, after 12 weeks of abrocitinib treatment.

Furthermore, 14 patients who had previously failed other JAK inhibitors (baricitinib ($n=7$) and upadacitinib ($n=7$)) were included. Interestingly, eight of these patients (8/14) showed good clinical response to abrocitinib treatment. The different pharmacodynamic properties of JAK inhibitors and especially different selectivity for JAK isoforms may explain these findings.[17] For instance, baricitinib inhibits both JAK1 and JAK2 tyrosine kinases, while abrocitinib and upadacitinib are more selective for JAK1.[18–20] Different affinity for JAK1 and concomitant inhibitory activity on JAK2 and JAK3 pathways may explain why abrocitinib was effective in a subset of patients previously treated with other JAKi.[19,21]

The percentage of patients experiencing AEs in our study was 60.9%, which is slightly lower compared to previous clinical trials (reported 65.8%–62.7% and 69%–78% (JADE mono and DARE) of patients with at least 1 AE).[8,10,12] However, the most frequently reported AEs such as gastrointestinal symptoms and respiratory tract infections were consistent with previous clinical trials. However, we observed acne in 20% (six patients) of the patients, which was higher compared to 13.0% ($n=48$) reported in the JADE DARE trial.[12] However, most of the acne cases were considered mild and were no reason for treatment discontinuation. Although most of the other reported AEs were mild, seven patients discontinued abrocitinib treatment due to AEs (e.g. anaemia, severe nausea and pneumonia).[22,23]

Strengths of this study are the prospective design, the relatively large daily practice cohort, and the long median follow-up period of 28 weeks of treatment. Additionally, this study provides better insights into the effects of abrocitinib treatment in patients with difficult-to-treat AD, including those who have not responded to baricitinib and/or upadacitinib. One of the limitations of this study is missing data (e.g. EASI scores), which was partly due to rescheduled visits, no shows and the increased frequency of remote visits during the pandemic. Furthermore, only short-term safety data in daily practice are available, and long-term follow-up is necessary to monitor important AEs like MACE and VTE in daily practice.

In conclusion, abrocitinib can be an effective treatment in patients with difficult-to-treat AD. Patients who previously failed on baricitinib and/or upadacitinib achieved favourable clinical response on abrocitinib treatment. This suggests that switching from one JAK inhibitor to another may be successful in daily practice. Moving forward, it is crucial to conduct further research on the long-term efficacy and safety of abrocitinib.

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None.

CONFLICT OF INTEREST STATEMENT

JO: none, AS: none, PC: 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 the publication of their case details.

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