Received: 20 June 2022 | Revised: 1 August 2022 | Accepted: 8 September 2022

DOI: 10.1002/jvc2.64

ORIGINAL ARTICLE

Baricitinib for atopic dermatitis patients who responded inadequately to dupilumab treatment: First daily practice results

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Funding information
None

Abstract

Background: Baricitinib is the first JAK inhibitor registered for the treatment of moderate-to-severe atopic dermatitis (AD). Efficacy and safety were shown in clinical trials, but daily practice data is sparse.

Objectives: To evaluate the effectiveness and safety of baricitinib treatment in daily practice in AD patients who have inadequately responded to dupilumab.

Methods: In this prospective observational cohort study, AD patients who failed dupilumab treatment and started baricitinib treatment in context of standard care at the Erasmus MC (the Netherlands) were included. We analysed physician-reported scores and patient-reported outcome measure scores (PROMs).

Results: Twenty-five patients were included. Baricitinib treatment resulted in significant improvement of Eczema Area and Severity Index (EASI) scores and PROMs. Seven patients showed a good and sustained response (EASI50), eight patients showed no response (<EASI50), and five patients showed an initial response but worsening of EASI scores in time. Overall, baricitinib was well tolerated. Four patients discontinued baricitinib treatment due to ineffectiveness or side effects.

Conclusions: Baricitinib can be an effective treatment for a subset of AD patients who failed dupilumab treatment in daily practice. We found three different treatment response groups including responders, temporarily responders, and non-responders.

KEYWORDS
atopic dermatitis, baricitinib, dupilumab, immunosuppressive agents

[Correction added on 5 November 2022, after first online publication: Acknowledgements has been changed to Ethics Statement.]

Linde de Wijs, Corine Schreurs, and Anne Schlösser contributed equally.

INTRODUCTION

Atopic dermatitis (AD) is a highly prevalent chronic inflammatory skin disease characterised by pruritus and eczematous skin lesions. It is associated with a large impact on patients'; quality of life.[1] In most patients, the eczema can be adequately controlled with topical therapy. In some AD patients, systemic immunosuppressive– or immunomodulatory therapy is needed to achieve adequate disease control.[2–4]

Until recently, dupilumab was last resort therapy for patients with moderate-to-severe AD. At this moment, multiple targeted treatments are available, including JAK inhibitors and biologics.[2] Baricitinib, a small-molecule Janus kinase (JAK) inhibitor, was the first JAK 1-2 inhibitor registered for the treatment of moderate-to-severe AD.[5] Two selective JAK-1 inhibitors, abrocitinib and upadacitinib, were recently registered.[3,6,7] By selectively blocking JAK 1 and 2, baricitinib inhibits multiple cytokine pathways that are implicated in the pathogenesis of AD, including thymic stromal lymphopoietin (TSLP), Interleukin (IL)-4, IL-5, IL-13, IL-22, and IL-31.[8–10]

Phase II and III clinical studies reported promising efficacy and favourable safety of baricitinib (in combination with TCS) in adult patients with moderate-to-severe AD.[9,11–15] After one week, baricitinib treatment resulted in rapid improvement of itch, night-time awakenings, and skin pain. During the first 16 weeks of baricitinib treatment, AD symptoms further improved. All dosages of baricitinib (1 mg, 2 mg, and 4 mg) were well-tolerated, with nasopharyngitis and headache as most common side effects.[9,11,12,14–17]

Until now, data on the effectiveness and safety of baricitinib for adults with AD in daily practice is limited.[18,19] Recently, previous daily practice studies showed an improvement of AD symptoms, a significant decrease in EASI score in patients who started baricitinib treatment, and no serious adverse events were observed.[20,21]

It is known that effectiveness (daily practice) might differ from efficacy (clinical trials). This may partially be caused by stringent inclusion and exclusion criteria in clinical trials, such as exclusion of patients who previously have been treated with dupilumab. Therefore, there is a need for observational studies conducted in clinical care to get a better insight in the real-life effectiveness.[22] In our study, we aimed to investigate the effectiveness and safety of baricitinib in patients with moderate-to-severe AD who have inadequately responded to dupilumab.

MATERIALS AND METHODS

Study design and patient population

This prospective, observational cohort study was conducted at the Department of Dermatology at the Erasmus MC University Medical Center (Rotterdam, the Netherlands). All adult AD patients who failed dupilumab treatment (due to insufficient effectiveness and/or side effects) and started baricitinib treatment in context of standard care between December 2020 and June 2021 were eligible. Patients were included after consent was obtained to publish pseudonymized information relating to them.

Baricitinib was administered 4 mg once daily, in accordance with the product label.[23] Dupilumab and systemic immunnosuppressants were discontinued before starting baricitinib treatment. If needed, systemic corticosteroids were used as bridging therapy. During baricitinib treatment, patients were encouraged to continue the use of moisturisers, topical corticosteroids (TCSs) and topical calcineurin inhibitors (TCIs).

Patients visited the outpatient clinic at start of treatment, after 4 and 12 weeks of treatment. Data were collected in the context of the 'Erasmus MC IMID Quality of Care Registry', Medical Research Ethics Committee MEC-2017-1123; W18_097#18.123. At baseline, demographic and patient characteristics were recorded. Clinical examinations were performed by a small group of trained raters. Physician-reported severity was scored using the Eczema Area and Severity Index (EASI; 0–72) and Investigator Global Assessment (IGA; 0–4). Patient-reported outcome measures (PROMs) included Numeric Rating Scale (NRS; 0–10) pruritus (worstand mean weekly), the Atopic Dermatitis Control Tool (ADCT; 0–24), Dermatology Life Quality Index (DLQI; 0–30), and Patient-Oriented Eczema Measure (POEM; 0–28). Outcome measures were in line with the Core Outcome Set of the global Harmonising Outcome Measures for Eczema (HOME) initiative.[24] Safety was monitored by clinical laboratory tests (including haematological-, hepatic-, renal analysis, lipid parameters, creatinine kinase and serology) at scheduled visits. Other safety assessments included a chest radiograph (i.e. tuberculosis screening) before baseline and pregnancy tests at all scheduled visits. Potential side effects of baricitinib treatment were recorded during follow-up.

Treatment effectiveness was evaluated by comparing EASI scores and PROMs at all visits. Also, the proportions of patients achieving 50% and 75% improvement in EASI scores (EASI50, EASI75) at Weeks 4 and 12

compared with baseline, were calculated. In addition, the proportions of patients achieving an IGA score of 0 (clear) or 1 (almost clear) were determined. Response types were determined as good responders with EASI50 at both visits; non-responders for patient not achieving EASI50 at both visits; and temporarily responders with EASI50 at Week 4, and a relative EASI improvement of <50% at Week 12.

Patients with missing EASI scores at one or more time points were excluded from the response analysis.

Statistical analyses

Outcomes were analysed using the Wilcoxon signed-rank test (nonparametric, numerical outcomes) and the Fisher exact test (categorical outcomes). Patients who discontinued baricitinib during follow-up, were determined as not achieving IGA 0/1, EASI50/75, and not in control according to ADCT al all visits. In the statistical analyses, differences with two-sided p-values < 0.05 were regarded as statistically significant. Analyses were performed using IBM SPSS Statistics version 25.0.

RESULTS

Population

Table 1 represents the baseline characteristics of 25 patients included in our cohort. Two eligible patients were not included because consent was not provided. Sixty-four percent of the patients were male, with a median age of 29 years (IQR 24–51) and median BMI of 26 kg/m^2 (24–28) at baseline. The median age of AD onset was 3 years (IQR 0-17). Allergic rhinitis (68%) and allergic conjunctivitis (48%) were the most frequently reported atopic comorbidities.

The majority of patients (84%) was previously treated with ≥2 immunosuppressive therapies, mainly cyclosporine A (96%) and (short term) systemic corticosteroids (68%). All patients were previously treated with dupilumab, for a median duration of 7 months (IQR 4–15). Dupilumab treatment was prescribed according to the product label.[25] However, the interval was shortened to weekly administration due to insufficient effectiveness in seven patients, and extended to every 3 weeks due to blepharoconjuctivitis in one patient. Dupilumab was discontinued because of ineffectiveness in 11 patients, side effects in one patient and a combination of both in 12 patients. Reported side effects were (blepharo) conjunctivitis ($n = 7$), head-neck dermatitis ($n = 3$), joint complaints ($n = 2$), hair loss ($n = 1$), peripheral oedema ($n = 1$), and fatigue ($n = 1$).[26,27] Most patients ($n = 17$) directly switched from dupilumab to baricitinib treatment. The median duration between those treatments was 7 days (IQR 0–35). Conventional systemic immunosuppressants (excluding systemic corticosteroids) were

TABLE 1 Demographic and baseline characteristics ($n = 25$)

Baseline characteristics	
Male – *n* (%)	16 (64)
BMI (kg/m^2), median (IQR)	26 (24–28)
(Atopic) comorbidities, *n* (%)	
- Asthma	8 (32)
- Allergic rhinitis	17 (68)
- Allergic conjunctivitis	12 (48)
- Allergic contact dermatitis	11 (44)
- Food allergy	2 (8)
Fitzpatrick, *n* (%)	
- I	1 (4)
- II	17 (68)
- III	5 (20)
- IV	1 (4)
- V	1 (4)
Age of onset AD (years), median (IQR)	3 (0–17)
Age at start baricitinib, median (IQR)	29 (24–51)
Previous use of systemic immunosuppressive drugs, *n* (%)	
- Cyclosporine A	24 (96)
- Methotrexate	11 (44)
- Azathioprine	5 (20)
- Mycophenolic acid/Mycophenolate mofetil	10 (40)
- Systemic corticosteroids	17 (68)
Number of previous systemic immunosuppressive drugs, *n* (%)	
- 0	1 (4)
- 1	3 (12)
- 2	8 (32)
- 3	6 (24)
- 4	5 (20)
- 5	2 (8)
Previous UV therapy, *n* (%)	14 (56)
Previous dupilumab therapy, *n* (%)	25 (100)
Duration of dupilumab therapy, months	
- Median (IQR)	7 (4–15)
- Minimum, maximum	1, 32

Abbreviations: BMI, body mass index; IQR, interquartile range.

discontinued 7 days (IQR 0–19) before baricitinib therapy. In three patients the transition to baricitinib was bridged with a two-week tapering course of prednisone, with a starting dose of 30 mg.

Outcomes

Twenty-five patients consulted our department at 4 weeks of treatment, 18 patients at 12 weeks of treatment. Four patients discontinued baricitinib treatment before 12 weeks of treatment and three patients were still in follow-up (4–12 weeks of treatment). EASI scores at baseline and 4 weeks of treatment were available for 22 patients (missing: $n = 3$), whereas scores of 17 patients (missing: $n = 4$, discontinued before 12 weeks of treatment: $n = 4$) were available at baseline and 12 weeks of treatment.

EASI scores significantly decreased from baseline (median 12.8; IQR 10.0–25.0) to Week 4 (median 6.2; IQR 3.3–17.9) ($p = 0.003$). Although there was a significant decrease from baseline to Week 12 (median 9.6; IQR 3.1–15.0) ($p = 0.006$), median EASI scores increased between Weeks 4 and 12 (Table 2).

Thirteen patients (62%) achieved EASI50 at 4 weeks of treatment, of which 5 (24%) achieved EASI 75. EASI50 and EASI75 were reached by 7 (33%) and 4 (19%) patients at 12 weeks of treatment. IGA 0 or 1 was achieved by 3/25 (12%) patients and 4/22 (18.2%) at Weeks 4 and 12. As shown in Table 2, most PROMs showed statistically significant improvement from baseline to Weeks 4 and 12. Between Weeks 4 and 12, DLQI, POEM, and both NRS pruritus scores increased, indicating worse disease. Eight patients achieved disease control according to the ADCT outcome at Week 4, whereas five patients at Week 12.

We observed three treatment response groups (Figure 1). The first group included seven patients that showed a good response during 12 weeks of follow-up (EASI50 at Weeks 4 and 12). The second group of five patients showed a good response to baricitinib treatment at Week 4 (EASI50) but worsening of outcome measures at Week 12 (<EASI50). The third group, including eight patients, showed no response (<EASI50) at Week 4, nor at Week 12 (or discontinued before Week 12 because of ineffectiveness). EASI scores of five patients were lacking for at least one time point, and were therefore not included in the response analysis.

TABLE 2 Physician- and patient-reporting outcome measures indicating baricitinib effectiveness

	Baseline $n = 25$[†]	Week 4 $n = 25$[†]	p-value[¶]	Week 12 $n = 18$[†]; $n = 4$[‡]	p-value[¶]
EASI (0–72) (median, IQR)	12.8 (10.0–25.0)[a]	6.2 (3.3–17.9)[b]	$p = 0.003$	9.6 (3.1–15.0)	$p = 0.006$
Relative EASI improvement from baseline					
- EASI50 (n (%))	-	13 (62)	-	7 (33)	-
- EASI75 (n (%))	-	5 (24)		4 (19)	
NRS peak pruritus past 24 h (0–10) (median, IQR)	7.0 (4.5–8.5)	3.0 (2.0–6.0)	$p = 0.001$	4.0 (0.8–7.3)	$p = 0.003$
NRS pruritus past 7 days (0–10) (median, IQR)	6.0 (4.0–7.5)	2.0 (2.0–5.0)	$p = 0.001$	4.0 (1.0–5.3)	$p = <0.001$
ADCT (0–24) (median, IQR)	13.5 (10.0–16.8)[c]	6.0 (2.0–12.5)[c]	$p = 0.010$	6.5 (2.5–13.8)[a]	$p = 0.007$
ADCT					
- In control (n (%))	0 (0)	−8 (36)	$p = 0.004$	−5 (25)	$p = 0.018$
- Not in control (n (%))	−22 (100)	−14 (64)		−15 (75)	
DLQI (0–30) (median, IQR)	8.5 (5.0–12.5)[d]	3.0 (0.3–9.5)[d]	$p = 0.014$	4.0 (2.0–9.0)[e]	$p = 0.289$
POEM (0–28) (median, IQR)	18.5 (14.3–20.0)[d]	11.0 (4.3–17.8)[d]	$p = 0.010$	12. 0 (8.5–20.0)[e]	$p = 0.041$

Abbreviations: ADCT, atopic dermatitis control tool; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EASI50, relative improvement of ≥50%; EASI75, relative improvement of ≥75%; IQR, interquartile range; NRS, numeric rating scale; POEM, patient-oriented eczema measure.

Missing values:

[a] $n = 2$.

[b] $n = 1$.

[c] $n = 3$.

[d] $n = 9$.

[e] $n = 5$.

[†] n = number of patients who reached the time point in follow-up, [‡] n = patients who pre-maturely discontinued baricitinib treatment; [¶] p-values: Scores at Week 4 and Week 12 were compared with baseline scores.

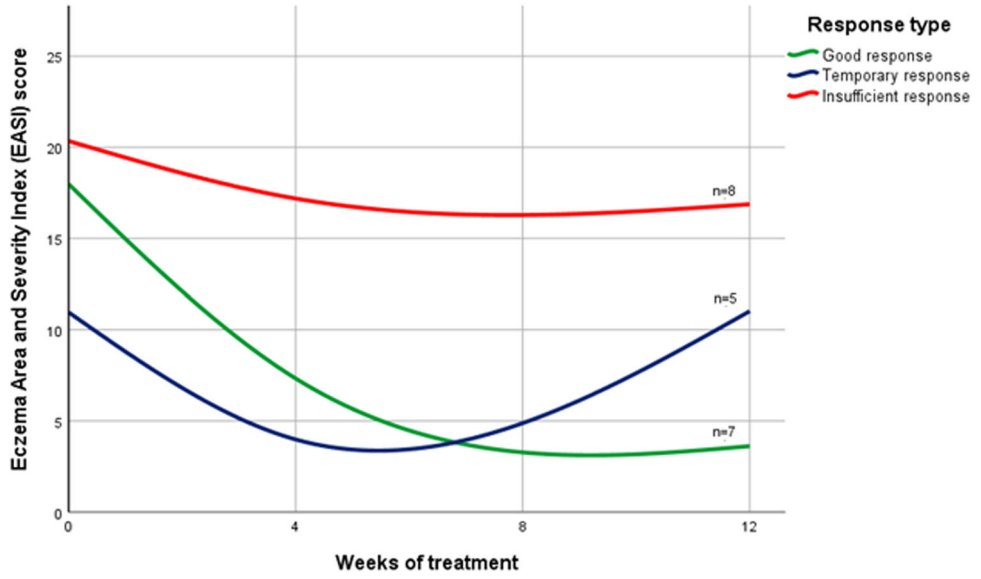

FIGURE 1 Treatment response types in baricitinib treatment in daily practice. EASI, Eczema Area and Severity Index. n = number of patients included in treatment response group. Note that in five patients EASI scores were missing at one or more time points. These patients were not included in the response analysis.

Side effects

Abnormal laboratory test results included increased serum creatinine kinase (CK) levels ($n = 6$, range 210–595 U/L), hypercholesterolaemia ($n = 1$), and ALAT increase ($n = 1$). The exact course of the serum abnormalities could not be adequately evaluated during 12 weeks of follow-up. All abnormalities were asymptomatic, there was no medical intervention needed.

Other reported side effects included oral sores ($n = 2$), eczema herpeticum ($n = 1$), gastro-enteritis ($n = 2$), acne vulgaris ($n = 2$), nausea ($n = 2$), erythema and burning sensation of the face ($n = 2$), headache ($n = 2$), fatigue ($n = 2$), joint complaints of the hands ($n = 1$), sleep loss ($n = 1$), nasopharyngitis ($n = 1$), hair loss ($n = 1$), weight gain ($n = 1$, 4 kg), and secondary impetiginisation ($n = 1$). The patient with secondary impetiginisation was successfully treated with oral antibiotics. Eczema herpeticum was treated with oral antiviral therapy and systemic corticosteroids. One patient experienced an AD flare after 6 weeks of treatment and required systemic corticosteroids, resulting in disease improvement.

The side effects attributed to previous dupilumab treatment, such as (blepharo)conjunctivitis resolved in all patients; dupilumab induced paradoxical head and neck dermatitis resolved in one out of three patients, within the first 12 weeks of baricitinib treatment.

Baricitinib dose adjustments and discontinuation

In total, four patients discontinued baricitinib treatment within 12 weeks of follow-up. In two patients the dosage of baricitinib was increased to either 6 mg or 8 mg once daily due to insufficient effectiveness. In none of these patients dose adjustment increased effectiveness, one patient developed eczema herpeticum 7 days after increasing the dose of baricitinib to 8 mg/day. This resulted in discontinuation of baricitinib at 4 and 5 weeks, respectively. One patient experienced a severe AD flare after 5 weeks of treatment (EASI 31.5) and discontinued baricitinib. In another patient baricitinib was discontinued at 11 weeks of treatment due to a combination of moderate effectiveness and side effects.

DISCUSSION

Dupilumab has been a real game changer in the treatment of AD. Nonetheless, a subset of patients has inadequate response to dupilumab treatment or experiences side effects.[28–30] Until recently, there were no therapeutic alternatives for these patients. Therefore baricitinib, as the first approved JAK inhibitor for AD, is an important new option for treatment of moderate-to-severe AD.[31,32] However, previous use of dupilumab was an exclusion criterium in clinical trials with baricitinib,

and there are no publications on this patient population.[11] We present the first cohort of patients (who responded inadequately to dupilumab) treated with baricitinib in daily practice.

In this prospective study, the effectiveness of baricitinib treatment up to 12 weeks was evaluated in a cohort of 25 moderate-to-severe AD patients who responded inadequately to dupilumab and prior systemic immunosuppressants. Baricitinib treatment resulted in a statistically significant improvement of EASI and PROM scores from baseline to Week 12 (except for DLQI) (Table 2). However, a subset of patients experienced a worsening of scores between 4 and 12 weeks of treatment (Figure 1). IGA 0 or 1 was achieved by 3/25 (12%) patients and 4/22 (18.2%) patients, at Weeks 4 and 12. Overall, baricitinib was well tolerated. Four patients discontinued baricitinib treatment in the first 12 weeks due to ineffectiveness, combined with side effects in two of them.

Baseline demographics of the patients in our cohort were comparable to those of clinical trials with baricitinib.[11] Baseline physician (EASI, IGA) and patient-reported outcomes (DLQI, POEM, and NRS pruritus) were lower in our cohort, which probably results from the direct transition from dupilumab or conventional systemic immunosuppressants to baricitinib, without a wash-out period. This is in contrast to the above-mentioned clinical trials, which applied a wash-out period of 4 weeks for conventional systemic immunosuppressants.[11] In our cohort, all patients had previously been treated with dupilumab and conventional systemic immunosuppressants. We consider these patients to be at the very severe end of the disease spectrum, compared to patients in clinical trials.

The percentage of patients reaching IGA 0 or 1 at 12 weeks of treatment is slightly lower compared to the clinical trials with baricitinib that allowed the use of TCS rescue therapy. In BREEZE-AD1 and –AD2, 22.4% and 22.0% of patients achieved IGA 0 or 1 after 16 weeks of treatment.[11] In addition, a smaller percentage of our cohort (19%) achieved EASI75 after 12 weeks of treatment compared to clinical trials (36% and 35.8% at 16 weeks of treatment, respectively).[11] This might be explained by the lower baseline severity scores and the facts that these patients might be difficult-to-treat. Furthermore, Rogner et al. showed a smaller improvement in clinical scores (EASI) in patients with previous dupilumab treatment compared with patients without. It is likely that patients with previous therapies have severe AD and are more difficult to treat.[21]

We observed three groups of patients with different treatment responses (Figure 1). Responders tend to be older (median age 55 years (IQR22–58)) compared with temporarily responders and non-responders (median 29 (IQR24–41). Decreased renal clearance in older patients may be related to better response, but because the groups were relatively small, we did not perform statistical analyses on these groups.

Dose adjustments in patients with inadequate response did not result in clinical disease improvement. A 36-year-old male patient developed eczema herpeticum in his face, 7 days after increasing the dose to 8 mg/day. He reported a history of similar symptoms during prior cyclosporine A treatment, but PCR analysis has never been performed. Although a causal relationship with baricitinib could not be proven, vigilance to the potentially increased rate of side effects at higher dosages of baricitinib is recommended.[33] The reported side effects are comparable with previous studies.[11,16] Asymptomatic increases of serum CK levels were found in 6 patients. Queeney et al., recently hypothesised that JAK inhibitors may restore muscle differentiation resulting in increased CK levels.[34]

In our cohort, 16% of the patients ($n = 4$) discontinued baricitinib. This percentage was much higher compared to the RCTs, which showed discontinuation rates of 4% for baricitinib 4 mg. This may be explained by the selection bias in our cohort (i.e. patients who failed dupilumab treatment).[11] In the Netherlands, dupilumab treatment is prescribed for patients with moderate-to-severe AD who responded inadequately to at least 1 systemic immunosuppressant for a minimum of 4 months.[35] Remarkably, patients in our cohort who discontinued baricitinib used a median of 4 (IQR 2–5) immunosuppressants before starting baricitinib treatment. As baricitinib treatment is often last resort therapy for our patients, baricitinib is tended to be continued even when there is a suboptimal therapeutic effect. If alternative treatment options would have been available, discontinuation rates may have been even higher. For patients with limited effect of baricitinib monotherapy, concomitant treatment with methotrexate could be considered. In rheumatoid arthritis, this has shown to be an effective and safe treatment strategy.[36]

There are several limitations. Because baricitinib was only the second targeted therapy registered for treatment of AD, patients described in this study mostly represent difficult-to-treat, severe AD patients that had previously been treated with several conventional systemics and dupilumab. The number of patients included in this study is relatively small, but with the recent registration of two selective JAK-1 inhibitors that showed better effectivity in clinical trials, the numbers of patients treated with baricitinib in daily practice are unlikely to grow fast. In this study, we only analysed clinical outcomes up to 12 weeks of treatment, and the discontinuation rate is relatively high, most likely to result from the above-mentioned bias towards a very

severe patient population. Future studies are needed to examine long-term effectiveness of baricitinib treatment in moderate-to-severe AD patients in daily practice.

In conclusion, in our daily practice cohort we found that baricitinib can be an effective treatment for a subset of AD patients who failed dupilumab and systemic immunosuppressive treatment. We described three groups of patients with different treatment responses. The patients with the best response to baricitinib treatment in this cohort were relatively older compared to the non-responders or patients with a suboptimal treatment response. Future studies including the use of predictive (serum) biomarkers may help to identify the patients with the best response to baricitinib treatment.

CONFLICTS OF INTEREST

LdW: None, CS: none, AS: None, TN: None, DH: investigator for AbbVie, LEO pharma, MedImmune/AstraZeneca, Novartis, Sanofi/Regeneron; consultancies for Regeneron/Sanofi, LEO pharma, MedImmune/AstraZeneca, Novartis, Incyte, Janssen, Pfizer.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The patients in this manuscript have given written informed consent to publication of their case details. Patients were included after consent was obtained to publish pseudonymized information relating to them. Data were collected in the context of the 'Erasmus MC IMID Quality of Care Registry', Medical Research Ethics Committee MEC-2017-1123; W18_097#18.123.

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How to cite this article: de Wijs L, Schreurs C, Schlösser A, Nijsten T, Hijnen DJ. Baricitinib for atopic dermatitis patients who responded inadequately to dupilumab treatment: first daily practice results. JEADV Clin Pract. 2022;1:364–371. https://doi.org/10.1002/jvc2.64