SHORT COMMUNICATION

Treatment of Atopic Dermatitis with Baricitinib: First Real-life Experience

Danielle ROGNER, Tilo BIEDERMANN and Felix LAUFFER
Department of Dermatology, Technical University of Munich, DE-80802 Munich, Germany. E-mail: daniellefranziska.rogner@mri.tum.de
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Atopic dermatitis (AD) (also termed atopic eczema) is a chronic inflammatory skin disease, affecting approximately 20% of children and 1–5% of the adult population in western countries (1). The disturbed skin barrier and inflammation in AD are treated with emollients and anti-inflammatory therapy. Mild AD can be controlled with this treatment, but moderate-to-severe manifestations require systemic therapy for sufficient response. In the past, unspecific immunosuppressive drugs were used, which lacked efficacy and caused side-effects (2, 3). The development of new therapy concepts and increased understanding of the pathophysiology of AD has provided the basis for development of new drugs (3). A breakthrough came with the development of dupilumab, which is directed against interleukin-4 and interleukin-13 receptors. The most common undesirable side-effect is conjunctivitis, which occurs in up to 10% of patients (2, 4–6).

In addition, baricitinib has been approved in Europe (2020), the first approved oral selective inhibitor of Janus-kinase-1 and Janus-kinase-2. Phase III studies (BREEZE-AD1, BREEZE-AD2, BREEZE-AD7) showed significant improvements in clinical signs (75% improvement in clinical signs on Eczema Area and Severity Index (EASI-75) in 48% of the study population at week 16, 31% achieved validated investigator global assessment 0 or 1) and symptoms in patients within 16 weeks and induced rapid reduction in itch (44% of participants showed a reduction in itch by 4 points on the numerical rating scale (NRS)) (7–9). However, in real-life, most patients do not fulfil the criteria to enter a clinical study, and effectiveness might differ dramatically in clinical trials (10).

We present here real-life data from patients with AD treated with baricitinib at our outpatient clinic.

MATERIALS, METHODS AND RESULTS

This study reports observations of clinical routine; hence, institutional review board approval is not necessary. Patients provided informed consent.

A total of 12 patients (1 woman and 11 men) with moderate-to-severe AD starting baricitinib 4 mg at the dermatological department of the Technical University of Munich, Germany, from November 2020 to January 2021 were included in the study and evaluated at initiation, 1 month and 3 months (**Table I**). Eight patients had a history of treatment with at least 1 immunosuppressive therapy, which were discontinued due to insufficient disease control or side-effects. Six of the patients (50%) had received dupilumab treatment, which was discontinued due to severe conjunctivitis. All patients used concomitant moisturizers and topical corticosteroids/calcineurin inhibitors. Ten of the patients drastically reduced their use of topical steroids, reporting use of medium-to-high potency corticosteroid only 1×/week.

Table I. Characteristics and history of treatment of the patients with atopic dermatitis (AD) initiating treatment with baricitinib

Patient characteristics	
Sex, *n* (%)	
Women	1/12 (8.3)
Men	11/12 (91.7)
Age at onset of AD, median (min–max)	5 (0–57)
Age at baricitinib initiation, years, median (min–max)	33.5 (27–65)
History of asthma, % (*n*/*n*total)	25% (4/12)
History of hay fever % (*n*/*n*total)	83% (10/12)
Previous treatment, *n* (%)	
Topical steroids	12 (100)
Topical calcineurin inhibitors	12 (100)
Systemic steroids	7 (58)
Other[a]	7 (58)
Phototherapy	10 (83)
Previous dupilumab therapy % (*n*/*n*total)	50% (6/12)
Contraindication or intolerance (e.g. conjunctivitis)	100 (6/6)
Due to lack of efficacy	50 (3/6)

[a]Methotrexate, azathioprine, cyclosporine A, other biologic drug (apart from dupilumab).

At each visit, disease severity was assessed by the same dermatologist using the Eczema Area and Severity Index (EASI) (11), quality of life (QoL) was assessed using the Dermatology Life Quality Index (DLQI) (ranging from 0 to 30; 30 indicating the worst score) (12). In addition, NRS pruritus of 0–10 points was used to assess itch intensity and impact on sleep (insomnia NRS) (13, 14). Blood samples were taken at each visit (see below). Before treatment initiation, a hepatitis-screening and quantiferon-test was performed.

Data were visualized using GraphPad Prism 7.00 software and paired *t*-test was used as a statistical test. Significance level was $p<0.05$ (*), $p<0.01$ (**) and $p<0.001$ (***).

At baseline, median EASI score was 16.85 points, mean reduction was 10.7 points (64%) at 1-month follow-up and 17.81 points (83.1%) at 3-month follow-up (Fig. S1). At 1-month follow-up, 83% experienced at least a 50% reduction in EASI-score from baseline (EASI-50), whereas at 3-month follow-up 100% achieved EASI-50. At 1-month-follow-up, 42% achieved EASI-75, and at 3-month follow-up, 90.1% achieved EASI-75. One patient discontinued due to lack-of-efficacy (Table SI).

The results showed a significant reduction in DLQI, NRS-itch and NRS-insomnia between baseline and 3-month follow-up. The decrease was most pronounced from baseline to 1 month. Mean percentage reduction in NRS pruritus from baseline was 65% at 1-month follow-up and 65.88% at 3-month follow-up. Mean percentage reduction in NRS insomnia from baseline was 73% at 1-month follow-up and 85.56% at 3-month follow-up (Fig. S2). Comparing patients regarding dupilumab therapy in the past, we found that patients without previous therapy showed an 82.45%, reduction in EASI score, in comparison with 52% in patients with previous therapy (Fig. S3).

Furthermore, this study found that NRS-pruritus, NRS-insomnia and DLQI showed bigger improvement in patients without previous dupilumab therapy.

Three patients had side-effects (headache, facial acne, night sweats). Blood samples drawn at each visit comprised full blood count (including eosinophil count), kidney function, liver function serum creatinine kinase (CK) and lipid status (including cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), lipoprotein A). One patient showed a reduction in lymphocytes (<750/µl), which recovered rapidly. Patients with increased creatinine phosphokinase ($n=3$) reported having performed weight-lifting exercises <24 h before bloods were drawn. Lipid status changed in some patients (7% showed an increase in triglycerides to high (≥2.26 mmol/l)), 7% had an increase in cholesterol to high (≥6.21mmol/l), 3% had an increase in LDL cholesterol to high (≥4.14 mmol/l or very high ≥4.91mmol/l) (15).

DISCUSSION

Baricitinib is a selective JAK1- and JAK2-inhibitor, it was the first in-its-class approved oral drug showing significant improvement in patients with AD with moderate-to-severe disease manifestation. The small molecule inhibits various cytokines that play a role in the pathogenesis of AD, including thymic stromal lymphopoietin (TSLP), interleukin (IL)-4, IL-5, IL-13, IL-22 and IL-31, offering new therapy (9).

The current study cohort showed improved signs and symptoms of AD, with a statistically significant reduction in EASI, DLQI, pruritus and sleep score from baseline, at 1- and 3-month follow-up. No further significant differences in the scores were present between 1- and 3-month follow-up, indicating that the main improvement takes place within the first month. At 3-month follow-up, the overall percentage reduction in EASI-score for all patients was 64% (EASI-50: 83%; EASI-75: 42%). Several of the patients had comorbidities that exclude them from clinical studies. The current study results are better than those of previously reported studies on the efficacy of baricitinib in phase-3 clinical trials (BREEZE-AD1, BREEZE-AD2, BREEZE-AD7) (see below) (8, 9).

Effectiveness evaluated by the percentage reduction in EASI score, EASI-50 and EASI-75 at 3 months was superior to results obtained from clinical trials especially from the BREEZE-AD7 study (EASI-75 after 16 weeks: 50%; EASI-75 after 16 weeks: 90%).

Patients reduced their use of topical steroids, which implies better efficacy than shown in published phase-III studies, in which concomitant therapy with topical steroids was mandatory.

One patient discontinued treatment due to lack of efficacy, which is comparable with findings of phase-3 clinical trials (1–2% drop-out), whereas the current study cohort was smaller.

Pruritus and impacted sleep quality have a negative impact on quality of life in patients. According to the participants, pruritus decreased rapidly. Median NRS pruritus score was reduced from 6.75 at baseline to 2.58 at 1-month and to 2.18 at 3-month follow-up. This emphasizes the rapid effects of JAK1/2 inhibition on itch, which might be based on inhibition of IL-31-signalling. Quality of life improved in all, starting from a mean score of 12.66 at baseline and reducing to 0.82 at 3 months.

As mentioned, this study observed that patients with previous dupilumab therapy showed a smaller improvement in EASI score compared with in patients without (Fig. S3). This observation is in concordance with the impression that patients with multiple previous therapies tend to present with difficult-to-treat AD. Switching to baricitinib might be a therapeutic option in patients with severe conjunctivitis under dupilumab.

In conclusion, these first real-life data on treatment with baricitinib show promising effectiveness and tolerability, even in patients with comorbidities or previous systemic treatment. The real-life profile appears to be comparable to the results of phase-3 clinical trials.

Conflicts of interest: DR has no conflicts of interest to declare. FL is member of advisory boards and/or speaker for Novartis, Abbvie, Lilly, Janssen, UCB, Amgen, Almirall, Sanofi, LEO Pharma and Roche, not related to this study. TB gave advice to or got an honorarium for talks or research grant from the following companies: Alk-Abelló, Celgene-BMS, Galderma, GlaxoSmithKline, Leo Pharma, Lilly Deutschland GmbH, Mylan, Novartis, Phadia-Thermo Fisher, Sanofi-Genzyme and Regeneron.

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