ORIGINAL REPORT

Impact of Baricitinib on Patients' Quality of Life after One Year of Treatment for Atopic Dermatitis in Real-World Practice: Results of the Observatory of Chronic Inflammatory Skin Diseases Registry

Ziad REGUIAI[1], Pierre André BECHEREL[2], Jean Luc PERROT[3], Anne Claire FOUGEROUSSE[4], Edouard BEGON[5], Claire POREAUX[6], Claire BOULARD[7], Guillaume CHABY[8], Charlotte FITE[9], Inès ZARAA[9], Dominique LONS-DANIC[9], Anne-Laure LIEGEON[10], Josiane PARIER[11,12], Nathalie QUILES-TSIMARATOS[13], Laurene DAVID[13] and François MACCARI[4,12] for the OMCCI GROUP

[1]Department of Dermatology, Polyclinique Courlancy, Reims-Bezannes, [2]Dermatology and Clinical Immunology Unit, Antony Hospital, Antony, [3]Department of Dermatology, CHU Saint Etienne, Saint-Etienne, [4]Department of Dermatology, Hôpital d'Instruction des Armées Begin, Saint Mandé, [5]Department of Dermatology, Centre hospitalier René Dubos, Pontoise, [6]Centre médical Stanislas-Nancy, Nancy, [7]Department of Dermatology, Centre hospitalier du Havre, Le Havre, [8]Department of Dermatology, CHU Amiens-Picardie, Amiens, [9]Department of Dermatology, Hôpital Paris Saint Joseph, Paris, [10]Department of Dermatology, Centre hospitalier régional Metz-Thionville, Thionville, [11]Centre de Santé Sabouraud, Hôpital Saint-Louis, Paris, [12]Cabinet Médical, Saint-Maur-des-Fossés, [13]Department of Dermatology, Hôpital Saint Joseph, Marseille, France

The efficacy and safety of baricitinib for treatment of atopic dermatitis have been demonstrated in clinical trials; however, very few real-life studies have been published to date. The Observatory of Chronic Inflammatory Skin Diseases (OMCCI) registry was initiated to prospectively determine the long-term impairment caused by chronic inflammatory dermatoses on patients' lives. The study included 88 patients starting baricitinib for treatment of atopic dermatitis. Clinical evaluation and patient-reported outcomes were recorded at baseline and after 6 and 12 months. After 6 months and 1 year of follow-up, 65 and 47 patients, respectively, were still being treated with baricitinib. Treatment failure was the main reason for discontinuation. Only 1 patient stopped baricitinib because of a side-effect. After 1 year of follow-up, the mean Eczema Area and Severity Index score decreased significantly from 20.7 to 6.4; the percentage of patients with severe atopic dermatitis decreased from 42.9% to 6.5% and a significant improvement in most patient-reported outcomes was noted. There was no difference in terms of efficacy whether or not patients were previously treated with dupilumab. The results remained stable after 6 and 12 months of treatment, which suggests a sustained efficacy of the treatment in patients who initially responded well.

Key words: atopic dermatitis; baricitinib; Janus kinase inhibitors; quality of life; registry.

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Corr: Ziad Reguiai, Department of Dermatology, Polyclinique Courlancy-Bezannes, 89 rue Louis-Victor de Broglie, FR-51430 Reims-Bezannes, France. E-mail: dr-reguiai@orange.fr

SIGNIFICANCE

Very few real-life studies have been published on the effectiveness and safety of baricitinib treatment in patients with atopic dermatitis. The current study of 88 adult patients treated with baricitinib with a follow-up of 1 year in daily clinical practice highlights that baricitinib is an effective and well-tolerated treatment option for patients with moderate-to-severe atopic dermatitis, including those with previous inadequate response to dupilumab. The clinical improvement in the disease was coupled with a significant improvement in patients' quality of life in the initial 6 months and remained stable in the subsequent 6 months.

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease, with a reported prevalence in adults of approximatively 5% (1, 2). Moderate-to-severe AD may greatly impact the quality of life (QoL) of affected patients and their families, with a potential high economic burden (3, 4). The impact of AD on health-related QoL may accumulate with time or change in terms of the affected dimensions (physical, psychological, socio-professional, and patients' feelings about their illness or treatments). In recent years, 2 biologics (dupilumab and tralokinumab) and 3 Janus kinase (JAK) inhibitors (abrocitinib, baricitinib, upadacitinib) have been approved in France for the treatment of adult patients with moderate-to-severe AD after failure or contraindication to cyclosporine. Baricitinib is an oral selective Janus kinase (JAK)1 and 2 inhibitor whose efficacy and safety have been demonstrated in clinical trials (5–9). In France, baricitinib was the first oral JAK inhibitor to be made commercially available for treatment of moderate-to-severe AD, in March 2021. Very few real-life studies on the effectiveness and safety of baricitinib treatment in patients with AD have been published to date (10–14).

The Observatory of Chronic Inflammatory Skin Diseases (OMCCI) registry has been initiated to prospectively determine the long-term impairment caused by the 4 most frequent and impacting chronic inflammatory diseases (CID) (psoriasis, AD, hidradenitis suppurativa, and chronic urticaria) on several aspects of patients' lives. This registry was driven by RESO-dermatologie,

a French national network of approximately 400 dermatologists involved in CID management at various centres (university/public/military/private hospitals, private practices). Patients are included in the OMCCI at the initiation or modification of a conventional, biological, or JAK inhibitor systemic therapy. The registry is ongoing and aims to include at least 1,000 adult patients for each of the 4 CID. The planned long-term follow-up (4 years) will allow accumulation of data on the impact of therapeutic choices on patient-reported outcomes (PROs) and may also permit real-world assessment of the tolerability of new emerging treatments, such as JAK inhibitors. We present herein data from the OMCCI registry of patients with moderate-to-severe AD at baricitinib initiation and after one year of follow-up.

MATERIALS AND METHODS

A prospective multicentre observational cohort study was performed, which included adult patients with moderate-to-severe AD who have been participating in the OMCCI registry since December 2020. Patients consulting in routine care who had given written consent to participate in the study were consecutively included at the initiation of baricitinib treatment. Patients were treated in real-life conditions with the standard dosage of baricitinib 4 mg once daily monotherapy or in combination with topical treatments (corticosteroids or tacrolimus). No washout period was required before baricitinib initiation.

In the OMCCI registry a 4-year follow-up is planned with annual physician assessment and bi-annual input from patients on several PROs. AD severity was assessed using the Eczema Area and Severity Index (EASI) score (range 0–72) (15) (mild AD: EASI score <7, moderate AD: EASI score ≥ 7 and <21, severe AD: EASI score ≥ 21). Patients' information was recorded every 6 months covering: sociodemographic details; age at diagnosis; hospital admissions, sick leave in the preceding 6 months; compliance with treatment; short questionnaires; namely, the Dermatology Life Quality Index (DLQI) (16), the 12-item Short-Form Health Survey (SF-12) (17), and patient's perceptions of disease impact on their daily, familial, and professional life over the week preceding each onsite visit using a numerical rating scale (NRS) (scale 0–10. 0="my skin condition doesn't bother me at all"; 5="my skin condition bothers me moderately"; 10="my skin condition bothers me enormously (I can't imagine anything worse)"). Finally, patients were asked to make an overall evaluation of the impact of AD on their daily life (no impact, minor impairment, moderate impairment, severe impairment preventing the patient from having a normal life) and their sleep (see Appendix S1). Outcome measures were in line with the Core Outcome Set of the global Harmonising Outcome Measures for Eczema (HOME) initiative (18). Investigators could choose from 4 reasons for baricitinib discontinuation: lack of efficacy, side-effect, patient's willingness, and other (without detailing the reason). Only serious side-effects or side-effects leading to treatment discontinuation were recorded.

Data management and statistical analysis were undertaken using SAS® software (Version 9.4; SAS Institute, Cary, NC, USA). Continuous variables were described by number of observations, number of non-missing observations, mean, standard deviation (SD), range, median and 95% confidence interval (95% CI), if relevant. Categorical variables were described by the frequency and percentage of patients in each category. The groups were compared using Student's *t*-test for normally distributed quantitative variables or non-parametric Wilcoxon test in other cases; the χ^2 test for qualitative variables or Fisher's exact test. Evolutions (including mean EASI score) were evaluated with the Student's *t*-test or Wilcoxon signed-rank test for matched series. All statistical tests were 2-tailed, with a type I error of 5%.

The study was approved by the French National Data Protection Commission and the Committee for the Protection of individuals (CPP Paris X) (19).

RESULTS

Overall, 2,391 patients were included in the OMCCI registry, 524 of whom had moderate-to-severe AD. At the inclusion visit, 88 started baricitinib treatment in 14 centres. Twenty-five patients had been previously treated with dupilumab and 63 had never been treated with a biologic or another JAK inhibitor. The main reason for switching from dupilumab to baricitinib was failure for 14 patients (66.7%), side-effects for 3 (14.3%), patient willingness for 3 (14.3%), and unspecified reason for 5.

Baricitinib initiation

Patient baseline characteristics are summarized in **Table I**. Most patients were affected on several areas of the body (60%), 8% had a head and neck exclusive phenotype and 6.9% had only hand eczema (Table SI). Considering treatment compliance, 22.9% of patients felt

Table I. Patient characteristics and atopic dermatitis (AD) severity at baricitinib initiation

	Non-naïve	Naïve	Total	*p*-value
Patients, *n* (%)	25 (28.4)	63 (71.6)	88	–
Sex; female, *n* (%)	16 (64)	42 (66.7)	58 (65.9)	0.812
Age, years, mean±SD	34.4±16.6	34.5±14.7	34.5±15.2	0.967
Age 18–35 years, *n* (%)	14 (56)	37 (58.7)	51 (58)	
Age >65 years, *n* (%)	2 (8)	4 (6.3)	6 (6.8)	–
Eczema Area and Severity Index score, mean±SD[a]	15.4±9.1	22.8±13.6	20.7±12.9	0.022
Eczema Area and Severity Index score <7, *n* (%)	5 (20)	6 (9.7)	11 (12.6)	0.070
Eczema Area and Severity Index score 7–21, *n* (%)	14 (56)	25 (40)	39 (44.8)	
Eczema Area and Severity Index score ≥21, *n* (%)	6 (24)	31 (50)	37 (42.5)	
Duration of the disease; years, mean±SD	14.3±22.1	12.0±13.7	12.7±16.4	0.584
In the last 6 months, *n* (%)				
Patients who were hospitalized for AD, *n* (%)	0 (0)	4 (6.3)	4 (4.5)	0.574
Patients who had AD flares[a]	18 (72)	49 (79)	67 (77)	0.651
Patients who had AD-related sick-leave[b]	3 (21.4)	12 (34.3)	15 (30.6)	0.502

[a]Missing data = 1; [b]Missing data = 3; Non-naïve: patients who had been previously treated with dupilumab; Naïve: patients who had never been treated with a biologic or another Janus kinase inhibitors.

that they had too many drugs to take; 67.7% reported to be at least frequently fed up with daily treatments (26.4% reporting being continuously fed up), and 22% considered themselves as seriously non-compliant.

In the 6 months preceding the inclusion visit, 77% of patients experienced AD flares, which were described as severe by 61.5%. These flares had a major impact on patients' work, daily living activities, social, family, or personal relationships, and on their self-esteem (**Table II**). Overall, using the NRS (from 0 to 10), AD had a major impact globally on patient QoL parameters with a mean score of 8 for their personal life, 6 for their familial life, and 7 for their professional life. SF-12 results showed substantial impact on both physical (function, health, pain, general state of health, and vitality) and mental (social functioning, emotional health, and mental state) dimensions (Table SII). According to the DLQI, 54.5% of patients experienced "major" or "very high" impact (DLQI > 10). Many patients commented that their condition had interfered with their sleep (often: 19.5%, very often: 23%, continuously: 23%) and that a great deal of time was spent taking care of their skin (often: 30.7%, very often: 10.2%, continuously: 22.7%). In response to the question "When you think about your current skin problem, how troublesome do you consider it?" 49.2% answered "Quite bothersome with some consequences in my daily life" and 42.9% answered "Very bothersome, because it impedes my ability to live normally."

Six to 12 months after baricitinib initiation

After 6 months and 1 year, 65 patients and 47 patients, respectively, were still being treated with baricitinib. Only 1 patient stopped baricitinib after 1 month because of a side-effect (acne), and 3 discontinued due to "patient willingness" after 6 months. For all other patients, the reason for stopping treatment was lack of efficacy.

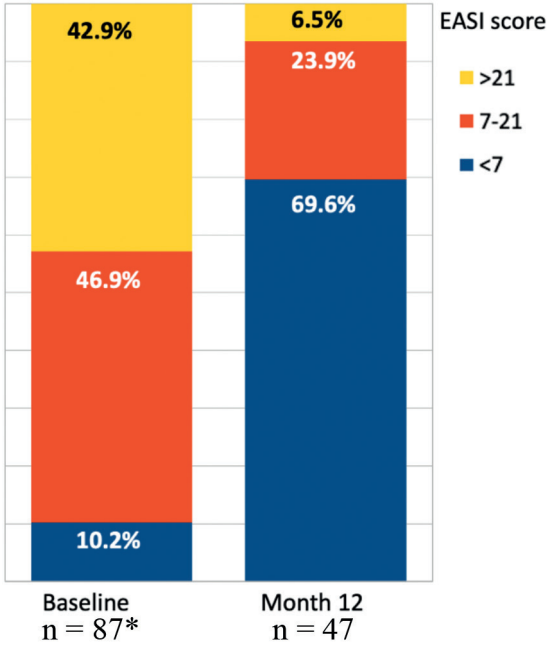

Fig. 1. Percentage of patients with mild/moderate/severe atopic dermatitis at baricitinib initiation and after 12 months of treatment according to the Eczema Area and Severity Index (EASI) score.
*Missing data = 1

After 1 year of follow-up, mean EASI score decreased significantly from 20.7 (95% CI 17.9–23.4) to 6.4 (95% CI 4.1–8.7) ($p<0.001$) and the percentage of patients with severe AD (EASI >21) decreased from 42.9% to 6.5% (**Fig. 1**). Of the patients who were still treated with baricitinib 61.7% achieved a 75% improvement in their baseline EASI score (EASI75) and 40.4% a 90% improvement (EASI90). There was no difference in terms of efficacy whether or not patients were previously treated with dupilumab ($p=0.739$ for EASI75, $p=0.675$ for EASI90).

Table II. Patient perceptions of the impact of the disease on their quality of life at baseline and after 6 and 12 months from baricitinib treatment initiation

	At baricitinib initiation ($n=88$)	After 6 months of baricitinib treatment ($n=65$)	After 1 year of baricitinib treatment ($n=47$)
NRS impact on daily life[a] mean±SD	7.2±1.9[b]	3.4±3.1	3.8±3.2
NRS impact on family life[a] mean±SD	5.5±2.7[b]	2.4±2.9[b]	2.8±3.0
NRS impact on professional life[a] mean±SD	6.7±2.6[a]	2.8±3.1[&]	3.5±3.3[b]
Patients who had AD flares in the last 6 months, *n* (%)*	67 (77)[b]	22 (33.8)	24 (51)
Described as severe by patients	40 (61.5)[c]	7 (33.3)	8 (36.4)
With major impact on daily activities	29 (43.3)	4 (18.2)	9 (39.1)
With major impact on work	29 (44.6)[b]	4 (18.2)	10 (45.5)
With major impact on social, familial, and personal life	28 (41.8)	6 (27.3)	5 (21.7)
SF-12 physical, mean±SD	50.63±7.51[d]	53.26±7.00	53.50±6.45
SF-12 mental, mean±SD	37.84±10.61[d]	44.76±11.93	43.24±12.13
DLQI, mean±SD	11.5±5.9	5.6±6.1	5.6±5.8
Impact on sleep at least frequently, *n* (%)**	57 (65)[b]	13 (20.4)[b]	14 (29.8)
Impact on sleep continuously, *n* (%)**	20 (23)[b]	4 (8.5)b	2 (4.3)

[a]Missing data = 4; [b]Missing data = 1; [c]Missing data = 2; [d]Missing data = 3.
*Assessment of patients' perceptions of the impact of the disease on their daily, familial, and professional life over the week preceding the onsite visit using a numerical rating scale (scale from 0 to 10) with higher scores indicating greater impact (major impact was defined with a score ≥7) (see Appendix S1). **Patients were asked to specify the impact of their eczema on their sleep over the last 7 days, with a predefined choice between "Not concerned/Never/Rarely/Sometimes/Often/Very often/Continuously" (see Appendix S1).
DLQI: Dermatology Life Quality Index; NRS: numerical rating scale (range 0–10); SD: standard deviation; SF: Short-Form Health Survey.

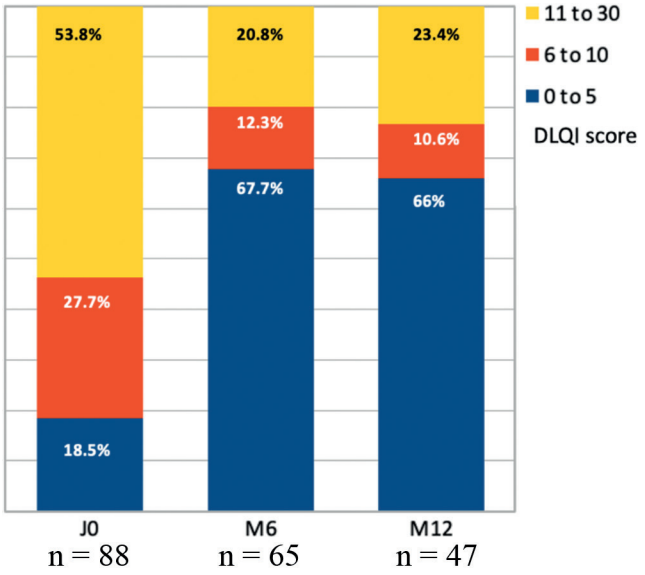

Fig. 2. Dermatology Life Quality Index (DLQI) score at baseline and after 6 months and 12 months of baricitinib treatment. J0: starting of baricitinib treatment; M6: 6 months after starting baricitinib treatment; M12: 12 months after starting baricitinib treatment.

Six months after baricitinib initiation the mean DLQI score decreased significantly from 11.5 (95% CI 10.3–12.8) at baseline to 5.6 (95% CI 4.1–7.1) ($p<0.001$) and remained stable at 5.6 (95% CI 3.9–7.3) 1 year after the inclusion visit (**Fig. 2,** Table II). Twenty percent of patients had a DLQI score >10 at 6 months and 23.4% at 1 year. At inclusion, 4.6% of patients ($n=3$) had a DLQI 0/1 (no impact on patients' life), 33.8% ($n=22$) after 6 months, and 31.9% ($n=15$) at 1 year. Overall AD impact on all patients' QoL also decreased from baseline to 6 months after baricitinib initiation and remained stable at 1 year (**Fig. 3**). In response to the question "When you think about your current skin problem, how troublesome do you consider it?", 21.9% of patients answered "Quite bothersome with some consequences in my daily life" at 6 months and 21.7% after 1 year of follow-up, and 17.2% answered "Very bothersome, because it impedes my ability to live normally" at 6 months and 17.4% after 1 year of follow-up. Of patients who were still being treated with baricitinib after 1 year, 80% were satisfied with their AD treatment.

One year after baricitinib initiation, 22 patients (47.8%) continued treatment and 23 had stopped. The main reason for stopping was "other reason".

DISCUSSION

Data from the OMCCI registry on patients with moderate-to-severe AD who have initiated treatment with baricitinib have already proved very informative as regards the effectiveness and safety of baricitinib. To our knowledge, the current real-world study is the largest to date in terms of the number of patients with a 1-year follow-up. The OMCCI registry captures PROs at inclusion and then every 6 months for 4 years. By focusing on patients' perception of their AD and its long-term impact, the current study differs from other published studies centred on treatment efficacy or safety.

Available data for the treatment of AD with baricitinib are largely derived from clinical trials. This may lead to potential biases related to the inclusion and exclusion criteria of these trials and the risk of under-representation of at-risk patients or those with comorbidities; significant differences may also be seen between efficacy in clinical trials vs daily practice (20, 21). In baricitinib phase III studies, more patients achieved an EASI75 score in the baricitinib 4 mg and 2 mg arms compared with placebo. Significant improvements were also observed as early

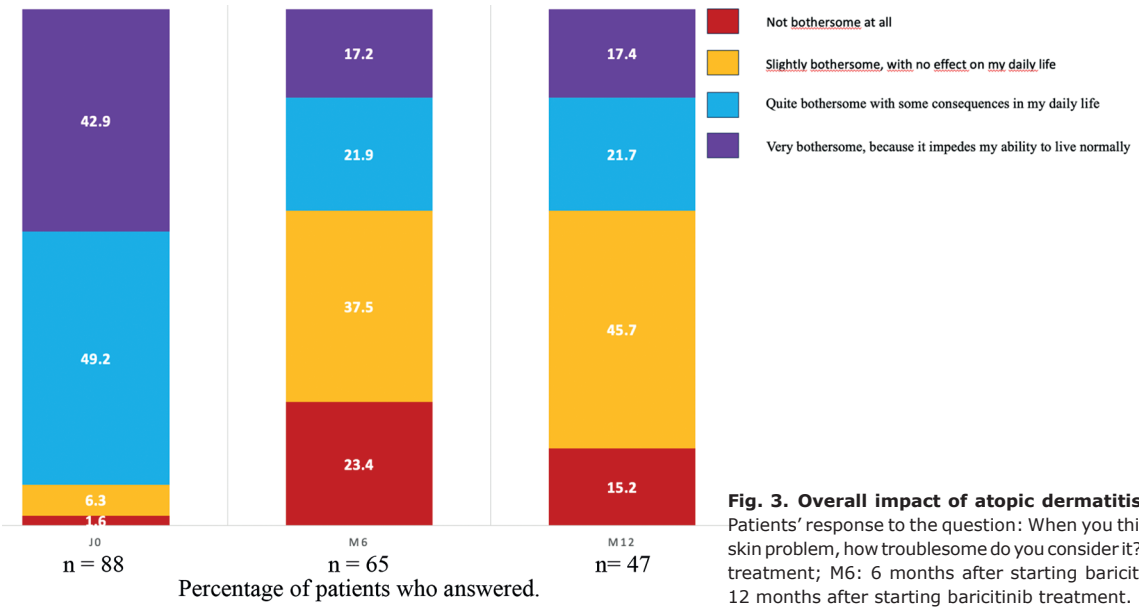

Fig. 3. Overall impact of atopic dermatitis on patients' lives. Patients' response to the question: When you think about your current skin problem, how troublesome do you consider it? J0: starting baricitinib treatment; M6: 6 months after starting baricitinib treatment; M12: 12 months after starting baricitinib treatment.

as Week 1 in terms of pruritus, night-time awakenings, skin pain, DLQI, and Patient-Oriented Eczema Measure (POEM) (5, 6).

Very few studies evaluating the real-world use of baricitinib have been published to date (10–14). The first series, published in 2022 by Rogner et al. (10), concerned 12 German patients who were followed for up to 3 months (13). Hagino et al. analysed data from 36 Japanese patients during a 12-week period. Vittrup et al. (11) recently published short-term real-world experience in Danish adults (44 patients with follow-up to Week 16). Finally, data from the Dutch Bio-Day registry (51 patients) evaluated the efficacy and tolerability of baricitinib in daily practice after 16 weeks of treatment (14).

In the current study, after 1 year of follow-up, only 1 patient stopped baricitinib treatment because of a side-effect (acne). In clinical trials, the most frequently reported side-effects with baricitinib were infections, acne, and gastrointestinal disorders (5–9). In January 2023, the European Medicines Agency endorsed measures recommended by the Pharmacovigilance Risk Assessment Committee (PRAC) to minimize the risk of serious side-effects, including cardiovascular conditions, venous thromboembolism, cancer, and serious infections, in patients receiving JAK inhibitors. As in baricitinib clinical trials (22) and other real-life studies (10–13, 23), we did not observe these specific side-effects in the current study.

The need for real-life data is not only crucial for these safety elements, but is also important when evaluating efficacy. Previous treatment with dupilumab was one of the exclusion criteria for clinical trials of baricitinib. Very few data are thus available concerning this subgroup of patients who had an insufficient response or safety issues with dupilumab before starting baricitinib treatment. In the current study, 25 patients were in this category. The current study did not observe any difference between this subgroup of patients and patients who were dupilumab-naïve before starting baricitinib. This result is consistent with the Bio-Day registry data (14). In the current study, 65 patients were still being treated with baricitinib at 6 months and 47 at 12 months, representing a maintenance rate of 76% at 6 months and 53% at 1 year. This is higher than the Bio-Day data, where 53.7% of patients maintained baricitinib treatment at Week 16, but is lower than in the monocentric German series where only 1 of 12 patients had stopped treatment due to inefficiency.

In randomized phase 3 studies, 24.8% of patients achieved an EASI75 and 16% an EASI90 after 16 weeks of treatment with baricitinib 4 mg monotherapy. When using rescue topical corticosteroids (which reflects daily practice), this percentage increased to 36% and 20% for EASI75 and EASI90, respectively (5). EASI scores at 1 year were available for 46 of the 47 patients still receiving baricitinib treatment; 29 patients achieved EASI75 and 19 EASI90. For the EASI75 score, this represented 61.7% (29/47) of patients still being treated with baricitinib and 32.9% (29/88) of all patients since the inclusion visit. For the EASI90 score, this represented 40.4% (19/47) of patients still being treated with baricitinib and 21.6% (19/88) of all patients since the inclusion visit. Our real-life data at 1 year therefore align very closely with data from the phase III studies at 16 weeks.

The patients included in the OMCCI registry were heavily impacted by their AD. Their initial characteristics and PROs reflect the extent of their disease and the high burden it can impose. AD is much more than a simple skin disease and can impact on many aspects of a patient's life. Not surprisingly, the clinical improvement in EASI score with baricitinib, with nearly 7 out of 10 patients achieving an EASI score <7 after 1 year of treatment, was coupled with a clear improvement in most PROs. Decreases were seen in DLQI score and overall impact on family, personal and professional life, and an increase was seen in the proportion of patients who felt little or not at all negatively affected by their AD. Notably, PRO data obtained after 12 months of treatment with baricitinib were almost identical to those obtained 6 months earlier, which suggests the sustained efficacy of treatment in patients who were initially good responders. However, despite a clinical improvement in patients' AD with baricitinib, only 31.9% of patients achieved a DLQI 0/1 score and 39.1% were still impacted in their daily life after 1 year of treatment, which may reflect the long-term burden of this disease.

The current results are strengthened by the diversity of the participating centres (university/general/private hospitals and independent practitioners), which improves the representation of the enrolled patients. Very few missing data were observed. However, this study has some limitations. There is a potential positive selection bias, as most patients who experienced ineffectiveness stopped the treatment after 6 and 12 months. Dupilumab marked a real breakthrough for the treatment of moderate-to-severe AD and was, for a certain period, the only treatment available to us. Baricitinib was the second available treatment. Therefore, for several months, only these 2 treatments were available for moderate-to-severe AD in patients who failed treatment or had a contraindication to cyclosporine. Thus, the high maintenance rate can be partially explained by the absence of other therapeutic alternatives in clinical practice, even in cases of partial efficacy. In the Japanese series, Higano et al. concluded that a high baseline EASI of the lower limbs might predict good treatment response at Week 12, while high baseline EASI of the head and neck might predict poor treatment response at Week 4 (10). In the current study some patients were very good responders (achieving EASI90) and experienced sustained efficacy. However, we were not able to characterize this subgroup of good long-term responders (based on AD location and/or initial severity) more precisely due to a lack of power in

the current study. Finally, only 2 follow-up time-points were planned (6 and 12 months after inclusion) in this first analysis. Longer follow-up will be analysed during the 4-year planned follow-up of the OMCCI registry.

After Visit 3 (corresponding to 1 year after baricitinib initiation), 22 patients (47.8%) continued baricitinib and 23 stopped treatment. The main reason for stopping was stated as "other reason" by investigators. The case report form of the registry did not allow us to record more details. Nevertheless, after interviewing some investigators, it seems that baricitinib was sometimes stopped even in patients in whom it was effective and well tolerated after PRAC recommendations.

The daily life data of the current study highlight the good benefit–risk profile of baricitinib, which has proved to be an effective and well-tolerated treatment for patients with moderate-to-severe AD, including patients for whom previous treatment with dupilumab has failed. The clinical improvement in AD symptoms was associated with a great impact on several facets of patients' QoL, which was maintained after 1 year of treatment. Long-term evaluation of the changes brought by baricitinib on the evolution of patients' lives and on AD clinical manifestations will be studied prospectively during the 4-year follow-up of the OMCCI registry.

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The study was approved by the National Data Protection Commission ("Commission Nationale de l'Informatique et des Libertés") and the Committee for the Protection of individuals (CPP Paris X).

Patients providing data for this manuscript gave oral informed consent to the publication of their case details in line with revised French Research Standard MR003.

Conflicts of interest: ZR has received consulting fees and honoraria from: Abbvie, Almirall, Amgen, Avene, BMS, Celgene, GSK, Janssen-Cilag, Leo-Pharma, Lilly, Medac, MSD, Novartis, Pierre Fabre Dermatologie, Pfizer, UCB, Sanofi. Investigator for: AbbVie, Actelion, Almirall, Amgen, Bayer, Boehringer-Ingelheim, BMS, Forward Pharma, GSK, Galderma, Genentec, Incyte, Janssen Cilag, Leo-Pharma, Novartis, Pfizer, Roche, Regeneron, UCB, Sanofi. PAB has received consultant and/or member of boards and/or speaker fees from: AbbVie, Amgen, Boehringer-Ingelheim, Bristol-Myers-Squibb, Celgene, Janssen, Léo-pharma, Lilly, Novartis, Pfizer, Sanofi, UCB. JLP has received consultant fees from: Sanofi, Lilly, Leo, Pharma, Pfizer. A-CF has received speaker, consultant or investigator fees from: AbbVie, Leo-Pharma, Lilly, Pfizer, Sanofi. EB: Lilly, AbbVie, UCB, Novartis, Sanofi, Janssen. CB: AbbVie, Janssen, Leo Pharma, Novartis, Sanofi, UCB, Lilly, Almirall. CF: AbbVie, Sanofi, Janssen, UCB, Novartis, Almirall, Lilly. IZ: AbbVie, Novatis, Lilly, Leo, Sanofi, UCB, Janssen, Almirall. DL-D: AbbVie, Almirall, Janssen, Leo Pharma, Lilly, Sanofi, UCB. A-LL: Novartis, Janssen, UCB, AbbVie. JP: Leo, Amgen, UCB, Almirall, Janssen, AbbVie, Novartis, Medac, Lilly, Sanofi. NQ-T: AbbVie, Amgen, BMS, Janssen Cilag, Léo Pharma, Lilly, Novartis. FM has received consulting fees from: Almirall, AbbVie, Leo Pharma, Lilly, Pfizer, Sanofi. GC: Abbvie, Pfizer, Janssen, UCB. CP and LD have no conflicts of interest to declare.

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