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LETTER TO THE EDITOR

Successful response of upadacitinib in different clinical phenotypes of atopic dermatitis

Dear Editor,

Adult atopic dermatitis (AD), specifically late-onset phenotypes, is characterized by a notable degree of clinical heterogeneity in terms of morphologic and topographic characteristics.[1–4] Alongside the classic flexural AD presentation, adult patients can manifest other less common phenotypes, including prurigo nodularis-like, nummular eczema and generalized/erythrodermic,[2] that may exhibit variations in immune and skin barrier proteins with potential influence on topical and systemic therapies' efficacy.[5] Upadacitinib, a JAK 1 inhibitor indicated for treatment of patients aged ≥12 years with moderate-to-severe AD, has shown good short- and long-term efficacy and a favourable safety profile both in randomized clinical trials and real-world studies.[6–8] However, the effectiveness of upadacitinib in distinct AD clinical phenotypes has not been investigated.

We performed a multicentre retrospective study on adult patients with moderate/severe AD treated with upadacitinib recruited from October 2020 to September 2022 at seven Italian university hospitals. The objective of our study was to characterize the effectiveness of upadacitinib in the most prevalent clinical AD phenotypes, including flexural, prurigo nodularis-like, nummular eczema and erythrodermic, with a view towards identifying clinical predictors of treatment response.

A total of 245 adult patients, 105 women and 140 men with a mean age of 35.9 years (SD ±13.9), with moderate-to-severe AD were included in the study. Table 1 illustrates patients' demographic and clinical characteristics. A significant reduction of mean Eczema Area and Severity Index (EASI) score (from 22.1 ± 13.3 to 2.6 ± 4.4, $p < 0.0001$) as well as an improvement of Worst Pruritus (WP)-Numeric Rating Scale (NRS) and Dermatology Life Quality Index (DLQI) were observed at week 16 and were then maintained throughout the 52 weeks of treatment (Table 1). By week 16, 84.2%, 65.2% and 40.8% of patients achieved EASI75, 90 and 100, respectively, with sustaining response throughout 12 months of treatment. In addition, at week 16, a significant improvement (≥4 point) of WP-NRS, NRS-sleep and DLQI 0/1 were recorded for 74.8%, 78.2% and 53.3% of patients, respectively, with slight improvement thereafter (Table 1, $p < 0.0001$ for each time point from baseline). Disease phenotype did not affect the likelihood of achieving a good or optimal clinical response as evidenced by a similar proportion of patients reaching EASI75/90/100 throughout the study period among each phenotype (Table 2). We also sought to identify clinical variables influencing the likelihood of achieving a minimal disease activity (MDA) after 16 weeks of treatment, as defined by a recent international consensus (EASI90 plus absolute WP-NRS ≤ 1).[9] The multivariable analysis highlighted that the erythrodermic AD phenotype was associated with a 78% reduced likelihood of achieving MDA at week 16 (OR = 0.22, 95% CI = 0.08–0.63, $p = 0.005$), regardless of the age at treatment initiation and disease severity (EASI) at baseline (Prob > $chi^2 = 0.030$, Number of observations = 154), underlying the challenge of attaining such an optimal outcome in this severely debilitating phenotype. Recently, a multicentre real-world experience including 221 moderate/severe AD patients, described a good and comparable clinical response of dupilumab in six different clinical phenotypes after 16 and 52 weeks of treatment, thus supporting the central role of IL-4 and IL-13 across different clinical phenotypes.[10] It should be noted, however, that the aforementioned study is limited by the absence of a comprehensive efficacy analysis including more stringent end points such as EASI 90/100 and MDA. In conclusion, the present study confirms that upadacitinib, due to its broad cytokine inhibitory spectrum, can be an effective and safe option for the treatment of a significant proportion of AD patients across different clinical phenotypes, with no notable differences in the extent of clinical response. We recognise the retrospective nature of the study as a limitation, along with the relatively small number of non-classic AD phenotype included in the analysis.

TABLE 1 Clinical and demographic characteristics of patients and disease, with a focus on upadacitinib efficacy throughout different time points.

Overall population	*N* tot = 245 patients[a], *n* (%)
Males	152 (62)
Age (mean ± SD)	35.9 ± 13.9
Atopic comorbidities (*N*[b] tot = 233)	126 (54.1)
Allergic rhinitis	78 (33.5)
Allergic asthma	67 (28.8)
Allergic conjunctivitis	78 (33.5)
Early onset (<18 years old)	168 (69.4)
Late onset (≥18 years old)	74 (30.6)
Flexural phenotype	179 (74.0)
Nummular eczema	26 (10.7)
Erythrodermic AD	27 (11.2)
Prurigo nodularis-like AD	10 (4.1)
Head and neck involvement *N* tot = 233	206 (84.4)
Hand involvement *N* tot = 240	147 (45.0)
Genital involvement *N* tot = 240	61 (25.4)
Patients previously treated with SCS	202 (84.4)
Patients previously treated with CsA	185 (75.5)
Previous treatment with dupilumab	173 (70.6)

Response end points	Week 0	Week 16 (*N* tot = 184)[b]	Week 52 (*N* tot = 126)[b]
EASI (mean ± SD)[c]	22.1 (13.3)	2.6 (4.4)	2.6 (4.9)
WP-NRS (mean ± SD)[c]	7.5 (2.4)	2.0 (2.4)	1.9 (2.5)
NRS-sleep (mean ± SD)[c]	5.5 (3.6)	1.2 (2.1)	1.1 (4.2)
DLQI (mean ± SD)[c]	15.3 (8.3)	3.1 (4.1)	3.0 (5.2)
EASI75, *n* (%)		155 (84.2)	108 (85.7)
EASI90, *n* (%)		120 (65.2)	89 (70.6)
EASI100, *n* (%)		75 (40.8)	43 (34.1)
NRS-itch reduction, ≥4 point, *n* (%)		166 (74.8)	96 (73.9)
DLQI reduction, ≥4 point, *n* (%)		169 (78.2)	105 (82.0)
DLQI, 0/1, *n* (%)		98 (53.3)	77 (60.2)

Note: Clinical response was assessed at 16, 32 and 52 weeks during treatment using the following tools: Eczema Area and Severity Index (EASI), ranging from 0 to 72 points; Worst Pruritus (WP) Numeric Rating Scale (NRS), a 0–10 scale used to quantify the worst pruritus experienced by the subject in the past 24 h; NRS-sleep, ranging from 0 to 10 points and evaluating the sleep impairment in the last 24 h; and Dermatology Life Quality Index (DLQI), ranging from 0 to 30 points.

Abbreviations: CsA, cyclosporine A; SCS, systemic corticosteroids.

[a]The sum does not always matched the total due to missing data.

[b]The reduction in the number of patients at each follow-up visit was due to the fact that patients started treatment at different times and that not all patients had completed 12 months of treatment by the time of the present study. The discontinuation rate was low, with 6.9% (17/245) of patients ceasing treatment at week 16, 3.8% (7/182) at week 32 and 11.45% (15/131) at week 52. Adverse events were the most common reason for discontinuation, accounting for 45.8% and 50% of cases at 6 and 12 months of treatment, respectively, with the most frequently reported being thrombosis, paraesthesia/tremor, hypertrichosis, nausea and fatigue, proteinuria and creatine phosphokinase elevation.

[c]Paired *t* test for the comparison between baseline and subsequent time points shows $p < 0.0001$.

TABLE 2 Clinical efficacy in terms of achieving EASI 75, 90 and 100 in the four different clinical phenotypes of AD.

	Flexural phenotype, *n* (%)	Prurigo nodularis, *n* (%)	Nummular eczema, *n* (%)	Erythrodermic AD, *n* (%)
Week 16 (*N* = 184 pts)				
EASI 75	116 (84.7)	5 (100)	16 (88.9)	18 (75.0)
EASI 90	91 (66.4)	2 (40.0)	14 (77.8)	13 (54.2)
EASI 100	60 (43.8)	2 (40.0)	6 (33.3)	7 (29.2)
Week 32 (*N* = 171 pts)				
EASI 75	113 (89.0)	4 (80.0)	15 (88.2)	17 (77.3)
EASI 90	85 (68.2)	3 (75.0)	10 (58.8)	15 (68.1)
EASI 100	47 (37.0)	0 (0.0)	6 (29.6)	9 (40.9)
Week 52 (*N* = 126)				
EASI 75	82 (87.2)	3 (100.0)	9 (81.8)	14 (77.8)
EASI 90	70 (74.5)	2 (66.7)	8 (72.7)	9 (50.0)
EASI 100	31 (32.9)	1 (33.3)	5 (45.5)	6 (33.3)

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CONFLICT OF INTEREST STATEMENT

Outside of the submitted work, the authors declare the following conflicts of interest: **Niccolò Gori** served as advisory board member and received honoraria for lectures for AbbVie, Sanofi and Leo-Pharma. **Andrea Chiricozzi** has served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Boehringer-Ingelheim, Bristol Myers Squibb, Leo Pharma, Lilly, Janssen, Novartis, Pfizer and Sanofi Genzyme. **Angelo Valerio Marzano** reports consultancy/advisory boards disease-relevant honoraria from AbbVie, Amgen, Boehringer-Ingelheim, Bristol Myers Squibb, Incyte, Leopharma, Novartis, Pfizer, Sanofi and UCB. **Giampiero Girolomoni** has received personal fees from AbbVie, Almirall, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli-Lilly, Leo Pharma, Merck Serono, Novartis, Pfizer, Pierre Fabre, Samsung Bioepis and Sanofi. **Silvia Mariel Ferrucci** served as advisory board member, principal investigator in clinical trials and speaker for Almirall, AbbVie, Amgen, Leo Pharma, Galderma, Elli Lilly, Novartis, Pfizer and Sanofi. **Maria Concetta Fargnoli** has served on advisory boards, received honoraria for lectures and/or research grants from AMGEN, Almirall, AbbVie, Boehringer-Ingelheim, BMS, Galderma, Kyowa Kyrin, Incyte, LEO Pharma, Pierre Fabre, UCB, Lilly, Pfizer, Janssen, MSD, Novartis, Sanofi, Regeneron and Sun Pharma. **Marco Galluzzo** has acted as a speaker and/or consultant for AbbVie, Almirall, Eli-Lilly, Janssen-Cilag, LeoPharma, Novartis and Sanofi outside the submitted work. **Maria Esposito** has served as speaker/consultant for AbbVie, Amgen, Almirall, Eli Lilly, Janssen, Leopharma, Novartis, Pfizer, Sanofi and UCB. **Ketty Peris** has served on advisory board and received honoraria for lectures from Abbvie, Almirall, Lilly, Galderma, Leo Pharma, Pierre Fabre, Philogen, Novartis, Sanofi, Sun Pharma and Janssen. The other authors have no competing interests to declare.

DATA AVAILABILITY STATEMENT

Enquiries related to the data generated or analysed during this study can be directed to the corresponding author.

ETHICAL APPROVAL

Approval of this study was obtained by the Local Ethics Committee—Comitato Etico Territoriale (CET) Lazio Area 3, Prot. ID: 5909.

ETHICS STATEMENT

The patients included in this study have given written informed consent to publication of their case details.

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REFERENCES

1. Gori N, Chiricozzi A, Marsili F, Ferrucci SM, Amerio P, Battarra V, et al. National Information Campaign Revealed Disease Characteristic and burden in adult patients suffering from atopic dermatitis. J Clin Med. 2022;11(17):5204.
2. Silvestre Salvador JF, Romero-Pérez D, Encabo-Durán B. Atopic dermatitis in adults: a diagnostic challenge. J Invest Allergol Clin Immunol. 2017;27(2):78–88.
3. Girolomoni G, de Bruin-Weller M, Aoki V, Kabashima K, Deleuran M, Puig L, et al. Nomenclature and clinical phenotypes of atopic dermatitis. Ther Adv Chronic Dis. 2021;12:20406223211002979.
4. Bosma AL, Ascott A, Iskandar R, Farquhar K, Matthewman J, Langendam MW, et al. Classifying atopic dermatitis: a systematic review of phenotypes and associated characteristics. J Eur Acad Dermatol Venereol. 2022;36(6):807–19.
5. Czarnowicki T, He H, Krueger JG, Guttman-Yassky E, Czarnowicki T, He H, et al. Atopic dermatitis endotypes and implications for targeted therapeutics. J Allergy Clin Immunol. 2019;143(1):1–11.
6. Thyssen JP, Thaçi D, Bieber T, Gooderham M, de Bruin-Weller M, Soong W, et al. Upadacitinib for moderate-to-severe atopic dermatitis: stratified analysis from three randomized phase 3 trials by key baseline characteristics. J Eur Acad Dermatol Venereol. 2023;37(9):1871–80.
7. Chiricozzi A, Ortoncelli M, Schena D, Gori N, Ferrucci SM, Babino G, et al. Long-term effectiveness and safety of Upadacitinib for atopic dermatitis in a real-world setting: an interim analysis through 48 weeks of observation. Am J Clin Dermatol. 2023;24(6):953–61.
8. Schlösser AR, Boeijink N, Olydam J, Nijsten TEC, Hijnen D. Upadacitinib treatment in a real-world difficult-to-treat atopic dermatitis patient cohort. J Eur Acad Dermatol Venereol. 2024;38(2):384–92.
9. Silverberg JI, Gooderham M, Katoh N, Aoki V, Pink AE, Binamer Y, et al. Combining treat-to-target principles and shared decision-making: international expert consensus-based recommendations with a novel concept for minimal disease activity criteria in atopic dermatitis. J Eur Acad Dermatol Venereol. 2024;38(11):2139–48.
10. Tavecchio S, Angileri L, Pozzo Giuffrida F, Germiniasi F, Marzano AV, Ferrucci S. Efficacy of Dupilumab on different phenotypes of atopic dermatitis: one-year experience of 221 patients. J Clin Med. 2020;9(9):2684.