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BRIEF REPORT

Real-Life Effectiveness and Safety of Upadacitinib in Adults and Adolescents with Moderate-to-Severe Atopic Dermatitis: A Single-Center 16-Week Study

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ABSTRACT

Introduction: The treatment of severe atopic dermatitis (AD) includes cyclosporine and recently approved biologics and small molecules. Among these, upadacitinib is a selective inhibitor of Janus kinase 1, approved for the treatment of severe AD in adolescents/adults. Upadacitinib has shown efficacy and safety in several phase 3 clinical trials, but data on real-life patients are still lacking.

Methods: We conducted a retrospective real-life observational study to evaluate the effectiveness and safety of upadacitinib up to week 16 in a cohort of both bio-naïve and bio-experienced patients. This study was carried out by analyzing the AD database records of an Italian referral hospital. Thirty-eight patients were included in this study, and 35 completed 16 weeks of treatment.

Results: At week 16, out of 35 patients, the percentages of Eczema Area and Severity Index (EASI) 50, EASI 75, EASI 90 and EASI 100 responses were 94.29, 91.43, 74.29, and 60%, respectively. A decrease of at least 4 points from baseline of itch-NRS was reported by 94.74 and 91.43% of patients at weeks 8 and 16. Regarding the safety of upadacitinib, 26.32% of patients experienced at least one adverse event (AE), and a total of 13 AEs were recorded, including blood test abnormalities and papulopustular acne. None of our patients interrupted the drug because of an AE.

Conclusions: We observed higher rates of EASI75/EASI90/EASI100 responses at week 16, compared with data from clinical trials. The safety profile of upadacitinib was favorable, as no AEs leading to discontinuation were experienced by our patients up to week 16.

Keywords: Atopic dermatitis; Eczema; JAK inhibitors; Real-life; Therapy; Upadacitinib

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Key Summary Points

The efficacy and safety of upadacitinib have been assessed in multiple clinical trials, but data on real-life patients are limited.

We conducted a retrospective observational real-life study to assess further the effectiveness and safety profiles of upadacitinib in patients affected by moderate-to-severe atopic dermatitis.

In our experience, we observed higher rates of EASI 75, EASI 90 and EASI 100 responses at week 16 compared with data from clinical trials.

Our findings, although limited, highlight the high effectiveness of upadacitinib in patients naïve to biological drugs, suggesting a role of upadacitinib as a first choice in adults who failed cyclosporine.

INTRODUCTION

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases, affecting up to 4.9% of the adult population worldwide [1]. From a clinical point of view, atopic dermatitis is characterized by recurrent eczematous skin lesions, intense itch, and a chronic-relapsing course [2]. AD can present along with other atopic-related comorbidities, including conjunctivitis, asthma, allergic rhinitis, and food allergy, but it can also be associated with other immune-mediated diseases, including inflammatory bowel disease, arthritis, and psychological disease [3]. The impact of AD on patients may be profound, significantly affecting their quality of life, leading to sleep loss, anxiety and depression [4].

According to the most recent guidelines [5, 6], systemic drugs should be used to treat moderate-to-severe cases. Conventional immunosuppressive drugs, including cyclosporine, have limited efficacy and present a high risk of adverse events leading to discontinuation [7]. A better understanding of the pathogenesis of AD has led in the last 5 years to the development of new drugs with different mechanisms of action [8]. Dupilumab, a monoclonal antibody that targets the alpha subunit of the interleukin (IL)-4 receptor, blocking both IL-4 and IL-13 signaling, is currently approved for the treatment of AD in both adults and adolescents/children who are candidates for systemic treatment [9]. According to the 2022 European Guidelines, Janus kinase (JAK) inhibitors are also recommended in AD patients who are candidates for systemic treatment. Upadacitinib, a selective JAK inhibitor, which predominantly targets JAK1 [10, 11], has been recently approved for the treatment of moderate-to-severe AD in both adults and adolescents across two different dosages (15 and 30 mg) after being evaluated in multiple phase 3 clinical trials, showing superiority compared with placebo and dupilumab at week 16 [12–14]. In two replicate multicenter phase 3 clinical trials, Measure Up 1 and Measure Up 2, patients treated with upadacitinib in monotherapy achieved higher EASI-75 responses (75% reduction in EASI, Eczema Area and Severity Index) compared with placebo at week 16. In Measure Up 1, at week 16, an EASI-75 response was achieved by 70% of patients receiving upadacitinib 15 mg, 80% in the upadacitinib 30 mg group, compared with 16% of those treated with placebo [12]. Similar rates were observed in Measure Up 2 (60% in upadacitinib 15 mg group, 73% in upadacitinib 30 mg group, and 13% in placebo group) [12].

However, data on the effectiveness and safety of upadacitinib in a real-life setting are lacking, as only limited experiences are currently available [15]. We conducted a single-center study to evaluate the short-term effectiveness and safety of upadacitinib in 38 patients with moderate-to-severe AD.

METHODS

This non-interventional retrospective study was carried out by analyzing the AD database records of IRCCS Humanitas Research Hospital – Rozzano (Milan) between March and September 2022. Thirty-eight patients were included in this study. Patient eligibility for upadacitinib treatment was assessed in accordance with the most recent European guidelines on the systemic treatment of atopic dermatitis in adults and adolescents [5, 6].

All patients received upadacitinib, 15 mg or 30 mg daily, according to the summary of product characteristics [16]. They had inadequate response or intolerance or contraindications to treatment with cyclosporine. According to the Italian Medical Agency (named AIFA), the use of either 15 mg or 30 mg is based on the physician's decision. In our experience, patients aged between 12 and 18 years old and elderly people (> 65 years old) received upadacitinib 15 mg, one capsule daily, while all the other patients received 30 mg daily. Before starting upadacitinib, a wash-out period of at least 4 weeks was recommended in patients using systemic treatments for atopic dermatitis.

Patient characteristics, comorbidities, previous treatments, and the EASI (Eczema Area and Severity Index) and IGA (Investigator Global Assessment) scores at each visit (baseline, week 8, and week 16) were retrieved from the electronic medical records. Per our routine clinical practice, patients were seen every 2 months (8 weeks). In addition, itch-NRS (Numerical Rating Scale) score, sleep-NRS score and DLQI (Dermatology Life Quality Index) were also reported at each visit. The effectiveness of upadacitinib was evaluated at each time point by assessing the percentages of patients achieving 50, 75, 90, and 100% (EASI 50, EASI 75, EASI 90, and EASI 100) improvement in EASI with respect to baseline EASI. Moreover, we evaluated the proportion of patients reaching an IGA score of 0/1 (clear or almost clear). At weeks 8 and 16, we also evaluated the percentages of patients achieving an absolute EASI score ≤ 7, a reduction of at least 4 points in the absolute itch-NRS score, an absolute itch-NRS ≤ 4, an absolute DLQI score of 0/1 (no impact on quality of life). Effectiveness endpoints were selected according to those analyzed in pivotal phase 3 clinical trials Measure Up 1 and Measure Up 2 [12]. Previous use, or not, of dupilumab before starting upadacitinib was recorded, along with the reason for discontinuation.

Safety was evaluated according to reported adverse events (AEs), including serious AEs, AEs leading to discontinuation, AEs requiring dosage modification, laboratory values (hematology, clinical chemistry, and urinalysis) and physical examination. Serious adverse events were defined as AEs that result in death, require either inpatient hospitalization or the prolongation of hospitalization, are life-threatening, result in a persistent or significant disability/incapacity, or result in a congenital anomaly/birth defect [17]. The occurrence of AEs was collected at weeks 8 and 16. As patient recruitment took place over a 7-month period from March to September 2022, not all the patients were seen for a full 16 weeks. Data for any follow-up visits they had not yet attended were deemed missing.

Institutional review board approval was exempted, as the study protocol did not deviate from standard clinical practice. All patients received upadacitinib as in good clinical practice, in accordance with European guidelines. For some of the patients, AbbVie provided the drug upadacitinib through a Compassionate Use Program activated according to the DM 7/9/2017. All included patients provided written consent for retrospective study of data collected during routine clinical practice (demographics, clinical scores). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Data collection and handling complied with applicable laws, regulations, and guidance regarding patient protection, including patient privacy.

Statistical analysis was guided by the intention-to-treat principle, with the full analysis set being 38 patients treated with upadacitinib. Microsoft Excel software was used for analysis and to generate tables. Continuous parameters were reported using frequency, mean, and standard deviation (SD) values. Discrete parameters were reported as count and

percentage. Mean EASI and the percentage of patients achieving an absolute EASI ≤ 7 and EASI75, EASI90, and EASI100 responses with upadacitinib treatment were examined in relation to previous exposure to dupilumab. The categorical variables were analyzed using the chi-square test. The continuous variables were analyzed by with Student's *t* test and the Mann–Whitney *U* test if the parametric test assumption were not met.

Statistical significance was defined as a probability value (*p* value) of less than 0.05.

RESULTS

A total of 38 patients were recruited to this study. All of them completed at least 8 weeks of treatment, with 35 patients reaching week 16.

Regarding the patients' gender, 20 (52.63%) were males, with a mean age of 41.53 (SD 16.56). Twenty-three patients (60.53%) had a history of atopic dermatitis since childhood/adolescence, while the other 15 (39.47%) had an adult onset of atopic dermatitis. The mean disease duration was of 19.58 years (SD 14.55). Thirty-three were previously treated with cyclosporine, experiencing partial remission or intolerance. The other patients did not receive cyclosporine because of concomitant arterial hypertension. Thirty-five patients had also received multiple courses of systemic corticosteroids in the past. A total of 22 patients (57.89%) had previously received dupilumab: all of them discontinued dupilumab because of inefficacy, with one patient also experiencing a severe conjunctivitis, unresponsive to topical corticosteroids. A total of 21 patients (55.26%) had an anamnesis of at least one other systemic disease, with seven (18.42%) having at least one atopy-related comorbidity. Five patients (13.16%) also had a diagnosis of asthma, five (13.16%) were affected by arterial hypertension, four had an allergic rhinitis (10.53%), three had alterations of the thyroid function (7.89%), and two (5.26%) also had an allergic conjunctivitis. The demographic characteristics of our population at baseline are summarized in Table 1.

The mean absolute EASI scores at baseline and weeks 8 and 16 are summarized in Fig. 1.

Table 1 Demographic characteristics and disease severity scores at baseline of our population

Number of patients	38
Male	20/38 (52.63%)
Age (years)	41.53 SD 16.56
Adult onset	15 (39.47%)
Mean disease duration	19.58 SD 14.55
Comorbidity	21/38 (55.26%)
Atopic comorbidities	7/38 (18.42%)
Previous exposure to cyclosporine	33/38 (86.84%)
Previous exposure to systemic corticosteroids	35/38 (92.11%)
Previous exposure to dupilumab	22/38 (57.89%)
Mean EASI at baseline	17.48 (SD 4.69)
Mean IGA at baseline	3.61 (SD 0.50)
Mean DLQI at baseline	15.82 (SD 5.38)
Mean Itch-NRS at baseline	8.42 (SD 1.24)

DLQI Dermatology Life Quality Index, *NRS* Numerical Rating Scale, *IGA* Investigator Global Assessment, *EASI* Eczema Area and Severity Index

Twenty-six patients (68.42%) received 30 mg of upadacitinib per day, while 12 (31.58%) started with 15 mg daily. Over the course of the study, our patients saw their absolute EASI scores decrease from a mean (SD) of 17.48 (4.69) at baseline to 2.56 (3.32) at week 8 and 1.45 (3.11) at week 16. Regarding the IGA score, at baseline, all patients had an IGA ≥ 3, with a mean IGA of 3.61 (SD 0.50); at week 8 mean IGA was 0.87 (SD 0.96), and at week 16, it was 0.51 (SD 0.74). An IGA score of 0/1 (clear or almost clear) was

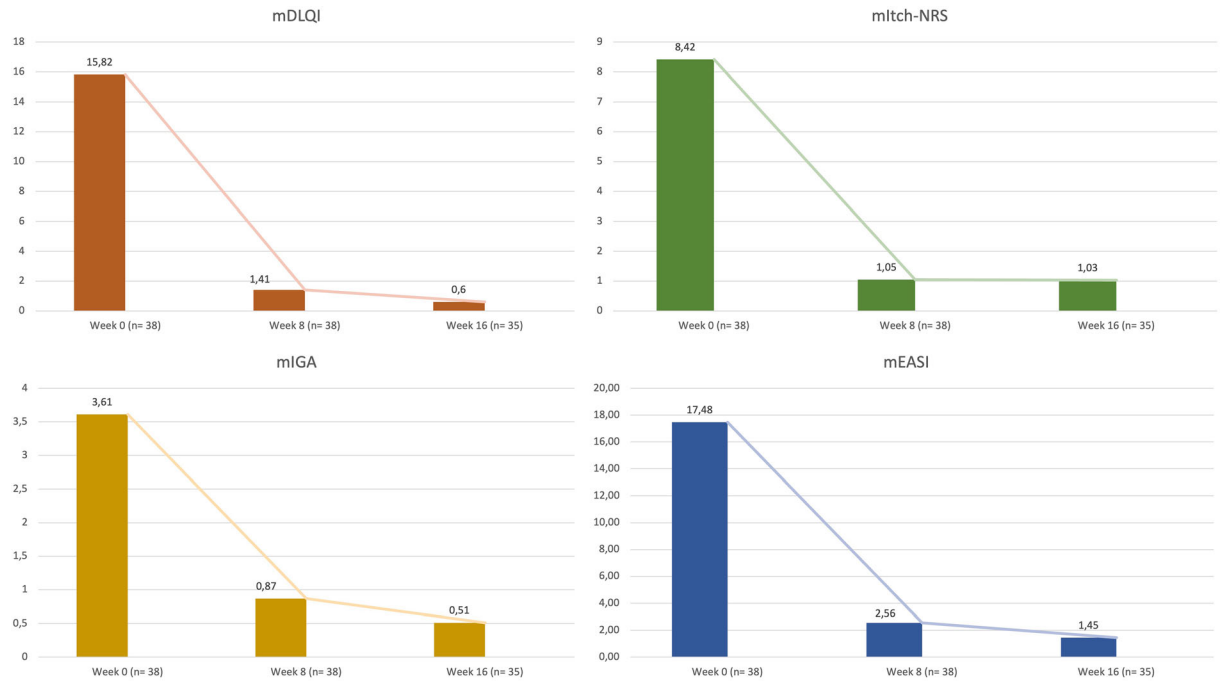

Fig. 1 Mean DLQI, itch-NRS, IGA, and EASI scores of our population at baseline, week 8 and week 16. *DLQI* Dermatology Life Quality Index, *NRS* Numerical Rating Scale, *IGA* Investigator Global Assessment, *EASI* Eczema Area and Severity Index

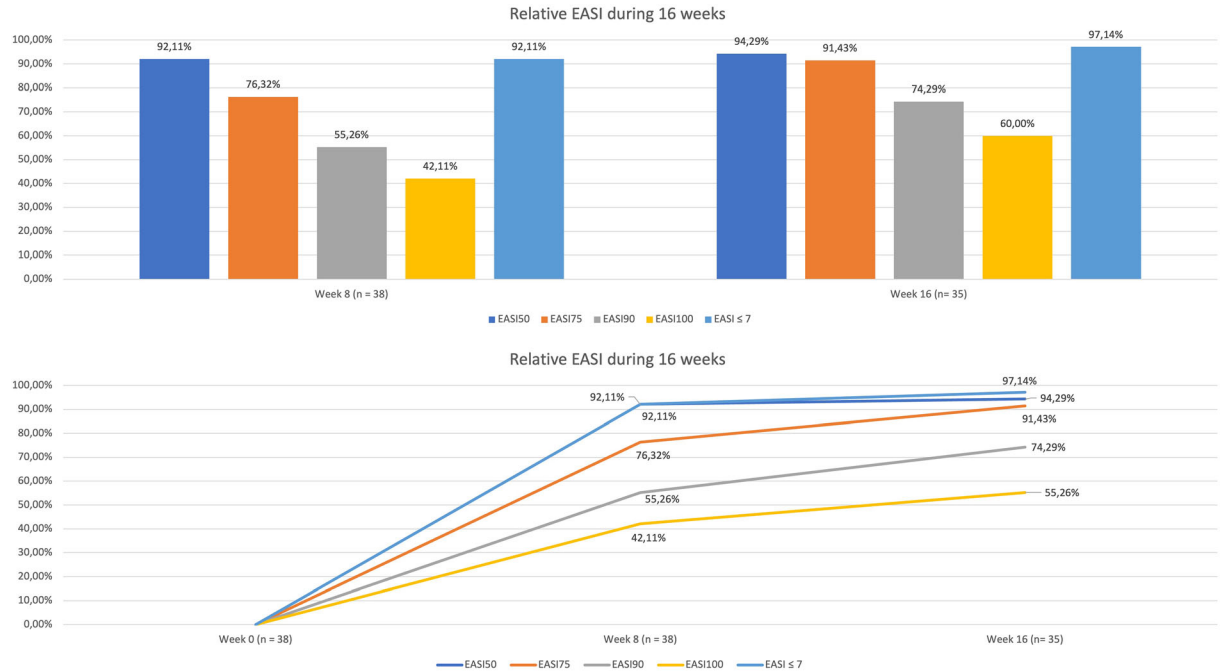

Fig. 2 Percentages of patients achieving EASI 50, EASI 75, EASI 90, EASI 100, and absolute EASI ≤ 7 at weeks 8 and 16. *EASI* Eczema Area and Severity Index

Table 2 Efficacy endpoints at weeks 8 and 16

Therapeutic goals	Week 8	Week 16
EASI 50	35/38 (92.11%)	33/35 (94.29%)
EASI 75	29/38 (76.32%)	32/35 (91.43%)
EASI 90	21/38 (55.26%)	26/35 (74.29%)
EASI 100	16/38 (42.11%)	21/35 (60%)
EASI ≤ 7	35/38 (92.11%)	34/35 (97.14%)
Mean EASI	2.56 (SD 3.32)	1.45 (SD 3.11)
IGA 0/1	27/38 (71.05%)	32/35 (91.43%)
Mean IGA	0.87 (SD 0.96)	0.51 (SD 0.74)
DLQI 0/1	27/38 (71.05%)	31/35 (88.57%)
Mean DLQI	1.41 (SD 1.98)	0.60 (SD 1.52)
Itch-NRS ≤ 4	35/38 (92.11%)	31/35 (88.57%)
Δ Itch-NRS ≥ 4	36/38 (94.74%)	32/35 (91.43%)
Mean Itch-NRS	1.05 (SD 1.86)	1.03 (SD 2.13)

DLQI Dermatology Life Quality Index, *NRS* Numerical Rating Scale, *IGA* Investigator Global Assessment, *EASI* Eczema Area and Severity Index. *Δitch-NRS* reduction of at least 4 points from baseline of reported itch-NRS

achieved by 27 (71.05%) patients at week 8 and by 32 (91.43%) at week 16.

At week 8, 35 (92.11%), 29 (76.32%), 21 (55.26%), and 16 (42.11%) patients achieved EASI 50, EASI 75, EASI 90, and EASI 100, respectively. At week 16, out of 35 patients, the percentages of EASI 50, EASI 75, EASI 90, and EASI 100 responses were 94.29, 91.43, 74.29, and 60%, respectively. Regarding absolute EASI, 35 (92.11%) and 34 (97.14%) patients achieved an EASI ≤ 7 at weeks 8 and 16, respectively. Data regarding EASI 50, EASI 75, EASI 90, EASI 100, and EASI ≤ 7 of our cohort of patients are summarized in Fig. 2.

Regarding the impact on patient's quality of life, mean DLQI decreased from 15.82 (SD 5.38) at baseline to 1.41 (SD 1.98) at week 8 and 0.60 (SD 1.52) at week 16. A DLQI of 0/1 was reported from 27 (71.05%) and 31 (88.57%) patients at weeks 8 and 16, respectively (Fig. 1). The treatment with upadacitinib had a significant impact on itch-NRS, which decreased from a mean (SD) of 8.42 (1.24) at baseline to 1.05 (1.86) at week 8 and 1.03 (2.13) at week 16. Regarding itch-NRS, a decrease of at least 4 points from baseline was reported by 36 (94.74%) and 32 (91.43%) patients at weeks 8 and 16, respectively (Fig. 1). Additional effectiveness endpoints are reported in Table 2.

Among patients without previous exposure to dupilumab, at week 8, EASI 75 was reached by 81.25%, EASI 90 by 62.5%, and EASI 100 by 50%. All patients had an EASI score ≤ 7 at week 8. At week 16, EASI 75 was achieved by 84.62% of patients, EASI 90 by 76.92%, and EASI 100 by 61.54%. In this subset of patients, mean EASI decreased from a baseline score of 17.63 to 1.94 at week 8 and 2.11 at week 16. Regarding patients with previous exposure to dupilumab, at week 8, EASI 75 was reached by 72.73%, EASI 90 by 50%, and EASI 100 by 36.36%. EASI ≤ 7 was observed in 86.36% of patients, with a mean EASI score that decreased from 17.38 to 3.01. At week 16, 95.45% of patients achieved EASI75, 72.73% EASI90, and 59.09% EASI100. All patients had an absolute EASI of seven or less, and mean EASI score was 1.06. No significant differences between the two sub-groups

Table 3 Safety profile of upadacitinib up to week 16

Adverse events	Numbers (% on total of AEs)
Elevated liver enzymes	2 (15.38%)
Anemia	1 (7.69%)
Hypercholesterolemia	4 (30.77%)
Papulopustular acne	5 (38.46%)
Infection from SARS-CoV-2	1 (7.69%)
Total	13
Severe AEs	0
AEs leading to discontinuation	0
AEs leading to dose reduction	5 (38.46%)

AE adverse event

were observed at weeks 8 and 16 in terms of effectiveness endpoints.

Regarding the safety of upadacitinib, ten (26.32%) experienced at least one adverse event (AE). A total of 13 AEs were recorded. The most common AE was papulopustular acne (five cases, 38.46% of the total AEs), followed by hypercholesterolemia (four cases, 30.77%), mild elevation of liver enzymes (two cases, 15.38%). No severe AEs were reported from our patients up to week 16. None of the AEs led to the discontinuation of upadacitinib. In five patients, three with papulopustular acne and two with an elevation of liver enzymes, the development of an AE led to the modification of the dose, as they were all receiving 30 mg daily and were subsequently switched to 15 mg per day with an improvement of those AEs. Data concerning the safety of upadacitinib in our cohort of patients are shown in Table 3.

DISCUSSION

Multiple clinical trials have evaluated the safety and efficacy of upadacitinib in patients with severe atopic dermatitis, but real-life experiences are currently limited. Our retrospective single-center study included 38 patients, more than half of them unresponsive to dupilumab, different from clinical trials which excluded patients previously treated with dupilumab.

In our study, we observed higher rates of EASI 75/ EASI 90/ EASI 100 responses at week 16, compared with data from clinical trials. In the two replicate phase 3 clinical trials, Measure Up 1 and Measure Up 2, 79.7 and 72.9% of patients, respectively, achieved EASI 75 after treatment with upadacitinib 30 mg daily in monotherapy [12]. The high effectiveness rates we observed in our study could be due to the concomitant application of medium/high potency topical corticosteroids when needed. Regarding other demographic characteristics, our population was comparable with clinical trials, with similar mean age and disease duration. Moreover, during the treatment, the patients were allowed to apply topical corticosteroids when needed, as per good clinical practice.

Compared with the phase 3 clinical trials AD Up [13], in which patients were allowed to apply topical low-to-medium potency corticosteroids up to week 16, we observed better clinical responses in terms of EASI 75 (91.43% in our population versus 77.1 and 64.6% for upadacitinib 30 mg and 15 mg, respectively in the AD Up study). A higher proportion of our patients achieved EASI 90 at week 16 (74.29%) compared with the same clinical trial (63.1 and 42.8%). Complete skin clearance (EASI 100) was observed in 55.26% in our study (compared with 22.6% of patients receiving upadacitinib 30 mg in AD Up study) [13].

Compared with other real-life studies, we found similar responses in terms of IGA [18] and EASI75 [19]. Regarding another real-life experience from Hagino et al. [20], we observed better clinical responses. However, in this study, the time points were slightly different as patients were evaluated at weeks 4 and 12.

Patients who had previously failed the treatment with dupilumab achieved comparable clinical responses compared with patients naïve to biologics. Our data on this subpopulation are consistent with a multicenter real-life study from Chiricozzi et al. [15], who analyzed only patients unresponsive or contraindicated to dupilumab.

In our experience, the subset of patients naïve to biologics achieved slightly better responses than the general study population, although statistical significance was not reached. Given the small sample size, larger studies are needed to assess further the role of upadacitinib as a first-line therapy in patients who failed cyclosporine. To date, there are no real-life studies on the effectiveness of upadacitinib in patients without previous exposure or contraindications to dupilumab.

In our population, the rapid improvement of cutaneous lesions was associated with a reduction of the itch and an improvement in the quality of life. The impact of the treatment with upadacitinib on the itch-NRS was dramatic, as 94.74% of our patients experienced a decrease of at least 3 points from baseline already at week 8. Upadacitinib also had a significant impact on the quality of life of the patients, as at week 16,

88.57% of our patients reported a DLQI of 0 or 1.

Our real-life experience included difficult-to-treat patients, as most of them had several comorbidities and had previously failed therapy with dupilumab. Overall, the safety profile of upadacitinib (both 15 mg and 30 mg) up to week 16 was favorable, as no cases of herpes infection/reactivation were reported in our experience, differently from phase 3 clinical trials [21]. None of our patients discontinued upadacitinib because of treatment-related AEs. Regarding laboratory anomalies, routine examinations showed plasma creatine phosphokinase elevation, mild anemia, and transaminases elevation, which did not lead to discontinuation. Among our patients, only one patient discontinued upadacitinib at the week 16 visit because of primary inefficacy. All the other patients are still on treatment to date.

Our study has a few limitations, the first being its retrospective nature. Other limitations are the limited sample size, although larger than most published real-life studies to date, and the short follow-up period (16 weeks of treatment).

CONCLUSIONS

Our experience supports data from both clinical trials and other real-life studies, highlighting the effectiveness of upadacitinib also in a difficult-to-treat population with inadequate response to cyclosporine and dupilumab. The safety profile of upadacitinib also was favorable, as no AEs leading to discontinuation were experienced by our patients up to week 16.

Our experience, although limited, highlights the high effectiveness of upadacitinib in patients naïve to biological drugs, suggesting a role of upadacitinib as a first choice after the failure of cyclosporine [5]. Longer and larger studies are needed to assess further the effectiveness and safety profiles of upadacitinib in a real-life setting.

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Author Contribution. All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Luigi Gargiulo, Luciano Ibba, Andrea Cortese, Jessica Avagliano, Mario Valenti, Antonio Costanzo, and Alessandra Narcisi. The first draft of the manuscript was written by Luigi Gargiulo, Luciano Ibba and Andrea Cortese and all authors commented on previous versions of the manuscript. Funding acquisition: Antonio Costanzo. Resources: Antonio Costanzo. Super- vision: Alessandra Narcisi. All authors read and approved the final manuscript.

Disclosures. A. Costanzo has been a consultant and/or speaker for Abb-Vie, Almirall, Amgen, Janssen, Leo Pharma, Eli Lilly, Galderma, Boehringer, Novartis, Pfizer, Sandoz, and UCB. A. Narcisi has served on advisory boards, received honoraria for lectures and research grants from Almirall, AbbVie, Leo Pharma, Celgene, Eli Lilly, Janssen, Novartis, Sanofi-Genzyme, Amgen and Boehringer Ingelheim. M. has been a consultant and/or speaker for Sanofi, Leo Pharma, Eli Lilly and Boehringer Ingelheim. L. Gargiulo, L. Ibba, A. Cortese, J. Avagliano have nothing to disclose.

Compliance with Ethics Guidelines. Institutional review board approval was exempted, as the study protocol did not deviate from standard clinical practice. All patients received upadacitinib as in good clinical practice, in accordance with European guidelines. For some of the patients AbbVie provided the drug upadacitinib through a Compassionate Use

Program activated according to the DM 7/9/2017. All included patients had provided written consent for retrospective study of data collected during routine clinical practice (demographics, clinical scores). The study was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. Data collection and handling complied with applicable laws, regulations, and guidance regarding patient protection, including patient privacy.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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