Effectiveness and Safety of Upadacitinib in the Treatment of Moderate-Severe Atopic Dermatitis: A Multicentric, Prospective, Real-World, Cohort Study

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Abstract

Background The efficacy and safety of upadacitinib in atopic dermatitis (AD) have been defined in clinical trials, but no real-world data are currently available. We aimed to assess the safety and effectiveness of upadacitinib in a real-world AD patient cohort that mostly included patients who failed the available systemic therapies, including dupilumab.

Methods Prospective cohort study collecting data on upadacitinib-treated AD adult patients completing at least 16 weeks of therapy.

Results Forty-three patients showed rapid and marked response to upadacitinib with significant reduction of all disease severity scores since the first follow-up visit. At week 16, Eczema Area and Severity Index (EASI) 75, EASI 90, and EASI 100 response was observed in 97.5%, 82.1%, and 69.2% of patients, respectively. EASI 90 response reflected the achievement of a clear or almost clear condition (POEM 0-2), self-evaluated by 79.5% of patients. Patients’ quality of life improved as suggested by the achievement of DLQI 0/1 by 38.5% of patients at week 4, and by 76.9% at week 16.

Conclusion Elevated effectiveness and favorable safety of upadacitinib were confirmed in patients unresponsive to dupilumab, who were not included in upadacitinib trials.

Key Points

- Real-world data on upadacitinib in the treatment of atopic dermatitis are limited.
- Upadacitinib demonstrated effectiveness in patients excluded from trials because of prior failure on dupilumab.

1 Introduction

Atopic dermatitis (AD) is a chronic-relapsing, highly itchy, inflammatory skin disease that is associated with a negative impact on patients’ quality of life (QoL) [1]. It represents a common skin condition with an increasingly higher prevalence in adulthood that in Italy is estimated at 8.1% [2]. Because of the complex immune mechanism underlying AD pathogenesis, topicals and/or conventional systemic immunosuppressive/immunomodulant therapies (i.e., cyclosporine) are prescribed, though their use is often limited by the lack of effectiveness or safety risks related with their long-term use [3, 4]. Dupilumab, a subcutaneous monoclonal antibody inhibiting the signaling of two pathogenic cytokines, interleukin (IL)-4 and IL-13 [5], is now available in most European countries for the treatment of moderate-to-severe AD in adults and adolescents/children. Although many patients benefit from dupilumab therapy, persistence of AD was reported in a consistent proportion of dupilumab-exposed patients in pivotal trials and in real-world studies.
were treated with 30 mg upadacitinib. The objective of the compassionate use program was to provide upadacitinib to adult patients with moderate-to-severe AD who were non-responders, intolerant, or had a contraindication to drugs approved for the treatment of AD. Patients were eligible if aged between 18 and 75 years, and had completed the prespecified washout from prior treatments, according to criteria applied for upadacitinib trials [17, 18].

Prior to upadacitinib initiation, a washout period of at least 4 weeks was recommended in patients using systemic immunosuppressive agents that included corticosteroids, methotrexate, cyclosporine, azathioprine, phosphodiesterase type 4 (PDE-4) inhibitors, interferon-γ, and mycophenolate mofetil. A washout period of five half-lives or within 12 weeks (whichever was longer) was considered in case of targeted biologic treatments [17, 18].

All patients were encouraged to use emollients daily, while topical corticosteroids of different potencies or topical calcineurin inhibitors were applied during the study according to the physician’s recommendations.

Follow-up visits were scheduled according to an appointment timetable at each center and patient availability, optionally after 4 weeks and, as required, after 16 weeks from baseline. Signed informed consent was obtained from patients in order to extract data from their clinical records. Approval of this study was obtained by the Local Ethics Committee—Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Prot N.: 4434.

2.2 Data Collection

Patients who achieved at least 16 weeks of treatment and those who discontinued treatment prior to week 16 were included in the study. Physicians were asked to report data derived from the medical records in an electronic case report form. Although the intermediate timepoint at week 4 was additionally considered, both baseline and week 16 information were required for each patient. Baseline characteristics included age, gender, occupation, smoking habits (smoker, former smoker, or non-smoker), AD history and severity, prior treatments, atopic and non-atopic comorbidities, and concomitant therapies. At baseline and at each follow-up visit, Eczema Area and Severity Index (EASI) and Body Surface Area (BSA) were used to assess disease severity and skin involvement, respectively, whilst itch severity was assessed by a 0–10 Numeric Rating Scale (itch-NRS), sleep disturbances/sleeplessness by a 0–10 NRS scale (sleep-NRS), pain intensity by a 0–10 Numeric Rating Scale (pain-NRS), patient’s QoL by the Dermatology Life Quality Index (DLQI) and global patient-oriented disease severity by the Patient-Oriented Eczema Measure (POEM).

Safety was assessed by physical examination and laboratory tests (i.e., complete blood count, transaminases,
creatinine, blood glucose, prothrombin time, activated partial thromboplastin time, international normalized ratio, creatine phosphokinase). Adverse events (AEs) were defined as any abnormal physical condition or blood test alteration collected by the physicians throughout the study period every 16 weeks or more tightly based on clinical needs.

### 2.3 Statistical Analyses

Data were summarized as mean and standard deviation, median and interquartile range, or as absolute number and percentage, as appropriate. The within-group comparison of study outcomes (between baseline with week 4 and week 16) was performed listwise by the Wilcoxon-rank test for dependent observations. Different endpoints of response were considered: the achievement of EASI 50, EASI 75, and EASI 90 at weeks 4 and 16 as compared to baseline; an absolute DLQI value of 0/1 at the follow-up visit, meaning no impact of the disease on the patient’s QoL; and an absolute POEM value of 0–2 corresponding to patient-assessed clear or almost clear condition. As identified by an international expert consensus on the treat-to-target approach in AD, we also considered other treatment goals, though the timepoints identified by the consensus to assess the achievement of these therapeutic targets differed from our real-world setting [19]. At week 4, as an early timepoint, we evaluated the number of patients achieving a reduction of at least 3 points in the absolute itch-NRS score, a reduction of absolute DLQI score of at least 4 points, and a reduction of absolute POEM score of at least 4 points. At week 16, as a late timepoint, we evaluated the number of patients achieving an absolute EASI score ≤ 7, an absolute itch-NRS score ≤ 4, an absolute DLQI score ≤ 5, and an absolute POEM score ≤ 7. A p value < 0.05 was considered statistically significant. Data are reported and analyzed “as observed”. Thus, no missing imputation was performed. Data analysis was performed by STATA 13 for Windows (College Station, TX, USA).

### 3 Results

Forty-three patients (15 females and 28 males) were treated with 30 mg upadacitinib daily for an observation period of 16 weeks. Baseline demographic and clinical characteristics of the study population are illustrated in Table 1. All patients had been previously treated with at least one systemic agent. In particular, dupilumab was prescribed in 42/43 patients, while in one case it was not prescribed as it was considered not indicated (severe conjunctivitis with marked facial involvement). The most common reason for dupilumab discontinuation was inefficacy (39 cases, 92.9%), followed by the occurrence of AEs (three cases: two for recalcitrant conjunctivitis and one for head/neck eczema).

Thirty-nine of 43 patients completed 16 weeks of treatment, whereas two withdrew from treatment due to AEs, while two were lost to follow-up.

#### 3.1 Upadacitinib Improves Clinical Manifestations and Symptoms

The EASI score significantly reduced over time, and, similarly, symptoms (itch and pain) as well as sleeplessness and QoL improved throughout the study period. The baseline median EASI score (26.0; interquartile range (IQR) 23.0–28.0) rapidly dropped (3.5; IQR 1.0–5.0) at week 4 and

| Table 1 Demographic characteristics of the study population |
|-------------------------------------------------------------|
| Characteristics                                             |
| Total population                                            | 43 patients |
| M/F, n (%)                                                 | 28 (65.1)/15 (34.9) |
| Mean age, years (± SD)                                      | 45.91 (± 15.8) |
| Mean BMI, kg/m² (± SD)                                      | 24.6 (± 3.5) |
| Median age at the onset of disease (25–75 percentile)       | 6 (1–27) |
| Allergic rhinitis, n (%)                                    | 15/43 (34.9) |
| Asthma, n (%)                                               | 12/43 (27.9) |
| Allergic conjunctivitis, n (%)                              | 10/43 (23.3) |
| Chronic rhinosinusitis with nasal polyposis, n (%)          | 1/43 (2.3) |
| Food allergy, n (%)                                         | 10/43 (23.3) |
| Patients previously treated with CsA, n (%)                 | 42/43 (97.7) |
| Patients previously treated with dupilumab, n (%)           | 42/43 (97.7) |
| Patients previously treated with methotrexate, n (%)        | 20/43 (46.5) |
| Patients previously treated with oral corticosteroids, n (%)| 14/43 (42.4) |
| Patients previously treated with tralokinumab, n (%)        | 2/43 (4.6) |

*BMI* body mass index, *CsA* cyclosporine, *n* number, *SD* standard deviation

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a further reduction was observed at the following visits (0.0; IQR 0.0–2.0; \( p \) for changes at different timepoints compared to baseline <0.001; Table 2). Skin involvement (BSA score) reduced similarly to the EASI score (Table 2). Symptoms, both itch and pain, and sleep disturbances improved from week 4. Response rates in terms of EASI 50, EASI 75, EASI 90, and EASI 100 were high from week 4 (Fig. 1). After 4-week treatment, all patients achieved EASI 50, whilst EASI 75, EASI 90, and EASI 100 were reached in 88.5%, 42.3%, and 23.1% of patients, respectively. Further improvements were observed at week 16 with 97.5%, 82.1%, and 69.2% of patients achieving EASI 75, EASI 90, and EASI 100 responses, respectively (Fig. 1).

This significant \(( p < 0.001)\) and rapid decrease in disease severity was associated with an improvement of patients’ QoL. A significantly lower median value of DLQI scoring was detected at visit 16 (0.0; IQR 0.0–1.0) compared to baseline (16.0; IQR 10.0–20.0). The achievement of DLQI 0/1 (no impact on QoL) was reported in 38.5% and 76.9% at weeks 4 and 16, respectively. Based on the POEM criteria, patients considered their skin condition as clear or almost clear (POEM 0–2) in 42.3% and 79.5% of cases after 4 and 16 weeks of therapy, respectively. According to the recently proposed treatment goals, the vast majority of patients could be considered as responsive to upadacitinib therapy. More than 88% of patients achieved early treatment goals after

| Table 2: Disease severity reported as median scores (and interquartile range) for EASI, BSA, itch-NRS, sleep-NRS, pain-NRS, POEM, and DLQI, at baseline, at week 4, and at week 16 |
|---------------------------------------------------------------|
| **Patients** | Baseline | Week 4 | Week 16 | \( p \) value* |
|----------------|----------|--------|---------|----------------|
| EASI score     | 26.0 (23.0–28.0) | 3.5 (1.0–5.0) | 0.0 (0.0–2.0) | \(< 0.001\) |
| BSA score      | 24.0 (20.0–30.0) | 2.0 (0.0–4.0) | 0.0 (0.0–2.0) | \(< 0.001\) |
| Itch-NRS score | 9.0 (7.0–10.0) | 2.0 (0.0–2.0) | 0.0 (0.0–0.0) | \(< 0.001\) |
| Sleep-NRS score| 8.0 (5.0–9.0) | 1.0 (0.0–2.0) | 0.0 (0.0–0.0) | \(< 0.001\) |
| Pain-NRS score | 7.0 (0.0–8.0) | 1.0 (0.0–1.0) | 0.0 (0.0–0.0) | \(< 0.001\) |
| POEM score     | 18.0 (15.0–23.0) | 3.5 (0.0–6.0) | 0.0 (0.0–2.0) | \(< 0.001\) |
| DLQI score     | 16.0 (10.0–20.0) | 2.5 (0.0–5.0) | 0.0 (0.0–1.0) | \(< 0.001\) |

*Wilcoxon rank test for dependent observations comparing baseline values with both week 4 and week 16 scores. The comparison was done list-wise.

BSA: Body Surface Area, DLQI: dermatology life quality index, EASI: eczema area severity index, NRS: numeric rating scale, POEM: patient-oriented eczema measure.

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Fig. 1: Treatment response to upadacitinib in terms of Eczema Area and Severity Index (EASI) 50, EASI 75, EASI 90, and EASI 100 responses. Percentage of patients achieving EASI 50, EASI 75, EASI 90, and EASI 100 responses at the follow-up visits.

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4 weeks of treatment and similar response rates, above 92%, for late therapeutic goals were detected after 16 weeks of treatment (Table 3).

### 3.2 Upadacitinib Safety

Sixteen of 43 patients (37.2%) reported at least one AE during the study period. A total of 19 AEs was recorded. Most of them were evaluated as mild and they did not cause treatment interruption, except for two cases: one case of metastatic pancreatic carcinoma and one case of thrombophlebitis, permanently discontinuing treatment after 4 and 8 weeks, respectively. The case of metastatic pancreatic carcinoma occurred within the first 4 weeks of upadacitinib treatment in a 72-year-old male subject without any known comorbid condition, whilst the case of thrombophlebitis was reported after 8 weeks of upadacitinib therapy in a 73-year-old male subject affected by two comorbid conditions (hypertension and hypothyroidism), both pharmacologically well controlled. The most common AEs were blood test abnormalities, detected in 16 cases (84.2% of all AEs), that included blood creatine phosphokinase elevation, blood cell count alterations, and decreased hemoglobin levels. AEs of special interest consisted of two cases of papulopustular, facial acne and two cases of Coronavirus Disease 2019 (COVID-19), these latter causing treatment suspension for a period of 4 weeks, with successful re-treatment thereafter. In addition, one case of viral warts was reported.

### 4 Discussion

Safety and effectiveness of upadacitinib have been shown in clinical trials, but real-world data are currently limited [18, 20–24]. This prospective, multicentric study provides insights into the short-term safety and effectiveness of 30 mg upadacitinib in the treatment of moderate-to-severe adult AD patients in a real-world setting. In particular, our patient population consisted of difficult-to-treat patients who were unresponsive or had contraindications to several lines of systemic therapies including dupilumab, which in 92.9% of cases failed to obtain a satisfactory clinical response. Notably, patients previously exposed to dupilumab or JAK inhibitors were not included in the upadacitinib clinical trials [18, 20–22].

Rapid and marked reduction of disease severity was observed from the first follow-up visit, corresponding to 4 weeks of treatment. Being a real-world study, intermediate follow-up visits (visit after 4 weeks of treatment, for instance) could be differently scheduled, thus, clinical data might result missing. In those patients evaluated after 4 weeks’ treatment, the clinical response obtained during the first weeks of treatment was maintained over time with further reductions in disease severity scores thereafter. According to therapeutic goals identified by an international expert consensus seeking to define treat-to-target recommendations for AD [19], we also detected the achievement of both early and late therapeutic goals in a large percentage of patients (above 88%). These goals were obtained in a shorter timeframe (within 4 months of treatment) compared to those timepoints (3 and 6 months) proposed by the international expert consensus [19], suggesting an eventual revision of the treat-to-target strategy and goals in the future that considers the upcoming therapeutic options available for the management of AD. At week 4 and week 16, our study revealed elevated percentages of patients achieving EASI 75, EASI 90, and EASI 100, which were higher than clinical trial outcomes [20, 21]. In the Measure Up 1 and Measure Up 2 trials, EASI 75 was obtained by 79.7% and 72.9% of patients treated with 30 mg upadacitinib, respectively, and the association with topical low-to-medium potency corticosteroids did not enhance upadacitinib efficacy in a phase III trial, AD Up (77.1% of EASI 75 response at week 16) [20, 21]. In our cohort, almost all subjects (97.5%) achieved EASI 75 after 16 weeks of treatment. Differences in clinical outcomes between trial setting and our real-world experience were more marked in terms of EASI 90 and EASI 100. In our study, EASI 90 at week 16 was reached by 82.1%

| Therapeutic goals                                  | Week 4     | Week 16    |
|----------------------------------------------------|------------|------------|
| Patients achieving absolute EASI score ≤ 7, n (%)   | 38/39 (97.4)|           |
| Patients achieving the reduction of at least 3 points in the absolute itch-NRS score, n (%) | 24/26 (92.3) | 37/39 (94.9) |
| Patients achieving the absolute itch-NRS score ≤ 4, n (%) | 24/26 (92.3) |            |
| Patients achieving the reduction of absolute DLQI score of at least 4 points, n (%) | 23/26 (88.5) | 36/39 (92.3) |

**Table 3** Response to upadacitinib therapy evaluated through the achievement of additional treatment goals proposed by De Bruin Weller et al. [19]

**DLQI** dermatology life quality index, **EASI** eczema area severity index, **NRS** numeric rating scale, **POEM** patient-oriented eczema measure

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of patients, reflecting a self-assessed clear or almost clear condition (POEM 0–2) reported in 79.5% of treated cases.

This high rate of effectiveness could be related to the characteristics of our patient cohort, which consisted of high-need patients with moderate-to-severe AD, who had shown multifailure to systemic therapies, and had no other valid therapeutic options than upadacitinib. Additional inclusion/exclusion criteria of the compassionate use program could possibly have selected a sub-population of great responders. Another factor that might contribute to the better responses documented in this real-world study is the allowed combination of topical potent-ultrapotent corticosteroids based on the physician’s choice. Similarly, real-world outcomes related to other targeted therapies used in AD, such as dupilumab, showed higher response rates in comparison with clinical trials [25–27]. As is commonly seen, in our study the improvement of skin manifestations was associated with a decrease of itch, an amelioration of sleep disturbances, as well as better QoL. In particular, at week 4 about one-third of patients achieved DLQI 0/1, which was obtained by a greater number of patients (76.9% of cases) at week 16. A significant improvement in patients’ QoL was also reported in the Measure Up 1 trial, with 41.1% of patients reaching DLQI 0/1 at week 16 [20]. No upadacitinib-treated patients withdrew from therapy because of ineffectiveness; the two cases of discontinuation were due to the occurrence of AEs. Overall, the safety profile was favorable and in line with clinical trials, showing plasma creatine phosphokinase elevation, anemia, and acne as the most frequently reported treatment-emergent AEs, the majority of which were mild and transient and did not cause treatment withdrawal.

Our study describing the safety and effectiveness of upadacitinib in patients unresponsive to dupilumab provides evidence with meaningful clinical implications as no data are currently available on dupilumab-exposed patients [5, 28, 29]. Long-term data on a larger patient population will be of great interest to confirm the persistence of treatment response and safety in upadacitinib-treated patients [30].

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Declarations

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