

Treatment of severe atopic dermatitis with upadacitinib in real clinical practice. Short-term efficacy and safety results

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Atopic dermatitis (AD) is a chronic, inflammatory and pruritic skin disease, with a prevalence of 7.3% in the adult population[1]. In 2017, dupilumab was the first approved biologic for the treatment of moderate-to-severe AD. However, despite its efficacy, some patients are still refractory[2]. Treating these severely ill patients who have failed multiple therapies is therefore challenging, with new therapeutic alternatives still needed.

Recently, upadacitinib, a selective JAK-1 inhibitor, has been incorporated into the therapeutic arsenal for AD. Upadacitinib has shown the highest short-term efficacy rates in two recent network metaanalysis[3,4]. However, real clinical practice studies are scarce with only isolated case series published [2,5–8]. We considered of interest to analyze the short-term effectiveness and safety of a series of patients with AD treated with upadacitinib in a real clinical practice setting.

We included patients that started upadacitinib during a compassionate use program and an early access program (october 2020 to March 2022). Patients had a confirmed diagnosis of AD performed by experienced dermatologists from 16 participating reference hospitals in Spain. Patients older than 12 years were eligible to access these programs. In addition to failure of systemic therapy, adult patients had to have some contraindication to the use of dupilumab or intolerance, adverse effect, or inefficacy (the

monitoring and financing protocol in Spain requires at least EASI 50 and improvement of 2 IGA points from baseline). No washout period was required for previous medications. Approved 15 or 30 mg daily doses were prescribed at the discretion of the prescribing physician. Patients under 18 years of age and those over 65 years of age received 15 mg daily.

Data collected included age, disease duration time, comorbidities and previous systemic and biological treatments. Disease severity was measured by Scoring Atopic Dermatitis (SCORAD), Eczema Area and Severity Index (EASI), Body Surface Area (BSA), and peak pruritus Numerical Rating Scale (PP-NRS) at the baseline visit and at weeks 4 and 16 in the follow up. Quality of life was assessed with the Dermatology Life Quality Index (DLQI). We registered adverse events related to the drug and blood test parameters including eosinophil count, total IgE, haemoglobin, LDL/HDL cholesterol, triglycerides, CPK, GGT, GOT and GPT levels.

The ethics committee of the Virgen del Rocio Hospital approved the study protocol. All patients signed a written consent before participating in the study.

Statistical analysis and graphs were performed with GraphPad v.9.2. Descriptive statistics were calculated for each variable. The differences observed in the different scales were compared with the Wilcoxon test, because they did not reach normality.

Forty-three patients (23 male, 53.4%) were included in the study. The mean age was 34.4 ± 13.5 years old, ranging from 12 to 71 years. The mean disease duration time was 21.1 ± 11.3 years. The mean body mass index was 24.5 ± 4.9 . Concomitant atopic diseases were present as follows: allergic rhinitis 39.5%, asthma 32.6%, conjunctivitis 23.3%, food allergies 23.2% and nasal polyps 2.3%. All patients had received corticosteroids and nearly all cyclosporine (90.7%) and dupilumab (74.4%). Upadacitinib 30 mg daily was

the most prescribed dose (60.4%). With regard to concomitant medications, 39.5% used topical corticosteroids, 6.9% oral corticosteroids (prednisone between 0.1-0.3 mg/kg daily in weeks 0-4), 2.3% (weeks 4-16) and 2.3% received phototherapy.

The mean baseline values for disease severity were: SCORAD 57.6 ± 17.42 , EASI 24.9 ± 9.6 , DLQI 17.4 ± 6.8 and PP-NRS 8.0 ± 1.4 . 62.7% of patients had an IGA of 4. Mean EASI decreased to 4.1 ± 4.6 (83.5% improvement), SCORAD to 15.9 ± 15.1 (72.3% improvement) and PP-NRS to 2.5 ± 2.8 (69.1% improvement) at week 16. ($p < 0.0001$ for all assessments) (Fig 1). 76.7% of the patients reached EASI 75 (76.9% with 30 mg and 76.5% with 15 mg) and 51.1% EASI 90 (50.0% with 30 mg and 52.9% with 15 mg) at week 16. 62.8% showed IGA 0/1 at the end of the follow-up period.

The safety profile was overall good. 30.2% of patients reported mild adverse events, being acne the most frequent (18.6%). One patient (2.3%) discontinued the drug due to adverse effects (weakness and asthenia). Only one patient had recurrent oral herpes simplex (3 episodes), self-limited without the need for treatment. Other adverse effects were: one case of insomnia, one case of dermatitis of the head-neck and upper part of the thorax, and one case of epigastric pain and nausea. Laboratory abnormalities were only found in 1 case (2-point drop in haemoglobin) during follow-up.

The patients included in our series had an important baseline severity and several comorbid atopic conditions. They had a clinical history of multiple treatment failures, including cyclosporin and dupilumab in more than 90% and 70% of them, respectively.

This clinical effectivity and safety of upadacitinib observed in our study is similar to that of clinical trials, both in monotherapy[9] and in combination with topical corticosteroids[10]. 76.7% of our patients treated with either 30 or 15 mg daily reached

EASI 75 at week 16 whereas the values for EASI75 were 76.3% (30 mg) and 64.9% (15 mg) in the Measure Up 1 and 2 studies and 77.1% (30 mg) and 64.6% (15 mg) in the Measure Up AD study at week 16. The EASI percentage change from baseline in our series was -83.5%, which is in somewhat in the middle of the reduction obtained in the Measure Up 1 and 2 studies (-87.7%, -84.7%, (30 mg) and -80.2%, -74.1% (15mg) respectively) and Measure Up AD study (-97.3% (30 mg) and -78.0% (15 mg)). Regarding itch, patients experienced a quick reduction in peak pruritus NRS (69.1% compared to baseline), even greater than that obtained in the trials of upadacitinib in combination with TCS (66.9% (30 mg) and 58.1% (15 mg)) [9,10]

Despite the promising clinical trials results of upadacitinib in AD, we have little data on its use in real conditions. Our patients had a profile of severe disease and refractoriness to multiple treatments, including biological therapy. Patients with this lack of response to biological therapy were not included in clinical trials. On the other hand, the use in real clinical practice conditions allowed patients to use medication such as oral or topical corticosteroids and no prior washout period was required. This situation has also been recently evaluated in other real-world evidence studies in patients treated with other molecules[11]. Although these facts should undoubtedly be taken into account when interpreting these results, they are valuable in the management of patients with severe atopic dermatitis.

This study has some limitations such as the small sample size, the short follow-up period, lack of a placebo/control group, and washout period, retrospective nature, and lack of blinding. However, the main strength of our study is precisely to show the response in real conditions of a series of patients with severe AD.

Conflict of interests

Jose Juan Pereyra-Rodriguez has received Honoraria for research from Novartis, Abbvie and Sanofi, and for lecturing and other financial benefit from Abbvie, Almirall, Galderma, Janssen, Gebro-Pharma, Leo-Pharma, Novartis, Lilly, Novartis, Pfizer, Sanofi and UCB.

Pedro Herranz has been an investigator, speaker and/or consultant for: AbbVie, Almirall, Amgen, Bristol Myers Squibb, Janssen, Lilly, Galderma, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi Genzyme, and UCB Pharma

Ignasi Figueras Nart has been an investigator, speaker and/or advisor for: AbbVie, Amgen, Lilly, Galderma, Pierre Fabre, LEO Pharma, Novartis, Regeneron and Sanofi Genzyme.

Bibiana Perez has received Honoraria for speaker and/or advisor as well as funding to attend conferences for Sanofi, Abbvie, Boheringer Ingelheim, Lilly, Galderma, Leo Pharma, Pierre Fabre, Meda Pharma, FAES Pharma

Marta Elosua González has been an investigator and/or speaker for: AbbVie, Lilly, Galderma, LEO Pharma, Pfizer, UCB Pharma and Sanofi Genzyme

Violeta Zaragoza Ninet has been an investigator, speaker and/or advisor for: AbbVie, Amgen, LEO Pharma, Novartis, Pfizer and Sanofi Genzyme

Juan Francisco Silvestre has been an investigator, speaker and/or advisor for: AbbVie, Amgen, Astra Zeneca, Bristol Myers Squibb, Lilly, Galderma, Incyte, LEO Pharma, Novartis, Pfizer, Regeneron and Sanofi Genzyme

Javier Miquel has received speaker and consultancy fees from Abbvie, Leo Pharma, Novartis, Sanofi, UCB, Janssen and Lilly, and have participated as PI in clinical trials sponosized by Abbvie and Novartis.

Sara Alcantara-Luna has received honoraria for research from Abbvie, and lecturing and other financial benefits from Sanofi, AbbVie, LEO, Lilly and Almirall

Pablo de la Cueva has received consulting fees; payment or honoraria for lectures, presentations, speaker's bureaus, manuscript writing or educational events; support for attending meetings and/or travel; participation on a Data Safety Monitoring Board or Advisory Board from AbbVie, Pfizer, UCB, Leo Pharma, Almirall S.A., Lilly, Sanofi, MSD, BMS, Novartis and Janssen

Esther Serra-Baldrich has been an investigator, speaker and/or advisor for: AbbVie, Amgen, Lilly, Galderma, Pierre Fabre, LEO Pharma, Novartis, Regeneron and Sanofi Genzyme.

Jose-Carlos Armario-Hita research from Novartis, Abbvie and Sanofi, and lecturing and other financial benefits from Abbvie, Almirall, Galderma, Janssen, Gebro-Pharma, Leo-Pharma

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FIGURE LEGENDS

Fig.1 Mean variation of the SCORAD, EASI, PP-NRS and DLQI from baseline to weeks 4 and 16. Statistical significance was assessed by the Wilcoxon test. * $p < 0.05$; **** $p < 0.0001$. ns not significant

