Treatment of Severe Atopic Dermatitis With Upadacitinib in Clinical Practice: Short-Term Efficacy and Safety Results

Pereyra-Rodriguez JJ[1]*, Herranz P[2], Figueras-Nart I[3], Perez B[4], Elosua M[5], Munera-Campos M[6], Melgosa-Ramos J[7], Zaragoza V[8], Silvestre JF[9], Campos-Domínguez M[10], Guilabert A[11], Miquel J[12], Alcantara-Luna S[13], de la Cueva P[14], Serra-Baldrich E[15], Armario-Hita JC[16]

[1]*Department of Dermatology, University Hospital Virgen del Rocío, Sevilla, Spain*
[2]*Department of Dermatology, University Hospital La Paz, Madrid, Spain*
[3]*Department of Dermatology, University Hospital de Bellvitge, Barcelona, Spain*
[4]*Department of Dermatology, University Hospital Ramón y Cajal, Madrid, Spain*
[5]*Department of Dermatology, University Hospital Puerta del Hierro, Madrid, Spain*
[6]*Department of Dermatology, University Hospital Germans Trias i Pujol, Badalona, Spain*
[7]*Department of Dermatology, University Hospital Doctor Peset, Valencia, Spain*
[8]*Department of Dermatology, University Hospital General de Valencia, Valencia, Spain*
[9]*Department of Dermatology, University Hospital of Alicante, Alicante, Spain*
[10]*Department of Dermatology, University Hospital Gregorio Marañón, Madrid, Spain*
[11]*Department of Dermatology, General Hospital of Granollers, Barcelona, Spain*
[12]*Department of Dermatology, University Hospital Arnau de Vilanova, Valencia, Spain*
[13]*Department of Dermatology, Juan Ramón Jiménez Hospital, Huelva, Spain*
[14]*Department of Dermatology, Infanta Leonor Hospital, Madrid, Spain*
[15]*Department of Dermatology, Sant Pau Hospital, Barcelona, Spain*
[16]*Department of Dermatology, University Hospital Puerto Real, Puerto Real, Spain*

J Investig Allergol Clin Immunol 2023; Vol. 33(3): 211-213
doi: 10.18176/jiaci.0831

Key words: Atopic dermatitis. Atopic eczema. Upadacitinib. JAK-inhibitors. Real-world evidence.

Palabras clave: Dermatitis atópica. Eccema atópico. Upadacitinib. Inhibidores de JAK. Evidencia en el mundo real.

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 became the first approved biologic for the treatment of moderate-to-severe AD. However, despite the drug's efficacy, the disease remains refractory in some patients [2]. Treating severely ill patients for whom multiple therapies have failed is challenging, and new therapeutic alternatives are still needed.

Upadacitinib, a selective JAK-1 inhibitor, was recently incorporated into the therapeutic arsenal for AD and shown to have very favorable short-term efficacy in 2 recent network meta-analyses [3,4]. However, clinical practice–based studies are scarce, with only isolated case series published [2,5-8]. We considered it of interest to analyze the short-term effectiveness and safety of upadacitinib in a series of patients with AD treated in a clinical practice setting.

We included patients who started upadacitinib during a compassionate use program and an early access program (October 2020 to March 2022). Patients were diagnosed with AD by experienced dermatologists from 16 participating reference hospitals in Spain. Those older than 12 years were eligible for access to these programs. In addition to failure of systemic therapy, adult patients had to have some contraindication to the use of dupilumab or intolerance, adverse effects, or inefficacy (the monitoring and financing protocol in Spain requires an Eczema Area and Severity Index [EASI] of at least 50 and an improvement of 2 points from baseline on the Investigator Global Assessment [IGA] scale). 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.

The data collected included age, disease duration, comorbidities, and previous systemic and biological treatments. Disease severity was measured based on the SCORing Atopic Dermatitis tool (SCORAD), EASI, Body Surface Area (BSA), and the Peak Pruritus Numerical Rating Scale (PP-NRS) at the baseline visit and at weeks 4 and 16. Quality of life was assessed using the Dermatology Life Quality Index (DLQI). We registered adverse events related to the drug and blood test parameters including eosinophil count and total IgE, hemoglobin, LDL/HDL cholesterol, triglycerides, CPK, GGT, AST, and ALT levels.

The Ethics Committee of Virgen del Rocio Hospital approved the study protocol. All patients signed a written informed consent document before participating in the study.

The statistical analysis was performed, and graphs were generated using GraphPad v.9.2. Descriptive statistics were calculated for each variable. The differences between the scales were compared using the Wilcoxon test, since the data were not normally distributed.

The study population comprised 43 patients (23 males, 53.4%). The mean (SD) age was 34.4 (13.5) years, ranging from 12 to 71 years. The mean disease duration was 21.1 (11.3) years. The mean body mass index was 24.5 (4.9). Concomitant atopic diseases included the following: 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 had received 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% received topical corticosteroids, 6.9% oral corticosteroids (prednisone 0.1-0.3 mg/kg daily) during

weeks 0-4, 2.3% oral corticosteroids during weeks 4-16, and 2.3% phototherapy.

The mean (SD) baseline values for disease severity were as follows: SCORAD, 57.6 (17.42); EASI, 24.9 (9.6); DLQI, 17.4 (6.8); and PP-NRS 8.0 (1.4). The IGA was 4 in 62.7% of patients. 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<.0001 for all assessments) (Figure). At week 16, EASI75 was reached by 76.7% of patients (76.9% with 30 mg and 76.5% with 15 mg) and EASI-90 by 51.1% (50.0% with 30 mg and 52.9% with 15 mg). The IGA was 0/1 in 62.8% at the end of the follow-up period.

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

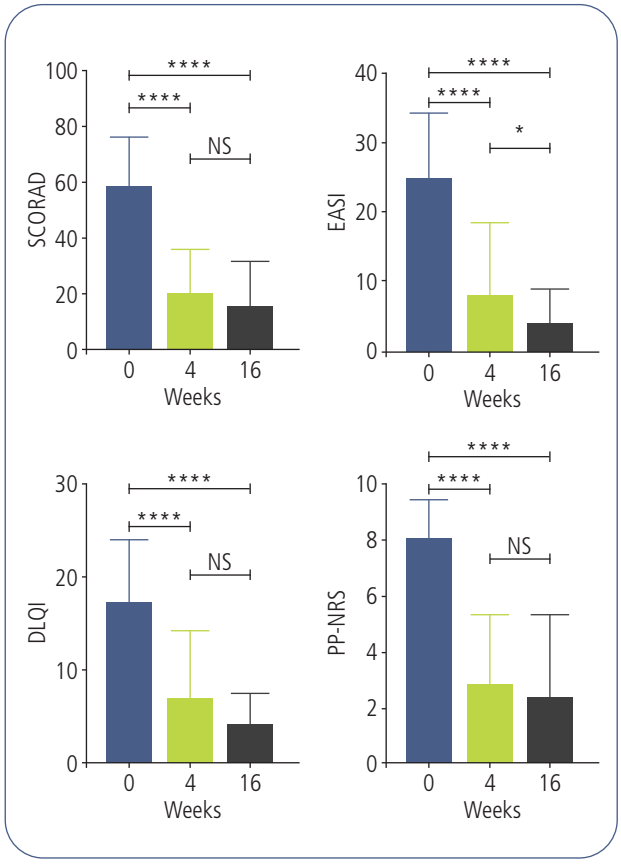

Figure. Mean variation in the SCORAD, EASI, PP-NRS, and DLQI from baseline to weeks 4 and 16. Statistical significance was assessed using the Wilcoxon test. SCORAD indicates SCORing Atopic Dermatitis tool; EASI, Eczema Area Severity Index; BSA, Body Surface Area (BSA); PP-NRS, Peak Pruritus Numerical Rating Scale; DLQI, Dermatology Life Quality Index. *P<.05; ****P<.0001; NS indicates not significant.

The patients included in our series had considerably severe disease at baseline and several comorbid atopic conditions. They had a clinical history of multiple treatment failures, especially cyclosporine and dupilumab, which had failed in more than 90% and 70% of cases, respectively.

The clinical effectiveness and safety of upadacitinib observed in our study is similar to that reported in clinical trials when the drug was administered in monotherapy [9] and in combination with topical corticosteroids [10]. Of the patients treated with either 30 or 15 mg daily, 76.7% reached EASI-75 at week 16. In the Measure Up 1 and 2 studies, the week-16 values for EASI-75 were 76.3% (30 mg) and 64.9% (15 mg); in the Measure Up AD study they were 77.1% (30 mg) and 64.6% (15 mg). The EASI percentage change from baseline in our series was –83.5%, which lies somewhere in the middle of the reductions obtained in the Measure Up 1 and 2 studies (–87.7%, –84.7% [30 mg] and –80.2%, –74.1% [15 mg], respectively) and Measure Up AD study (–97.3% [30 mg] and –78.0% [15 mg]). Regarding itch, patients experienced a rapid reduction in PP-NRS (69.1% compared to baseline), even greater than that obtained in trials where upadacitinib was combined with topical corticosteroids (66.9% [30 mg] and 58.1% [15 mg]) [9,10].

Despite the promising clinical trial results for upadacitinib in AD, few data have been reported on its use in real-world conditions. Our patients had severe disease that was refractory to multiple treatments, including biological therapy. Patients whose disease did not respond to biological therapy were not included in the clinical trials. Therapy with upadacitinib in clinical practice, on the other hand, enabled patients to use medication such as oral or topical corticosteroids without the need for a prior washout period. This situation was recently evaluated in other real-world evidence studies in patients treated with other molecules [11]. While these observations should undoubtedly be taken into account when interpreting the results, they are valuable in the management of patients with severe AD.

Our study is limited by its small sample size, the short follow-up period, the lack of a placebo/control group and washout period, its retrospective design, and the lack of blinding. However, the main strength of our study is that we confirm the response to upadacitinib in a series of patients with severe AD under real-world conditions.

Funding

The authors declare that no funding was received for the present study.

Conflicts of Interest

Jose Juan Pereyra-Rodriguez has received honoraria for research from Novartis, AbbVie, and Sanofi and lecturing fees and other financial benefits 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 as a speaker and/or advisor and funding to attend conferences from Sanofi, AbbVie, Boheringer Ingelheim, Lilly, Galderma, Leo Pharma, Pierre Fabre, Meda Pharma, and 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 has participated as PI in clinical trials sponsored by AbbVie and Novartis.

Sara Alcantara-Luna has received honoraria for research from AbbVie and lecturing fees 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, payment for 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 has received payment for research from Novartis, AbbVie, and Sanofi and lecture fees and other financial benefits from AbbVie, Almirall, Galderma, Janssen, Gebro-Pharma, Leo-Pharma, Novartis, Lilly, Novartis, Pfizer, Sanofi, and UCB.

The remaining authors declare that they have no conflicts of interest.

References

1. Chiesa Fuxench ZC, Block JK, Boguniewicz M, Boyle J, Fonacier L, Gelfand JM, et al. Atopic Dermatitis in America Study: A Cross-Sectional Study Examining the Prevalence and Disease Burden of Atopic Dermatitis in the US Adult Population. J Invest Dermatol . 2019;139:583-90.
2. Licata G, Gambardella A, Tancredi V, Calabrese G, De Rosa A, Alfano R, et al. Face atopic dermatitis resistant to dupilumab: a case series of three patients successfully treated with upadacitinib. J Eur Acad Dermatology Venereol. 2022;36:e150-2.
3. Pereyra-Rodriguez JJ, Alcantara-Luna S, Domínguez-Cruz J, Galán-Gutiérrez M, Ruiz-Villaverde R, Vilar-Palomo S, et al. Short-Term Effectiveness and Safety of Biologics and Small Molecule Drugs for Moderate to Severe Atopic Dermatitis: A Systematic Review and Network Meta-Analysis. Life (Basel). 2021;11:927.
4. Drucker AM, Morra DE, Prieto-Merino D, Ellis AG, Yiu ZZN, Rochwerg B, et al. Systemic Immunomodulatory Treatments for Atopic Dermatitis: Update of a Living Systematic Review and Network Meta-analysis. JAMA Dermatology. 2022;158:523-32.
5. Nguyen J, Chen JK, Honari G, Pol-Rodriguez M, Ko JM, Chiou AS. Bridging to a selective Janus kinase 1 inhibitor in severe atopic dermatitis: An instructive case with upadacitinib. JAAD Case Reports. 2021;7:65-7.
6. Ferrucci SM, Buffon S, Marzano AV, Maronese CA. Phenotypic switch from atopic dermatitis to psoriasis during treatment with upadacitinib. Clin Exp Dermatol. 2022;15104:2021-2.
7. Cantelli M, Martora F, Patruno C, Nappa P, Fabbrocini G, Napolitano M. Upadacitinib improved alopecia areata in a patient with atopic dermatitis: A case report. Dermatol Ther. 2022;35:e15346.
8. Gao DX, Kahn JS, Cohen SR, Griffiths DM, Fiumara K, Lam A, et al. Results of Switching From Tofacitinib to Upadacitinib in Patients With Atopic Dermatitis: A Retrospective Medical Record Review. Dermatitis. 2021;32:e165-6.
9. Guttman-Yassky E, Teixeira HD, Simpson EL, Papp KA, Pangan AL, Blauvelt A, et al. Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised controlled phase 3 trials. Lancet. 2021;397:2151-68.
10. Reich K, Teixeira HD, de Bruin-Weller M, Bieber T, Soong W, Kabashima K, et al. Safety and efficacy of upadacitinib in combination with topical corticosteroids in adolescents and adults with moderate-to-severe atopic dermatitis (AD Up): results from a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2021;397:2169-81.
11. Nettis E, Ferrucci S, Ortoncelli M, Pellacani G, Foti C, Di Leo E, et al. Use of Dupilumab for 543 Adult Patients with Moderate-To-Severe Atopic Dermatitis: A Multicenter, Retrospective Study. J Investig Allergol Clin Immunol. 2020;32:1-28.

Manuscript received April 30, 2022; accepted for publication June 1, 2022.

Jose Juan Pereyra Rodríguez
Department of Dermatology
University Hospital Virgen del Rocío
Avda. Manuel Siurot s/n
41013 Sevilla (Spain)
E-mail: jpereyra@us.es

