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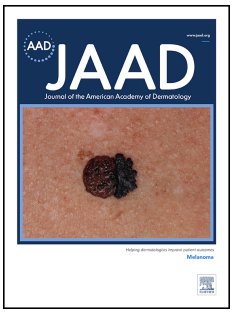

Upadacitinib dose increase to 45 mg daily for refractory atopic dermatitis

Joan Ceravalls, MD, Ignasi Figueras-Nart, PhD, Marc Julià Manresa, Alvaro Prados-Carmona, MD, Lucia Prieto-Torres, MD, Lydia Corbalan Escortell, MD, Gemma Melé-Ninot, MD, Maribel Iglesias-Sancho, MD, Montserrat Salleras Redonnet, PhD, Mónica Munera-Campos, MD, Francisco Javier Melgosa Ramos, MD, Sergio Santos Alarcón, MD, Leandra Reguero del Cura, MD, Pablo Coto-Segura, MD, Luis Alfonso Pérez González, MD, Alberto Guerrero Torija, MD, Ricardo Ruiz-Villaverde, PhD

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Authors: Joan Ceravalls MD,[a] Ignasi Figueras-Nart PhD, [b] Marc Julià Manresa,[c] Alvaro Prados-Carmona MD,[d] Lucia Prieto-Torres MD, [e] Lydia Corbalan Escortell MD,[e] Gemma Melé-Ninot MD,[a] Maribel Iglesias-Sancho MD,[a] Montserrat Salleras Redonnet PhD,[a] Mónica Munera-Campos MD,[f] Francisco Javier Melgosa Ramos MD,[g] Sergio Santos Alarcón MD,[h] Leandra Reguero del Cura MD, [i] Pablo Coto-Segura MD,[j] Luis Alfonso Pérez González MD,[j] Alberto Guerrero Torija MD, [k] Ricardo Ruiz-Villaverde PhD,[d]

Affiliations:

[a] Department of Dermatology, Hospital Universitari Sagrat Cor, Grupo Quirónsalud, Barcelona, Spain.

[b] Department of Dermatology, Hospital Universitari Bellvitge, L'Hospitalet de, Llobregat, Spain.

[c] Department of Dermatology, Hospital Universitario de Basurto, Bilbao, Vizcaya, Spain

[d] Department of Dermatology, Hospital Universitario San Cecilio, Instituto biosanitario de Granada, Ibs, Granada, Spain

[e] Department of Dermatology, Hospital Clínico Universitario Lozano Blesa, Zaragoza, Spain

[f] Department of Dermatology, Hospital Universitari Germans Trias i Pujol, Departament de Medicina, Universitat Autonoma de Barcelona (UAB), Germans Trias i Pujol Research Institute (IGTP). Badalona, Barcelona, Spain.

[g] Department of Dermatology, Hospital Lluís Alcanyís de Xàtiva, Valencia, Spain

[h] Department of Dermatology, Hospital Virgen De Los Lirios, Alcoy, Alicante, Spain

[i] Department of Dermatology, Hospital de Sierrallana, Santander, Spain

[j] Department of Dermatology, Hospital Vital Álvarez-Buylla, Mieres, Spain

[k] Department of Dermatology, Hospital Universitario Infanta Cristina, Parla, Spain

Corresponding author:

Joan Ceravalls, MD

Department of Dermatology, Hospital Universitari Sagrat Cor, Grupo Quirónsalud.

Viladomat Street, 288, E-08029 Barcelona, Spain.

E-mail: drceravalls@gmail.com

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Ethical statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of GRUPO HOSPITALARIO QUIRÓNSALUD-CATALUNYA (2025/106-DER-HUSC).

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Dr. Alberto Guerrero Torija has served as an advisory board member, consultant, or speaker for AbbVie, Almirall, Leo Pharma, Lilly, Pfizer, and Sanofi, for which he has received honoraria. Dr. Gemma Melé-Ninot has served as an advisory board member or speaker for AbbVie, Sanofi, Lilly, Almirall, and Leo Pharma, for which she has received honoraria. Dr. Francisco Javier Melgosa Ramos has served as an advisory board member, consultant, or speaker for AbbVie, Almirall, Amgen, Janssen, Leo Pharma, Lilly, Novartis, Pfizer, Sanofi, and UCB, for which he has received honoraria. Dr Pablo Coto has served as a consultant or speaker for AbbVie, Amgen, Almirall, Incyte, Leo Pharma, UCB, and Sanofi, for which he has received honoraria. Dr. Mónica Munera-Campos has served as a speaker or investigator for Lilly, Sanofi, Almirall, AbbVie, Pfizer, Leo Pharma, and Galderma, for which she has received honoraria. Dr. Lucía Prieto-Torres has served as a speaker for AbbVie, Lilly, Janssen, Kiowa Kirin, Amgen, and Novartis, for which she has received honoraria. Dr. Marc Julià Manresa has served as an advisory board member, consultant, or speaker for AbbVie, Leo Pharma, Sanofi, Lilly, and Pfizer, for which he has received honoraria. Dr Sergio Santos-Alarcón has served as an advisory board member, consultant, or speaker for Almirall, Abbvie, Amgen, Pfizer, Novartis, Janssen, Lilly, Leo Pharma, UCB Pharma, Pierre Fabre, Isdin, Sanofi, Boheringer and Bristol Meyers.

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To the editor,

Upadacitinib, a selective Janus kinase 1 inhibitor, is among the most effective systemic therapies for moderate-to-severe atopic dermatitis (AD), approved at daily doses of 15mg and 30mg.[1] However, a subset of patients fails to achieve or maintain adequate disease control at these doses. A potentially accessible and cost-effective strategy is an off-label dose escalation to 45mg, supported by its approved induction use in Crohn's disease and by data from inflammatory bowel disease flares.[2,3]

We conducted a multicenter retrospective study (September 2021–January 2025), including patients with severe AD who received upadacitinib 45mg. The primary objective was to evaluate clinical response tolerability; secondary endpoints included treatment duration, dose modifications, and reasons for reduction or discontinuation. Applying a last observation carried forward approach, efficacy was assessed using the last observation obtained at 45mg. The study was approved by the QuirónSalud Ethics Committee (2025-36-DERM-HUSC), and written informed consent was obtained due to the off-label use.

Twenty-one patients were included (71% male; median age 31 years; BMI 26 kg/m^2; Table 1). Most (76%) had atopic comorbidities, and 10% presented with autoimmune or cardiovascular risk factors. Seventeen (81%) had previously received biologics or JAK inhibitors (median 2), including upadacitinib in 24% (n=5) and tralokinumab + upadacitinib in 5% (n=1). Eighteen (86%) started at standard doses (84%, 30mg; 16%, 15mg) and required escalation after a median of 266 days (IQR 138–682), mostly for secondary failure (77%). The remaining three (14%) started directly on 45 mg, two for disease severity and one as reintroduction after prior biologic failure.

Before updosing, mean EASI was 16±7.3, BSA was 26±13.4%, and IGA was 3.3±0.6. Patients received 45mg for a median of 120 days (IQR 95–150), during which 90% (n=19) improved (Figure 1, Supplementary Figure 2). Adverse events were mild and occurred in 38% (n=8), including herpes simplex recurrence (18%), acne (18%), asymptomatic lymphopenia (6%), and hypercholesterolemia (12%), although none led to discontinuation. Overall, 67% (n=14) successfully de-escalated to 30mg while maintaining disease control, including the three patients who had started at 45mg. Of the remaining seven, four showed good response but

could not taper due to disease severity, two did not achieve adequate control, and one had only 16 weeks of follow-up with ongoing response.

The 45mg upadacitinib dose escalation provided marked improvement in most patients with refractory AD. The strategy was generally limited to a few months, suggesting a favorable tolerability profile, although long-term data are lacking. The incidence of adverse events was consistent with that reported for standard dosing. Notably, in the pivotal Crohn's disease phase III trial, 45mg induction dosing did not result in higher adverse event rates than 30mg.[3] Our findings highlight two clinical contexts in which this approach proved beneficial. First, 30% of patients previously treated with upadacitinib improved upon reintroduction at the higher dose, possibly reflecting JAK-inhibitor resensitization,[4] and second, one patient on combination therapy achieved disease control after discontinuing the biologic and increasing the JAK-inhibitor dose.[5]

In conclusion, short-term 45mg upadacitinib dosing appears to provide clinical benefit with good tolerability for patients with refractory AD, including those with suboptimal response to standard upadacitinib dosage. Although limited by a small sample size, retrospective design, heterogeneous prior treatments, and short follow-up, these findings suggest that temporary upadacitinib dose escalation represents a practical rescue strategy for difficult-to-treat AD cases, warranting further investigation.

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Figure legends.

Figure 1. Mean EASI (black) and BSA (dark grey) evolution following upadacitinib 45mg intensification.

Supplementary Figure 2. Mean NRS-pruritus and DLQI evolution following upadacitinib 45mg intensification.

224 Table 1. Overall clinical, demographic, and therapeutic characteristics.

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Variable	Total (n=21)
Age (years, Q1 Q3)	33 (26, 38)
Patient sex, n (%)	
Male	15 (71%)
Female	6 (29%)
BMI (kg/m², Q1 Q3)	26 (23.4, 29)
Atopic comorbidities n (%)	16 (76%)
Food allergy	8 (38%)
Asthma	14 (66%)
Rhinitis	10 (47%)
Eosinophilic esophagitis	1 (5%)
Autoimmune comorbidities n (%)	2 (10%)
Crohn's disease	1 (50%)
Areata Alopecia	1 (50%)
History of neoplasia (last 5 years) n (%)	2 (10%)
Basal cell carcinoma	1 (50%)
Conjunctival squamous metaplasia with low-grade dysplasia	1 (50%)
Predominant clinical subtype of AD n (%)	
Generalized	11 (53%)
Flexural	10 (47%)
Involvement of special areas n (%)	
At least one	21 (100%)
Hands	16 (76%)
Face and/or neck	21 (100%)
Genitalia	9 (43%)
Patients previously treated with biologics/JAKi n (%)	17 (81%)
Number of treatments (median, Q1 Q3)	2 (1–3)
Prior upadacitinib exposure with switched therapy n (%)	5 (24)
Prior combination therapy JAKi + biologic n (%)	1 (5)
Prior combination therapy JAKi/biologic + systemic therapy n (%)	5 (24)
Previous systemic treatments, n (%)	21
Dupilumab n (%)	15 (71%)
Tralokinumab n (%)	7 (33%)
Lebrikizumab n (%)	4 (19%)
Nemolizumab n (%)	0 (0%)
Upadacitinib n (%)	5 (24%)
Baricitinib n (%)	4 (19%)
Abrocitinib n (%)	6 (30%)
Methotrexate n (%)	5 (24%)
Cyclosporine n (%)	20 (95%)
Phototherapy n (%)	10 (47%)

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