

Practical Use of Upadacitinib in Patients with Severe Atopic Dermatitis in a Real-World Setting: A Systematic Review

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Abstract: Upadacitinib is a selective Janus kinase inhibitor approved for the treatment of severe atopic dermatitis (AD). This systematic review aims to summarize the most recent data in terms of effectiveness and safety of upadacitinib in the treatment of severe AD in a real-world setting. The review included a comprehensive search of databases, including PubMed, Google Scholar and Web of Science, according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines. The literature search initially identified 242 studies. Of these, 214 were excluded after reviewing their titles and abstracts. We then conducted a full-text review of 25 studies, of which 17 met our inclusion criteria and were therefore included in our systematic review. The analysis of real-world studies showed high effectiveness of upadacitinib, in terms of both clinical signs and subjective symptoms, in different patient populations, including those resistant to other treatments. No new significant safety concerns have emerged as compared to randomized clinical trials.

Keywords: JAKi, real-life, upadacitinib, atopic dermatitis, systematic review

Introduction

Atopic Dermatitis

Atopic dermatitis (AD) is one of the most prevalent inflammatory dermatological conditions, affecting both children and adults with a significant impairment of quality of life and work productivity.^{1,2} During the last ten years, the pathogenesis of AD has been deeply explored, and interleukins (ILs) such as IL-4, IL-13 and IL-31 have emerged as the pivotal cytokines in the inflammatory cascade of AD, along with barrier defects such as filaggrin mutations.³

Novel Treatment Options for Severe Atopic Dermatitis

A better understanding of AD pathophysiology has led to the development of several new drugs that selectively target the key molecules responsible for this disease. In particular, monoclonal antibodies, which block IL-13 and IL-4 (dupilumab) or IL-13 only (tralokinumab and lebrikizumab), are currently indicated for the treatment of severe AD.⁴ Another class of systemic treatments for adults with severe AD is represented by the inhibitors of Janus Kinase (JAKi), including abrocitinib, baricitinib and upadacitinib.⁴ These three drugs have shown efficacy and safety in phase-III clinical trials, compared with placebo and therefore have been approved for the treatment of severe AD.⁵⁻⁷ Upadacitinib and abrocitinib have also demonstrated superior rapidity and effectiveness compared with dupilumab in head-to-head clinical trials.⁸⁻¹⁰ To date, several real-world experiences are available regarding the effectiveness and safety of upadacitinib, while only a few studies have been published on abrocitinib and baricitinib in the treatment of severe AD.^{11,12} Regarding baricitinib, real-life studies have been recently published on its effectiveness also in the treatment of alopecia areata.^{13,14} According to European Guidelines, both JAKi and IL inhibitors, along with cyclosporine, are recommended in adults with severe AD.⁴ Abrocitinib, baricitinib, cyclosporin, dupilumab, tralokinumab

and upadacitinib are all indicated as systemic treatments for severe AD in adult patients, with the same grade of recommendation, according to European Guidelines.⁴ However, there is no specific indication regarding the place in therapy of JAKi, including their possible role as a first or second-line systemic treatment. Moreover, recently the Pharmacovigilance Risk Assessment Committee (PRAC) of EMA published a reassessment (EMA/PRAC/68283/2022) of the benefit–risk balance of oral JAKi, with increasing concerns regarding their safety profiles in patients with AD.¹⁵ In addition, current guidelines do not give enough evidence on patients' management during treatment with JAKi regarding laboratory and clinical monitoring or how to handle concomitant medical procedures. In this setting, the summary of product characteristics (SmPC) of each drug can give the clinicians a little information. However, of course, these are very limited and do not cover all the possible issues that can emerge when managing these patients.^{16–18}

Upadacitinib

Upadacitinib, a selective JAK inhibitor primarily targeting JAK1, has been approved for the treatment of severe AD in both adolescents and adults at two different daily dosages, 15 and 30 mg. This approval followed its evaluation in multiple phase-3 clinical trials where it demonstrated efficacy superior to both placebo and dupilumab after 16 weeks.^{5,8,19}

Materials and Methods

Search Strategy

We conducted a systematic review of the English-language medical literature utilizing PubMed, Google Scholar and Web of Science databases from the earliest records through October 2023.

The search strategy was performed using the following key terms: “upadacitinib” and “atopic dermatitis or atopic eczema” not “Review”. Titles and abstracts of all identified studies underwent screening with the established selection criteria.

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram from the PRISMA statement (Figure 1).²⁰

Selection Criteria

Articles were selected for full-text review by evaluating their titles and abstracts, with selection criteria based on their relevance to the issue of interest. The following inclusion criteria were applied with no restriction to the dosage of upadacitinib: patients with severe atopic dermatitis; identification of effectiveness data from real-world studies or case series; identification of safety data from real-world studies or case series. In particular, effectiveness was assessed by the reduction in mean/median EASI (Eczema Area and Severity Index), the proportion of patients who achieved a reduction of 75%, 90% and 100% of EASI compared with baseline (EASI 75, EASI 90, EASI 100, respectively) and the mean/median reduction in itch-Numerical Rating Scale (NRS).

We excluded case series in which the effectiveness outcomes were not reported. Clinical trials and post hoc analyses were excluded. Systematic reviews and meta-analyses were excluded from the research.

Data Extraction

Two researchers (L.I. and C.A.V.) extracted data independently from the refined papers (Tables 1 and 2), and any discrepancies were resolved by a third author (L.G.). The following information was extracted from each article: name of first author, year of publication, type of study, sample size, effectiveness outcomes, safety findings and relevant comments about the paper. Authors were not contacted to provide further information.

Results

A total of 242 studies were retrieved from the literature search after removal of duplicates (Figure 1). Two hundred and fourteen were excluded based on their title and abstracts. The full text of 25 studies was reviewed, of which 17 met the inclusion criteria, and were included in our study. The main reason for the exclusion of articles was the lack of clear

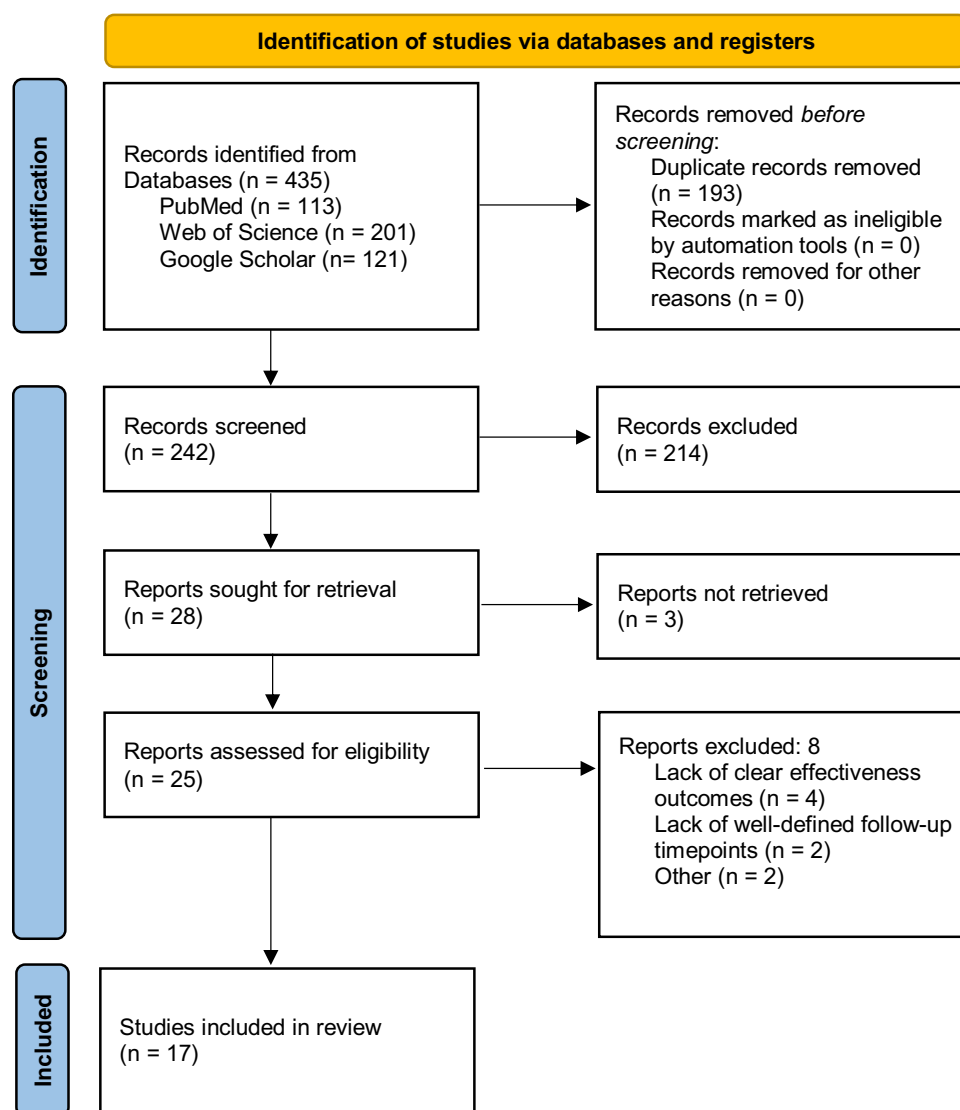


Figure 1 PRISMA Flowchart of study selection. The diagram illustrates the process used to retrieve, assess, and either select or exclude relevant studies from the databases. Adapted from Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA Statement. *Open Med.* 2009;3(3):e123–e130. doi:10.1136/bmj.327.7423.1083.²⁰

effectiveness outcomes. Data from 660 patients were included in the review. The most common type of study was observational retrospective, and most of the articles were published in 2023 (Table 1).

Effectiveness

Only five studies reached a follow-up of at least 48/52 weeks, while the other 12 reached a follow-up of 16 weeks (Table 2).

An observational retrospective multicenter study by Melgosa Ramos et al²¹ showed high effectiveness of upadacitinib through 52 weeks of treatment. In particular, the mean EASI decreased from 19.8 to 3.1 after 4 weeks, 0.9 after 16 weeks, 0.6 after 24 weeks, 0.8 after 32 weeks and 0.6 after one year of follow-up. At the same time points, the Authors also observed improvement in subjective symptoms with an itch-NRS that went from 7.6 at baseline to 1.5 after 4 weeks, 1.1 after 16 weeks, 0.9 after 24 weeks, 0.8 after 32 weeks and 1.4 after 52 weeks of follow-up. Moreover, all patients in this study achieved an EASI 75 response after just 4 weeks of treatment with upadacitinib.

Table 1 Baseline Characteristics of Reviewed Studies

Authors	Year	Type of Study	Sample Size	Mean Age (SD or Range)	Dosage	mEASI at Baseline	mP-NRS at Baseline	Reference
Melgosa Ramos et al	2023	Multicenter Retrospective	21	37.8 (10–71)	15 mg = 6 patients 30 mg = 15 patients	19.8	7.6	[21]
De Greef et al	2023	Single-Center Retrospective	29	Median: 37 (IQR= 37)	15 mg = 10 patients 30 mg = 19 patients	22		[22]
Chiricozzi et al	2023	Multicenter Prospective	146	37.83 (14.4)	15 mg = 28 patients 30 mg = 118 patients	25		[23]
Gargiulo et al	2023	Single-Center Retrospective	71	41.44 (17.33)	15 mg = 39 patients 30 mg = 32 patients	18.62	8.42	[24]
Gori et al	2023	Single-Center Retrospective	8	Median: 42 (IQR= 25.75–54.25)	15/30 mg; not specified	17.3		[25]
Napolitano et al	2023	Single-Center Retrospective	9	28.7 (10.3)	30 mg	27.2	8.9	[26]
Patruno et al	2023	Case Series	4	16.25 (0.96)	15 mg	27.5	9.25	[27]
Tran et al	2023	Single-Center Retrospective	10	41.9 (13.5)	15 mg	27.3		[28]
Chiricozzi et al	2022	Multicenter Prospective	43	45.91 (15.8)	30 mg	26	9	[29]
Gargiulo et al	2023	Single-Center Retrospective	38	41.53 (16.56)	15 mg = 12 patients 30 mg = 26 patients	17.48	8.42	[30]
Georgakopoulos et al	2023	Multicenter Retrospective	39	46.3 (14.8)	15 mg = 28 patients 30 mg = 11 patients	16.7		[31]
Boesjes et al	2023	Multicenter Prospective	47	Median: 33 (26–43)	15 mg = 40 patients 30mg = 7 patients	16.6	7	[32]
Hagino et al	2022	Single-Center Retrospective	31	41.2 (16.5)	15 mg + twice daily topical corticosteroids	23.4	8	[33]
Hagino et al	2023	Single-Center Retrospective	39	Median: 14 (13–16)	15 mg + twice daily topical corticosteroids	21.3	8	[34]
Napolitano et al	2023	Dual-Center Retrospective	16	29.88 (10.15)	30mg	25.88	8.44	[35]
Pereyra-Rodriguez et al	2023	Multicenter Retrospective	43	34.4 (13.5)	15 mg = 17 patients 30 mg = 26 patients	24.9	8	[36]
Vanlerberghe et al	2022	Multicenter Retrospective	66	Median: 34 (26–47)	15 mg = 54 patients 30 mg = 12 patients	15.6		[37]

Abbreviations: SD, Standard Deviation; IQR, Interquartile Range; EASI, Eczema Area and Severity Index; P-NRS, pruritus-Numerical Rating Scale.

Table 2 Effectiveness Outcomes of Reviewed Studies

Authors	mEASI	mP-NRS	EASI 75	EASI 90	EASI 100	IGA 0/I
Melgosa Ramos et al ²¹	W4 = 3.1 W16 = 0.9 W24 = 0.6 W32 = 0.8 W52 = 0.6	W4 = 1.5 W16 = 1.1 W24 = 0.9 W32 = 0.8 W52 = 1.4	W4 = 100% W16 = 100% W24 = 100% W52 = 100%	W16 = 90.50% W24 = 100% W52 = 100%		
De Greef et al ²²			W16 = 58.60% W52 = 82.70%	W16 = 90.50% W52 = 58.60%		W16 = 79.30% W52 = 79.30
Chiricozzi et al ²³	W16 = 5.4 W32 = 2.0 W48 = 2.6	W16 = 1.8 W32 = 1.3 W48 = 1.4	W16 = 78.2% W32 = 92.0% W48 = 87.6% W8 = 69%	W16 = 47.6% W32 = 71.4% W48 = 69.1% W8 = 36.62%	W16 = 28.2% W32 = 51.80% W48 = 44.3% W8 = 23.90%	
Gargiulo et al ²⁴			W16 = 85.70% W32 = 87.20% W52 = 87.90%	W16 = 71.40% W32 = 76.60% W52 = 75.80%	W16 = 55.60% W32 = 55.30% W52 = 57.60%	W8 = 60.60% W16 = 84.10% W32 = 83% W52 = 90.90%

(Continued)

Table 2 (Continued).

Authors	mEASI	mP-NRS	EASI 75	EASI 90	EASI 100	IGA 0/I
Gori et al ²⁵	W4 = 1.2 W52 = 0.5	W4 = 0.7 W52 = 0			W4 = 62.50% W52 = 62.50%	
Napolitano et al ²⁶	W4 = 7.3 W16 = 3.3	W4 = 0.3 W16 = 0.2	W16 = 77.78%			
Patruno et al ²⁷	W4 = 9.75 W16 = 2.25	W4 = 1.50 W16 = 0.75				
Tran et al ²⁸	W12 = 6.8		W12 = 60%			
Chiricozzi et al ²⁹	W4 = 3.5 W16 = 0	W4 = 2 W16 = 0	W4 = 88.5% W16 = 97.50%	W4 = 42.30% W16 = 82.10%	W4 = 23.1% W16 = 69.20%	
Gargiulo et al ³⁰	W8 = 2.56 W16 = 1.45	W8 = 1.05 W16 = 1.03	W8 = 76.32% W16 = 91.43%	W8 = 55.26% W16 = 74.29%	W8 = 42.11% W16 = 60%	
Georgakopoulos et al ³¹	W16 = 1.4		W16 = 76.9%*			W16 = 76.9%*
Boesjes et al ³²	W4 = 7.5 W16 = 5.7	W4 = 3.9 W16 = 3.7				W4 = 36.20% W16 = 32.90%
Hagino et al ³³			W4 = 51.6% W16 = 67.7%	W4 = 22.6% W16 = 41.9%		W4 = 16.7% W16 = 36.7%
Hagino et al ³⁴	W4 = 4.4 W12 = 4.4	W4 = 3 W12 = 2	W4 = 64.1% W12 = 62.5%	W4 = 12.8% W12 = 15.6%	W4 = 12.8% W12 = 15.6%	W4 = 11.6% W12 = 18.6%
Napolitano et al ³⁵	W4 = 9.56 W16 = 4.31	W4 = 2.69 W16 = 1.19				
Pereyra-Rodriguez et al ³⁶	W16 = 4.1	W16 = 2.5	W16 = 76.7%	W16 = 51.1%		W16 = 62.8%
Vanlerberghe et al ³⁷			W12 = 35.7% (15 mg); 57.1% (30 mg) W24 = 37.5% (15 mg); 100% (30 mg)	W12 = 7.1% (15 mg); 57.1% (30 mg)		

Notes: *The endpoint was the achievement of EASI75 or IGA 0/I.

Abbreviations: EASI, Eczema Area and Severity Index; P-NRS, pruritus-Numerical Rating Scale.

De Greef et al²² conducted a retrospective cohort study including patients with severe atopic dermatitis treated with upadacitinib 15 or 30 mg. In this study, an EASI 75 response was obtained by 58.6% and 82.70% of patients after 12/16 weeks and 52 weeks of treatment, respectively. In addition, 58.60% of patients achieved an EASI 90 after one year.

In a prospective multicenter study of 146 patients conducted by Chiricozzi et al.²³ EASI 75 was reached by 78.2%, 92.0%, and 87.6% of patients after 16, 32, and 48 weeks of treatment. At the same time points, 47.6%, 71.4% and 69.1% of patients achieved EASI 90. A complete skin clearance was observed in 28.2%, 51.80%, and 44.3% of patients after 16, 32, and 48 weeks, respectively. In this study, the mean EASI decreased consistently throughout the study period (from 25.0 at baseline to 5.4 after 16 weeks, 2.0 after 32 weeks, and 2.6 after 48 weeks). Moreover, the mean itch-NRS decreased significantly, from 7.1 before the start of upadacitinib to 1.4 after 48 weeks of follow-up.

Gargiulo et al²⁴ showed an excellent response to upadacitinib in adults with severe atopic dermatitis over 52 weeks of follow-up. In particular, after 16 weeks of treatment, 85.7%, 71.4% and 55.6% of patients achieved EASI 75, EASI 90, and EASI 100, respectively. After one year of treatment, 87.9%, 75.8% and 57.6% reached EASI 75, EASI 90 and EASI 100, respectively. Subjective symptom improvement was also excellent, with 81.8% of patients achieving at least a 4-point reduction in itch-NRS from baseline after 52 weeks of treatment.

Gori et al²⁵ performed a retrospective analysis of eight patients with AD involving sensitive areas (head/neck, genitalia and hands) who were resistant to dupilumab and treated with upadacitinib 15 or 30 mg. At baseline, the mean EASI score was 17.30, which decreased to 1.2 after 4 weeks and 0.5 after 1 year of treatment. Complete skin clearance (EASI 100) was observed in five patients (62.5%) at weeks 4 and 52, while the remaining three patients had minimal residual disease (EASI ≤ 1). In terms of subjective symptoms, the mean itch-NRS decreased from 6.1 at baseline to 0.7 at week 4 and 0 at week 52.

According to a real-life study by Napolitano et al,²⁶ upadacitinib showed a rapid improvement in pruritus after 4 and 16 weeks of treatment. In particular, the mean itch-NRS at baseline was 8.9, which decreased to 0.3 at week 4 and 0.2 at week 16. The Authors also found excellent effectiveness of upadacitinib in terms of mean EASI, which decreased from 27.2 at baseline to 7.3 at week 4 and 3.3 at week 16. In addition, 77.78% of patients achieved EASI 75 after 16 weeks of treatment with upadacitinib.

Patrino et al²⁷ published a case series of four adolescents with severe AD treated with upadacitinib 15 mg. The mean EASI score decreased from 27.5 at baseline to 9.75 at week 4 and 2.25 after 16 weeks of treatment. Mean itch-NRS decreased from 9.25 to 1.50 and 0.75 at the same time points.

In an Australian retrospective cohort study by Tran et al,²⁸ the mean EASI score at baseline was 27.3. After 3 months of treatment with upadacitinib, the mean EASI score was 6.8, and 60% of patients achieved EASI 75.

In a 16-week prospective multicenter study by Chiricozzi et al.²⁹ After 4 weeks of treatment with upadacitinib, 88.5%, 42.3% and 23.1% of patients reached EASI 75, EASI 90 and EASI 100, respectively. At week 16, almost all patients (97.5%) achieved EASI 75, while 82.1% and 69.2% of patients achieved EASI 90 and EASI 100, respectively.

Similar results were reported in a 16-week retrospective study by Gargiulo et al³⁰ in which the EASI score decreased from a mean of 17.48 at baseline to 2.56 at week 8 and 1.45 after 16 weeks. At week 8, the percentages of EASI 75, EASI 90 and EASI 100 responses were 76.32%, 55.26%, and 42.11%, respectively. At week 16, out of 35 patients, 91.43%, 74.29%, and 60% of them achieved EASI 75, EASI 90, and EASI 100, respectively. At the same time points, the Authors also observed a significant impact on itch-NRS, which decreased from a mean of 8.42 at baseline to 1.05 at week 8 and 1.03 at week 16.

In a multicenter retrospective study, Georgakopoulos et al³¹ showed high effectiveness of upadacitinib even in patients who had previously failed dupilumab. The mean EASI score decreased from 16.7 at baseline to 1.4 at week 16. At the same time point, EASI 75 or IGA 0/1 was achieved by 76.9% of patients. Complete skin clearance (EASI 100 or IGA 0) was achieved by 56.4% of patients after 16 weeks of treatment with upadacitinib.

Boesjes et al³² conducted a multicenter prospective study to evaluate the effectiveness of upadacitinib in patients with severe AD, including those who have failed dupilumab and/or baricitinib. The mean EASI score improved from 16.6 at baseline to 7.5 after 4 weeks and 5.7 at week 16, while an IGA of 0 or 1 was reached by 36.2% and 32.9% of patients at the same time points. Regarding subjective symptoms, the authors observed a significant reduction of mean itch-NRS, which decreased from 7.0 at baseline to 3.9 at week 4 and 3.7 at week 16.

Two studies by Hagino et al^{33,34} were included in this systematic review. The first one was a retrospective analysis of 31 patients affected by severe AD treated with upadacitinib 15 mg plus twice/daily topical corticosteroids.³³ At baseline, the mean EASI score was 23.4. An EASI75 achievement rate of 51.6% and 67.7% was observed at weeks 4 and 12, respectively, and an EASI 90 in 22.6% and 41.9% at weeks 4 and 12, respectively. The median IGA score at baseline was 3, and a reduction to IGA 0/1 was observed in 16.7% and 36.7% at weeks 4 and 12, respectively. The second publication by Hagino et al³⁴ consisted of a retrospective study conducted on 39 Japanese adolescent patients (aged 12 to 17 years) suffering from severe AD treated with oral upadacitinib 15mg/day plus twice daily topical corticosteroids. The median EASI at baseline amounted to 21.3. It reached 4.4 at weeks 4 and 12. The median IGA at baseline was 3, and it decreased to 1 at weeks 4 and 12. A reduction of median PP-NRS was observed, descending from 8 at baseline to 3 and 2 at weeks 4 and 12, respectively. The achievement rates at weeks 4 and 12 were respectively 64.1% and 62.5% for EASI 75, 12.8% and 15.6% for EASI 90, 12.8% and 15.6% for EASI 100, and 11.6% and 18.6% for IGA 0/1.

A retrospective two-center study by Napolitano et al³⁵ of 16 adults with severe AD treated with upadacitinib 30 mg showed a significant reduction in mean EASI score (from 25.88 at baseline to 9.56 at week 4 and 4.31 at week 16). The improvement in clinical signs was accompanied by a reduction in subjective symptoms. The mean itch-NRS decreased from 8.44 at baseline to 2.69 and 1.19 at the same time points.

A retrospective multicentric study on a population of 43 patients affected by AD treated with 15- or 30-mg daily doses of upadacitinib was conducted by Pereyra-Rodriguez et al.³⁶ Upadacitinib 30mg was prescribed in the majority of patients (60.4%), 39.5% received topical corticosteroids, 6.9% received oral corticosteroids during weeks 0–4, and 2.3% of the patients received oral corticosteroids during weeks 4–16. The mean EASI was 24.9 at baseline and decreased to 4.1 at week 16. The EASI 75 was achieved by 76.7% of patients, and the EASI 90 was achieved by 51.1% after 16 weeks of treatment with upadacitinib. At baseline, the mean PP-NRS amounted to 8.0 and reached 2.5 at week 16. Most patients had an IGA score of 4 at baseline (62.7%), while after 16 weeks, most patients had an IGA score of 0/1 (62.8%).

Vanlerberghe et al³⁷ published a multicenter French real-world study to evaluate the effectiveness of JAK inhibitors for the treatment of severe AD. After three months of treatment, the Authors found that 35.7% and 7.1% of patients achieved EASI 75 and EASI 90, respectively, with the dosage of 15 mg, while 57.1% reached EASI 75 and EASI 90 with upadacitinib 30 mg. Only a small proportion of patients reached 6 months of treatment, with 37.5% and 100% of patients achieving EASI 75 with upadacitinib 15 and 30 mg, respectively.

Safety

A safety evaluation was performed in 16 articles out of 17 included in this review, as a retrospective study was not included because it did not report AEs.²⁶ Among the articles analyzed, a total of 359 AEs were reported (Tables 3 and 4).

The most common clinical AE reported was papulopustular acne, which was found in 77 patients, followed by Herpes Simplex infections (n = 27), upper respiratory tract infections (n = 22), nausea (n = 12), headache (n = 10) and Herpes Zoster (n = 9). Moreover, four patients experienced thrombophlebitis, including three patients with multiple risk factors for thrombosis.

Table 3 Safety Evaluation of Reviewed Studies. The Table Specified the Most Common and Relevant Adverse Events

Authors	Total AEs	AEs Leading to Discontinuation	Hematochemical AEs	Clinical AEs
Melgosa Ramos et al ²¹	3	0	Lymphopenia= 3	0
De Greef et al ²²	21	0	Lymphopenia= 1 Neutropenia= 2 Anemia= 1 Hypercholesterolemia= 7 Elevated liver enzymes= 2	Papulopustular acne= 6 Headache= 1
Chiricozzi et al ²³	29	4	Anemia= 1 Hypercholesterolemia= 4 Elevated liver enzymes= 2	Papulopustular acne= 5 URTI= 6 Herpes simplex= 2 Neoplasm= 1 Thrombophlebitis= 3 (≥ 65 years) Acute myocardial infarction= 1
Gargiulo et al ²⁴	17	6	Anemia= 3 Hypercholesterolemia= 3 Elevation of CPK= 2	Papulopustular acne= 6 Herpes zoster= 2 Papulopustular acne= 2
Gori et al ²⁵	5	0	NA	NA
Napolitano et al ²⁶	NA	NA	NA	NA
Patruno et al ²⁷	1	0	Elevation of CPK= 1	0
Tran et al ²⁸	10	3	Hypercholesterolemia= 1	Papulopustular acne= 2 URTI= 3 Herpes simplex= 3 Herpes zoster= 1
Chiricozzi et al ²⁹	23	1	16 (Not Specified)	Papulopustular acne= 3 URTI= 2 Neoplasm= 1 Thrombophlebitis= 1
Gargiulo et al ³⁰	13	0	Anemia= 1 Hypercholesterolemia= 4 Elevated liver enzymes= 2	Papulopustular acne= 5 URTI= 1
Georgakopoulos et al ³¹	12	0	0	Papulopustular acne= 3 Herpes simplex= 4 Herpes zoster= 1 Nausea= 4

(Continued)

Table 3 (Continued).

Authors	Total AEs	AEs Leading to Discontinuation	Hematochemical AEs	Clinical AEs
Boesjes et al ³²	57	5	Hypercholesterolemia= 3 Elevated liver enzymes= 2 Elevation of CPK= 4	Papulopustular acne= 10 URTI= 4 Herpes simplex= 6 Herpes zoster= 2 Headache= 3 Nausea= 4 Fatigue= 1
Hagino et al ³³	17	1	Elevated liver enzymes= 1 Elevation of CPK= 3	Papulopustular acne= 5 Nausea= 1 Herpes simplex= 1 Herpes zoster= 1
Hagino et al ³⁴	25	2	Elevation of CPK= 7	Papulopustular acne= 8 URTI= 2 Nausea= 1 Herpes simplex= 3 Herpes zoster= 2
Napolitano et al ³⁵	22	3	Anemia= 3 Hypercholesterolemia= 2 Elevated liver enzymes= 2 Elevation of CPK= 3	Papulopustular acne= 2 URTI= 4 Herpes simplex= 1 Headache= 2
Pereyra-Rodriguez et al ³⁶	25	1	Anemia= 1	Papulopustular acne= 8 Herpes simplex= 1 Nausea= 1 Fatigue= 1
Vanlerberghe et al ³⁷	94	4	Lymphopenia= 3 Neutropenia= 2 Anemia= 1 Hypercholesterolemia= 14 Elevated liver enzymes= 8 Elevation of CPK= 8	Papulopustular acne= 12 Herpes simplex= 6 Headache= 4 Nausea= 1

Abbreviations: AE, Adverse Event; URTI, Upper Respiratory Tract Infection; NA, Not Applicable; CPK, Creatine phosphokinase.

Table 4 Most Frequent Clinical and Laboratory Adverse Events

Laboratory AEs*	N (%)^
Lymphopenia	7 (1.08)
Anemia	11 (1.69)
Neutropenia	4 (0.61)
Hypercholesterolemia	38 (5.84)
Elevation of liver enzymes	19 (2.92)
Elevation of CPK	28 (4.30)
Hypertriglyceridemia	13 (2)

(Continued)

Table 4 (Continued).

Clinical AEs	N (%) [^]
Papulopustular acne	77 (11.83)
Herpes simplex infection	27 (4.15)
URTIs	22 (3.38)
Nausea	12 (1.84)
Headache	10 (1.54)
Herpes Zoster	9 (1.38)
Trombophlebitis	4 (0.61)
Neoplasm	2 (0.31)
Fatigue	2 (0.31)
Acute myocardial infarction	1 (0.15)
Total AEs	359
AEs leading to discontinuation	33

Notes: *Laboratory adverse events reported by Chiricozzi et al did not specify number of patients with each alteration. They cited 16 blood test abnormalities including anemia, neutropenia, lymphopenia and CPK elevation. [^]The percentage is calculated on the number of patients included in the studies that reported the number of adverse events (n= 591 patients).

Abbreviations: AE, Adverse Event; CPK, Creatine phosphokinase; URTI, Upper Respiratory Tract Infection.

Among laboratory AEs, hypercholesterolemia was the most reported (n = 38), followed by elevation of creatine phosphokinase (CPK) (n = 28), elevation of liver enzymes (n = 19), hypertriglyceridemia (n = 13), anemia (n = 11) and lymphopenia (n = 7). One study by Chiricozzi et al reported 16 blood test abnormalities, including anemia, neutropenia, lymphopenia and CPK elevation, without specifying the number of patients with each alteration.²⁹

Moreover, 33 AEs led to discontinuation of the treatment with upadacitinib.

In the two studies by Chiricozzi et al, six patients discontinued the treatment due to AEs. Two patients had thrombophlebitis, two were diagnosed with a neoplasm (one with metastatic pancreatic carcinoma and one with bladder metaplasia), one had a myocardial infarction, and one patient experienced limb heaviness and pain associated with diffuse swelling.^{23,29}

In a French retrospective observational study, four patients discontinued treatment with upadacitinib due to cytotoxicity, hypercholesterolemia, dyspnea, and a facial papular eruption.³⁷ In the cohort studied by Napolitano et al,³⁵ three patients discontinued treatment due to anemia, restless leg syndrome, and elevated blood CPK. In a Spanish retrospective observational study, one patient discontinued treatment due to asthenia and weakness.³⁶ AD flares led to discontinuation in three patients within the cohorts of subjects studied by Hagino et al^{33,34} Among the 47 patients from the Dutch BioDay Registry, seven patients interrupted the treatment with upadacitinib for various reasons, including dyspnea, nausea, recurrent herpes simplex infections, reactive lymphoid infiltrate, the elevation of liver enzymes, a combination of headache and acne, and finally, a combination of headache, nausea, and acne.³²

In an Australian real-world study by Tran et al, three patients experienced AEs that led to discontinuation of upadacitinib (one because of eczema herpeticum, one because of herpes zoster ophthalmicus and one because of worsening of his acne).²⁸

In the 52-week retrospective study by Gargiulo et al, six patients discontinued upadacitinib due to AEs.²⁴ Two patients experienced a severe manifestation of herpes zoster, three patients interrupted the treatment because of blood test abnormalities and one due to unplanned pregnancy.

Discussion

To the best of our knowledge, this is the first systematic review aiming to provide real-world data, specifically on patients' characteristics, treatment regimens, clinical effectiveness and safety related to upadacitinib for the treatment of severe AD.

In most real-world studies, the patient cohorts were slightly older than in randomized clinical trials (RCTs), except for two studies that included adolescent patients.^{27,34} Moreover, the baseline level of disease activity was lower, as the mean EASI scores in Measure Up 1 and 2 were higher than in the studies included in this systematic review.⁵ The number of patients treated with upadacitinib 15 mg was comparable to the number of patients treated with upadacitinib 30 mg.

In terms of effectiveness, the percentage of patients achieving EASI 75 in most of the real-world studies analyzed was higher compared to the data from the RCTs. In the Measure Up 1 and Measure 2 clinical trials, EASI 75 was achieved by 69.6% and 60.1% of patients treated with upadacitinib 15 mg and 79.7% and 72.9% of patients treated with upadacitinib 30 mg, respectively, after 16 weeks of treatment.⁵ The percentages of patients achieving EASI 75 in the AD Up clinical trial were 64.6% and 77.1% for upadacitinib 15mg and 30mg, respectively.¹⁹ In the Phase 3b Heads Up clinical trial comparing the efficacy of upadacitinib 30 mg with dupilumab, the rate of EASI 75 after 16 weeks of treatment was comparable to other RCTs (71% of patients).⁸

The percentage of patients reaching EASI 90 and complete skin clearance (EASI 100) was also comparable or slightly better in most real-world studies than in RCTs. After 16 weeks of treatment with upadacitinib 30 mg, EASI 90 was achieved by 63.1% and 60.6% of patients in the AD Up and Heads Up clinical trials, respectively. Complete skin clearance was achieved by 22.6% and 27.9% of patients in the same clinical trials.^{8,19}

In this systematic review, there was significant heterogeneity regarding the effectiveness data, likely due to differences in study methods, such as baseline patient characteristics and sample size. However, improvement in disease activity was often observed within 16 weeks of starting upadacitinib and was sustained over time, as also confirmed by an open-label extension study of the Heads Up trial.³⁸

Real-world studies also confirmed the effectiveness of upadacitinib among different patient phenotypes, as it showed comparable responses in those with prominent involvement of the head/neck district or hands.^{24,25} Recently, upadacitinib has also been successfully used for the treatment of concomitant psoriasis and AD due to its broader action on inflammatory cytokines involved in both diseases.³⁹

Regarding safety, papulopustular acne, herpes simplex infection, and upper respiratory tract infection were the most common AEs observed in the real-world setting. No new safety concerns have been identified despite the large number of patients who are older and have more comorbidities than those enrolled in RCTs. The number of AEs of special interest (including malignancies, major adverse cardiovascular events, deep vein thrombosis and serious infections) also remained stable, with only two real-world studies reporting thrombophlebitis in patients older than 65 years.^{23,29} According to EMA recommendations, JAKi should be used cautiously in patients older than 65 years, and IL-13 or IL-4/13 inhibitors should be primarily considered in this cohort due to their different safety profiles, according to clinical trials and real-world experiences.⁴⁰⁻⁴² However, some of the studies analyzed in this review also included patients older than 65 without significant safety findings, which is consistent with a recent case series on seven over-65 patients treated with upadacitinib for at least 32 weeks.⁴³

According to this systematic review, patients who may benefit most from upadacitinib are those with high levels of pruritus and AD affecting sensitive areas such as the face/neck, hands and genitalia. Upadacitinib has been effective in patients with features of both psoriasis and AD, likely due to the broad spectrum of action of JAKi on cytokines involved in the pathogenesis of both conditions. Although data are limited, JAKi, and in particular upadacitinib, could be considered for patients with concomitant asthma or allergic rhinitis, especially those with mild to moderate symptoms.⁴⁴ This systematic review has a few limitations. First, the reliability of the summary of a systematic review depends on the strength of the methods used in each underlying study. Second, real-world studies have inherent biases, such as the selection bias and the presence of confounders. Third, the heterogeneity of all included studies, in terms of concomitant AD treatment, wash-out from previous therapies and dosage of upadacitinib, could possibly affect the conclusion of our review. Last, given the inclusion of several real-world experiences from the same geographic area, it is likely that some patients could have been enrolled in multiple studies.

Conclusion

Upadacitinib represents one of the most recent treatment options for severe AD. This systematic review evaluated available real-world data in order to offer an overview of the practical use of this drug in a clinical setting.

In the future, it will be critical to conduct longer studies to further assess the effectiveness and safety of upadacitinib since only very few experiences reported a follow-up longer than 4 months.

Disclosure

L. Gargiulo has been a consultant for Almirall. L. Ibba has been a consultant for Almirall.

A. Costanzo has served as an advisory board member, consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Biogen, LEO Pharma, Lilly, Janssen, Novartis, Pfizer, Sanofi Genzyme, and UCB-Pharma. 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 Valenti reports personal fees from AbbVie, personal fees from Eli-Lilly, personal fees from Almirall, personal fees from Novartis, personal fees from UCB, personal fees from Leopharma, personal fees from Boehringer-Ingelheim, personal fees from Sanofi, outside the submitted work. The authors report no other conflicts of interest in this work.

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