

JAK inhibitors in the treatment of atopic dermatitis

Inibidores de JAK no tratamento da dermatite atópica

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ABSTRACT

Atopic dermatitis is the most common inflammatory skin disease worldwide. The JAK/STAT pathway plays an important role in the disease mechanism, and small-molecule JAK inhibitors are drugs with great potential for use in atopic dermatitis. We systematically reviewed PubMed using the search terms “atopic dermatitis” AND/OR “JAK inhibitors” AND/OR “small molecules” for studies published between 2017 and 2022. Results from phase III trials evaluating both topical and systemic application of JAK inhibitors were included. Of 646 studies retrieved, 37 evaluating the efficacy and safety of JAK inhibitors in humans were selected for analysis. When properly indicated, the use of JAK inhibitors yielded positive results, some of which were superior to those of recommended treatments for the control of atopic dermatitis, with a good safety profile.

Keywords: Atopic dermatitis, JAK inhibitors, small molecules.

Introduction

Atopic dermatitis, a chronic, recurrent inflammatory disease also known as atopic eczema, is the most prevalent inflammatory skin disease. Furthermore, recent evidence reveals that it is among the top 30 chronic diseases with the highest non-fatal burden of disease, or years lived with disease (YLD), worldwide.^{1,2}

It is characterized by pruritus and eczema, and its morphology are seen in different anatomical locations

RESUMO

A dermatite atópica é a doença inflamatória cutânea mais prevalente mundialmente. A via JAK/STAT tem papel importante no mecanismo da doença e as pequenas moléculas inibidores de JAK são fármacos com grande potencial de uso na dermatite atópica. Foi realizada uma revisão sistemática da literatura na base de dados PubMed, utilizando os termos “atopic dermatitis” e/ou “JAK inhibitors” e/ou “small molecules” entre 2017 e 2022. Foram incluídos os resultados disponíveis de estudos de fase 3, avaliando o uso de inibidores de JAK em apresentações tópicas e sistêmicas. Entre 646 estudos, foram selecionados 37 em humanos que avaliaram a eficácia e segurança dos inibidores de JAK. Os resultados do uso, quando bem indicados, mostraram-se positivos e em alguns casos superiores a outros tratamentos já preconizados para o controle da dermatite atópica, com um bom perfil de segurança.

Descritores: Dermatite atópica, inibidores de JAK, pequenas moléculas.

that may vary depending on the age of the patient, and is manifested with a broad spectrum of clinical presentations. Considering its clinical heterogeneity, epidemiological data on its prevalence are variable.

The International Study of Asthma and Allergies in Childhood (ISAAC) was a study designed to estimate the prevalence of allergic diseases among children and adolescents in different regions of the world. In the first phase, children aged 6 to 7 years and adolescents

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aged 13 to 14 years from 56 and 38 countries, respectively, answered a standardized questionnaire. The results for the prevalence of atopic dermatitis varied between 0.3% and 20.5%, depending on the geographical region, and the disease showed to be more prevalent in regions of lower latitude and with smaller temperature variations. In Brazil, the mean prevalence of eczema was 11.5% among participants of 20 Brazilian cities, assessed from 2002 to 2003.³

Disease pathophysiology is well understood. Atopic dermatitis is caused by genetic factors, changes in immunological and inflammatory response, and changes in skin barrier. Patients with atopic dermatitis present an exacerbated type 2 immunological response. Type 2 inflammatory cytokines, especially interleukin (IL)-4, IL-5 and IL-13, can inhibit proteins and lipids in the skin barrier, contributing to its disruption. Furthermore, it is known that these type 2 cytokines participate also in the activation of eosinophils and mast cells, in addition to increasing the production of IgE.⁴

Janus kinase (JAK) enzymes are important mediators of the intracellular action of several substances, including inflammatory cytokines. When their receptors are activated, there is phosphorylation of signal transducers and activators of transcription (STATs), which may be translocated to the cell nucleus, inducing transcription and regulation of expression of the selected genes. This pathway stimulates the expression of several molecules and cytokines that facilitate leukocyte mobilization and cell proliferation. Therefore, the JAK/STAT pathway has a crucial role in the function of hematopoietic and immunological cells, and recent studies show that this pathway may have higher susceptibility to activation in patients with asthma, atopic dermatitis, and allergic rhinitis, diseases characterized by increased type 2 inflammatory interleukins^{5,6} (Figure 1).

Patients with moderate-to-severe atopic dermatitis who did not respond to topical treatments require systemic immunosuppressant drugs. With improved understanding on disease pathophysiology, the use of immunobiological agents was approved for atopic dermatitis. Dupilumab is the only agent approved for the treatment of atopic dermatitis.^{7,8} It was considered a hallmark in the direction that disease treatment could take. It is a monoclonal IgG4 antibody that inhibits IL-4 receptor and IL-13 in type 2 inflammatory response.⁹ It is a well-tolerated medication with a good response in groups of adults and children over 6 years of age. Despite promising results, there is a group of patients

who did not respond to treatment, either partially or totally, reinforcing the need to continue scientific studies for the development of new therapeutic classes.

JAK inhibitors are small molecules, i.e., low-molecular-weight drugs, which can easily pass through the cell membrane and reach intracellular targets. Thus, they act inhibiting signaling mediated by specific cytokines, acting in chains of specific receptors of Janus Kinase subtypes (JAK-1, JAK-2, JAK-3) and/or Tyrosine-Kinase 2 (TYK-2).^{10,11} The first JAK-inhibitor drug was approved for clinical practice in 2011, for autoimmune disease.¹² Its clinical use is comprehensive, ranging from oncology up to combat of viral diseases, and shows great potential of action in allergic diseases with type 2 immunological response. Future perspectives of JAK inhibitors have been increasingly assessed in atopic dermatitis, and its use have been recently regulated in several countries, both in topical and systemic forms.

Methodology

A systematic literature review was conducted, using the PubMed/MEDLINE database as the research source. The terms “atopic dermatitis” and/or “JAK inhibitors” and/or “small molecules” were used, from 2017 to July 2022. The choice for this date was based on the fact that 2017 was the year when dupilumab was approved for use in atopic dermatitis both by the FDA and by ANVISA, being the first biological drug approved.

This review selected clinical trials on atopic dermatitis in humans treated with systemic or topical JAK inhibitors that assessed drug efficacy and safety.

The selection excluded studies characterized as literature reviews, case reports, expert opinions, laboratory or animal experimental studies, studies focusing only on drug pharmacokinetics, and studies that assessed the use of JAK inhibitors in other diseases.

Results

A total of 646 studies were found, of which 609 were excluded because they were literature reviews, laboratory or animal experimental studies, duplicate results, or because they did not meet the other inclusion criteria. Thirty-seven publications showing the results

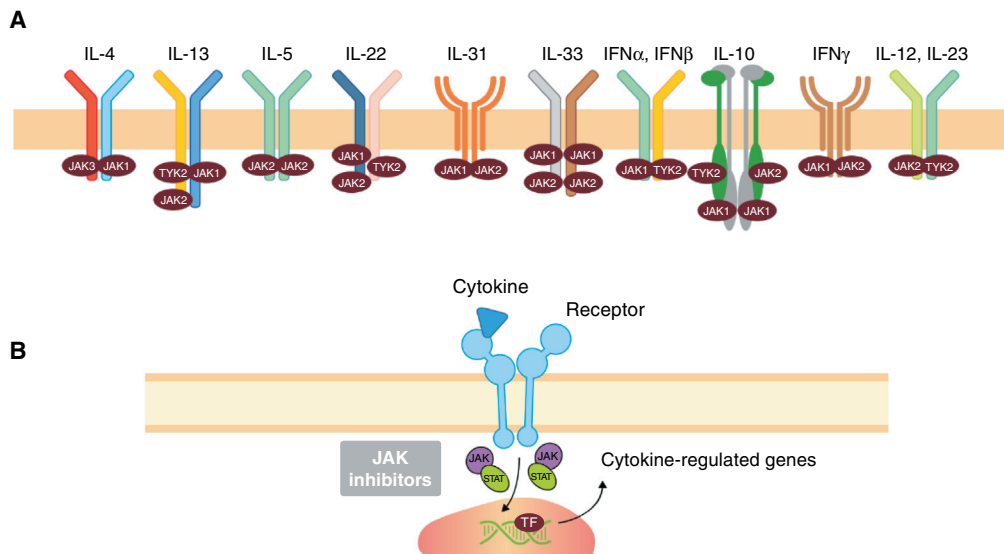


Figure 1
 A) JAK signaling with cytokines involved in immunological response and immune-mediated diseases
 B) JAK/STAT pathway
 Adapted from Ahn J, et al.⁵⁶

of clinical trials involving JAK inhibitors were selected. Considering that some publications display different points of analysis based on the same population, i.e., they are derived from the same controlled trial, it was observed that the 37 selected articles were based on 25 clinical multicenter randomized trials.

The selected articles analyzed the effects of different drug doses, compared with a placebo group and in some cases with other treatments already established in the literature. The main scores used to assess disease evolution were the Eczema Score and Severity Index (EASI) and the Investigator Global Assessment (IGA). The EASI score consists of rater's assessment to define the extent of the lesion in each body region and then the severity of erythema, edema, excoriation, and lichenification is classified from 0 to 3. The sum of the points classifies disease severity, with a score above 21 points indicating severe disease. Previous studies assessed the EASI scores of patients before

treatment and improvement in percentage after using the medications. One of the outcomes assessed was the proportion of patients who showed 75% improvement from baseline, named EASI-75, or 90% clinical improvement, EASI-90, for example. The IGA, in turn, consists of the morphological description of lesions, ranging from 0 to 4. Most studies established an IGA score of 0/1 (asymptomatic or mild disease) as a therapeutic target.

In addition to also using other scales to assess control of lesions and quality of life, some studies assessed the severity of patients' pruritus through the Pruritus Numerical Rating Scale (NRS), which consists of two questions scored from 0-10. Significant improvement was considered when patients showed a decrease of 4 points or more in the NRS scale.

The main results of phase 3 studies found when applying the search terms on PubMed, considering systemic and topical drugs, are shown in Table 1.

Table 1
Phase 3 studies with JAK inhibitors in atopic dermatitis

Drug	Target	Phase 3 study	Inclusion criteria	Population	Time of assessment	EASI-75	IgA 0/1 (Improvement ≥ 2 points)	Most common adverse effects
Upadacitinib (Up.)	JAK-1	MEASURE UP 1 (NCT03569293)	EASI ≥ 16	847 (12 - 75 years)	16 weeks	Up. 15 mg: 69.6%	Up. 15 mg: 48.1%	Acne, URTI, nasopharyngitis, headache, increased CPK
			IGA ≥ 3			Up. 30 mg: 79.7%	Up. 30 mg: 62.0%	
			NRS ≥ 4			Placebo: 16.3%	Placebo: 8.4%	
Oral route	JAK-1	MEASURE UP 2 (NCT03607422)	EASI ≥ 16	836 (12 - 75 years)	16 weeks	Up. 15 mg: 60.1%	Up. 15 mg: 38.8%	Acne, URTI, nasopharyngitis, headache, increased CPK
			IGA ≥ 3			Up. 30 mg: 72.9%	Up. 30 mg: 52.0%	
			NRS ≥ 4			Placebo: 13.3%	Placebo: 4.7%	
Oral route	JAK-1	AD UP (NCT03568318)	EASI ≥ 16	901 (12 - 75 years)	16 weeks	Up. 15 mg: 64.6%	Up. 15 mg: 39.6%	Acne, nasopharyngitis, URTI, herpes oral, increased CPK, headache
			IGA ≥ 3			Up. 30 mg: 77.1%	Up. 30 mg: 58.6%	
			NRS ≥ 4			Placebo: 26.4%	Placebo: 10.9%	
Oral route	JAK-1	HEADS UP (NCT03738397)	EASI ≥ 16	692 (18 - 75 years)	16 weeks	Up. 30 mg: 71.0%	Not reported	Acne, URTI, increased CPK, nasopharyngitis
			IGA ≥ 3			Dup. 300 mg: 61.1%		
			NRS ≥ 4					
Abrocitinib (Ab.)	JAK-1	JADE MONO-1 (NCT03349060)	EASI ≥ 16	387 (12 - 75 years)	12 weeks	Ab. 100 mg: 39.7%	Ab. 100 mg: 23.7%	Nausea, nasopharyngitis, headache, URTI
			IGA ≥ 3			Ab. 200 mg: 62.7%	Ab. 200 mg: 43.8%	
			NRS ≥ 4			Placebo: 11.8%	Placebo: 7.9%	
Oral route	JAK-1	JADE MONO-2 (NCT03575871)	EASI ≥ 16	391 (12 - 75 years)	12 weeks	Ab. 100 mg: 44.5%	Ab. 100 mg: 38.1%	URT, nasopharyngitis, headache, nausea, vomiting, acne
			IGA ≥ 3			Ab. 200 mg: 61.0%	Ab. 200 mg: 28.4%	
			NRS ≥ 4			Placebo: 10.4%	Placebo: 9.1%	
Oral route	JAK-1	JADE COMPARE (NCT03720470)	EASI ≥ 16	837 (≥ 18 years)	12 weeks	Ab. 100 mg: 58.7%	Ab. 100 mg: 36.6%	Similar to the previous studies
			IGA ≥ 3			Ab. 200 mg: 70.3%	Ab. 200 mg: 48.4%	
			NRS ≥ 4			Dup. 300 mg: 58.1%	Dup. 300 mg: 36.5%	
Oral route	JAK-1	JADE TEEN (NCT03796676)	EASI ≥ 16	285 (12 - 17 years)	12 weeks	Ab. 100 mg: 68.5%	Placebo: 14.0%	URT, headache, nasopharyngitis, dizziness, acne, vomiting
			IGA ≥ 3			Ab. 200 mg: 72.0%	Ab. 100 mg: 41.6%	
			NRS ≥ 4			Dup. 300 mg: 41.5%	Ab. 200 mg: 46.2%	

Table 1 (continuation)
Phase 3 studies with JAK inhibitors in atopic dermatitis

Drug	Target	Phase 3 study	Inclusion criteria	Population	Time of assessment	EASI-75	IgA 0/1 (Improvement ≥ 2 points)	Most common adverse effects
Baricitinib (Bar.)	JAK-1 JAK-2	BREEZE 1 (NCT03334396)	EASI ≥ 16 IGA ≥ 3	624 (≥ 18 years)	16 weeks	Bar. 1 mg: 17.3%	Bar. 1 mg: 11.8%	Nasopharyngitis, URTI, diarrhea, headache
						Bar. 2 mg: 18.7%	Bar. 2 mg: 11.4%	
						Bar. 4 mg: 24.8%	Bar. 4 mg: 16.8%	
					Placebo: 8.8%	Placebo: 4.8%		
Oral route	JAK-1 JAK-2	BREEZE 2 (NCT03334422)	EASI ≥ 16 IGA ≥ 3	615 (≥ 18 years)	16 weeks	Bar. 1 mg: 12.8%	Bar. 1 mg: 8.8%	Herpes simplex, nasopharyngitis, increased CPK, headache
						Bar. 2 mg: 17.9%	Bar. 2 mg: 10.6%	
						Bar. 4 mg: 21.1%	Bar. 4 mg: 13.8%	
					Placebo: 6.1%	Placebo: 4.5%		
Oral route	JAK-1 JAK-2	BREEZE 4 (NCT03428100)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10% Contraindication to ciclosporin	463 (≥ 18 years)	16 weeks	Bar. 1 mg: 22.6%	Bar. 1 mg: 12.9%	Nasopharyngitis, herpes simplex, influenza, headache, back and abdominal pain, diarrhea, conjunctivitis
						Bar. 2 mg: 27.6%	Bar. 2 mg: 15.1%	
						Bar. 4 mg: 31.5%	Bar. 4 mg: 21.7%	
					Placebo: 17.2%	Placebo: 9.7%		
Ruloxitinib (Rul.)	JAK-1 JAK-2	BREEZE 5 (NCT03435081)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10%	440 (≥ 18 years)	16 weeks	Bar. 1 mg: 12.9%	Bar. 1 mg: 12.9%	Nasopharyngitis, URTI
						Bar. 2 mg: 29.5%	Bar. 2 mg: 24.0%	
						Placebo: 8.2%	Placebo: 5.4%	
Topic	JAK-1 JAK-2	BREEZE 7 (NCT03733301)	EASI ≥ 16 IGA ≥ 3 BSA ≥ 10%	329 (≥ 18 years)	16 weeks	Bar. 2 mg: 43.1%	Bar. 2 mg: 23.9%	Folliculitis, URT, nasopharyngitis
						Bar. 4 mg: 47.7%	Bar. 4 mg: 30.6%	
						Placebo: 22.9%	Placebo: 14.7%	
Ruloxitinib (Rul.)	JAK-1 JAK-2	TRuE-AD 1 (NCT03745638)	IGA 2/3 BSA 3-20% (except for scalp)	631 (≥ 12 years)	8 weeks	Rux. 0.75%: 56.0%	Rux. 0.75%: 50.0%	Nasopharyngitis, URTI, headache
						Rux. 1.5%: 62.1%	Rux. 1.5%: 53.8%	
						Vehicle: 24.6%	Vehicle: 15.1%	
Topic	JAK-1 JAK-2	TRuE-AD 2 (NCT03745651)	IGA 2/3 BSA 3-20% (except for scalp)	618 (≥ 12 years)	8 weeks	Rux. 0.75%: 51.5%	Rux. 0.75%: 39.0%	URT, nasopharyngitis
						Rux. 1.5%: 61.8%	Rux. 1.5%: 51.3%	
						Vehicle: 14.4%	Vehicle: 7.6%	
Delgocitinib (Del.)	pan-JAK	OBA 4-1 (JapicCTI-173554)	EASI ≥ 10 BSA 10-30%	158 (≥ 16 years)	4 weeks	Del. 0.5%: 26.4%	Del. 0.5%: 10.4%	Contact dermatitis
						Vehicle: 5.8%	Vehicle: 3.8%	
							FACE:	
Topic	pan-JAK	JapicCTI-184064)	EASI ≥ 5 IGA 2-4 BSA 5-30%	137 (2 - 15 years)	4 weeks	Del. 0.25%: 37.7%	Del. 0.5%: 22.8%	Nasopharyngitis, folliculitis
						Vehicle: 4.4%	Vehicle: 4.0%	
							Not reported	

Upadacitinib

Upadacitinib is a selective JAK-1 inhibitor that blocks the action of the main pro-inflammatory cytokines. It has been previously approved for use in rheumatoid arthritis in several countries.

The first phase 2 study of upadacitinib for atopic dermatitis assessed the use of monotherapy at doses of 7.5 mg, 15 mg and 30 mg compared to placebo, in 167 patients aged from 18 to 75 years and diagnosed with moderate-to-severe atopic dermatitis, who were followed for 16 weeks. Patients' clinical improvement was shown to be proportionally greater as the dose increased. These findings supported the decision to maintain 15 mg and 30 mg doses in phase 3 studies. Nearly 69% of patients on upadacitinib 30 mg achieved EASI-75, followed by 52% in the group treated with 15 mg, 29% in the group using the lowest dose (7.5 mg), and 10% in the placebo group.^{13,14}

Measure Up 1 and 2 were two replicate multicenter, double-blind, phase 3 trials that involved 847 and 836 volunteer patients, respectively, aged from 12 to 75 years, in more than 150 international specialized centers, who were assigned to receive upadacitinib 15 mg, upadacitinib 30 mg, or placebo, and were initially followed up for 16 weeks. In the two studies, patients who received any dose of the medication already started to have a significant improvement in EASI scores with two weeks of treatment, with 42.7% and 38.5% of patients treated with upadacitinib achieving EASI-75 in Measure Up 1 and Measure Up 2, respectively, compared with 3.6% of patients from the placebo group in both studies. At week 16, considering the sum of the populations in the two study groups, nearly 76.3% of patients treated with upadacitinib 30 mg and 64.9% of patients treated with 15 mg achieved EASI-75, compared with only 14.8% in the placebo group. Pruritus was evaluated using the NRS scale, and nearly 9.8% of patients started to have an improvement of 4 points or more as early as after 2 days of treatment with 30 mg, and 9.9% of participants after 3 days of treatment with 15 mg.¹⁵

The AD Up trial assessed a population of 901 patients aged 12-75 years receiving topical corticosteroids in combination with upadacitinib, allocated into three groups: upadacitinib 15 mg, upadacitinib 30 mg, or placebo. Combined medications were well tolerated by patients, and efficacy after 16 weeks was also higher in patients who used JAK inhibitor, with 77.1% of patients obtaining EASI-75 with 30 mg, and 64.6% with 15 mg, *versus* 26.4% of

the placebo group. With regard to control of pruritus, 63.9% of patients receiving 30 mg achieved a 4 point reduction or more in NRS, 51.7% of patients treated with 15 mg, and only 15.0% in the placebo group at the end of 16 weeks.¹⁶

In the Measure Up 1 and 2 trials, the incidence of adverse effects was similar in the 15 mg and 30 mg groups. The incidence of serious infections was below 1% in all groups that received treatment. Patients who received the highest dose had more hematological changes, and up to 5% of patients in the 30 mg group presented with neutropenia in Measure Up 1, mostly transient, and none led to treatment discontinuation. In the two groups, the most frequent adverse effects were: acne (9.7% with 15 mg and 15.9% with 30 mg), upper respiratory tract infection and nasopharyngitis (14.7% with 15 mg and 18.7% with 30 mg), headache (5.7% with 15 mg and 6.9% with 30 mg), and elevation in creatine phosphokinase levels (4.5% with 15 mg and 4.9% with 30 mg). In the AD Up trial, the most common adverse effects were similar to the aforementioned ones, and there was no difference in serious adverse effects between treatment and placebo groups.^{15,16}

One of the main effects observed in these two large phase 3 trials (Measure Up and AD Up) was the onset of acne vulgar (more than 5%). Most cases were of mild-to-moderate acne, with only one case of severe acne. Overall, three patients discontinued treatment due to acne. This adverse effect was more commonly observed in adult, female, and non-White patients, and its incidence was proportionally higher as the dose increased. The face was the most common location of acne. The onset of lesions occurred on nearly 40-43 days of treatment, and about 40-46% of the cases did not require additional treatment.¹⁷ Eczema herpeticum was more reported in studies that assessed upadacitinib in atopic dermatitis than in others diseases. In the Measure Up trials, 20 patients who received medication presented with cases of herpes zoster versus only 2 patients in the placebo group.¹⁵

Studies were extended to observe patients using upadacitinib up to 52 weeks of treatment. In the Measure Up trial, 82.0% of patients in the 15 mg group and 84.9% of those in the 30 mg group achieved EASI-75, showing greater potential for clinical improvement with maintenance of medication for longer periods.¹⁸ In the AD Up trial, in turn, nearly 69.0% of patients in the upadacitinib 30 mg group and 50.8% in the 15 mg group achieved EASI-75 at

week 52, with no significant changes from the results obtained at week 16, showing a slight loss of efficacy with the two doses.¹⁹ No differences were observed in adverse effects in the two studies with more prolonged treatment. The participants of the studies continued follow-up, and further analyses are planned when completing 260 weeks of treatment.

Furthermore, upadacitinib was compared with dupilumab in a study with 692 patients aged from 18 to 75 years, divided into two groups, one receiving treatment with upadacitinib, 30 mg daily, and the other receiving dupilumab, 300 mg, every 14 days. It was observed that, at the end of 16 weeks of treatment, 60.6% patients in the group treated with JAK inhibitor achieved EASI-90, compared with 38.7% in the group who received the immunobiological agent ($p = 0.006$).²⁰

Two studies were found on the PubMed platform that reported the experience of using upadacitinib in populations of specific countries. The Rising UP trial was conducted in Japan and included 272 patients aged from 12 to 75 years, receiving 15 mg, 30 mg, or placebo. Results similar to the findings of studies with international population, in which 65.3% of patients using 15 mg, and 76.2% using 30 mg, achieved EASI-75 at the end of 16 weeks.²¹ In Spain, a study by Pereyra-Rodriguez et al., with a smaller sample of only 43 participants over 12 years of age, showed that 76.3% of patients treated with 30 mg and 64.9% of those treated with 15 mg achieved EASI-75. In this study, all patients below 18 years and over 65 years received 15 mg.²²

With the promising results published, upadacitinib was approved for the treatment of atopic dermatitis in patients over 12 years by the European Union in August 2021,²³ by the FDA in January 2022,²⁴ and by the ANVISA in May of the same year, for use with initial doses of 15 mg/day.²⁵

Abrocitinib

Abrocitinib is also a systemic selective JAK-1 inhibitor administered orally. A phase 2 study assessed 267 patients aged from 18 to 75 years for 12 weeks. They were stratified into groups receiving 200 mg, 100 mg, 30 mg, 10 mg, or placebo. The groups that received doses higher than 100 mg or 200 mg showed significant results compared with placebo, with the improvement of disease severity and pruritus, whereas patients who received lower doses did not show significant improvement.^{26,27}

The group of studies named JADE is the largest phase 3 clinical trials of abrocitinib and evaluated several populations with different purposes. JADE MONO-1 was the first study to assess the effect of abrocitinib monotherapy in 387 patients aged from 12 to 75 years, predominantly with moderate atopic dermatitis. The patients were randomized to receive 100 mg, 200 mg, or placebo for 12 weeks. In this study, 62.7% of the patients treated with the highest dose, and 39.7% of those treated with the lowest dose, achieved EASI-75, versus 11.8% in the placebo group. Control of pruritus was assessed with 2 weeks of treatment, showing improvement in 46% and 20% of patients treated with 200 mg and 100 mg, respectively. This proportion increased at the end of the 12 weeks, and nearly 57.2% and 37.7% of patients showed an improvement of 4 points or more in their NRS score.²⁸

With regard to adverse effects, 69% of patients treated with 100 mg, and 78% of those treated with 200 mg, reported some reaction potentially related to the treatment. The most frequent symptom was nausea, present in 20% of patients who received 200 mg, and in 9% of those who received the reduced dose, versus 3% in the placebo group. Other common symptoms were nasopharyngitis (12% with 200 mg and 15% with 100 mg), headache (10% with 200 mg and 8% with 100 mg), and upper respiratory tract infection (7% in both groups). Nearly 14% of patients treated with 100 mg presented with worsening of dermatitis symptoms. In the control group, this percentage was of 17%, and decreased to 5% in patients treated with 200 mg. Serious adverse effects that were considered related to treatment were reported for two patients, one who developed intestinal inflammatory disease while using abrocitinib 200 mg, and other who evolved with pancreatitis while using abrocitinib 100 mg, but no deaths were reported. Overall, 22 patients (14%) developed herpes virus-related infections (herpes simplex, zoster, oral, or eczema herpeticum) while receiving treatment with any dose, and only 1 patient had eczema herpeticum in the placebo group. A trend of dose-dependent thrombocytopenia was observed at nearly week 4 of treatment. One patient discontinued treatment due to persistent thrombocytopenia.²⁸

JADE MONO 2 was a replicate study with 391 patients that used the same methodology as the previous one and showed similar results. At the end of 12 weeks, 61% of patients treated with 200 mg and

44.5% of those treated with 100 mg achieved EASI-75. Control of pruritus was also similar, and median time for improvement was 29 days in the 200 mg group and 58 days in the 100 mg group.²⁹

With regard to IGA score, in the JADE MONO 1 trial, 43.8% of patients treated with 200 mg and 23.9% of those treated with 100 mg achieved IGA 0/1 in the analysis of the 12 weeks of treatment. In JADE MONO 2, even few patients achieved the target, with 38.1% in the 200 mg group and 28.4% in the 100 mg group. Overall, nonresponders according to the IGA score had more severe atopic dermatitis at baseline. Considering the entire population assessed in the phase 2b study, along with that assessed in JADE MONO 1 and 2 trials, a higher percentage of patients who achieved the desired IGA score was classified as having moderate atopic dermatitis at baseline, compared with nonresponders (72.7% versus 58.8% of patients with IGA 3 at baseline). When considering other scales to assess dermatitis, many patients who did not achieve the target IGA score obtained improvement in clinical status and in scores of others tools, suggesting that the assessment of drug efficacy by IGA may be limited. Among nonresponders according to the IGA score, 41.0% of those who received abrocitinib 200 mg were found to achieve EASI-75 at week 12, followed by 27.0% of those who received abrocitinib 100 mg.³⁰

The JADE REGIMEN trial was designed to assess maintenance therapy. Firstly, patients with moderate/severe atopic dermatitis were selected to receive treatment with abrocitinib 200 mg for 12 weeks. At end of period, only responder patients were stratified, considering IGA, EASI and NRS scores, into three groups: the first would continue to receive 200 mg, other would receive 100 mg, and the last would receive placebo, to be evaluated for 40 weeks. During this period, the rate of failure of maintenance treatment was significantly higher in the 100 mg group compared with the group that received the highest dose (HR 0.36; $p < 0.0001$). It was observed that 39.6% of patients treated with 100 mg and 16.5% of those treated with 200 mg had a therapeutic flare, defined as a 50% reduction in EASI compared to that obtained at week 12 or IGA score of 2 or more. With regard to placebo, the two groups who received the medication exhibited a significant decrease in the rate of therapeutic flare, whereas 77.5% of the patients in the placebo group had a flare.³¹

The JADE COMPARE trial assessed 837 patients randomized to receive abrocitinib 100 mg or 200

mg, dupilumab 300 mg, or placebo. There was no difference in the outcome of patients treated with abrocitinib 100 mg and dupilumab – in both groups, 36% of patients had an IGA score of 0/1 and 58% achieved EASI-75 after 12 weeks of treatment. However, patients in the abrocitinib 200 mg group showed better results, with 48% of them having an IGA 0/1 and 70% achieving EASI-75. The patients with the highest dose present with slightly more mild adverse effects, such as nausea.³² With regard to time to clinical improvement, patients using abrocitinib 200 mg also had better results, with a mean of 29 days to achieve EASI-75. In the group of 100 mg, mean time to achieve EASI-75 was 32 days, and could reach up to 57 days for improvement of lesions in head, neck, and upper limbs, a result similar to that of the dupilumab group.³³

Patients treated with dupilumab after 12 weeks were randomized again to receive treatment with abrocitinib 100 mg or 200 mg until completing 40 weeks of treatment. Of the 54 patients who obtained an improvement of 75 to 90% in EASI with dupilumab, 61.1% achieved EASI-90. Of the 29 patients who did not respond to dupilumab, 8 showed improvement by changing medication. However, some patients who had responded to dupilumab, achieving EASI-75, IGA 0/1 and/or improvement of 4 points or more in the NRS score, did not maintain response using abrocitinib, at percentages ranging from 7.6% to 23.1%, depending on the dose and on the scale used.³⁴

JADE MONO 1 and 2 trials included a small portion of adolescents from 12 to 17 years (21.7% and 10.2% of the sample, respectively). The findings in these populations followed the trend of efficacy observed in the general population, with 54.5% and 60% of patients in JADE MONO 1 and 2 achieving EASI-75 with abrocitinib 200 mg, and 44.1% and 43.8% with abrocitinib 100 mg, respectively. The JADE TEEN trial included 295 adolescents and showed that the difference in results between the different doses was smaller (EASI-75 in 72.0% with 200 mg, and in 68.5% with 100 mg). However, the participants in this study could combine abrocitinib with a topical drug, which was also related to the fact that a higher percentage of patients in the control group showed better clinical response, since 24.5% of patients who received placebo achieved EASI-75 within weeks.^{35,36}

The drug was also approved for use in patients with atopic dermatitis by the FDA for patients over 18 years in the United States in January 2022.³⁷

Baricitinib

Baricitinib is a JAK-1 and 2 inhibitor, and its use in atopic dermatitis has been studied since 2016, when phase 2 studies started.³⁸ The BREEZE-AD program includes 7 phase 3 studies to assess baricitinib efficacy. The first studies, named BREEZE-AD 1 and 2, were two double-blind identical studies that analyzed 624 and 615 participants, respectively, over 18 years of age for 16 weeks, who received placebo or baricitinib 1 mg, 2 mg, or 4 mg. In these first studies, the use of the JAK inhibitor pruritus severity with doses of 2 mg and 4 mg, but improvements in EASI were not equally relevant.³⁹

BREEZE 4 included 463 participants over 18 years of age to analyze patients' response to baricitinib combined with topical corticosteroids versus placebo. Patients who received 4 mg of the medication achieved EASI-75 in 32% of the cases, whereas 28% of those who received 2 mg reached EASI-75, with no significant difference from placebo (17%).⁴⁰

BREEZE 5 is a study that includes only the American and Canadian population, with 440 participants, and analyses the effect of smaller doses of baricitinib 1 mg and 2 mg compared with placebo. It was observed that only baricitinib 2 mg had a significant result compared with placebo, after 16 weeks of use, EASI-75 and IGA score of 0/1 in was achieved by 37.1% and 31.7% of baricitinib 2-mg-treated patients with body surface area affected from 10-50, compared with 9.9% and 6.9%, respectively, in the placebo group ($p < 0.001$). In patients with greater body surface area affected and receiving 1 mg, there were no significant differences with regard to placebo.^{41,42}

Among the 329 patients of BREEZE 7, nearly 31% of those who received 4 mg had an IGA score of 0/1, compared with 15% of those in the placebo group. The difference between the baricitinib 2 mg and placebo groups were not statistically significant also, considering the IGA score. Furthermore, it was observed that 48% and 43% of 4-mg and 2-mg-treated patients, respectively, achieved EASI-75, versus 23% of those in the placebo group.⁴³

Considering all the studies, the percentage of patients who achieved EASI-75 with baricitinib 4 mg in the BREEZE AD 1, 2, 4 and 7 trials was 24.8%, 21.1%, 31.1%, and 47.7%, respectively. These results are inferior when compared with other JAK inhibitors.⁴⁴ In an indirect comparison with previous studies using dupilumab, the BREEZE trials were not

able to show superior results as compared with the immunobiological agent (51% of the sample achieved EASI-75 in SOLO 1, and 44% in SOLO 2, studies that validated dupilumab in atopic dermatitis).⁴⁵⁻⁴⁶

Although having a lower reported efficacy compared with the other two oral JAK inhibitors in phase 3 studies for atopic dermatitis, baricitinib was the first JAK inhibitor approved for eczema in Europe, in September 2020.⁴⁴

Ruxolitinib

Ruxolitinib is a JAK-1 and JAK-2 topical inhibitor developed to optimize drug action directly on the affected areas and reduce the risk of systemic adverse effects. In a phase 2 study, ruxolitinib promoted a rapid and sustained improvement of lesions, and no significant adverse effect was observed.⁴⁷ This study was conducted in the United States and Canada and evaluated 307 patients aged from 18 to 70 years to compare the effect of topical ruxolitinib at doses of 0.15%, 0.5%, and 1.5%, once or twice daily, with 0.1% triamcinolone and vehicle. Patients were initially assessed for a period of 4 weeks, and medications were not applied on the facial region. After the first month of treatment, lower concentrations of ruxolitinib did not lead to superior results compared with topical corticosteroids. Among patients who received ruxolitinib 1.5% twice daily, 56% achieved EASI-75, versus 47.1% in the corticosteroid group and 17.3% in the vehicle group. After week 4, patients who received triamcinolone used vehicle for 4 weeks and, after week 8, all patients received ruxolitinib 1.5% twice daily until completing 12 weeks of analysis. At that time, 73.2% of the 252 patients who completed the study achieved EASI-75, which indicates that changing to the topical JAK inhibitor led to additional improvement of lesions.⁴⁸

The TRuE-AD 1 and 2 trials were two parallel, double-blind, phase 3 studies that assessed the effect of topical ruxolitinib in patients over 12 years of age with mild/moderate atopic dermatitis, evaluated for 8 weeks. Overall, 631 patients were randomized in TRuE-AD 1, and 616 patients in TRuE-AD 2, to receive ruxolitinib cream 0.75%, 1.5% or a vehicle cream with no active compound, applied twice daily.⁴⁹

The two concentrations of ruxolitinib led to an improvement in lesions compared with vehicle. Among patients who used ruxolitinib 0.75% in TRuE-AD 1, 50% had an IGA score of 0/1 and 56% achieved EASI-75; conversely, among individuals who received

ruxolitinib 1.5%, 53.8% had an IGA score of 0/1, and 62.1% achieved EASI-75. In the TRuE-AD 2, it was found that 39% and 51.5% of patients who received the lowest concentration of the drug achieved an IGA score of 0/1 and EASI-75, respectively; whereas 51.3% of those who received the highest dose achieved an IGA score of 0/1, and 61.8% of them achieved EASI-75. In the vehicle group, 15.1% and 24.6% of patients reached an IGA score of 0/1 and EASI-75 in TRuE-AD 1, and 7.6% and 14.4% achieved the targets for IGA score and EASI in TRuE-AD 2, respectively.⁴⁹

The most common adverse effect observed in the study was application site burning sensation, which was reported in a higher percentage of patients in the vehicle group (4.4% versus 0.6% with ruxolitinib 0.75% and 0.8% with ruxolitinib 1.5%). No serious adverse effect was related to the use of the medication.⁴⁹

In September 2021, ruxolitinib was approved for use in atopic dermatitis by the FDA, being the first JAK inhibitor approved for use in the United States, at a concentration of 1.5%, in patients over 12 years of age.⁵⁰

Delgocitinib

Delgocitinib is a topical pan-Janus Kinase inhibitor, i.e., it inhibits JAK-1, JAK-2, JAK-3, and TYK-2. Results of phase 1, 2 and 3 studies conducted in Japan were found. In phase 1 studies, the drug was tested in adults, and topical application showed to be safe, with no immediate local reactions and apparent improvement after 7 days of use.⁵⁰

A phase 2 study involved 38 centers and included 366 participants aged from 16 to 65 years randomized to receive delgocitinib at 0.25%, 0.5%, 1%, or 3%, or the vehicle ointment, or tacrolimus 0.1% for 4 weeks. The vehicle group showed the highest rates of patients requiring rescue therapy, and these rates progressively decreased as the dose of delgocitinib increased. In this study, 23% of patients treated with delgocitinib 3% achieved an IGA score of 0/1, compared with 3% of those in the vehicle group. Only the highest dose of delgocitinib showed equal or superior results as compared to tacrolimus.⁵¹

Furthermore, a phase 2 study assessed the use of delgocitinib in the pediatric population, including 103 patients aged from 2 to 15 years with EASI greater than 5, excluding the head/neck region, IGA score equal or higher than 2, and eczema affecting 5 to 30% of the body surface area. Patients were randomized to receive delgocitinib 0.25%, 0.5%, or vehicle. At the

end of 4 weeks, EASI-75% was achieved by 50% of patients in the delgocitinib 0.5% group, 38.2% of those in the 0.25% group, and 8.6% of those in the control group. Improvement of pruritus were already observed at week 1 of treatment, with the two doses.⁵²

The phase 3 study with the pediatric population had two parts. In part 1, 137 patients were randomized to receive delgocitinib 0.25% or vehicle for 4 weeks, and 37.7% of patients receiving medication achieved EASI-75, compared to 4.4% of those in the control group. In part 2, patients were followed up for more 52 weeks while receiving delgocitinib 0.25% or 0.5%. Nearly 52.5% of patients achieved EASI-75. Treatment-related adverse effects were reported in 9.7% of patients, all of which were mild. The most common one was application site folliculitis, and one patient discontinued treatment due to acne.⁵³

Patients over 16 years of age were also included in phase 3 studies. The QBA4-2 study assessed the patients for 52 weeks, when all patients received delgocitinib 0.5%, without any control group. The proportion of patients who achieved EASI-75 was 10.9%, at week 4 and 27.5% at week 52. Serious adverse effects occurred in 1.4% of patients. One participant presented with Kaposi's varicelliform eruption that was considered related to the application, which developed on day 26 of treatment, and had to interrupt medication. Nearly 3.4% of patients discontinued treatment due to adverse effects, the most common of which was contact dermatitis.^{54,55}

Delgocitinib was approved for topical use in atopic dermatitis in Japan, at the concentrations of 0.25% and 0.5%, for the adult population and children over two years of age, in March 2021.⁵⁵

Conclusion

The use of JAK inhibitors has recently started to be regulated for use in atopic dermatitis in clinical practice across different countries. This type of small molecules showed promising results in the treatment of several diseases, such as cancer and autoimmune, viral, and allergic diseases. However, like all new medications, attention should be given to their potential adverse events. By studying the mechanism of action of these drugs, it is possible to raise concerns with regard to the remaining potential effects in other systems that these drugs may eventually affect. The JAK-STAT pathway is known to be present not only in type 2 inflammation, but also participates in the

modulation of other extremely important functions, such as immunity and hematopoietic pathways. When properly indicated, the use of JAK inhibitors yielded positive results, some of which were superior to those of recommended treatments for the control of atopic dermatitis.

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