Comparative efficacy of abrocitinib, baricitinib and upadacitinib for the treatment of atopic dermatitis.

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SUMMARY:
Purpose: To establish, through an indirect comparison (IC) against placebo, whether abrocitinib, baricitinib and upadacitinib can be considered equivalent alternatives in efficacy for the treatment of atopic dermatitis.
Methods: A Pubmed search was performed for pivotal clinical trials (CTs) of abrocitinib, baricitinib, and upadacitinib for atopic dermatitis, as monotherapy (MT) and in combination with topical corticosteroids (TC). The main variable for comparison was EASI75 (Eczema Area and Severity Index) at week 16 after start of treatment. Relative risk (RR) compared to placebo was calculated. Finally, an IC of these drugs was performed using the Bucher method (ITC calculator, Indirect Treatment Comparisons, of the Canadian Agency for Health Technology Assessment). Results were analyzed, seeing if there were statistically significant differences between these three drugs.
Results: Eight CT were found: two of abrocitinib (1 TC and 1 MT), three of baricitinib (1 TC and 2 MT) and three of upadacitinib (1 TC and 2 MT). All of them versus placebo as common comparator. None of the IC showed statistically significant differences, except in the comparison of baricitinib 2mg versus upadacitinib 15mg, and in baricitinb 4mg versus upadacitinib 30mg, in all cases in favor of upadacitinib.
Conclusion: Given that no statistically significant differences have been established between the different drugs in terms of efficacy, and in those in which it has been found we cannot know if it is a clinically relevant difference, the choice of one or the other should be based on safety and efficiency criteria.

Keywords: **abrocitinib, baricitinib, upadacitinib, atopic dermatitis, efficacy.**

Eficacia comparativa entre abrocitinib, baricitinib y upadacitinib en el tratamiento de la dermatitis atópica

RESUMEN:
Objetivo: Establecer, mediante una comparación indirecta (CI) frente a placebo, si abrocitinib, baricitinib y upadacitinib pueden considerarse alternativas equivalentes en eficacia para el tratamiento de la dermatitis atópica.
Métodos: Se realizó una búsqueda en Pubmed de ensayos clínicos pivotales (EC) de abrocitinib, baricitinib y upadacitinib para la dermatitis atópica, como monoterapia (MT) y en combinación con corticosteroides tópicos (CT). La variable principal de comparación fue el EASI75 (Eczema Area and Severity Index) en la semana 16 tras el inicio del tratamiento. Se calculó el riesgo relativo (RR) en comparación con placebo. Se realizó un CI de estos fármacos mediante el método Bucher (calculadora ITC, Indirect Treatment Comparisons, de la Agencia Canadiense de Evaluación de Tecnologías Sanitarias). Se analizó si existían diferencias estadísticamente significativas entre ellos.
Resultado: Se encontraron ocho EC: dos de abrocitinib (1 CT y 1 MT), tres de baricitinib (1 CT y 2 MT) y tres de upadacitinib (1 CT y 2 MT). Todos ellos frente a placebo como comparador común. Ninguno de las CI mostró diferencias estadísticamente significativas, excepto en la comparación de baricitinib 2mg vs upadacitinib 15mg, y en baricitinb 4mg vs upadacitinib 30mg, a favor de upadacitinib.
Conclusiones: Dado que no se han establecido diferencias estadísticamente significativas entre los distintos fármacos en términos de eficacia, y en aquellos en los que sí se han encontrado no podemos saber si es una diferencia clínicamente relevante, la elección de uno u otro debería basarse en criterios de seguridad y eficiencia.

Palabras clave: **abrocitinib, baricitinib, upadacitinib, dermatitis atópica, eficacia.**

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INTRODUCTION

Atopic dermatitis is an inflammatory skin disease, which usually presents with sensitive and dry skin, localized or disseminated eczematous lesions, generally accompanied by a strong itching sensation.[1]

The scarce information on the incidence and prevalence of this pathology could be due to the wide interindividual variability, the different definitions of the disease, the diagnostic criteria and the lack of a universally accepted index for classifying the severity of the disease, among others[2]. Atopic dermatitis is more common in children than in adults, and in overcrowded urban areas[3]. Regarding adults, a study published in 2018[4] reported a prevalence of atopic dermatitis in adults in the EU of 4.4 % (95 % CI: 4.2-4.6).

Optimal treatment of atopic dermatitis requires an approach that addresses different aspects, such as elimination of factors that trigger disease flares (heat, low humidity, anxiety, stress, skin infections, contact with allergens), restoration of skin barrier function and skin hydration, patient education and pharmacological treatment[5]. Measures such as moisturizing the skin well, the use of topical treatments, phototherapy and oral antihistamines are usually sufficient to control mild disease[6].

From the results obtained from different investigations over the years, it has been evidenced that the Janus kinase (JAK)/Signal Transducers and Activators of Transcription (STAT) pathway is one of the essential signaling pathways in various inflammatory diseases, such as atopic dermatitis. In addition, some interleukins such as IL-4, IL-13 and IL-31 have been found to be major contributors to the chronic pruritus of this disease, and these are transmitted through the JAK-STAT pathway. Therefore, it appears that JAK inhibitors could be promising candidates for the treatment of severe atopic dermatitis[7].

Several JAK inhibitor drugs have been approved in recent years for the treatment of severe atopic dermatitis, including baricitinib, upadacitinib and abrocitinib. However, clinical trials comparing all these alternatives with each other are not available to date. Therefore, the aim of this study is to establish, through an indirect comparison (IC) versus placebo, whether abrocitinib, baricitinib and upadacitinib can be considered equivalent alternatives in efficacy for the treatment of atopic dermatitis, when used both in monotherapy (MT) and concomitantly with topical corticosteroids (TC).

METHODS

A Pubmed search was conducted for pivotal clinical trials (CTs) of abrocitinib (200mg/24h, 100mg/24h), baricitinib (2mg/24h, 4mg/24h) and upadacitinib (15mg/24h, 30mg/24h) for atopic dermatitis, both in monotherapy and in combination with topical corticosteroids. The keywords used were: atopic dermatitis, abrocitinib, baricitinib, upadacitinib. The main characteristics of each trial were collected (randomization, arms of each trial, diagnosis, number of patients, mean age, EASI (Eczema Area and Severity Index) prior to treatment initiation) and assessed for important differences between them.

Table 1. Main characteristics of pivotal clinical trials of JAK inhibitors in the treatment of atopic dermatitis in combination with topical corticosteroids.

DRUG	ABROCITINIB	BARICITINIB	UPADACITINIB
Clinical Trial	Jade Compare[8]	Breeze-AD7[10]	AD UP[12]
Characteristics	Multicentre	Multicentre	Multicentre
	Randomised	Randomised	Randomised
	Double-blind	Double-blind	Double-blind
	Phase 3	Phase 3	Phase 3
Randomisation	2:2:2:1	1:1:1	1:1:1
Study gropus – no. patients	A100mg-226 A200mg-238 Placebo-131 Dupilumab-24	B2mg-109 B4mg-111 Placebo-109	U15mg-281 U30mg-285 Placebo-281
Diagnosis	Moderate/severe atopic dermatitis	Moderate/severe atopic dermatitis	Moderate/severe atopic dermatitis
Total no. of patients	838	329	847
Age - mean±SD	37.7±14.7	33.8±12.4	34.1 (12-75)*
EASI at baseline- mean±SD	30.9±12.8	29.6±12.3	29.7±15.1
Measured Variable	EASI 75 at week 12	EASI 75 at week 16	EASI 75 at week 16
Results obtained:	A 100mg 138/235 (58.7)	B2mg 47/109 (43)	U15mg 194/300 (65)
EASI75 no./total no. (%)[§]	A 200Mmg154/219 (70.3)	B4mg 53/111 (48)	U30mg 229/297 (77)
	Dupilumab 140/241 (58.1)	Placebo 2/1095 (23)	Placebo 80/304 (26)
	Placebo 35/129 (27.1)		

*Clinical trial does not provide data on standard deviation (SD), but rather a range of minimum and maximum values.

[§]Results obtained at week 16 after initiation of treatment, except in the Jade Mono-1 CT where results were measured at week 12.

A100mg: abrocitinib 100mg; A200mg: abrocitinib 200mg; B2mg: baricitinib 2mg; B4mg: baricitinib 4mg; EASI75: Eczema Area and Severity Index; EASI75 no./total no.: number of patients with EASI75/total number of patients; U15mg: upadacitinib 15mg; U30mg: upadacitinib 30mg.

The EASI75 results at week 16 after treatment initiation were used as the primary endpoint for comparison. With the EASI75 results (in %), the relative risk (RR) with respect to placebo was calculated. Finally, with these values, an IC of these drugs was performed using the Bucher method (ITC calculator, Indirect Treatment Comparisons, of the Canadian Agency for Health Technology Assessment). The lower doses of the 3 drugs (abrocitinib 100mg, baricitinib 2mg, upadacitinib 15mg) and the higher doses (abrocitinib 200mg, baricitinib 4mg, upadacitinib 30mg) were compared with each other, both in monotherapy and in combination with topical corticosteroids. The results were analyzed to see if there were statistically significant differences between these three drugs.

RESULTS

Eight CTs were found: 2 of abrocitinib[8,9] (1 with TC and 1 in MT), 3 of baricitinib[10,11] (1 with TC and 2 in MT) and 3 of upadacitinib[12,13] (1 with TC and 2 in MT). All of them versus placebo as a common comparator. The main characteristics of all the CEs are summarized in Table 1 (with TC) and Table 2 (in MT).

Regarding CTs in combination with TC, all studies presented a similar methodology (design, characteristics of the study population, inclusion criteria, primary endpoint). However, the pivotal trial of upadacitinib included patients younger than 18 years of age (corresponding to 12% of the total), unlike the other CTs only included population of legal age. In addition, the sample size differs between CTs (the sample size of the upadacitinib CT is approximately three times larger than that of baricitinib, while that of abrocitinib is in an intermediate position between the other two).

As for the CTs in MT, they also presented similar methodology. However, the abrocitinib CT was the only one not to include patients under 18 years of age (13.5% of patients in the upadacitinib CT and 22% in the baricitinib CT). Regarding the use of TC in these CTs, the abrocitinib CT specifies that no rescue medication or topical corticosteroids were allowed and that those who used them were excluded. The baricitinib CT performs a separate analysis of the patients who did not require rescue with TC, which are shown in Table 1, and which were used to calculate the RR and, therefore, the IC. The CT for upadacitinib points out that patients who used TC were considered non-responders.

Table 2. Main characteristics of pivotal clinical trials of JAK inhibitors for the treatment of atopic dermatitis in monotherapy.

DRUG	ABROCITINIB	BARICITINIB		UPADACITINIB	
Clinical Trial	Jade Mono-1[9]	BREEZE AD1[11]	BREEZE AD2[11]	MEASURE UP1[13]	MEASURE UP2[13]
Characteristics	Multicentre	Multicentre	Multicentre	Multicentre	Multicentre
	Randomised	Randomised	Randomised	Randomised	Randomised
	Double-blind	Double-blind	Double-blind	Double-blind	Double-blind
	Phase 3	Phase 3	Phase 3	Phase 3	Phase 3
Randomisation	2:2:1	1:1:1:2	1:1:1:2	1:1:1	1:1:1
Study gropus – no. patients	A100mg-156 A200mg-154 Placebo- 77	B1mg-127 B2mg-123 B4mg-125 Placebo-249	B1mg-125 B2mg-123 B4mg-123 Placebo-244	U15mg-281 U30mg-281 Placebo-285	U15mg-278 U30mg-276 Placebo-282
Diagnosis	Moderate/severe atopic dermatitis	Moderate/severe atopic dermatitis	Moderate/severe atopic dermatitis	Moderate/severe atopic dermatitis	Moderate/severe atopic dermatitis
Total no. of patients	385	624	615	847	836
Age - mean±SD	32.5±16.0	35.8±12.9	34.5±12.6	34 (12-75)*	34 (12-75)*
EASI at baseline-mean±SD	30.2±13.4	31.0±12.3	33.5±13.6	29.5±12.2	29.1±12.0
Measured Variable	EASI 75 at week 12	EASI 75 at week 16	EASI 75 at week 16	EASI 75 at week 16	EASI 75 at week 16
Results obtained: EASI75 no./total no. (%)[§]	A 100mg 62/156 (40)	B1mg 22/127 (17.3)	B1mg 16/125 (12.8)	U15mg 196/281 (69.6)	U15mg 166/276 (60.1)
	A 200mg 96/153 (63)	B2mg 23/123 (18.7)	B2mg 22/123 (17.9)	U30mg 227/285 (79.7)	U30mg 206/282 (72.9)
	Placebo 9/76 (12)	B4mg 31/125 (24.8)	B4mg 26/123 (21.1)	Placebo 46/281 (16.3)	Placebo 37/278 (13.3)
		Placebo 22/249 (8.8)	Placebo 15/244 (6.1)		

* CT does not provide standar desviation (SD) data, but only a range of minimum and maximum values.

[§]Results obtained at week 16 after initiation of treatment, except in the Jade Mono-1 CT where results were measured at week 12.

A100mg: abrocitinib 100mg; A200mg: abrocitinib 200mg; B1mg: baricitinib 1mg; B2mg: baricitinib 2mg; B4mg: baricitinib 4mg; EASI75: Eczema Area and Severity Index; EASI75 no./total no.: number of patients with EASI70/total number of patients; U15mg: upadacitinib 15mg; U30mg: upadacitinib 30mg.

Table 3. Relative risk calculated versus placebo, in combined therapy with topical corticosteroids and in monotherapy.

Topical corticosteroid therapy		Monotherapy	
RR (IC95%)		RR (IC95%)	
A100mg vs P	1.97 (1.48-2.61)	A100mg vs P	3.36 (1.76-6.38)
A200mgvsP	2.32 (1.76-3.06)	A200mg vs P	5.30 (2.83-9.90)
		B2mg-AD1 vs P	2.12 (1.23-3.64)
B2mg vs P	1.88 (1.25-2.82)	B2mg-AD2 vs P	2.91 (1.57-5.42)
		B4mg-AD1 vs P	2.81 (1.70-4.64)
B4mg vs P	2.08 (1.40-3.09)	B4mg-AD2 vs P	3.44 (1.89-6.25)
		U15mg-UP1 vs P	4.26 (3.24-5.61)
U15mg vs P	2.46 (2.00-3.02)	U15mg-UP2 vs P	4.52 (3.3-6.19)
		U30mg-UP1 vs P	4.87 (3.71-6,38)
U30mg vs P	2.93 (2.40-3.57)	U30mg-UP2 vs P	5,49 (4,03-7,47)

A100mg: abrocitinib 100mg; A200mg: abrocitinib 200mg; B2mg: baricitinib 2mg; B2mg-AD1: baricitinib 2mg from BREEZE AD1 clinical trial; B2mg-AD2: baricitinib 2mg from BREEZE AD2 clinical trial; B4mg: baricitinib 4mg; B4mg-AD1: baricitinib 4mg from BREEZE AD1 clinical trial; B4mg-AD2: baricitinib 4mg from clinical trial BREEZE AD2; 95% CI95%: 95% confidence interval; P: placebo; RR: Relative Risk; U15mg: upadacitinib 15mg; U15mg-UP1: upadacitinib 15mg from clinical trial MEASURE UP1; PU15mg-UP2: upadacitinib 15mg from clinical trial MEASURE UP2;U30mg: upadacitinib 30mg. U30mg-UP1: upadacitinib 30mg from the MEASURE UP1 clinical trial; U30mg-UP2: upadacitinib 30mg from the MEASURE UP2 clinical trial.

Table 4. Indirect comparisons (in OR) of JAK inhibitors for the treatment of atopic dermatitis in combination with topical corticosteroids and in monotherapy

	Topical corticosteroid therapy		Monotherapy					
Drugs	OR (IC95%)	p	Drugs	OR (IC95%)	p	Drugs	OR (IC95%)	p
A100mg vs B2mg	0.95 (0.58-1.57)	0.850	A100mg vs B2mg-AD1	0.63 (0.27-1.46)	0.284	A200mg vs B4mg-AD1	0.53 (0.24-1.18)	0.121
			A100mg vs B2mg-AD2	0.87 (0.35-2.12)	0.753	A200mg vs B4mg-AD2	0.65 (0.27-1.54)	0.328
A100mg vs U15mg	1.25 (0.88-1.77)	0.210	A100mg vs U15mg-UP1	1.27 (0.63-2.55)	0.506	A200mg vs U30mg-UP1	0.92 (0.46-1.82)	0.808
			A100mg vs U15mg-UP2	1.35 (0.66-2.75)	0.417	A200mg vs U30mg-UP2	1.04 (0.52-2.08)	0.921
B2mg vs U15mg	1.31 (0.83-2.06)	0.240	B2mg-AD1 vs U15mg-UP1	2.01 (1.09-3.69)	0.025	B4mg-AD1 vs U30mg-UP1	1.73 (0.98-3.07)	0.059
A200mg vs B4mg	0.90 (0.55-1.46)	0.650	B2mg-AD1 vs U15mg-UP2	2.13 (1.14-3.99)	0.018	B4mg-AD1 vs U30mg-UP2	1.95 (1.08-3.52)	0.026
A200mg vs U30mg	1.26 (0.9-1.78)	0.179	B2mg-AD2 vs U15mg-UP1	1.46 (0.74-2.88)	0.270	B4mg-AD2 vs U30mg-UP1	1.42 (0.73-2.73)	0.299
B4mg vs U30mg	1.41 (0.9-2.19)	0.129	B2mg-AD2 vs U15mg-UP2	1.55 (0.78-3.11)	0.214	B4mg-AD2 vs U30mg-UP2	1.60 (0.81-3.13)	0.173

A100mg: abrocitinib 100mg; A200mg: abrocitinib 200mg; B2mg: baricitinib 2mg; B2mg-AD1: baricitinib 2mg from BREEZE AD1 clinical trial; B2mg-AD2: baricitinib 2mg from BREEZE AD2 clinical trial; B4mg: baricitinib 4mg; B4mg-AD1: baricitinib 4mg from BREEZE AD1 clinical trial; B4mg-AD2: baricitinib 4mg from clinical trial BREEZE AD2; 95% CI95%: 95% confidence interval; OR: Odds Ratio; U15mg: upadacitinib 15mg; U15mg-UP1: upadacitinib 15mg from clinical trial MEASURE UP1;U15mg-UP2: upadacitinib 15mg from clinical trial MEASURE UP2;U30mg: upadacitinib 30mg. U30mg-UP1: upadacitinib 30mg from the MEASURE UP1 clinical trial;U30mg-UP2: upadacitinib 30mg from the MEASURE UP2 clinical trial.

In both situations (MT and TC), in the abrocitinib CTs the EASI75 is measured at 12 weeks from the start of treatment, while in the others at week 16.

Once the limitations for both scenarios had been analyzed, they were accepted for IC and the RR was calculated with respect to placebo for each drug in the 8 CTs, the results of which are summarized in Table 3. The data for baricitinib 1mg were excluded from the analysis because this presentation is not commercialized in Spain, as were those for dupilumab in the Jade Compare trial because it is not a JAK inhibitor. With these RR values, and after applying the Butcher method, the Odds Ratio (OR) values were obtained, which are summarized in Table 4.

None of the results of the indirect comparisons showed statistically significant differences, except in the comparison of baricitinib 2mg (CT BREEZE AD1) versus upadacitinib 15mg (CT MEASURE UP1 AND UP2), and baricitinb 4mg (CT BREEZE AD 1) versus upadacitinib 30mg (CT MEASURE UP2), in all three cases in favor of upadacitinib.

CONCLUSIONS

According to the results obtained in combination therapy with TC, given that no statistically significant differences have been established between the different drugs in terms of efficacy, the choice of one or the other for the treatment of atopic dermatitis should be based on safety and efficiency criteria.

Regarding the results obtained in the ICs of the CTs in MT, it could be that baricitinib had a more modest benefit than upadacitinib. However, of the 8 CTs performed between these two drugs, only 3 showed a statistically significant difference, and therefore it would also be necessary to assess whether this difference is clinically relevant. This, together with the limitations described with respect to the differences between the pivotal CTs, means that these results should be taken with caution and the drug should be individually adapted to each patient according to the interaction profile, adverse effects and cost.

For all these reasons, it would be of particular interest to have a direct comparison of these drugs to confirm equivalence.

The authors declare no conflict of interest

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