



Systematic Review

Efficacy and Safety of Oral Janus Kinase Inhibitors in Moderate-To-Severe Atopic Dermatitis: A Systematic Review and Meta-Analysis of Randomised Controlled Trials

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ABSTRACT

Background: Oral Janus kinase (JAK) inhibitors block several cytokines that drive inflammation and itch in atopic dermatitis. Abrocitinib, baricitinib and upadacitinib have been tested against placebo in randomised trials, but a pooled estimate of their benefit and harm is needed to guide practice.

Aim: To estimate the efficacy and short-term safety of oral JAK inhibitors compared with placebo in moderate-to-severe atopic dermatitis.

Materials and methods: PubMed was searched from inception to 31 December 2020 for placebo-controlled randomised trials of oral JAK inhibitors in moderate-to-severe atopic dermatitis. The efficacy outcomes were Investigator's Global Assessment (IGA) of clear or almost clear skin (0/1) and at least 75% improvement in the Eczema Area and Severity Index (EASI-75) at the end of the placebo-controlled period. The safety outcomes were any adverse event and serious adverse events. Risk ratios (RRs) were pooled with a random-effects model in Review Manager 5.4. Risk of bias was assessed with the Cochrane tool, and the certainty of evidence with GRADE.

Results: Seven reports describing eight trials with 2,904 randomised patients were included. Compared with placebo, JAK inhibitors increased IGA 0/1 response (26.5% vs 6.6%; RR 3.19, 95% CI 2.23 to 4.57; $I^2 = 35\%$) and EASI-75 response (41.3% vs 10.7%; RR 3.22, 95% CI 2.38 to 4.35; $I^2 = 48\%$). The numbers needed to treat were 7 for IGA 0/1 and 4 for EASI-75. The effect was larger with abrocitinib and upadacitinib than with baricitinib (p for subgroup difference = 0.028 for IGA). Higher doses gave numerically larger responses than lower doses. Any adverse event was more frequent with JAK inhibitors (66.1% vs 50.0%; RR 1.27, 95% CI 1.14 to 1.42), but serious adverse events were not increased (2.3% vs 3.1%; RR 0.68, 95% CI 0.38 to 1.19). The certainty of evidence was high for both efficacy outcomes.

Conclusion: Oral JAK inhibitors are clearly more effective than placebo for moderate-to-severe atopic dermatitis over 12 to 16 weeks. They cause more mild adverse events, such as nausea, acne and herpes infections, but no excess of serious events in the short term. Longer studies are needed to define their long-term safety.

Keywords: Abrocitinib; Atopic dermatitis; Baricitinib; Janus kinase inhibitors; Meta-analysis; Upadacitinib.

INTRODUCTION

Atopic dermatitis is a chronic, relapsing, itchy inflammatory skin disease. It affects up to one in five children and many adults, and it often begins in infancy [1,2]. In the Global Burden of Disease 2010 study, it ranked first among skin diseases for disability-adjusted life years [3]. Its burden goes beyond the skin: patients report sleep loss, anxiety, depression, missed work and school, and high out-of-pocket costs [4].

Most patients are treated with emollients, topical corticosteroids and topical calcineurin inhibitors. Some, however, have moderate-to-severe disease that is not controlled by topical therapy. Conventional systemic agents such as ciclosporin, methotrexate, azathioprine and mycophenolate are used off-label in many countries, and their use is limited by toxicity and the need for monitoring [5,6]. Dupilumab, the first biologic for atopic dermatitis, showed that targeting type 2 cytokines works [7]. It is an injectable, costly treatment, and some patients do not respond adequately.

Janus kinases (JAK1, JAK2, JAK3 and TYK2) are intracellular enzymes that transmit signals from many cytokine receptors. Interleukin-4, interleukin-13, interleukin-31, interleukin-22 and thymic stromal lymphopoietin, all central to atopic inflammation, signal through JAK pathways [8]. JAK1 signalling in sensory neurons also directly drives chronic itch [9]. Small oral molecules that block JAK1, alone or together with JAK2, could therefore reduce both inflammation and itch. Abrocitinib and upadacitinib are selective JAK1 inhibitors, and baricitinib inhibits JAK1 and JAK2.

Several phase 2 and phase 3 placebo-controlled trials of these three drugs were published in 2019 and 2020. The individual trials differed in drug, dose, duration, background therapy and patient population, and some were small. We therefore carried out a systematic review and meta-analysis of randomised controlled trials to estimate the efficacy and short-term safety of oral JAK inhibitors compared with placebo in moderate-to-severe atopic dermatitis, and to compare the drugs and doses.

MATERIALS AND METHODS

Protocol and reporting

This review was conducted and reported in line with the PRISMA statement [10]. It used only published data, so ethics committee approval was not needed. The protocol was not registered.

Search strategy

PubMed/MEDLINE was searched from inception to 31 December 2020. The search combined the drug terms abrocitinib, PF-04965842, baricitinib, LY3009104, upadacitinib, ABT-494, Janus kinase inhibitor and JAK inhibitor with the disease terms atopic dermatitis and eczema. No language or date filters were applied at the search stage. The reference lists of included trials and of review articles found by the search were checked by hand.

Eligibility criteria

Trials were included if they (a) were randomised, double-blind and placebo-controlled; (b) enrolled patients with moderate-to-severe atopic dermatitis; (c) tested an oral JAK inhibitor at a dose that was later studied in phase 3 trials (abrocitinib 100 or 200 mg, baricitinib 2 or 4 mg, or upadacitinib 15 or 30 mg once daily), either alone or with background topical corticosteroids; and (d) reported at least one of the outcomes of interest. Trials of topical JAK inhibitors, open-label studies, case series, post hoc or pooled re-analyses of trials already included, and trials of agents not taken forward to phase 3 were excluded.

Outcomes

The two efficacy outcomes were the proportion of patients achieving an IGA (or validated IGA for atopic dermatitis) score of 0 or 1 with at least a two-grade improvement from baseline, and the proportion achieving EASI-75, both at the end of the placebo-controlled period (week 12 or week 16). The EASI scores the extent and severity of erythema, induration, excoriation and lichenification in four body regions and is a reliable measure of disease severity [11]. The safety outcomes were the proportions of patients with any adverse event and with a serious adverse event during the placebo-controlled period. Specific adverse events of interest were nausea, acne, herpes infections and laboratory changes, and they were summarised narratively.

Data extraction and risk of bias

Data were extracted on a predesigned form and checked against the source article on a second occasion. The items extracted were trial name, phase, setting, population, sample size, drug and dose, background therapy, duration, primary end point, and the number of patients with each outcome in each arm. Where only percentages were reported, numbers were calculated from the percentage and the number analysed. For dose-ranging trials, only the arms with the doses defined above were used. The two active doses in each trial were combined for the main analysis, as recommended for multi-arm trials, so that the placebo group was counted only once. The risk of bias of each trial was assessed with the Cochrane Collaboration's tool across random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other bias [12].

Statistical analysis

For each trial, the risk ratio (RR) and its 95% confidence interval (CI) were calculated for each outcome. RRs were pooled with the DerSimonian and Laird random-effects model, using inverse-variance weighting [13]. Heterogeneity was assessed with the χ^2 test (significant at $p < 0.10$) and quantified with the I^2 statistic [14]. The number needed to treat (NNT) was calculated from the pooled RR and the pooled placebo response rate.

Prespecified subgroup analyses compared the three drugs, and higher doses (abrocitinib 200 mg, baricitinib 4 mg and upadacitinib 30 mg) with lower doses (abrocitinib 100 mg, baricitinib 2 mg and upadacitinib 15 mg). For the dose analysis, the placebo group of each trial was split equally between the two dose comparisons to avoid double counting. Sensitivity analyses were restricted to monotherapy trials and to phase 3 trials, removed each trial in turn, and repeated the main analyses with a fixed-effect model. Funnel plots and Egger's test were planned to assess publication bias if ten or more trials were available [15]. The certainty of evidence for each outcome was rated with the GRADE approach as high, moderate, low or very low [16]. Analyses were performed in Review Manager (RevMan) version 5.4 (The Cochrane Collaboration, 2020). A p value below 0.05 was regarded as statistically significant.

RESULTS

Study selection

The search identified 159 records, and no further records were found from reference lists (Figure 1). After title and abstract screening, 140 records were excluded, most of them reviews, commentaries, studies of other diseases, animal studies and case series. Nineteen full-text articles were assessed. Twelve were excluded: seven were trials of topical JAK inhibitors, two tested an oral agent that had not reached phase 3 and did not report IGA or EASI-75 response rates against placebo, and three were secondary or post hoc analyses of included trials. Seven reports describing eight trials were included [17-23].

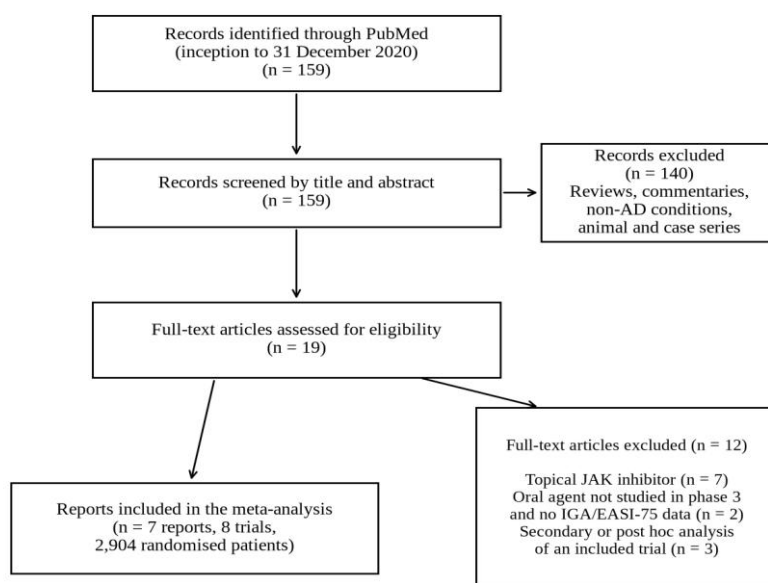


Figure 1: Flow diagram of study identification, screening and inclusion

The diagram follows the PRISMA statement. AD: atopic dermatitis; EASI-75: at least 75% improvement in Eczema Area and Severity Index; IGA: Investigator's Global Assessment; JAK: Janus kinase.

Characteristics of included trials

Table 1 summarises the eight trials, which randomised 2,904 patients. Three trials tested abrocitinib [17-19], four tested baricitinib [20-22] and one tested upadacitinib [23]. Five were phase 3 trials and three were phase 2 or 2b dose-ranging trials. Six trials used monotherapy, and two allowed background topical corticosteroids [20,22]. The placebo-controlled period lasted 12 weeks in the abrocitinib trials and 16 weeks in the others. The two JADE MONO trials included adolescents aged 12 years or older, while the other trials enrolled adults only. The baricitinib phase 2 trial did not report IGA 0/1 or EASI-75 response counts and contributed only to the safety analysis [20]. The two BREEZE monotherapy trials reported safety data for both trials combined, and these were entered as one comparison [21].

Table 1: Characteristics of the included randomised controlled trials

Trial	Phase; setting	Age group	n	Arms analysed	Add-on	Weeks	Primary end point
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Gooderham 2019 [17]	2b; 58 centres in 5 countries	Adults 18 to 75 years	267	Abrocitinib 200 mg, 100 mg, placebo	None	12	IGA 0/1
JADE MONO-1 2020 [18]	3; 69 sites in Australia, Canada, Europe and USA	12 years or older	387	Abrocitinib 200 mg, 100 mg, placebo	None	12	IGA 0/1 and EASI-75
JADE MONO-2 2020 [19]	3; 115 centres in 13 countries	12 years or older	391	Abrocitinib 200 mg, 100 mg, placebo	None	12	IGA 0/1 and EASI-75
Baricitinib phase 2 2019 [20]	2; USA and Japan	Adults	124	Baricitinib 4 mg, 2 mg, placebo	TCS	16	EASI-50
BREEZE-AD1 2020 [21]	3; multinational	Adults	624	Baricitinib 4 mg, 2 mg, placebo	None	16	vIGA-AD 0/1
BREEZE-AD2 2020 [21]	3; multinational	Adults	615	Baricitinib 4 mg, 2 mg, placebo	None	16	vIGA-AD 0/1
BREEZE-AD7 2020 [22]	3; 68 centres in 10 countries	Adults	329	Baricitinib 4 mg, 2 mg, placebo	TCS	16	vIGA-AD 0/1
Upadacitinib phase 2b 2020 [23]	2b; 8 countries	Adults 18 to 75 years	167	Upadacitinib 30 mg, 15 mg, placebo	None	16	Percentage change in EASI

n: number randomised; TCS: topical corticosteroids. Arms with doses not taken forward to phase 3 (abrocitinib 10 and 30 mg, baricitinib 1 mg and upadacitinib 7.5 mg) were not analysed. EASI: Eczema Area and Severity Index; EASI-50 or EASI-75: at least 50% or 75% improvement in EASI; IGA: Investigator's Global Assessment; vIGA-AD: validated IGA for atopic dermatitis.

Risk of bias

All eight trials were double-blind and used centralised or interactive web-based randomisation (Table 2). Outcome data were complete or handled by non-responder imputation, and all trials were registered with prespecified primary end points. All were funded by the manufacturers, which was judged an unclear risk of other bias. Overall, the risk of bias was low for the main domains in all trials.

Table 2: Risk of bias in the included trials (Cochrane Collaboration tool)

Trial	Random sequence	Concealment	Blinding	Missing data	Selective reporting	Other bias
Gooderham 2019	Low	Low	Low	Low	Low	Unclear
JADE MONO-1 2020	Low	Low	Low	Low	Low	Unclear
JADE MONO-2 2020	Low	Low	Low	Low	Low	Unclear
Baricitinib phase 2 2019	Low	Low	Low	Low	Low	Unclear
BREEZE-AD1 2020	Low	Low	Low	Low	Low	Unclear
BREEZE-AD2 2020	Low	Low	Low	Low	Low	Unclear
BREEZE-AD7 2020	Low	Low	Low	Low	Low	Unclear
Upadacitinib phase 2b 2020	Low	Low	Low	Low	Low	Unclear

Other bias was rated unclear because all trials were sponsored by the manufacturer of the study drug.

Efficacy

Seven trials with 2,367 patients in the analysed arms contributed to the IGA analysis. An IGA 0/1 response was achieved by 403 of 1,519 patients (26.5%) on JAK inhibitors and 56 of 848 (6.6%) on placebo. The pooled RR was 3.19 (95% CI 2.23 to 4.57; $p < 0.001$), with low to moderate heterogeneity ($I^2 = 35\%$) (Figure 2). The NNT was 7. Every trial favoured the JAK inhibitor.

(a) IGA 0/1 response

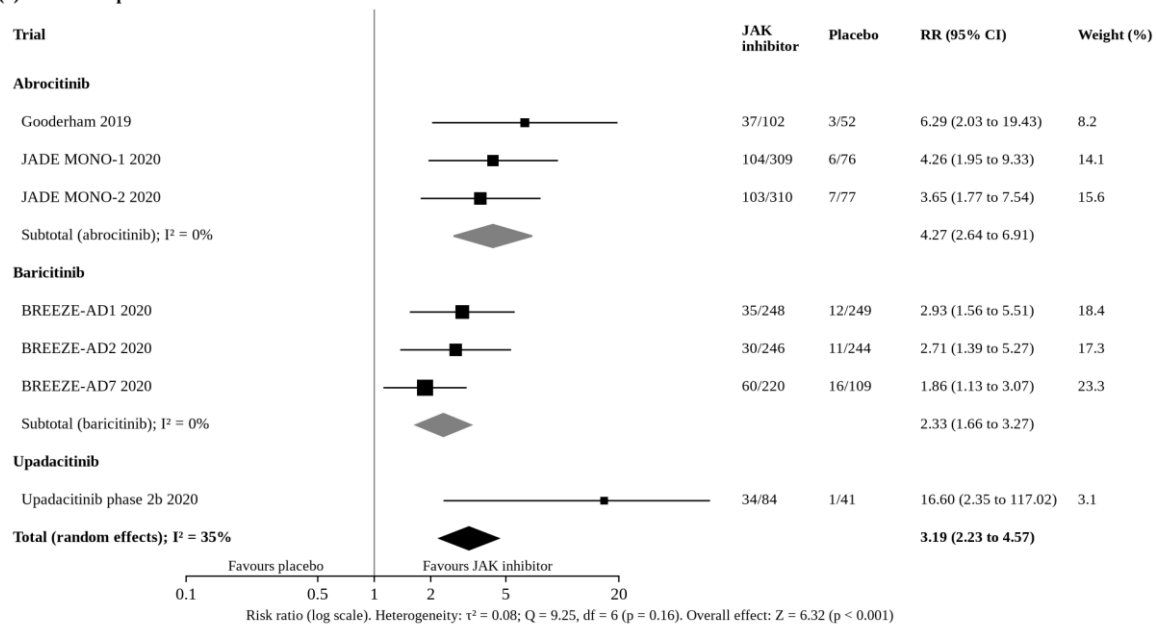


Figure 2: Forest plot of IGA 0/1 response with oral JAK inhibitors compared with placebo, by drug

Squares show trial risk ratios, sized by random-effects weight; horizontal lines show 95% confidence intervals; diamonds show pooled estimates. Event counts are responders/patients analysed, with both active doses of each trial combined. IGA: Investigator's Global Assessment; RR: risk ratio.

An EASI-75 response was achieved by 627 of 1,518 patients (41.3%) on JAK inhibitors and 91 of 848 (10.7%) on placebo, giving a pooled RR of 3.22 (95% CI 2.38 to 4.35; $p < 0.001$; $I^2 = 48\%$) (Figure 3). The NNT was 4.

(b) EASI-75 response

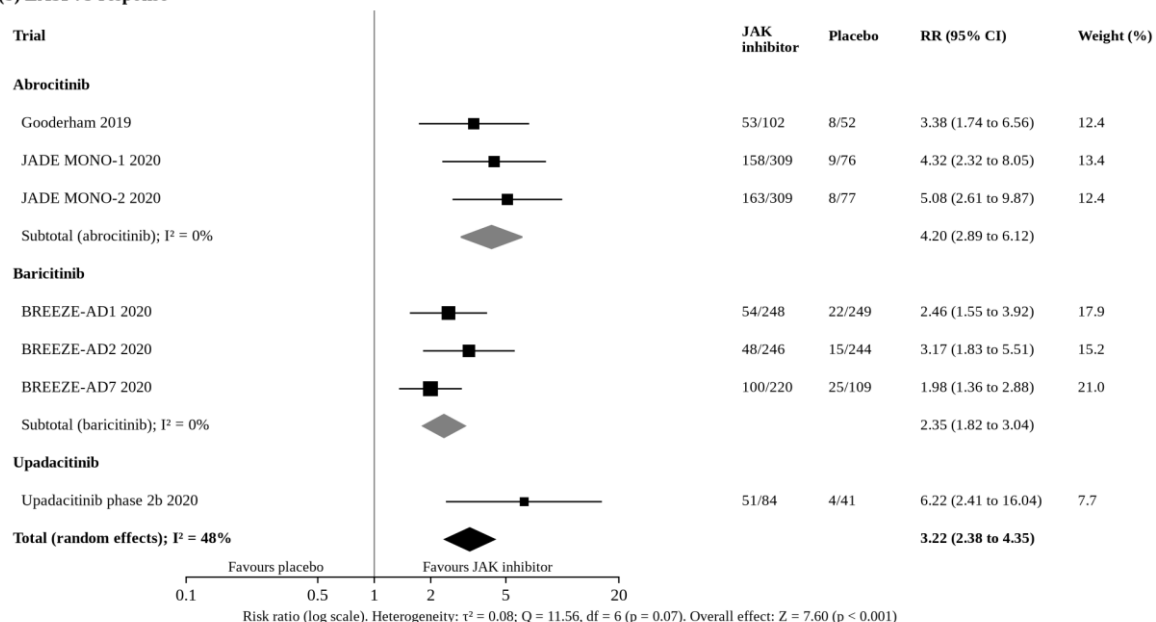


Figure 3: Forest plot of EASI-75 response with oral JAK inhibitors compared with placebo, by drug

EASI-75: at least 75% improvement in Eczema Area and Severity Index; RR: risk ratio.

Subgroup and sensitivity analyses

The size of the benefit differed between drugs (Table 3). For IGA 0/1, the RR was 4.27 (95% CI 2.64 to 6.91) for abrocitinib, 2.33 (95% CI 1.66 to 3.27) for baricitinib and 16.60 (95% CI 2.35 to 117.02) for upadacitinib, based on one small trial (p for subgroup difference = 0.028). The pattern was the same for EASI-75 ($p = 0.012$). Heterogeneity within each drug

subgroup was zero. Higher doses gave larger responses than lower doses for both IGA 0/1 (RR 3.44 vs 2.46) and EASI-75 (RR 3.44 vs 2.57), although these differences were not statistically significant ($p = 0.23$ and $p = 0.20$).

Restricting the analysis to monotherapy trials gave RRs of 3.59 for IGA 0/1 and 3.53 for EASI-75, both with little heterogeneity. Restricting it to phase 3 trials gave RRs of 2.72 and 3.01. Removing each trial in turn gave pooled RRs from 2.94 to 3.59 for IGA 0/1 and from 2.98 to 3.53 for EASI-75. Fixed-effect models gave similar results (RR 2.95, 95% CI 2.24 to 3.88, and RR 2.94, 95% CI 2.39 to 3.61). Because fewer than ten trials were available, publication bias was not assessed formally.

Table 3: Subgroup and sensitivity analyses for efficacy outcomes

Analysis	IGA 0/1: trials	IGA 0/1: RR (95% CI); I^2	EASI-75: trials	EASI-75: RR (95% CI); I^2
All trials	7	3.19 (2.23 to 4.57); 35%	7	3.22 (2.38 to 4.35); 48%
Abrocitinib	3	4.27 (2.64 to 6.91); 0%	3	4.20 (2.89 to 6.12); 0%
Baricitinib	3	2.33 (1.66 to 3.27); 0%	3	2.35 (1.82 to 3.04); 0%
Upadacitinib	1	16.60 (2.35 to 117.02); NA	1	6.22 (2.41 to 16.04); NA
Higher dose	7	3.44 (2.34 to 5.04); 0%	7	3.44 (2.47 to 4.78); 18%
Lower dose	7	2.46 (1.65 to 3.64); 0%	7	2.57 (1.91 to 3.46); 0%
Monotherapy trials only	6	3.59 (2.59 to 4.99); 0%	6	3.53 (2.72 to 4.57); 7%
Phase 3 trials only	5	2.72 (2.03 to 3.65); 4%	5	3.01 (2.13 to 4.24); 54%
Fixed-effect model	7	2.95 (2.24 to 3.88)	7	2.94 (2.39 to 3.61)

Test for subgroup differences: drug, $p = 0.028$ (IGA) and $p = 0.012$ (EASI-75); dose, $p = 0.23$ (IGA) and $p = 0.20$ (EASI-75). Higher dose: abrocitinib 200 mg, baricitinib 4 mg, upadacitinib 30 mg. Lower dose: abrocitinib 100 mg, baricitinib 2 mg, upadacitinib 15 mg. NA: not applicable; RR: risk ratio.

Safety

Five trials reported any adverse event by arm. Adverse events occurred in 662 of 1,002 patients (66.1%) on JAK inhibitors and 176 of 352 (50.0%) on placebo (RR 1.27, 95% CI 1.14 to 1.42; $I^2 = 0\%$) (Figure 4). Most events were mild or moderate. Six comparisons reported serious adverse events, which occurred in 35 of 1,532 patients (2.3%) on JAK inhibitors and 26 of 852 (3.1%) on placebo (RR 0.68, 95% CI 0.38 to 1.19; $p = 0.17$; $I^2 = 0\%$).

Nausea was the most typical adverse event with abrocitinib and was dose related. It occurred in 14.5% of patients on 200 mg compared with 1.8% on placebo in the phase 2b trial [17], and in 14.2% on 200 mg, 7.6% on 100 mg and 2.6% on placebo in JADE MONO-2 [19]. Acne was also more common with abrocitinib 200 mg (5.8% vs 0%) [19] and with baricitinib 4 mg plus topical corticosteroids (4% vs 1%) [22]. Herpes zoster occurred in two patients (1.3%) on abrocitinib 200 mg and none on placebo in JADE MONO-2 [19], and oral herpes was reported in 4% of baricitinib-treated patients in BREEZE-AD7 [22]. Abrocitinib caused a dose-dependent fall in platelet count that tended to recover after week 4 [17]. In the BREEZE monotherapy trials, no cardiovascular events, venous thromboembolism, gastrointestinal perforation or deaths were observed [21]. Fewer patients stopped treatment because of adverse events with abrocitinib than with placebo in JADE MONO-2 (3.2% to 3.8% vs 12.8%) [19].

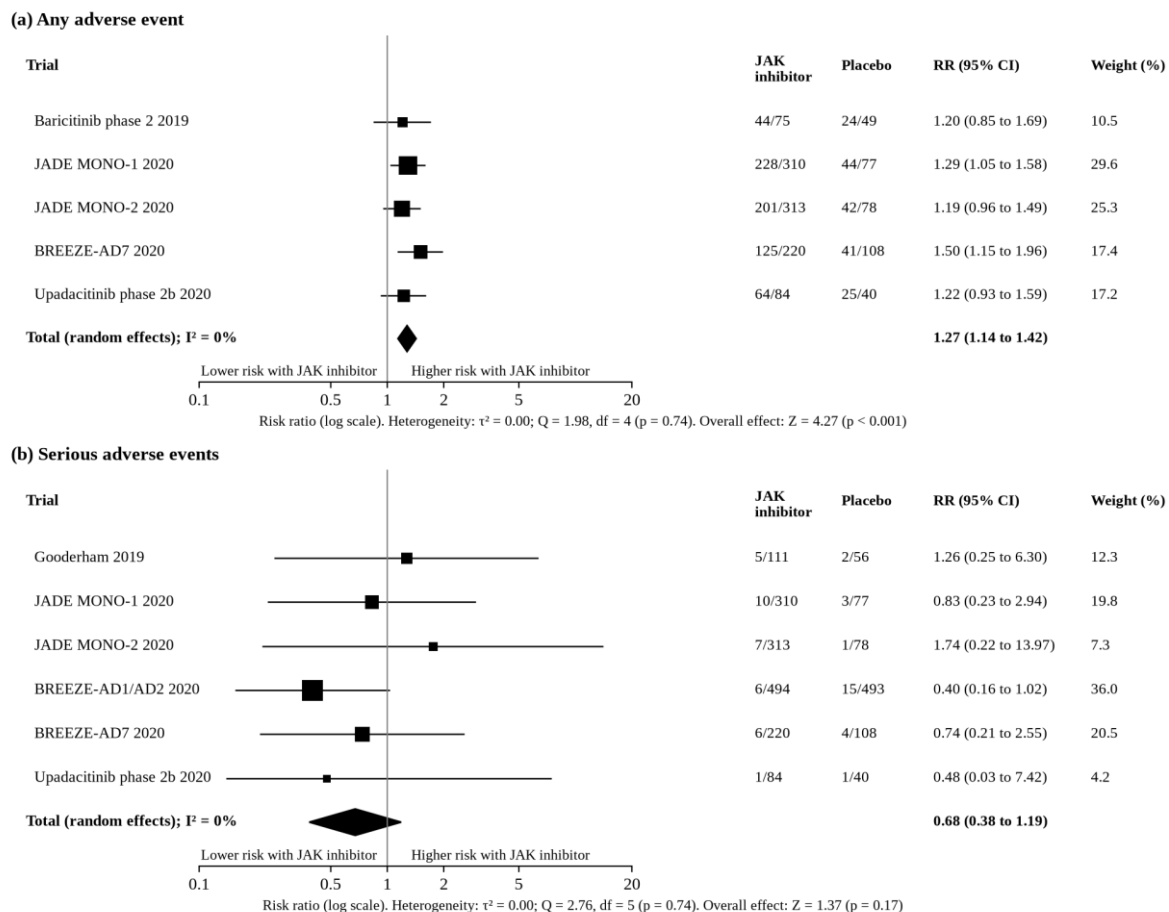


Figure 4: Forest plots of (a) any adverse event and (b) serious adverse events with oral JAK inhibitors compared with placebo

BREEZE-AD1 and BREEZE-AD2 reported serious adverse events combined, and they are shown as one comparison. RR: risk ratio.

Certainty of evidence

Using GRADE, the certainty of evidence was rated high for IGA 0/1 and EASI-75, since the trials had a low risk of bias and the results were consistent, direct and precise. It was rated moderate for any adverse event, because not all trials reported this outcome by arm. It was rated low for serious adverse events, because the events were few, the confidence interval was wide and the follow-up was short.

DISCUSSION

This meta-analysis of eight placebo-controlled trials found that oral JAK inhibitors roughly tripled the chance of clear or almost clear skin and of a 75% improvement in EASI after 12 to 16 weeks in patients with moderate-to-severe atopic dermatitis. About one in seven treated patients achieved clear or almost clear skin, and one in four achieved EASI-75, because of the drug. The results were consistent across trials and robust in sensitivity analyses. Any adverse event was about 27% more common with JAK inhibitors, but serious adverse events were not increased in the short term.

The benefit differed between drugs. Abrocitinib and upadacitinib, both selective JAK1 inhibitors, produced larger relative effects than baricitinib, which inhibits JAK1 and JAK2. A network meta-analysis of 39 trials of systemic treatments found that dupilumab and ciclosporin were the most effective established options over 16 weeks, and it described the JAK inhibitors as promising but supported only by small early-phase trials at that time [24]. The phase 3 trials pooled here now give much firmer evidence for these drugs. Part of the difference between drugs may reflect trial design, as patient populations, rescue rules and response rates in both arms differed between the abrocitinib and baricitinib programmes. The upadacitinib estimate came from a single phase 2b trial with only one placebo responder, so its very wide confidence interval should not be over-interpreted [23].

Higher doses gave numerically larger responses for all three drugs, consistent with the dose-response relationships reported in the dose-ranging trials [17,23]. The difference between doses was not statistically significant in our analysis, probably because the analysis had limited power. In practice, the choice of dose will need to balance the extra benefit of the higher

dose against its higher rates of nausea, acne and laboratory changes. When baricitinib was combined with topical corticosteroids, the relative effect was smaller because the placebo group, which also used topical corticosteroids, responded better [22]. This does not mean that combination therapy is less useful; the absolute response rates in BREEZE-AD7 were higher than in the monotherapy trials.

The safety findings over 12 to 16 weeks were reassuring for serious harm, but the trials were not designed to detect rare events. In rheumatoid arthritis, JAK inhibitors have been associated with herpes zoster, raised lipids, cytopenias and, at some doses, venous thromboembolism [25]. Patients with atopic dermatitis are generally younger and have fewer cardiovascular risk factors, but long-term extension studies and registries are needed. Clinicians should screen for latent tuberculosis and hepatitis, monitor blood counts and lipids, and consider herpes zoster vaccination where available.

For Indian practice, oral JAK inhibitors offer an alternative for patients whose disease is not controlled by topical therapy and who cannot take or do not respond to ciclosporin or methotrexate [5,6]. As oral drugs, they avoid the injections and cold-chain storage needed for biologics, which may help patients in smaller towns. Cost, access and the need for laboratory monitoring will still decide their place in treatment.

Strengths and limitations

This review included only double-blind, placebo-controlled trials with a low risk of bias, analysed standard and clinically meaningful end points, and avoided double counting of placebo groups. It also has limitations. Only PubMed was searched, although the main trials of all three drugs were found. The number of trials was small, and only one trial of upadacitinib published by 2020 was available. The trials lasted only 12 to 16 weeks, so long-term efficacy and safety could not be assessed. The trials were done mainly in North America, Europe, Australia and East Asia, which limits how far the results apply to Indian patients and health care settings. Finally, all trials were funded by the manufacturers.

CONCLUSION

Oral JAK inhibitors are effective short-term treatments for moderate-to-severe atopic dermatitis. Compared with placebo, they triple the chance of clear or almost clear skin and of a 75% improvement in EASI, with NNTs of 7 and 4. Abrocitinib and upadacitinib appear to give larger effects than baricitinib, and higher doses give larger responses. Mild adverse events are more common, but serious adverse events were not increased over 16 weeks. Long-term trials, head-to-head comparisons with dupilumab and studies in Indian patients are needed.

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Conflicts of interest

There are no conflicts of interest.

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