Effects of abrocitinib on pruritus and eczema symptoms and tolerance in patients with moderate-to-severe atopic dermatitis in randomized, double-blind and placebo-controlled trials: A systematic review and a meta-analysis

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Received January 11, 2024; Accepted March 8, 2024

DOI: 10.3892/br.2024.1772

Abstract. Abrocitinib is a highly selective Janus kinase 1 (JAK1) inhibitor that can block a multitude of inflammatory signaling pathways that underlie atopic dermatitis (AD). In addition, abrocitinib inhibits JAK1 signaling in sensory neurons to alleviate acute and chronic pruritus during AD. However, substantial variations in efficacy and safety risks remain due to variations in doses applied in clinical use. Therefore for the present study, differences in the efficacy and tolerability of 100 and 200 mg abrocitinib for treating pruritus and eczema symptoms in patients with moderate-to-severe AD were evaluated compared with placebo. Specifically, randomized controlled trials (RCTs) of abrocitinib compared with placebo for the treatment of moderate-to-severe AD were searched on Pubmed, E.B. Stephens Company, China National Knowledge Infrastructure, Wanfang Medical network, Web of Science and related Clinical Trials Registry up to November 2023. In total, two researchers evaluated the quality of the included literature according to the Cochrane Handbook of Systematic Reviews. RevMan 5.3 software was used to conduct a meta-analysis of the efficacy and safety indicators in a cross-comparison of the effects exerted by placebo and 100 and 200 mg abrocitinib. A total of 1,825 patients with moderate-to-severe AD were included across five double-blind, placebo RCTs. Compared with the placebo group, during the double-blind trial period, significant improvements were observed in the investigator's global assessment score, response rate of eczema area and severity index (EASI)-50, EASI-75, EASI-90 and pruritus numerical rating scale (P-NRS) in the 100 and 200 mg abrocitinib groups ($P<0.05$). However, pairwise control analysis of the 100 and 200 mg group yielded significant differences ($P<0.05$) in all of the aforementioned therapeutic indicators except for the P-NRS score. In terms of safety, compared with the placebo group, there were significantly higher incidence of nausea, upper respiratory tract viral infection, infections and infestations in the 100 mg abrocitinib group ($P<0.05$). In addition, there were significantly higher incidence of nausea, gastrointestinal disorder, headache and dizziness in the 200 mg group ($P<0.05$). There were also significant differences in the incidence of nausea, gastrointestinal disorder and dizziness between the 100 and 200 mg groups ($P<0.05$). For patients with moderate-to-severe AD, oral administration of 100 or 200 mg abrocitinib once/day was concluded to ameliorate skin pruritus and eczema symptoms to varying degrees, with the efficacy significantly superior at the 200 mg dose. However, the risk of a number of adverse reactions, such as headache, dizziness, nausea and gastrointestinal dysfunction, is also significantly increased. Therefore, patients should be made aware of the risk of adverse drug effects prior to the administration of long-term high abrocitinib doses. Furthermore, large-scale, multi-center, rigorous clinical trials remain necessary to validate the findings from the present study.

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Abbreviations: AD, atopic dermatitis; RCT, randomized controlled trial; EASI, eczema area and severity index; IGA, investigator's global assessment; P-NRS, pruritus numerical rating scale; OR, odds ratio; RR, risk ratio; M-H, Mantel-Haenszel; REM, random-effect model; FEM, fixed effects model

Key words: moderate-to-severe atopic dermatitis, abrocitinib, administration dose, randomized controlled trial, system review

Introduction

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease with pruritus and eczema as its primary symptoms, and the etiology is associated with genetic predisposition,

environmental factors, immune abnormalities and comorbidities (1). Itching is typically the most serious symptom of AD (2,3) and can worsen skin lesions by disrupting the skin barrier and exacerbating discomfort (4). In developed countries, especially those in Europe, AD affects nearly 20% of the population and is the most common type of inflammatory skin disease. By contrast, this figure is higher in low-income countries, such as those in Africa, Oceania and the Asian Pacific (28-34% (5,6). Due to ineffective local treatment, patients with moderate-to-severe AD frequently interrupt or abandon treatment and develop other systemic diseases, such as immune abnormalities, infection, osteoporosis and cardiovascular dysfunction (7-9). Therefore, the quality of life of patients with moderate-to-severe AD is greatly reduced.

AD management aims to decrease symptoms and severity and improve long-term disease control (10). Classical therapies for AD include emollients, topical corticosteroids and calcineurin inhibitors and phototherapy, which have been the primary treatment options for decades (11). Abrocitinib is a once-daily oral Janus kinase 1 (JAK1) inhibitor for long-term treatment of patients with moderate-to-severe AD (12) that rapidly relieves itching symptoms (13-17) and was first approved by the UK Medicines and Healthcare Products Regulatory Agency in September 2021. Due to good compliance, it was subsequently approved in Japan, South Korea, the European Union and the United States (18-20). On April 11, 2022, the China Food and Drug Administration approved abrocitinib for marketing in China for adult patients with refractory, moderate-to-severe AD who do not respond well to other systemic therapies, such as hormones or biological agents (21,22).

JAK is an intracellular enzyme that mediates signal transduction generated by the interaction of cytokines with growth factor receptors on the cell membrane, thereby regulating cell hematopoietic function and immune cell function (23). Abrocitinib reversibly and selectively inhibits JAK1 by blocking ATP binding sites. This drug therefore provides a novel treatment option for patients with AD (24). However, due to differences between abrocitinib dosage forms and specifications, studies on follow-up, follow-up and post-marketing reevaluation of abrocitinib after long-term use are still preliminary. Information on the safety comes from the randomized controlled trials (RCTs), with no post-marketing pharmacovigilance study data available yet (25). There remains a lack of decision-making modalities for guiding the optimal treatment strategy for patients, resulting in large differences in the benefit:risks ratio and in the evaluation results from drug economics studies (26-28).

Therefore, the present study aimed to establish a stringent literature quality screening and meta-analysis method for systematically evaluating the efficacy and safety of 100 and 200 mg abrocitinib for the treatment of moderate-to-severe AD, with placebo groups also being compared. The aim was to provide an evidence-based reference for the formulation of 100 and 200 mg standard abrocitinib clinical application program and pharmacoeconomic decision-making process.

Materials and methods

Inclusion criteria. According to the systematic review plan, inclusion criteria were determined in strict accordance with the patients, interventions, comparisons, outcomes and study design principles (29). Inclusion criteria were as follows: i) Patients with clinical diagnosis of moderate-to-severe AD (30); ii) patients aged ≥18 years; iii) test group received 100 and/or 200 mg abrocitinib (orally, once daily), whilst the control group received placebo; iv) investigator's global assessment (IGA) score was used as the efficacy indicator (31); v) 50, 75 and 90% response rates of eczema area and severity index (EASI) (32,33) and the pruritus numerical rating scale (P-NRS) were used (31); vi) adverse reaction symptoms with an event rate of >2 were used as the evaluation indices for safety; vii) double-blind RCT and viii) written in English or Chinese. Example of adverse events include gastrointestinal dysfunction, nausea, infection and infestation, upper respiratory tract infection, upper respiratory tract viral infection, dizziness, headache, skin and subcutaneous disease, elevated creatine phosphokinase, thrombocytopenia and serious adverse events (such as asthma, exacerbation of dermatitis, malignant melanoma and pulmonary embolism).

Exclusion criteria. Exclusion criteria were as follows: i) unable to provide valid data for analysis; ii) inappropriate statistical methods; iii) cohort study; iv) review and clinical reviews of the literature.

Search strategy. Pubmed (pubmed.ncbi.nlm.nih.gov/), Ovid Technologies; ovidsp.ovid.com/), E.B.Stephens Company (embase.com), China National Knowledge Infrastructure (cnki.net/), Wanfang Medical network (wanfangdata.com.cn/), Web of Science (webofscience.com) and relevant clinical trial registries, such as China Clinical Trial Registry (chictr.org.cn/), International Clinical Trial Registration Platform (trialsearch.who.int/), Hong Kong Clinical Trials Registry (ccrb.cuhk.edu.hk/web/) and North American Clinical Trial Data Center (clinicaltrials.gov/) were searched for clinical RCTs of abrocitinib compared with placebo in the treatment of moderate-to-severe AD. The retrieval period set was between the establishment of the database and November 2023 and the meta-analysis was performed according to the PRISMA guidelines (34). Default database expansion retrieval was performed supplemented with manual retrieval. The following terms were searched: 'atopic dermatitis' AND 'moderate to severe AD' AND 'abrocitinib' OR 'PF-04965842' OR 'Cibinqo' AND 'placebo' AND '100 mg' OR (AND) '200 mg' AND 'parallel control' OR 'cross-comparison' AND 'randomized clinical trial' OR' RCT'.

Literature screening and data extraction. To minimize selection bias, two researchers (XX and JZ) independently reviewed the literature according to the inclusion and exclusion criteria, screened the included literature and extracted the data. If there was any discrepancy, a third researcher (FH) analyzed and resolved it. The quality priority principle was adopted for the inclusion of multiple literature with the same data (35).

Literature quality evaluation. The RCT bias risk assessment tool in Cochrane Handbook of Systematic Reviews 5.1.0 was adopted (36,37). Specifically, a three-level risk assessment (low, unclear and high bias risk) was conducted in the included literature, including randomization, degree of blinded implementation,

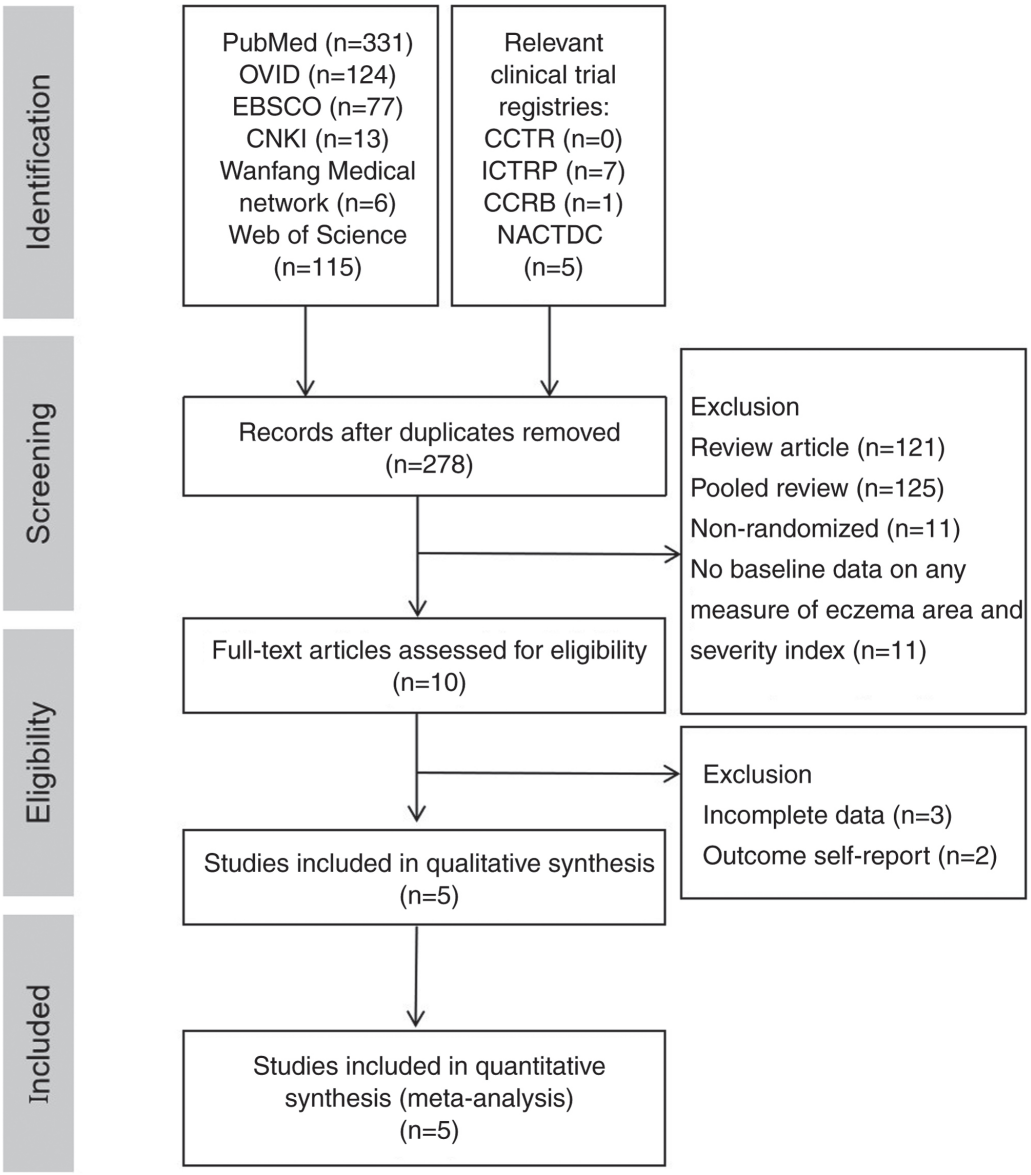

Figure 1. PRISMA flowchart of study selection. OVID, ovid technologies; EBSCO, E.B. stephens company; CNKI, China national knowledge infrastructure; CCTR, China Clinical Trial Registry; ICTRP, International Clinical Trial Registration Platform; CCRB, Hong Kong Clinical Trials Registry; NACTDC, North American Clinical Trial Data Center.

assignment concealment (unblinded), outcome data integrity (such as exit/loss rate) and selective reporting bias risk. Low bias risk indicates high reliability of the literature data.

Statistical analysis. Meta-analysis of each effect indicator was performed using RevMan 5.3 software recommended by the Cochrane Handbook of Systematic Reviews (38,39). Odds ratio (OR), risk ratio (RR) and 95%CI were used as efficacy and safety statistical effect sizes. OR and 95%CI were used as effect values for efficacy indicators and RR and 95%CI for safety indicators. Q-test was used to evaluate the heterogeneity of the literature. Studies with $I^2 \leq 50\%$ were considered to be homogenous, whereby all studies could be combined for meta-analysis using the fixed-effects model (FEM) with Mantel-Haenszel (M-H) test. Otherwise, the random-effects model (REM) was used for meta-analysis. Sensitivity analysis was used to verify the results of systematic evaluation. Funnel plot was used to evaluate risk of publication bias of associated indicators. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Literature search results. According to the search strategy, 679 publications were obtained during the preliminary search. Of these, 401 were excluded based on duplicate studies, 246 were excluded after reading the title and abstract, 241 were excluded after careful reading of the full text according to the exclusion criteria. In total, five English publications were included for meta-analysis (40-44) (Fig. 1).

Literature features

Basic information. The basic data of studies were complete, where the baseline levels of age, sex, duration of disease, blinded course of treatment and EASI score were balanced, with no statistical significance, indicating comparability (Table I).

Table I. Basic information of the enrolled patients.

First author, year	Interventions	Patients	Mean age, years	Sex F/M	Mean duration of illness, years	Trial duration, weeks	Mean EASI score	Mean IGA		SCORAD Index score	NRS	(Refs.)
								Moderate	Severe			
Bieber *et al*, 2021	Abr 100 mg	238	37.3±14.8	118/120	22.7±16.3	12	30.3±13.5	153.0±64.3	85.0±35.7	66.8±13.8	7.1±1.7	(40)
	Abr 200 mg	226	38.8±14.5	112/114	23.4±15.6		32.1±13.1	138.0±61.1	88.0±38.9	69.3±12.7	7.6±1.5	
	placebo	131	37.4±15.2	54/77	21.4±14.4		31.0±12.6	88.0±67.2	43.0±32.8	67.9±12.0	7.1±1.8	
Eichenfield *et al*, 2021	Abr 100 mg	95	16.0±7.8	50/45	9.8±5.4	12	31.0±12.8	57.0±60.0	38.0±40.0	67.6±13.5	7.0±1.8	(41)
	Abr 200 mg	94	15.0±6.4	38/56	9.7±5.3		29.5±12.2	61.0±64.9	33.0±35.1	66.2±13.3	6.8±2.0	
	placebo	96	14.0±9.3	52/44	10.5±4.8		29.2±12.7	57.0±59.4	39.0±40.6	68.5±13.4	7.2±1.7	
Gooderham *et al*, 2019	Abr 100 mg	56	41.1±15.6	31/25	23.8±14.3	12	26.7±11.8	29.0±52.7	26.0±47.3	65.4±13.7	7.4±2.2	(42)
	Abr 200 mg	55	38.7±17.6	28/27	19.6±12.8		24.6±13.5	34.0±63.0	20.0±37.0	62.7±13.7	6.9±2.7	
	placebo	56	42.6±15.1	21/35	25.6±15.2		25.4±12.9	34.0±61.8	21.0±38.2	65.0±12.1	7.6±1.8	
Silverberg *et al*, 2020	Abr 100 mg	158	37.4±15.8	94/64	21.1±14.8	12	28.4±11.2	107±67.7	51±32.3	63.8±11.4	7.1±1.6	(43)
	Abr 200 mg	155	33.5±14.7	88/67	20.5±14.8		29.0±12.4	106.0±68.4	49.0±31.6	64.1±13.1	7.0±1.6	
	placebo	78	33.4±13.8	47/31	21.7±14.3		28.0±10.2	52.0±66.7	26.0±33.3	64.3±12.4	6.7±1.9	
Simpson *et al*, 2020	Abr 100 mg	156	32.6±15.4	66/90	24.9±16.1	12	31.3±13.6	92.0±58.7	64.0±41.2	67.1±13.7	6.9±2.0	(44)
	Abr 200 mg	154	33.0±17.4	73/81	22.7±14.5		30.6±14.1	91.0±58.5	63.0±41.3	64.3±13.1	7.1±1.9	
	placebo	77	31.5±14.4	28/49	22.5±14.4		28.7±12.5	46.0±59.6	31.0±40.2	64.5±13.2	7.0±1.8	

Abr, abrocitinib; F, female; M, male; EASI, eczema area and severity index; IGA, investigator's global assessment; SCORAD, scoring of atopic dermatitis; P-NRS, pruritus numerical rating scale.

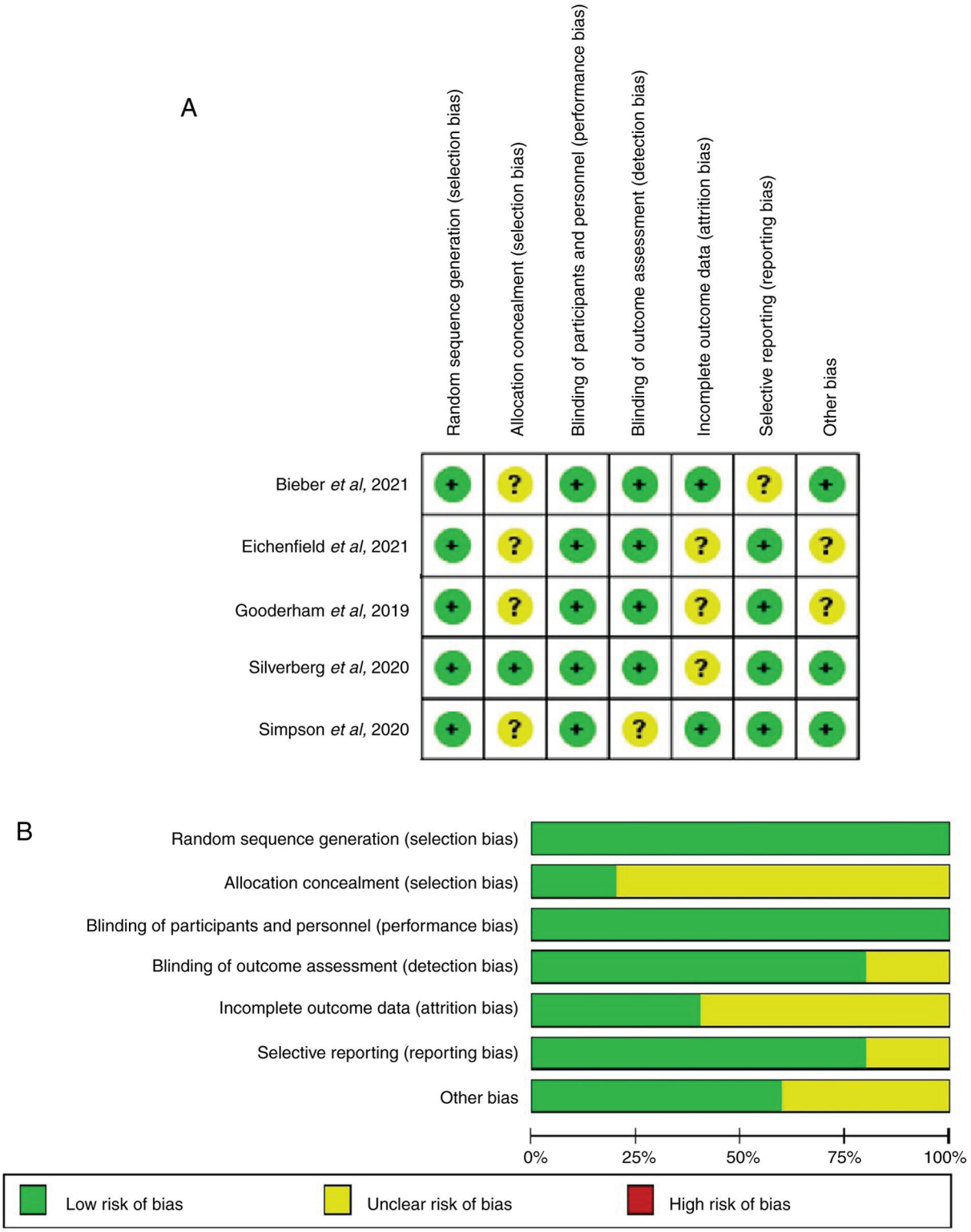

Figure 2. Risk of bias assessment. (A) Is the evaluation of each individual study. (B) Provides a graph for all studies.

Methodological quality characteristics. In the five RCTs (40-44) evaluated for each item in the Cochrane Handbook of Systematic Reviews 5.1.0, no item with high bias risk was found (Fig. 2).

Groups compared. Because there were two doses of abrocitinib compared with placebo, 100 and 200 mg, subgroup analysis was used for the analysis of both efficacy and safety indicators.

Evaluation of efficacy

IGA improvements. For the five RCTs (40-44) were included, results from the heterogeneity test (I^2<50%) indicated homogeneity. FEM analysis revealed that, compared with placebo, 100 (M-H OR, 4.21; 95% CI, 2.97-5.96) and 200 mg (M-H OR, 5.49; 95% CI, 3.96-7.61) significantly improved the IGA score (Fig. 3). FEM analysis showed that, the difference between 100 and 200 mg was significant, with the 200 mg

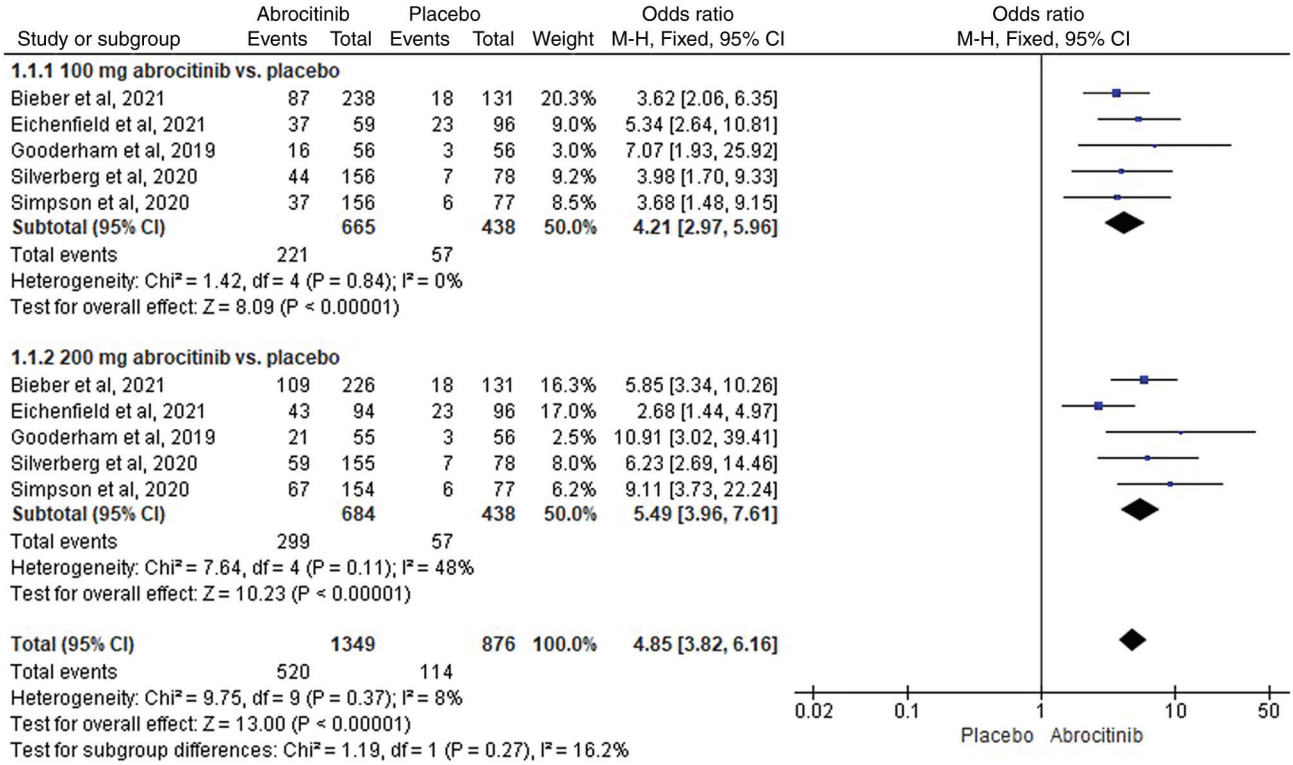

Figure 3. Subgroup analysis of investigator's global assessment scores of 100 and 200 mg abrocitinib compared with placebo in forest plots. M-H, Mantel-Haenszel.

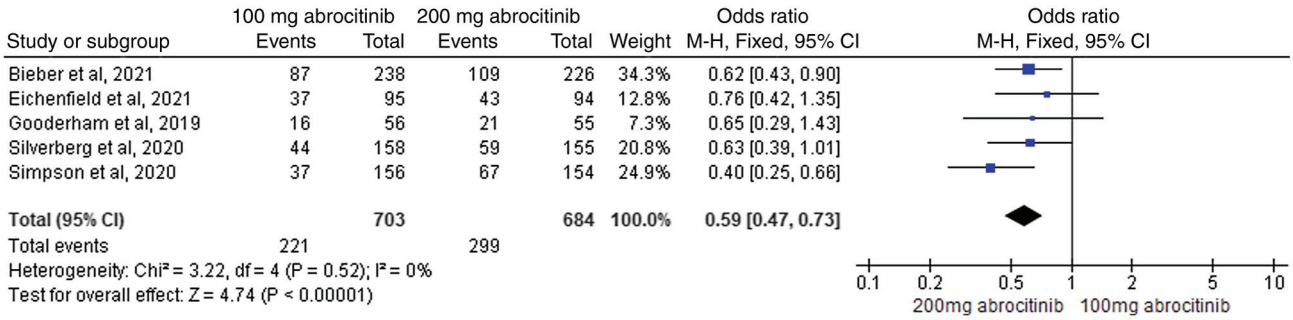

Figure 4. Forest plot of investigator's global assessment scores comparing 100 and 200 mg abrocitinib. M-H, Mantel-Haenszel.

abrocitinib group yielding superior improvements compared with the 100 mg group (M-H OR, 0.59; 95% CI, 0.47-0.73), This suggests that 200 mg dosage was superior at improving the IGA (Fig. 4).

EASI-50 response rate. In total, three RCTs (42-44) were included. Heterogeneity was detected (I^2>50%), therefore REM analysis was used. Compared with those in the placebo group, 100 (M-H OR, 5.39; 95% CI, 3.26-8.93) and 200 mg (M-H OR, 11.00; 95%CI, 6.89-17.55) abrocitinib significantly improved EASI-50 response rate (Fig. 5). For analysis of 100 and 200 mg abrocitinib, the heterogeneity test (I^2=0%) suggested homogeneity. FEM analysis showed the difference between the two groups was statistically significant, where 200 mg abrocitinib delivered greater EASI-50 response rate improvement compared with 100 mg group (M-H OR, 0.49; 95% CI, 0.36-0.67; Fig. 6).

EASI-75 response rate. In total, five RCTs (40-44) were included, where heterogeneity was detected (I^2>50%). Compared with those in the placebo group, 100 (M-H OR, 4.21; 95% CI, 2.89-6.15) and 200 mg (M-H OR, 8.07; 95% CI, 4.59-14.17) abrocitinib significantly improved the EASI-75 response rate (Fig. 7). A total of five RCTs (40-44) were included in comparative analysis of 100 and 200 mg abrocitinib, where the heterogeneity test (I^2=0%) suggested homogeneity. FEM analysis showed 200 mg abrocitinib yielded significantly greater improvement compared with 100 mg (M-H OR, 0.53; 95% CI, 0.43-0.66; Fig. 8).

EASI-90 response rate. In total, three RCTs (42-44) were included, where heterogeneity test (I^2<50%) suggested homogeneity. FEM analysis showed that compared with placebo, 100 (M-H OR, 4.87; 95% CI, 2.55-9.29) and 200 mg (M-H OR, 10.61; 95% CI, 5.63-20.01) significantly improved

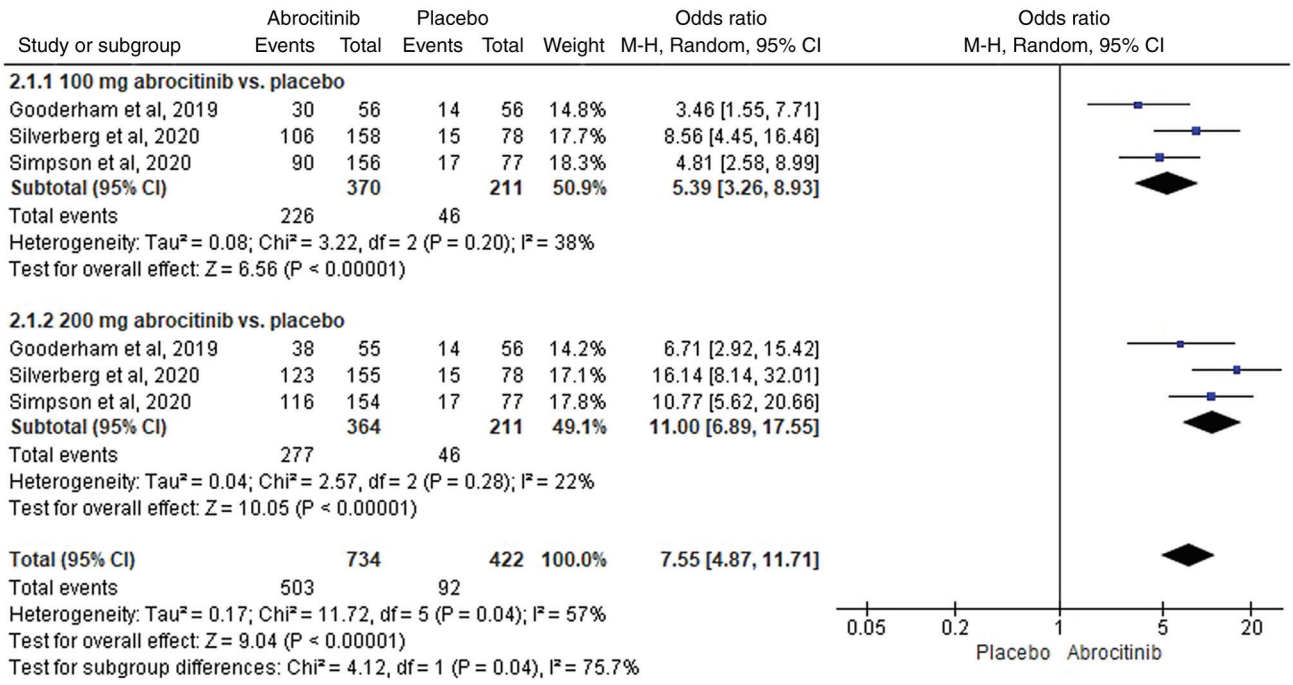

Figure 5. Sub-group analysis of eczema area and severity index-50 response rate. M-H, Mantel-Haenszel.

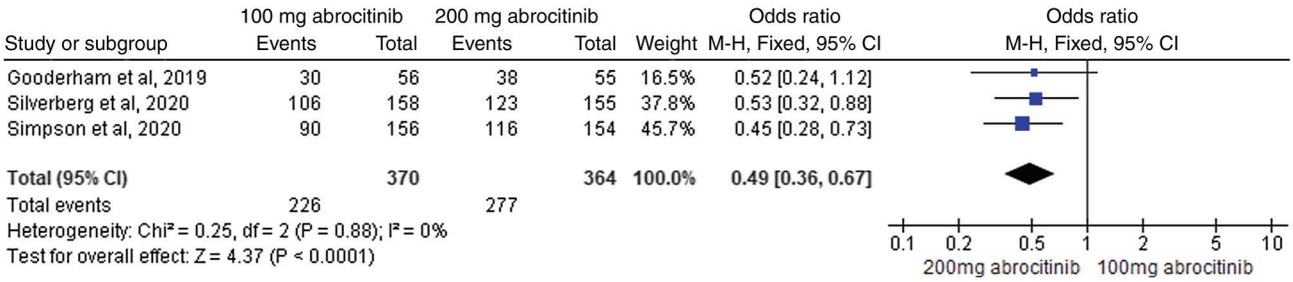

Figure 6. Meta-analysis of the eczema area and severity index-50 response rates. M-H, Mantel-Haenszel.

EASI-90 response rate (Fig. 9). In total, three RCTs (42-44) were included in subsequent comparative analysis of 100 and 200 mg abrocitinib, where homogeneity was suggested (I^2=0%) FEM analysis revealed that the difference between the two groups was significant, with the 200 mg abrocitinib group yielding superior EASI-90 response rates compared with those in 100 mg group (M-H OR, 0.45; 95% CI, 0.33-0.63; Fig. 10).

P-NRS improvement rate. In total, five RCTs (40-44) were included, where heterogeneity was suggested (I^2>50%). Compared with placebo, 100 (M-H OR, 3.03; 95% CI, 2.11-4.36) and 200 mg (M-H OR, 4.28; 95% CI, 2.46-7.47) significantly improved the P-NRS (Fig. 11). In the pairwise cross-control analysis of 100 and 200 mg abrocitinib, five RCTs (40-44) were included where heterogeneity was found (I^2>50%). No significant difference between the two groups were found in terms of P-NRS (Fig. 12).

Safety outcomes. A combined meta-analysis of the incidence of adverse drug reaction (ADR) in 100 and 200 mg abrocitinib and placebo groups was next conducted. A total of 11 symptoms were observed. Nausea (M-H RR, 3.25; 95% CI, 1.55-6.85), infection and infestation (M-H RR, 1.45, 95% CI, 1.06-1.98) and upper respiratory tract viral infection (M-H RR, 2.26; 95% CI, 1.11-4.60) had significantly higher incidence in the 100 mg abrocitinib compared with the placebo group. However, there was no significant difference in the incidence of gastrointestinal disorder, upper respiratory tract infection, dizziness, headache, skin and subcutaneous disorders, blood creatine phosphokinase increased, thrombocytopenia and severe adverse event between the two groups. In the 200 mg abrocitinib compared with the placebo group, there were significantly higher incidences of gastrointestinal dysfunction (RR, 5.35, 95%CI, 2.28-12.57), nausea (M-H RR, 8.03, 95% CI, 3.98-16.20), dizziness (M-H RR, 6.46; 95% CI, 1.17-35.62) and headache (M-H RR, 1.89, 95% CI, 1.11-3.19), but there were no significant differences in the incidence of other ADRs. In the 100 mg abrocitinib compared with the 200 mg abrocitinib, there were significant differences in the incidence of gastrointestinal disorder (M-H RR, 0.39; 95% CI, 0.22-0.69), nausea (M-H RR, 0.42; 95% CI, 0.30-0.58) and dizziness (M-H RR, 0.10; 95% CI, 0.01-0.76), but no significant differences in the incidence of other ADRs (Table II).

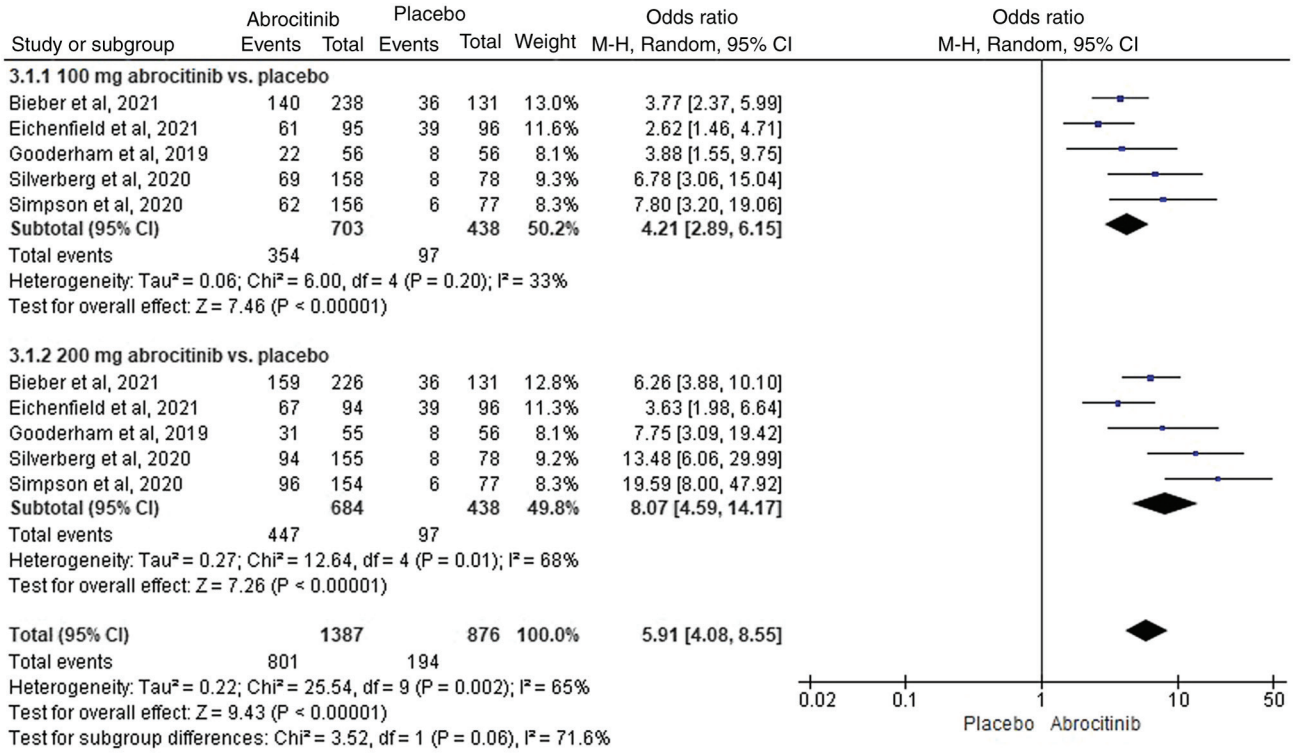

Figure 7. Subgroup analysis of eczema area and severity index-75 response rate. M-H, Mantel-Haenszel.

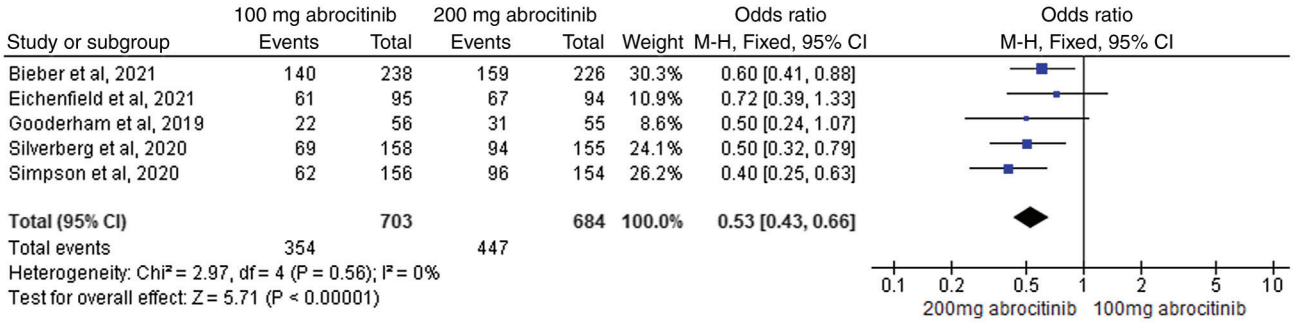

Figure 8. Meta-analysis of eczema area and severity index-75 response rates following 100 and 200 mg abrocitinib treatment. M-H, Mantel-Haenszel.

Publication offset evaluation. In a pairwise cross-control analysis of 100 and 200 mg of abrocitinib compared with placebo, funnel plots were constructed using IGA, EASI-75 response rate and P-NRS as the efficacy indicators. The results showed that asymmetry of the EASI-75 scattered points along the center line; scattered points of the IGA and P-NRS 2 evaluation indices were symmetrical along the center line, However, all of the aforementioned indices were scattered and stratified unevenly, suggesting that these three evaluation indices may have the risk of publication bias. These findings suggest that results should be judged with caution (Fig. 13).

Sensitivity analysis. Sensitivity correction was performed on results of the REM, before analysis was performed again after removing one research item with large differences in the weight ratio of each effect index at a time (45). The results showed that the effect value of P-NRS improvements in the control analysis of 100 and 200 mg abrocitinib showed instability. There were no changes in the statistical values of other effect indicators, suggesting that the results were stable (Table III).

Discussion

Pruritus is the most common clinical symptom in AD. Therefore, alleviating skin eczema symptoms and eliminating pruritus is key to the treatment of AD (46). Systemic treatment options for patients with moderate-to-severe AD are frequently based on those applied for patients with refractory AD who have failed local treatment or those who has not been cured for a long period time. Patients typically have unrealistically high expectations of the effect of these therapies (47). Based on five randomized, double-blind, parallel-controlled trials, the present study conducted a pairwise cross-control analysis of 1,825 patients with moderate-to-severe AD who received 200 and/or 100 mg abrocitinib orally or placebo once a day. The results showed that compared the placebo group, 100 and

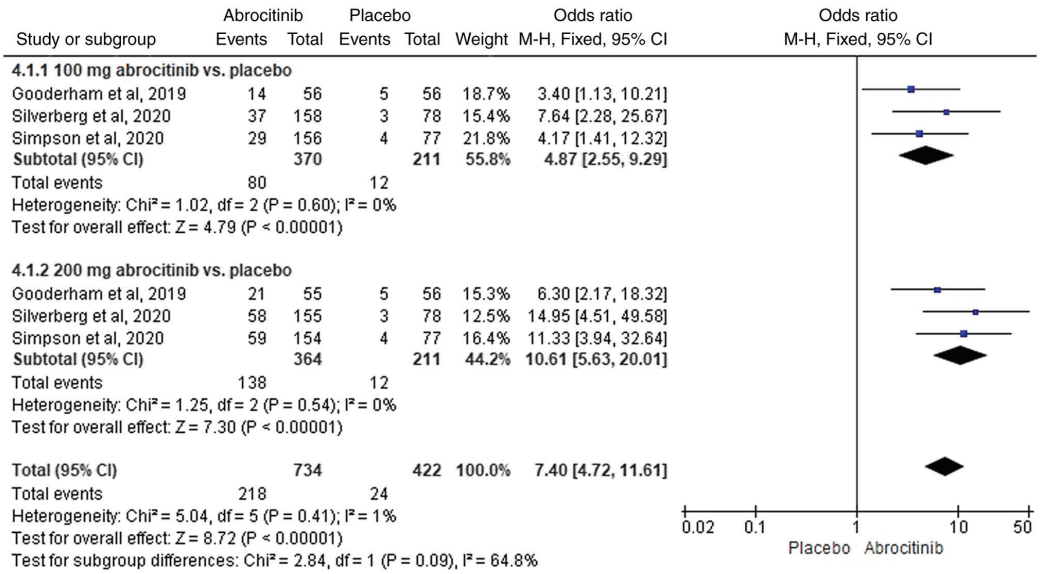

Figure 9. Subgroup analysis of eczema area and severity index-90 response rate. M-H, Mantel-Haenszel.

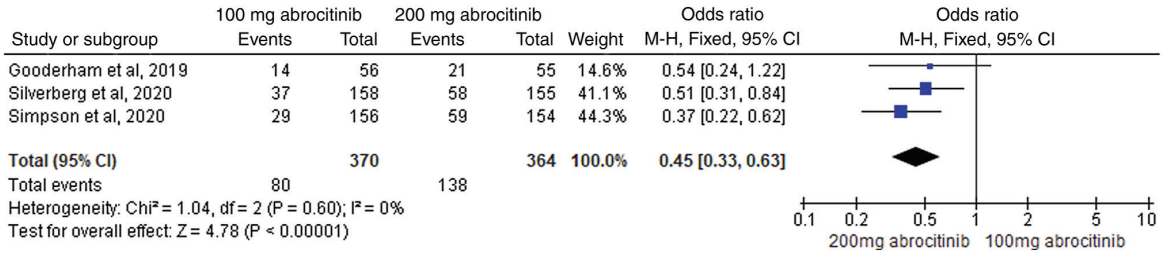

Figure 10. Meta-analysis of eczema area and severity index-90 response rates after 100 mg and 200 mg abrocitinib treatment. M-H, Mantel-Haenszel.

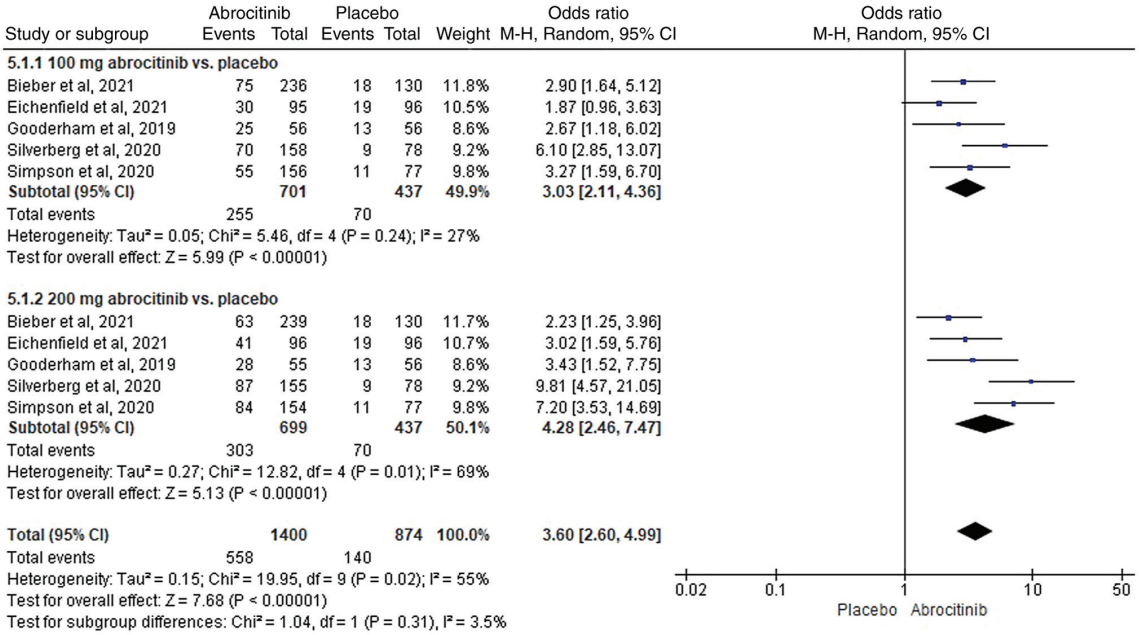

Figure 11. Subgroup analysis of pruritus numerical rating scale. M-H, Mantel-Haenszel.

200 mg abrocitinib significantly improved the therapeutic indices of IGA, EASI-50, -75 and -90 and P-NRS in patients. In particular, IGA score, skin eczema and pruritis symptoms of patients were more significantly improved when the dose of abrocitinib was increased to 200 mg. The results of these trials are consistent with the prominent role of JAK1 signaling

Table II. Safety profile in each treatment group.

Adverse drug reaction	Number of trials	100 mg abrocitinib vs. placebo		200 mg abrocitinib vs. placebo		100 vs. 200 mg abrocitinib	
		I^2, %	RR, 95% CI	I^2, %	RR, 95% CI	I^2, %	RR, 95% CI
Gastrointestinal disorder	3	0	2.16 (0.85-5.46)	0	5.35 (2.28-12.57)[a]	0	0.39 (0.22-0.69)[a]
Nausea	5	0	3.25 (1.55-6.85)[a]	0	8.03 (3.98-16.20)[a]	0	0.42 (0.30-0.58)[a]
Infection and infestation	5	0	1.45 (1.06-1.98)[a]	0	1.20 (0.87-1.65)	0	1.24 (0.96-1.60)
Upper respiratory tract infection	5	0	1.16 (0.75-1.80)	0	0.95 (0.61-1.50)	0	1.26 (0.85-1.87)
Upper respiratory tract viral infection	4	0	2.26 (1.11-4.60)[a]	21	1.75 (0.82-3.73)	0	1.24 (0.73-2.09)
Dizziness	2	0	0.34 (0.04-3.18)	0	6.46 (1.17-35.62)[a]	0	0.10 (0.01-0.76)[a]
Headache	5	0	1.41 (0.81-2.43)	0	1.89 (1.11-3.19)[a]	0	0.74 (0.50-1.10)
Skin and subcutaneous disorder	5	76	1.11 (0.49-2.49)	68	0.89 (0.42-1.91)	74	1.11 (0.57-2.17)
Increased blood creatine phosphokinase	2	56	2.05 (0.55-7.62)	32	2.50 (0.68-9.21)	0	0.77 (0.29-2.02)
Thrombocytopenia	2	0	1.57 (0.16-15.01)	0	4.27 (0.53-34.20)	0	0.19 (0.03-1.12)
Serious adverse events	5	0	0.88 (0.44-1.77)	0	0.59 (0.27-1.2)	0	1.52 (0.75-3.07)

[a]P<0.05.

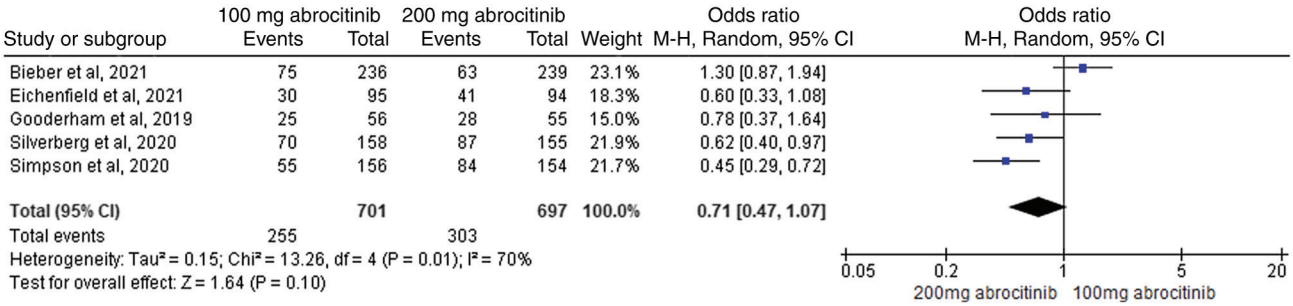

Figure 12. Meta-analysis of pruritus numerical rating scale after treatment with 100 and 200 mg abrocitinib. M-H, Mantel-Haenszel.

in the development of pruritus and skin inflammation in AD, demonstrating the potential therapeutic value of JAK1 inhibitors in patients with AD (48,49). AD has a complex pathophysiological mechanism that remains to be fully elucidated. However, it has been reported that immune disorders lead to the destruction of epidermal barrier function and aggravate symptoms of AD (50). At present, it is hypothesized that JAK inhibition alters the signaling mechanism of several immune and epidermal cell-derived cytokines involved in the pathogenesis of AD, such as thymus stromal lymphopoietin, IL-4, IL-13, IL-22 and IL-31 (51).

The reliability of the results of in a systematic review is dependent on quality of the original literature included, whereas the quantity of high-quality literature will determine the stability of the results (52). The five publications included in the present study were randomized and double-blinded studies, with 1,825 patients enrolled. The basic information of the publication was complete; research indicators were homogenous and data were complete. The risk of deviation from the experimental design by the authors of the original publication was low. In addition, high risk of deviation was not found in the evaluation results of the methodology quality in each study and the overall quality of the included literature was high.

In the present study, through the association analysis of the results of the main therapeutic indicators, it was concluded that the symptoms of pruritus and eczema in patients with moderate-to-severe AD could be relieved within 12 weeks after the oral administration of 100 mg abrocitinib. Specifically, the symptoms of pruritus and eczema could be

Table III. Sensitivity analysis of effect indicators with large differences in weight ratio.

A, 100 mg abrocitinib vs. placebo

	Before exclusion			After exclusion			
Effect index	RR	95%CI	P-value	RR	95%CI	P-value	Stability
Skin and subcutaneous disorder	1.11	0.49-2.49	0.81	0.96	0.43-2.16	0.93	Yes
Increased blood creatine phosphokinase	2.05	0.55-7.62	0.28	9.09	0.50-166.61	0.14	Yes

B, 200 mg abrocitinib vs. placebo

	Before exclusion			After exclusion			
Effect index	RR	95%CI	P-value	RR	95%CI	P-value	Stability
EASI-75	8.07	4.59-14.17	<0.01	8.39	5.79-12.17	<0.01	Yes
P-NRS	4.28	2.46-7.47	<0.01	5.29	3.71-7.55	<0.01	Yes
Skin and subcutaneous disorder	0.89	0.42-1.91	0.77	0.73	0.40-1.32	0.30	Yes

C, 100 vs. 200 mg abrocitinib

	Before exclusion			After exclusion			
Effect index	RR	95%CI	P-value	RR	95%CI	P-value	Stability
P-NRS	0.71	0.47-1.07	0.10	0.57	0.44-0.74	<0.01	No
Skin and subcutaneous disorder	1.11	0.57-2.17	0.77	0.99	0.43-2.31	0.98	Yes

P-NRS, pruritus numerical rating scale; EASI, eczema area and severity index.

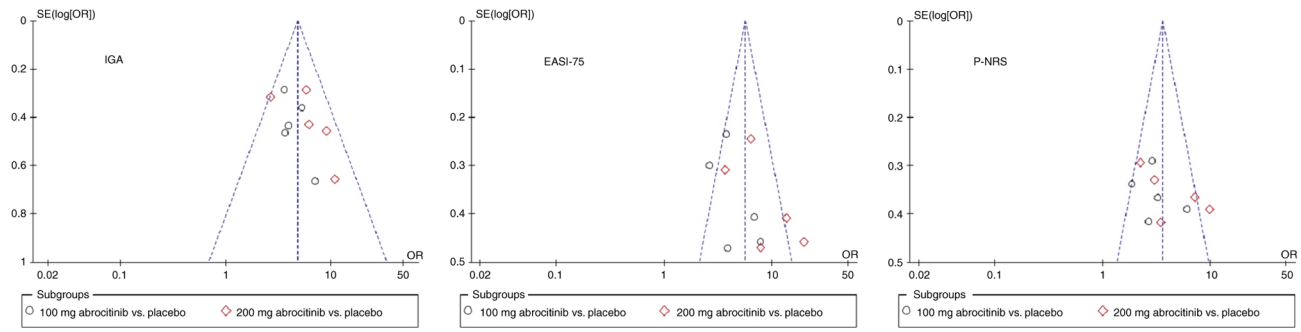

Figure 13. Offset evaluation funnel plot. IGA, investigator's global assessment; P-NRS, pruritus numerical rating scale; EASI, eczema area and severity index.

rapidly relieved, which was then effectively consolidated with the extension of the treatment course and increases in dosage. This finding is consistent with the results of a previous retrospective study of the effects of 100 mg abrocitinib once daily for the treatment of moderate-to-severe AD by Gooderham *et al* (53), which found that at week 12 after the commencement of treatment, the IGA score and EASI-75 improved significantly from the baseline. In the present study, significant improvements in IGA and EASI scores were observed compared with those receiving 100 mg when the dose was increased to 200 mg. To some extent, the efficacy of abrocitinib 200 mg appears to be more potent, in terms of both speed and intensity of action, suggesting that this dose may be the preferred dose for the majority of patients, which

was consistent with the results of Simpson *et al* (54). However, for patients with a higher risk of adverse reactions or those who do not tolerated abrocitinib, a dose of 100 mg may be a more appropriate starting dose. In addition, although 200 mg abrocitinib is generally well-tolerated by the majority of patients ≥65 years of age, dose-associated side effects, such as hematological changes and shingles, are particularly common in this age group (55). Therefore, appropriate dose selection in the adapted population before initiation is recommended to minimize the risks associated with abrocitinib. Due to the heterogeneity risk in the P-NRS score after 100 and 200 mg abrocitinib treatment and the high sensitivity of data variation found in the present study, there is likely to be a bias risk in the association analysis of P-NRS results in the 200 mg abrocitinib group, meaning these results should be interpreted with caution. In a pairwise cross-control safety comparison of 100 and 200 mg abrocitinib compared with placebo, both 100 and 200 mg abrocitinib exhibited different incidences of gastrointestinal and central nervous system symptoms, among which nausea, infection and infestation, upper respiratory tract viral infection were the main symptoms in the 100 mg abrocitinib group. By contrast, gastrointestinal dysfunction, nausea, dizziness and headache were the main symptoms in the 200 mg abrocitinib group. Reich *et al* (18) found that serious adverse reactions, such as inflammatory bowel disease, peritonsillitis, dehydration and asthma occurred after oral treatments with abrocitinib 200 mg, whereas one case of pneumonia was also found during follow-up. Serious adverse reactions, such as retinal detachment, acute pancreatitis, appendicitis, dizziness and epilepsy, were associated with 100 mg abrocitinib oral treatment (18), similar to the results of the present study. Although comparison between 100 and 200 mg abrocitinib found that incidence of gastrointestinal function, nausea and headache was more pronounced in the 200 mg group, incidence of infection and infestation (14.94 vs. 12.13%), upper respiratory tract infection (7.54 vs. 5.99%) and viral upper respiratory tract viral infection (5.32 vs. 4.35%) decreased as abrocitinib dosage increased. The association between the infection risk of patients and the dose of abrocitinib warrants further study.

To ensure the integrity of the included data and avoid missing literature or insufficient literature retrieval, the present study searched the universally used, recognized, authoritative and complete data collection databases. However, due to the limited number of included studies and tested patients, the results of each analysis are not strong and should be interpreted with caution. In terms of literature screening, data extraction, and quality evaluation, subjective selection bias or risk of omitting relevant literature may persist due to different researchers. The included analysis data may be confounded by uncertain factors, such as missing literature, differences in subjective judgments by each author and language restrictions. Furthermore, results of the present meta-analysis may contain volatility, necessitating further validation in future studies. The present systematic review focused on comparing 100 and 200 mg abrocitinib with the placebo group. The results serve as a basis for treatment decision-making at these doses, whilst excluding other major therapeutic drugs from the scope of this review. Despite the limitations in the present study, the present meta-analysis provides a systematic evaluation pathway for subsequent multi-arm studies on 100 mg abrocitinib and single-arm studies exploring the efficacy of its combined application. Additionally, it offers an avenue for further investigating the association between abrocitinib dosage and infection risk. Despite these limitations, the controversial effects of abrocitinib between 100 and 200 mg on pruritus, eczema symptoms and tolerance in patients with moderate-to-severe AD were mentioned.

Both 100 and 200 mg doses of abrocitinib can rapidly alleviate the clinical symptoms of pruritus and eczema in patients with moderate-to-severe AD, which are generally well tolerated compared with patients as demonstrated by the acceptable adverse reactions profile. However, there is risk of infection is different in patients treated with different doses of abrocitinib, rendering it necessary to perform additional benefit-risk assessments of patients. Due to the objective factors of the systematic review, the results of the present study are mainly for reference and require multi-center, strictly designed, high-quality and large-scale clinical trials for validation.

Acknowledgements

Not applicable.

Funding

The present study was supported by the Science and Technology Plan Fund from Yaan Science and Technology Bureau (grant no. 22KJJH0039); Beijing Medical Award Foundation 'Rui Ying IV phase' scientific research project (grant no. YXJL-2023-0866-0316).

Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XX and LF conceived and designed the study. XX performed the literature search, extracted and analyzed the data and wrote the manuscript. JZ and FH extracted and analyzed data and reviewed the manuscript. LF revised the manuscript. XX and JZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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