The safety of systemic Janus kinase inhibitors in atopic dermatitis: a systematic review and network meta-analysis

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Abstract

Purpose Janus kinase (JAK) inhibitors have been developed to treat moderate to severe atopic dermatitis, but there is little evidence comparing the safety profile of these drugs. The aim of this study is to compare the relative safety of the different systemic JAK inhibitors in atopic dermatitis.

Methods Medline, EMBASE, and clinicaltrials.gov were searched to identify phase 2/3, clinical trials (RCTs) designed to evaluate the efficacy and safety of systemic JAK inhibitors in atopic dermatitis. Outcomes were the risk of any adverse event (AE), serious AEs, AEs leading to treatment discontinuation, any infection, serious infections, herpes zoster infection, and any cardiac or vascular event.

Results Eighteen RCTs were included. Compared with placebo, baricitinib (odds ratio [OR] 1.25, 95% credible interval [CrI] 1.03–1.55), abrocitinib (OR 1.54, 95% CrI 1.25–1.90), and upadacitinib (OR 1.46, 95% CrI 1.19–1.81) increase the risk of any adverse event. Abrocitinib (OR 1.62, 95% CrI 1.70–2.72), upadacitinib (OR 1.67, 95% CrI 1.19–2.43), and dupilumab (OR 1.69, 95% CrI 1.02–2.79) increase the risk of infections when compared with placebo. Dupilumab has a reduced risk of herpes zoster infection when compared with upadacitinib (OR 0.23; 95% CrI 0.08–0.81) No further statistically significant risk differences between treatments were identified.

Conclusions The results suggest systemic JAK inhibitors for atopic dermatitis have a similar safety profile. However, as current data present limitations, postmarketing safety evidence will be crucial to draw definitive conclusions regarding the safety of JAK inhibitors.

Keywords Atopic dermatitis · JAK inhibitors · Safety · Systematic review · Meta-analysis

Introduction

Atopic dermatitis is a chronic, inflammatory, pruritic, relapsing skin disease affecting up to 20% of children and 2–8% of adults [1]. The majority of atopic dermatitis cases are considered mild, with 10% or less of patients suffering from severe eczematous skin lesions [1]. Patients with atopic dermatitis may have dry, itchy skin [1]. Acute phase lesions are characterized by being extremely pruritic, with erythematous papules and development of epidermal hyperplasia [2]. Hyperkeratosis of the skin characterizes chronic lesions of the disease. Skin lesions lead to recurrent infections, sleeping problems, and poor quality of life [2].

Topical treatment with corticosteroids and calcineurin inhibitors is considered the standard of care for most adults and children suffering from atopic dermatitis [1, 3]. For patients presenting a more severe condition, phototherapy and/or systemic therapy with anti-inflammatory and immunosuppressive agents are recommended [1, 3].

Systemic Janus kinase (JAK) inhibitors have been clinically developed to treat moderate to severe atopic dermatitis over the last years. Baricitinib and abrocitinib are already authorized in the European Union, while other drugs are currently being evaluated in phase 2/3 randomized clinical trials (RCTs) [4–6]. Results from clinical studies demonstrated that systemic JAK inhibitors are efficacious in treating atopic dermatitis, by alleviating itching, reducing skin pain and eczema, and improving sleeping levels [4–6]. However, the safety profile of JAK inhibitors has been subject to discussion since they first came into market.
Clinically important and potential risks, such as serious and opportunistic infections (e.g., herpes zoster reactivation, tuberculosis, or candidiasis), and cardiovascular events, like major adverse cardiac events (MACE), pulmonary embolism, and deep venous thrombosis, have been associated with JAK inhibitors [7, 8]. Safety concerns, including the risk of serious infections, delayed the approval of tofacitinib for rheumatoid arthritis in Europe until 2017 [9]. More recently, results from a postmarketing, phase IV, RCT identified an increased risk of myocardial infarction associated with tofacitinib in patients with rheumatoid arthritis and concomitant cardiovascular risk factors [10]. Furthermore, baricitinib initial marketing application was rejected by FDA because of an unfavorable overall benefit-risk assessment [11]. Lately, the regulatory authority approved baricitinib 2 mg, but not the 4 mg dose due to a potential risk of venous thromboembolism (VTE) [12].

A recently published network meta-analysis compared the risk of serious adverse events and adverse events leading to treatment discontinuation between systemic immunomodulatory treatments for atopic dermatitis, JAK inhibitors included, but the results are associated with low certainty, precluding robust conclusions [13]. Additional systematic reviews and pair-wise meta-analyses of RCTs have evaluated the safety profile of systemic JAK inhibitors when used in atopic dermatitis, although without establishing formal comparisons between treatments [14, 15]. Therefore, it is relevant to conduct additional analyses to the safety profile of systemic JAK inhibitors in patients with atopic dermatitis.

Materials and methods

This systematic review and network meta-analysis followed the Centre for Reviews and Dissemination’s guidance for undertaking reviews in healthcare and was reported in accordance with the PRISMA extension statement for reporting systematic reviews incorporating network meta-analyses of healthcare interventions (Supplemental Table 1) [16, 17]. This systematic review was registered at PROSPERO (CRD42022329007) and at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) (EUPAS46966).

Eligibility criteria

Studies were considered for inclusion if they fulfil the following criteria:

- Study design: phase II and phase III randomized controlled trials (RCTs);
- Population: patients diagnosed with atopic dermatitis according to one of the following criteria: American Academy of Dermatology; Hanifin and Rajka; Japanese Dermatological Association [18–20];
- Intervention: only studies assessing the effects of systemic JAK inhibitors (abrocitinib, baricitinib, gusacitinib, upadacitinib) in the treatment of patients with atopic dermatitis were included;
- Comparators: studies comparing the intervention against placebo, active treatment or no treatment;
- Outcomes: any adverse event; serious adverse events: defined as any untoward medical occurrence that at any dose may result in death, threat life, require hospital admission or prolongation of existing hospital stay, or result in persistent or significant disability or incapacity; adverse events leading to treatment discontinuation; any infection; serious infections; herpes zoster; any cardiac or vascular disorder (according to MedDRA vocabulary).
- Timing: no restrictions were applied to the length of follow-up of the studies;
- Language: only studies reported in English were included.

Information sources

Medline and EMBASE (using Ovid), and ClinicalTrials.gov were searched from their inception until February 17, 2022. Bibliographic reference list of all relevant studies, systematic reviews, and meta-analyses were hand searched to identify additional eligible studies.

Search strategy

Search terms comprised atopic dermatitis and drug names, including the thesaurus terms and the International Nonproprietary Names (INN). No language filters will be applied. The search strategy is described in detail in Supplemental Table 2.

Study records

Two researchers independently screened by hand the titles and abstracts and selected full articles for inclusion in accordance with the prespecified eligibility criteria. Disagreements were resolved by discussion and consensus with a third researcher.

Data items

The following data were extracted from each study: reference, year of publication, RCT phase (II or III), sample sizes, follow-up length, intervention (name, dosage, frequency, and
duration of treatment), comparators, and data on the safety outcomes (any adverse event, serious adverse events, adverse events leading to treatment discontinuation, any infection, serious infections, herpes zoster, and any cardiac or vascular disorder). Data was extracted from each included study by two researchers independently to a predeveloped form.

Risk of bias of the individual studies

The RoB 2 tool: a revised Cochrane risk of bias tool for randomized trials was used to assess the risk of bias of the individual studies [21]. The value of trial data on adverse effects relies on two major characteristics: the rigor of monitoring for the adverse effects during the study, in particular the infections, and the completeness of reporting.

Data synthesis

Bayesian network meta-analyses were performed using the Bayesian Markov Chain Monte Carlo (MCMC) sampling in WinBUGS, version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK) [22]. Convergence was achieved by 10,000 iterations. Further 50,000 iterations were run on three chains, giving a posterior sample of 150,000 values, on which the results of the study were based [23]. The convergence of models was assessed through Gelman-Rubin statistics and monitoring of the Monte Carlo error. Residual deviance and deviance information criteria were used to determine model fit for each outcome measure [24–26]. Odds ratios (OR) described with 95% credible intervals were chosen as effect size measures for the Bayesian network meta-analyses. The following non-informative prior distributions were initially proposed: uniform (0.2) for standard deviation of the random-effects model and normal (0, tau = 0.0001) for log[OR]. However, if any outcome measure was characterized by sparse data (0 events observed in one or both arms), a strong prior was used: uniform (−2.10; 1.58) for standard deviation of the random-effects model and normal (−2.34, tau = 1.62) [27, 28]. The probability of each drug being the best (safest) among all drugs for each outcome measure was estimated by ranking the relative safety of all treatments [23]. R statistical software (R version 4.1.2) was used to perform network maps.

Results

Supplemental Fig. 1 presents the flow of the search strategy criteria. The electronic database search returned 562 references. After excluding duplicates and other studies with inadequate design, 18 studies met the inclusion criteria [Supplemental References w1-w16]. Two publications reported the results of two RCTs each [w8,w14]. The main characteristics of the studies (design and follow-up duration, participants’ demographic characteristics, drugs under evaluation, and sample) are presented in Table 1. All except one study included patients using background topical therapy (n = 17). Most of the studies used placebo as a comparator (n = 17), while just 2 studies compared JAK inhibitors with dupilumab.

Supplemental Fig. 2 presents the assessment of the risk of bias of the studies included in this network meta-analysis. Sixteen RCTs were judged as having a low risk of bias, one generated some concerns in terms of bias and another one was judged as having a high risk of bias. Lack of information regarding the adverse event monitoring process and the allocation concealment/randomization method was identified as a methodological impairment.

Network maps

Network maps are illustrated in Supplemental Fig. 3. The thickness of the lines connecting two nodes indicates the amount of data available for that comparison.

Any adverse event

Compared with placebo, baricitinib (odds ratio [OR] 1.25, 95% credible interval [CrI] 1.03–1.55), abrocitinib (OR 1.54, 95% CrI 1.25–1.90), and upadacitinib (OR 1.46, 95% CrI 1.19–1.81) increase the risk of any adverse event (Supplemental Fig. 4). Dupilumab presents a reduced risk when compared with abrocitinib (OR 0.68, 95% CrI 0.48–0.92) and upadacitinib (OR 0.71, 95% CrI 0.51–0.96). The ranking suggests placebo is probably the safest treatment, followed by gusacitinib and dupilumab (Supplemental Table S3).

Serious adverse events

Compared with placebo, all treatments present a reduced risk of serious adverse events (Fig. 1). No further statistically significant risk differences were identified between the treatments. Dupilumab was found to be the safest treatment, followed by gusacitinib and upadacitinib (Supplemental Table S3).

Adverse events leading to discontinuation

All the treatments present a reduced risk of adverse events leading to discontinuation compared to placebo (Fig. 2). No further statistically significant risk differences were identified between the remaining treatments. The safest treatment
| Reference | Year of publication | RCT identifier | RCT phase | Region | Background therapy | Intervention Name | Dosage/frequency | Sample size (N) | Comparator Name | Sample size (N) | Follow-up (weeks) |
|-----------|---------------------|---------------|-----------|--------|--------------------|-------------------|-----------------|----------------|----------------|----------------|------------------|
| Blauvelt et al, 2022 | 2022 | NCT03627767 | III | Global | Topical (non-medicated emollients), oral antihistamines | Abrocitinib | 100 mg id 200 mg id | 265 266 | Placebo | 267 | 40 |
| Bieber et al, 2021 | 2021 | NCT03720470 | III | Global | Topical (gluc.; calc. in.; ph4 in.) | Abrocitinib | 100 mg id 200 mg id | 238 226 | Dupilumab | 242 131 | 16 |
| Eichenfield et al, 2021 | 2021 | NCT03796676 | III | Global | Topical (non-medicated emollients, gluc.; calc. in.; crisaborole) | Abrocitinib | 100 mg id 200 mg id | 95 94 | Placebo | 96 | 12 |
| Silverberg et al, 2020 | 2020 | NCT03575871 | III | Global | Topical (non-medicated emollients), oral antihistamines | Abrocitinib | 100 mg id 200 mg id | 158 155 | Placebo | 78 | 12 |
| Simpson et al, 2020 | 2020 | NCT03349060 | III | Global | Topical (non-medicated emollients), oral antihistamines | Abrocitinib | 100 mg id 200 mg id | 156 154 | Placebo | 77 | 12 |
| Gooderham et al, 2019 | 2019 | NCT02780167 | II | Global | Topical (non-medicated emollients), oral antihistamines | Abrocitinib | 10 mg id 30 mg id 100 mg id 200 mg id | 49 51 56 55 | Placebo | 55 | 12 |
| Reich et al, 2020 | 2020 | NCT03733301 | III | Global | Topical corticosteroids | Baricitinib | 2 mg id 4 mg id | 109 111 | Placebo | 108 | 16 |
| Simpson et al, 2020 | 2020 | NCT03334396 | III | Global | Topical corticosteroids | Baricitinib | 1 mg id 2 mg id 4 mg id | 127 123 125 | Placebo | 249 | 16 |
| Simpson et al, 2020 | 2020 | NCT03334422 | III | Global | Topical corticosteroids | Baricitinib | 1 mg id 2 mg id 4 mg id | 124 123 123 | Placebo | 244 | 16 |
| Simpson et al, 2020 | 2020 | NCT03435081 | III | USA, Canada | Topical (non-medicated emollients) | Baricitinib | 2 mg id 4 mg id | 147 145 | Placebo | 146 | 16 |

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| Reference | Year of publication | RCT identifier | RCT phase | Region | Background therapy | Intervention | Comparator | Sample size (N) | Follow-up (weeks) |
|-----------|---------------------|---------------|-----------|--------|--------------------|--------------|------------|---------------|-----------------|
| Guttman-Yassky et al, 2019 [w10] | 2019 | NCT02576938 | II | USA, Japan | Topical corticosteroids | Baricitinib 2 mg id 4 mg id | Placebo | 37 38 | 16 |
| NCT03428100 [w11] | 2019 | NCT03428100 | III | Global | Topical corticosteroids | Baricitinib 1 mg id 2 mg id 4 mg id | Placebo | 93 184 92 | 24 |
| Bissonnette et al, 2019 [w12] | 2019 | NCT03139981 | II | USA, Canada | None | Gusacitinib 20 mg id 40 mg id 80 mg id | Placebo | 9 9 9 | 4 |
| Blauvelt et al, 2021 [w13] | 2021 | NCT03738397 | III | Global | Topical (non-medicated emollients) | Upadacitinib 30 mg id | Dupilumab 300 mg weekly | 348 | 24 |
| Guttman-Yassky et al. 2021 [w14] (Measure Up 1) | 2021 | NCT03569293 | III | Global | Topical (non-medicated emollients) | Upadacitinib 15 mg id 30 mg id | Placebo | 281 285 | 16 |
| Guttman-Yassky et al. 2021 [w14] (Measure Up 2) | 2021 | NCT03607422 | III | Global | Topical (non-medicated emollients) | Upadacitinib 15 mg id 30 mg id | Placebo | 276 282 | 16 |
| Reich et al, 2021 [w15] | 2021 | NCT03568318 | III | Global | Topical corticosteroids | Upadacitinib 15 mg id 30 mg id | Placebo | 300 297 | 16 |
| Guttman-Yassky et al, 2021 [w6] | 2020 | NCT02925117 | II | Global | Topical (non-medicated emollients) | Upadacitinib 7.5 mg id 15 mg id 30 mg id | Placebo | 42 42 42 | 16 |

**RCT** randomized clinical trial, **gluc** glucocorticoids, **calc** calcineurin inhibitors, **ph4** phosphodiesterase 4 inhibitors, **USA** United States of America

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**Table 1** (continued)
was found to be gusacitinib, followed by dupilumab and upadacitinib (Supplemental Table S3).

**Any infection**

Abrocitinib (OR 1.62, 95% CrI 1.7–2.72), upadacitinib (OR 1.67, 95% CrI 1.19–2.43), and dupilumab (OR 1.69, 95% CrI 1.02–2.79) increase the risk of infections when compared with placebo (Supplemental Fig. 5). The ranking suggests that the placebo is probably the safest treatment, followed by baricitinib and gusacitinib (Supplemental Table S3).

**Serious infections**

No statistically significant risk differences were identified between the treatments (Supplemental Fig. 6). Dupilumab was found to be the safest treatment, followed by baricitinib and placebo (Supplemental Table S3).
Herpes zoster

All the treatments present a reduced risk of herpes zoster infection compared to placebo. Dupilumab has a reduced risk of herpes zoster infection when compared with upadacitinib (OR 0.23; 95% CrI 0.08–0.81) (Supplemental Fig. 7). Dupilumab was found to be the safest treatment, followed by baricitinib and abrocitinib (Supplemental Table S3).

Any cardiac or vascular disorder

A total of 42 cardiac or vascular disorder events occurred in the RCTs included in this systematic review. Of those, 5 occurred with dupilumab, 7 with placebo, and 30 with systemic JAK inhibitors (abrocitinib: 23; gusacitinib: 1; baricitinib: 3; upadacitinib: 3). It was not possible to perform a network meta-analysis due to the low frequency of these events.

Model fit, model consistency, heterogeneity, and convergence

The posterior mean residual deviances ($D_{res}$) for serious adverse events (55,32), adverse events leading to treatment discontinuation (49,17), and herpes zoster infection (91,59) meta-analyses are greater than the number of unconstrained data points (37) of the correspondent datasets, suggesting there may be some lack of model fit of the predictions from these network meta-analyses models (Supplemental Table S4). The $D_{res}$ estimates for the remaining networks suggest that the model gives...
predictions that fit well to the data. Supplemental Fig. 8 depicts the contribution of individual studies to the residual deviance. Blauvelt and colleagues (2022), two-arm, phase III RCT, evaluating abrocitinib, stands out as contributing largely for residual deviance among the serious adverse event meta-analysis [w1]. Breeze-AD2, a double-arm, phase III RCT evaluating baricitinib, contributes largely to the residual deviance among the adverse events leading to discontinuation network meta-analysis [w8]. Among the herpes zoster infection network, Measure Up 1, a phase III RCT evaluating upadacitinib, is the main contributor to the residual deviance [w14].

Except for any adverse effects dataset, between-studies heterogeneity (σ) was identified in the remaining meta-analyses, since the results are significantly different from zero (0), and the confidence intervals are slightly widened (Supplemental Table 4). Both posterior mean deviances (Dmodel) and Deviance Information Criteria (DIC) estimates suggest that the random-effects model is the most adequate to conduct these meta-analyses, except for herpes zoster infection (Supplemental Table 4). However, as a conservative approach, this analysis was carried out using the random-effects model.

According to the Gelman-Rubin statistics (Supplemental Fig. 9), convergence was achieved, but some difficulties were observed for the nodes including gusacitinib (treatment 2 in all meta-analyses, except for serious infections and herpes zoster infection, where it was not included). In those cases, plots only tended to stabilize around iteration 70,000 for most of the comparisons (R < 1.05). The main reason for this is that only one study of gusacitinib was included, with a small sample size. Yet, the Monte Carlo standard error (MC error) demonstrated was estimated as being <5% of the posterior standard deviation (sd), suggesting that sufficient posterior samples have been used for inference (Table S5).

Discussion

JAK inhibitors exert their immunosuppressive activity through the inhibition of the JAK-STAT pathway. This cascade plays an essential role in the immune dysregulation in atopic dermatitis, promoting Th2 cell and eosinophils response, upregulating epidermal chemokines, pro-inflammatory cytokines, and pro-angiogenic factors and downregulating the skin barrier function [29]. Although effective in the treatment of atopic dermatitis, JAK inhibitors are associated with serious adverse effects that may limit their use [30]. Moreover, there is evidence suggesting that patients with a history of atopy have an increased risk of suffering more severe adverse drug reactions [31]. Therefore, it is clinically relevant to compare the safety profiles of systemic JAK inhibitors when used to treat atopic dermatitis, aiming to improve the decision-making process in a skin condition with an already high burden of disease.

The results of this systematic review and network meta-analysis suggest that, based on current experimental clinical data, systemic JAK inhibitors present a comparable safety profile. No statistically significant risk differences were identified between systemic JAK inhibitors on both global safety outcomes and specific risks, such as infections and cardiac or vascular events. Statistically significant differences were observed only when systemic JAK inhibitors were compared with placebo or dupilumab. Topical administered JAK inhibitors were not considered in this network meta-analysis, since those formulations were developed for mild forms of atopic dermatitis, a different population from those candidates to receive systemic JAK inhibitors [32]. Moreover, systemic adverse events are uncommon, suggesting that the degree of systemic absorption of topical JAK inhibitors is low compared with systemic drugs [33, 34].

As far as it is known, this is the first network meta-analysis aimed at comparing several safety outcomes between the systemic JAK inhibitors. The network meta-analysis of Ducker and colleagues only evaluates the risks of serious adverse events and adverse events leading to treatment discontinuation associated with the drugs of this class, and did not try to assess specific events, such as infections or cardiovascular ones [13]. Infections and cardiac and vascular adverse events were specifically addressed in this network meta-analysis, given their clinical importance to the management of patients using JAK inhibitors. As per cardiovascular events, an increased incidence of myocardial infarction was observed with a JAK inhibitor, tofacitinib, when used in rheumatoid arthritis. Moreover, recent evidence shows that severe atopic eczema may increase the risk of cardiovascular disease [35–37]. Also, skin barrier defects and immunological dysfunction caused by atopic dermatitis increase the risk of both skin and systemic infections, and, although rare, some cases can be life-threatening [38, 39]. Since JAK inhibitors share the same mechanism of action, it is important to assess whether there are differences between them regarding the risks of infections and cardiac and vascular events; this information is useful to support clinical decision-making, namely to reduce the risk of patients’ morbidity associated with the adoption of new therapeutic options [40].

The rarity of the events evaluated and the relatively short-term duration of follow-up from the RCTs included in this network meta-analysis are its main limitations. Apart from any adverse events and any infections, the incidence of the events considered for the remaining outcomes was low, with some trials reporting zero events. In this sample of RCTs, no cases of tuberculosis, MACE, or thrombosis were identified among the patients treated with JAK inhibitors. Most of the cardiac and vascular events identified among the systemic JAK inhibitors occurred with abrocitinib (23 out of 30), yet all were considered non-serious adverse events. Few cases
of herpes zoster were identified as well. Nonetheless, the frequency of such adverse events in rheumatoid arthritis was higher than cardiac and vascular events. Since the data was found to be sparse in the RCTs of atopic dermatitis, a composite outcome of cardiac or vascular disorders was considered for this network meta-analysis. Even so, it was not possible to establish a network of studies to compare the risk of cardiovascular events between treatments. This may be related with differences in the background incidence of cardiovascular events between atopic dermatitis and rheumatoid arthritis. The risk of cardiovascular disease is increased among patients with rheumatoid arthritis, which seems to result from systemic inflammation characteristic of this autoimmune disease [41]. Findings suggest a 70% increase in myocardial infarction, a 40% increase in cerebrovascular events, almost a 90% increase in congestive heart failure, and an excess of cardiovascular mortality among patients with rheumatoid arthritis [42–44]. Despite the results from this study, long-term postmarketing evidence will be crucial to understand the safety profile of JAK inhibitors. Data included in this network meta-analysis was only collected up to 40 weeks of follow-up. According to the ORAL Surveillance study, an increased incidence of MACE and cancers was found among patients with rheumatoid arthritis treated with tofacitinib when compared with a TNF-alfa inhibitor after a median follow-up of 4 years [10]. Further long-term evidence from a 360-week extension study was needed to demonstrate similar incidence rates of VTE between the two doses of baricitinib (2 mg vs. 4 mg), of 0.5 events per 100 patient-years, which is in line with the incidence for rheumatoid arthritis populations [45].

Additional limitations should be considered when interpreting these results. As the datasets were characterized by rare events, sensitivity analyses to assess the robustness of these results could not be conducted. It was not possible to form networks of studies by disaggregating data according to predefined variables, such as studies’ methodological quality scores or patients’ background therapy. Second, although most studies (16 out of 18) were assessed as having a low risk of bias, two were judged as having methodological insufficiencies involving adverse event monitoring and unclear information regarding the allocation concealment/randomization methods. Nonetheless, not all RCTs had their protocols publicly available, which prevented carrying out a thorough assessment of their methodological quality. Third, between-studies heterogeneity was identified in these network meta-analyses. Although the clinical development programs of systemic JAK inhibitors for atopic dermatitis may present similarities, differences related with the background therapies, the follow-up duration (from 4 to 40 weeks), the sample sizes (few tents to hundreds), and geographic recruitment locations may be pointed as the cause of such heterogeneity. Fourth, data analysis suggests some lack of model fit of the predictions from the network meta-analysis models of serious adverse events, adverse events leading to treatment discontinuation, and herpes zoster infection. Such limitation was expected given the low rate of the events elected as outcomes, particularly among phase II RCTs including few patients. Fifth, this network meta-analysis was not designed to compare JAK inhibitors with other drugs used for atopic dermatitis, namely dupilumab. The literature was reviewed to identify only RCTs evaluating JAK inhibitors and the networks established in this meta-analysis do not include RCTs of other drugs. For this reason, the risk differences between JAK inhibitors and dupilumab lack statistical robustness. Sixth, only one study of gusacitinib was included, creating additional difficulties to establish a relative safety of profile between this drug and the remaining JAK inhibitors.

The results of this network meta-analysis suggest systemic JAK inhibitors used for atopic dermatitis have a similar safety profile. However, the results must be interpreted with caution given the limitations of the sparse data and between-study heterogeneity. Postmarketing safety evidence will be crucial to further investigate the risks associated with JAK inhibitors.

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Availability of data and materials Studies used in this systematic review and meta-analysis were retrieved from databases that are publicly available.

Declarations

Ethics approval Not applicable.

Competing interests The authors declare no competing interests.

References

1. Wollenberg A, Barbarot S, Bieber T et al (2019) Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part I [published correction appears in J Eur Acad Dermatol Venereol. 33(7):1436]. J Eur Acad Dermatol Venereol 32(5):657–682
2. Nemeth V, Evans J (2021) Eczema. https://www.ncbi.nlm.nih.gov/books/NBK538209/. Accessed 6 July 2022
3. Eichenfield LF, Tom WL, Berger TG et al (2014) Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. J Am Acad Dermatol 71(1):116–132
4. Guttman-Yassky E, Teixeira HD, Simpson EL et al (2021) Once-daily upadacitinib versus placebo in adolescents and adults with moderate-to-severe atopic dermatitis (Measure Up 1 and Measure Up 2): results from two replicate double-blind, randomised
controlled phase 3 trials [published correction appears in Lancet. et al 2021 Jun 5;397(10290):2150] Lancet 397(10290):2151–2168
5. Blauvelt A, Silverberg JI, Lynde CW et al (2022) Abrocitinib induction, randomized withdrawal, and retreatment in patients with moderate-to-severe atopic dermatitis: results from the JAK1 Atopic Dermatitis Efficacy and Safety (JADE) REGIMEN phase 3 trial. J Am Acad Dermatol 86(1):104–112
6. Simpson EL, Lacour JP, Spelman L et al (2020) Baricitinib in patients with moderate-to-severe atopic dermatitis and inadequate response to topical corticosteroids: results from two randomized monotherapy phase III trials. Br J Dermatol 183(2):242–255
7. European Medicines Agency. Human medicine European public assessment report (EPAR): Cibinico. Direct healthcare professional communications (DHPC). https://www.ema.europa.eu/en/medicines/human/EPAR/cibinico. Accessed 6 July 2022
8. European Medicines Agency. Human medicine European public assessment report (EPAR): Olumiant. Direct healthcare professional communications (DHPC). https://www.ema.europa.eu/en/medicines/human/EPAR/olumiant. Accessed 6 July 2022
9. Bechman K, Subesinghe S, Norton S et al (2019) A systematic review and meta-analysis of infection risk with small molecule JAK inhibitors in rheumatoid arthritis. Rheumatol (United Kingdom) 58(10):1755–1766
10. European Medicines Agency. Human medicine European public assessment report (EPAR): Xeljanz. Direct healthcare professional communications (DHPC). https://www.ema.europa.eu/en/medicines/dhpc/xeljanz-tofacitinib-increased-risk-major-adverse-cardiovascular-events-malignancies-use-tofacitinib. Accessed 6 July 2022
11. US Food and Drug Administration. Advisory Committee Meeting: Arthritis Advisory Committee Meeting. NDA 207924 Baricitinib Janus Kinase (JAK) inhibitor for RA. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000MedR.pdf. Accessed 6 July 2022
12. US Food and Drug Administration. Center for Drug Evaluation and Research Application. Number 207924Orig1s000. Summary Review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/207924Orig1s000ClinPharmacR.pdf. Accessed 6 July 2022
13. Drucker AM, Morra DE, Prieto-Merino D et al (2022) Systemic immunomodulatory treatments for atopic dermatitis: update of a living systematic review and network meta-analysis. JAMA Dermatol 158(5):523–532
14. Li C, Sun X, Zhao K et al (2021) Efficacy and safety of Janus kinase inhibitors for the treatment of atopic dermatitis: a systematic review and meta-analysis published online ahead of print, 2021 Aug 27. Dermatology 1–11
15. Le M, Berman-Rosa M, Ghazawi FM et al (2021) Systematic review on the efficacy and safety of oral Janus kinase inhibitors for the treatment of atopic dermatitis. Front Med (Lausanne) 8:682547
16. University of York, Centre for Reviews and Dissemination. Systematic reviews: CRD’s guidance for undertaking reviews in health care. https://www.york.ac.uk/media/crd/Systematic_Reviews.pdf. Accessed 6 July 2022
17. Hutton B, Salanti G, Caldwell DM et al (2015) The PRISMA extension statement for reporting of systematic reviews incorporating network meta-analyses of health care interventions: checklist and explanations. Ann Intern Med 162(11):777–784
18. Hanifin JM, Rajka G (1980) Diagnostic features of atopic dermatitis. Acta Derm Venereol 60(92):44–47
19. Eichenfield LF, Tom WL, Chamlin SL et al (2014) Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. J Am Acad Dermatol 70(2):338–51
20. Saeki H, Nakahara T, Tanaka A et al (2016) Clinical practice guidelines for the management of atopic dermatitis 2016. J Dermatol 43(10):1117–1145
21. Sterne JAC, Savović J, Page MJ et al (2019) RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 366:1–8
22. Lunn DJ, Thomas A, Best N et al (2000) WinBUGS - a Bayesian modelling framework: concepts, structure, and extensibility. Stat Comput 10(4):325–337
23. The Core Model (2018) In: Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ, editors. Network meta-analysis for decision-making. Hoboken, NJ: John Wiley & Sons, Ltd, pp 19–57
24. Model Fit, Model comparison and outlier detection (2018) In: Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ, editors. Network meta-analysis for decision-making. Hoboken, NJ: John Wiley & Sons, Ltd, pp 59–91
25. Venerito V, Lopalco G, Cacciapaglia F, Fornaro M, Iannone F (2019) A Bayesian mixed treatment comparison of efficacy of biologics and small molecules in early rheumatoid arthritis. Clin Rheumatol 38(5):1309–1317
26. Yan M, Kumachev A, Siu LL, Chan KK (2015) Chemoradiotherapy regimens for locoregionally advanced nasopharyngeal carcinoma: a Bayesian network meta-analysis. Eur J Cancer 51(12):1570–1579
27. Dias S, Welton NJ, Sutton AJ et al (2022) NICE DSU technical support document 2: a generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials. London: National Institute for Health and Care Excellence (NICE). https://www.ncbi.nlm.nih.gov/books/NBK31066/. Accessed 6 July 2022
28. Adverse events and other sparse outcome data (2018) In: Dias S, Ades AE, Welton NJ, Jansen JP, Sutton AJ, editors. Network meta-analysis for decision-making. Hoboken, NJ: John Wiley & Sons, Ltd, pp 179–187
29. Bao L, Zhang H, Chan LS (2013) The involvement of the JAK-STAT signaling pathway in chronic inflammatory skin disease atopic dermatitis. JAKSTAT 2(3):e24137
30. Wood H, Chandler A, Nezamololama N, Papp K, Gooderham MJ (2021) Safety of Janus kinase (JAK) inhibitors in the short-term treatment of atopic dermatitis published online ahead of print, 2021 Aug 22. Int J Dermatol. https://doi.org/10.1111/ijd.15853
31. Sher J, Hahn K, Paul M et al (2013) Incidence and severity of pediatric allergic/immunologic adverse drug reactions in a tertiary care center. J Allergy Clin Immunol 131(2):AB175
32. Chovatiya R, Paller AS (2021) JAK inhibitors in the treatment of atopic dermatitis. J Allergy Clin Immunol 148(4):927–940
33. Nakagawa H, Nemoto O, Igarashi A, Saeki H, Kaino H, Nagata T (2020) Delgocitinib ointment, a topical Janus kinase inhibitor, in adult patients with moderate to severe atopic dermatitis: a phase 3, randomized, double-blind, vehicle-controlled study and an open-label, long-term extension study [published correction appears in. 2021 Oct 85(4):1069 J Am Acad Dermatol 82(4):823–831
34. Papp K, Szepietowski JC, Kirkic L et al (2021) Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: results from 2 phase 3, randomized, double-blind studies. J Am Acad Dermatol 85(4):863–872
35. Silverwood RJ, Forbes HJ, Abuabara K et al (2018) Severe and predominantly active eczema in adulthood and long term risk of cardiovascular disease: population based cohort study. BMJ 361:k1786
36. Ascott A, Mullick A, Yu AM et al (2019) Atopic eczema and major cardiovascular outcomes: a systematic review and meta-analysis of population-based studies. J Allergy Clin Immunol 143(5):1821–1829
37. Nishida Y, Kubota Y, Iso H, Tamakoshi A; JACC Study Group (2019) Self-reported eczema in relation with mortality from cardiovascular disease in Japanese: the Japan Collaborative Cohort Study. J Atheroscler Thromb 26(9):775–782
38. Wang V, Boguniewicz J, Boguniewicz M, Ong PY (2021) The infectious complications of atopic dermatitis. Ann Allergy Asthma Immunol 126(3):3–12
39. Wang V, Keefer M, Ong PY (2019) Antibiotic choice and methicillin-resistant Staphylococcus aureus rate in children hospitalized for atopic dermatitis. Ann Allergy Asthma Immunol 122(3):314–317
40. Langan SM, Abuabara K, Henrickson SE, Hoffstad O, Margolis DJ (2017) Increased risk of cutaneous and systemic infections in atopic dermatitis—a cohort study. J Invest Dermatol 137(6):1375–1377
41. Crowson CS, Liao KP, Davis JM 3rd et al (2013) Rheumatoid arthritis and cardiovascular disease. Am Heart J 166(4):622-628.e1
42. Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D (2012) Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 71(9):1524–1529
43. Lindhardsen J, Ahlehoff O, Gislason GH et al (2011) The risk of myocardial infarction in rheumatoid arthritis and diabetes mellitus: a Danish nationwide cohort study. Ann Rheum Dis 70(6):929–934
44. Provan SA, Lillegraven S, Sexton J et al (2020) Trends in all-cause and cardiovascular mortality in patients with incident rheumatoid arthritis: a 20-year follow-up matched case-cohort study. Rheumatology (Oxford) 59(3):505–512
45. Genovese M, Smolen J, Takeuchi T et al (2020) Safety profile of baricitinib for the treatment of rheumatoid arthritis over a median of 3 years of treatment: an updated integrated safety analysis. Lancet Rheumatol 2(6):e347–e357

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