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SYSTEMIC REVIEW

Long-term Safety and Efficacy of JAK2 Inhibitors in the Treatment of Alopecia Areata and Atopic Dermatitis: A Systematic Review

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Abstract

Introduction: Alopecia areata (AA) and atopic dermatitis (AD) are chronic inflammatory diseases mediated by immune dysregulation involving the JAK-STAT pathway. JAK2, a key component of this pathway, has emerged as a promising therapeutic target. Small-molecule inhibitors like baricitinib and ruxolitinib show potential in mitigating disease severity, but long-term safety and efficacy data remain limited.

Objective: To systematically evaluate the long-term efficacy and safety profile of JAK2 inhibitors in treating AA and AD, with a focus on treatment durability, relapse after discontinuation, and adverse event trends.

Methods: A systematic review following PRISMA guidelines was conducted. Databases searched included PubMed, EMBASE, and CENTRAL up to April 2025. Randomized controlled trials and extension studies with at least 24 weeks of follow-up in adolescents and adults with AA or AD were included. Primary outcomes were long-term efficacy, relapse rates, and safety profiles.

Results: Ten studies met inclusion criteria. In AA, baricitinib 4 mg led to ≥80% scalp hair regrowth in 37–41% of patients at 52 weeks, with no new serious adverse events reported. Discontinuation resulted in >80% relapse rates within 6–12 months, though re-treatment recaptured response in most cases. In AD, ruxolitinib cream achieved Investigator's Global Assessment success rates of ~50% at 8 weeks and maintained efficacy and safety up to 52 weeks. Systemic baricitinib also improved EASI-75 scores but with moderate efficacy compared to biologics.

Discussion and results: JAK2 inhibitors demonstrate sustained efficacy and a favorable short-term safety profile in AA and AD. However, high relapse rates in AA after therapy cessation highlight the need for continuous treatment. Long-term safety beyond 2 years requires further study, particularly regarding malignancy and cardiovascular risks.

Keyword: alopecia areata; atopic dermatitis; janus kinase inhibitors; baricitinib; ruxolitinib

Introduction

Alopecia areata (AA) and atopic dermatitis (AD) are chronic inflammatory skin conditions with distinct yet overlapping immunopathogenic mechanisms, both substantially affecting patient quality of life. AA is an autoimmune condition characterized by the non-scarring loss of scalp and body hair, triggered by autoreactive CD8+ T cells that target hair follicle immune privilege zones. This cytotoxic activity is sustained and amplified by type I interferons (IFN-α/β) and IFN-γ, key mediators whose signaling is dependent on the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. AD, on the other hand, is driven by a Th2-skewed immune response with upregulation of cytokines such as IL-4, IL-13, and IL-31, which similarly utilize the JAK-STAT signaling axis, particularly through JAK1 and JAK2, to mediate epidermal inflammation, pruritus, and skin barrier dysfunction [1].

The JAK-STAT pathway functions as a central hub for numerous cytokine signals. It comprises four JAK proteins (JAK1, JAK2, JAK3, and TYK2) and seven STAT transcription factors. JAK2, in particular, is pivotal not only for hematopoietic growth factors like erythropoietin and thrombopoietin, but also for proinflammatory cytokine signaling (e.g., IL-6, IFN-γ, GM-CSF). Its pairing with JAK1 in several receptor complexes allows it to mediate downstream effects of both innate and adaptive immune signals. These features make JAK2 a promising therapeutic target in conditions like AA and AD where dysregulated immune activity drives chronic inflammation [2,3].

The therapeutic relevance of JAK inhibition emerged from studies demonstrating that small-molecule inhibitors, such as baricitinib (a selective JAK1/JAK2 inhibitor) and ruxolitinib (JAK1/JAK2), can downregulate aberrant cytokine responses involved in both diseases. In AA, clinical trials like BRAVE-AA1 and AA2 showed baricitinib induced significant hair regrowth in patients with ≥50% scalp hair loss, with response rates approaching 40% at 36 weeks for the 4 mg dose. Similarly, ruxolitinib has shown efficacy in AD both as a topical and systemic agent, rapidly reducing pruritus and inflammation, with an excellent short-term safety profile. These findings have led to regulatory approvals and incorporation into treatment guidelines. However, while efficacy is evident, concerns remain regarding the long-term immunosuppressive effects of JAK inhibition—particularly risks of serious infections, thromboembolic events, laboratory abnormalities, and malignancy, which have been reported in other indications like rheumatoid arthritis and myeloproliferative neoplasms [4].

Despite the growing adoption of JAK inhibitors for dermatologic conditions, substantial knowledge gaps remain regarding their long-term safety and efficacy, particularly in AA and AD. Most pivotal phase III trials report outcomes at 8–16 weeks (e.g., TRuE-AD1/2 for ruxolitinib in AD and BREEZE-AD trials for baricitinib), with only a minority extending beyond 36 or 52 weeks. Furthermore, while baricitinib and ruxolitinib have been evaluated in extension studies, data on relapse rates after discontinuation, the need for maintenance therapy, and the efficacy of re-treatment remain limited and heterogeneous [5,6].

There is also a lack of data on the chronic use of selective JAK2 inhibitors such as fedratinib and pacritinib in dermatologic diseases. These agents are approved primarily for hematologic malignancies like myelofibrosis and polycythemia vera, where their use has been associated with notable adverse effects including anemia, thrombocytopenia, and Wernicke's encephalopathy (for fedratinib). No published clinical trials to date have evaluated these compounds for AA or AD, leaving their dermatologic potential unexplored [7].

Moreover, existing studies often exclude key populations children, elderly patients, those with comorbidities limiting generalizability. The chronic, relapsing nature of AA and AD suggests that intermittent or indefinite therapy may be required. Yet, comparative data on continuous vs. Short-course treatment regimens are scarce, and the impact of prolonged immune modulation on systemic health remains uncertain [8].

This fragmented evidence base underscores the need for a comprehensive synthesis of existing long-term trial data. A systematic review focused on extended efficacy, adverse event patterns over time, and relapse dynamics following treatment cessation will help clinicians weigh risks and benefits, tailor treatment duration, and identify patients most likely to benefit from sustained JAK2 inhibition [9,10].

We hypothesize that JAK2 inhibitors, particularly baricitinib and ruxolitinib, provide sustained clinical benefit in AA and AD over extended periods, with an acceptable safety profile comparable to shorter-term use. However, the extent of durability, relapse risk after discontinuation, and cumulative adverse event patterns remain inadequately characterized.

Therefore, this review aims to answer the following research question: ¿What is the long-term safety and efficacy profile of JAK2 inhibitors in the treatment of alopecia areata and atopic dermatitis?, based on clinical trial evidence. This includes assessing therapeutic durability, relapse rates post-discontinuation, adverse event trends beyond 6 months, and the potential role of continuous versus intermittent therapy.

Methods:

Study design

This work was conducted as a systematic review of the literature aimed at synthesizing evidence from clinical trials regarding the long-term safety and efficacy of Janus kinase 2 (JAK2) inhibitors in the treatment of alopecia areata (AA) and atopic dermatitis (AD). The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Selection criteria

Types of studies

We included randomized controlled trials (RCTs) and extension studies evaluating JAK2 inhibitors with a minimum follow-up of 24 weeks. Open-label and dose-ranging trials were eligible if they reported long-term outcomes beyond 6 months.

Types of participants

Participants were adolescents or adults (≥12 years) diagnosed with alopecia areata or atopic dermatitis, with a focus on moderate to severe forms of the diseases. We included studies irrespective of sex, ethnicity, or geographic region.

Types of interventions

We included trials that evaluated systemic or topical JAK2 inhibitors, either as monotherapy or in combination with standard care. Relevant agents included:

- Baricitinib (JAK1/JAK2 inhibitor)
- Ruxolitinib (JAK1/JAK2 inhibitor)
- Fedratinib and pacritinib (selective JAK2 inhibitors; none identified in included studies)

Types of outcomes

Primary outcomes

- Long-term efficacy (≥24 weeks), defined by:
  - Hair regrowth in AA (e.g., SALT score improvements)
  - Eczema severity indices (e.g., EASI-75, IGA 0/1) in AD
- Sustained clinical benefit during maintenance therapy
- Relapse rates following treatment discontinuation

Secondary outcomes

- Adverse events (AEs) stratified by severity and duration
- Discontinuation rates due to AEs
- Recapture of response upon treatment reinitiation
- Use of concomitant therapies

Search methods for identification of studies

Electronic searches

A systematic search was conducted across the following databases:

- PubMed/MEDLINE
- EMBASE
- Cochrane Central Register of Controlled Trials (CENTRAL)

The search was last updated in April 2025 and included combinations of MeSH and free-text terms related to: alopecia areata, atopic dermatitis, JAK2 inhibitors, baricitinib, ruxolitinib, fedratinib, pacritinib, and long-term efficacy/safety. Filters for RCTs and clinical trials were applied.

Other Sources

We also screened:

- ClinicalTrials.gov for registered and completed studies with results
- References of included articles
- Major dermatology and immunology conference proceedings (e.g., AAD, EADV)

Data collection and analysis

Study selection

Titles and abstracts retrieved from the searches were screened independently by two reviewers. Full-text articles were then assessed for eligibility based on inclusion criteria. Disagreements were resolved by discussion or consultation with a third reviewer.

Data extraction and management

Data extraction was performed using a standardized and piloted data collection form. The following variables were extracted:

- Study characteristics: design, sample size, duration, funding
- Participant demographics and baseline characteristics
- Intervention details (drug, dose, route, duration)

- Primary and secondary outcomes
- Adverse events and withdrawals

Risk of bias assessment

The risk of bias in included randomized trials was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB2). Each study was independently evaluated by two reviewers across five domains:

1. Randomization process
2. Deviations from intended interventions
3. Missing outcome data
4. Measurement of the outcome
5. Selection of the reported result

Disagreements were resolved through consensus. Judgments were categorized as low risk, some concerns, or high risk of bias.

Bias management

Handling of missing data

We reported missing data as stated by the original studies. For trials with extension phases, follow-up data were summarized separately to reflect attrition or dropout patterns.

Assessment of reporting bias

Due to the absence of meta-analysis and limited number of trials per outcome, publication bias was not assessed with funnel plots. However, selective reporting was considered qualitatively during the RoB2 assessment.

Data synthesis strategy

No meta-analysis was conducted due to heterogeneity in study design, outcome definitions, and duration of follow-up. Instead, we performed a narrative synthesis, organizing results by:

- Disease (AA vs. AD)
- Intervention (baricitinib, ruxolitinib)
- Route (oral vs. topical)
- Duration (e.g., 36 weeks, 52 weeks, withdrawal phases)

Tables were constructed to summarize key findings, including efficacy outcomes and adverse event profiles at each time point.

Results

A total of 1,339 records were identified through database and registry searches. After removing 293 duplicates, 1,046 unique records remained for title and abstract screening, of which 1,012 were excluded. Thirty-four reports were then sought for retrieval, but six could not be obtained. The 28 retrieved reports underwent full-text assessment, and 18 were excluded—16 on grounds of study design and two because they did not enroll the target population—leaving 10 studies to be included in the review (Figure 1).

Alopecia areata: Several clinical trials have evaluated JAK inhibitors in severe alopecia areata (≥50% hair loss). In particular, two phase III trials (BRAVE-AA1 and BRAVE-AA2, King et al.) included adults with extensive AA (SALT score ≥50) and compared oral baricitinib (4 mg or 2 mg daily) versus placebo (Table 1) [11].

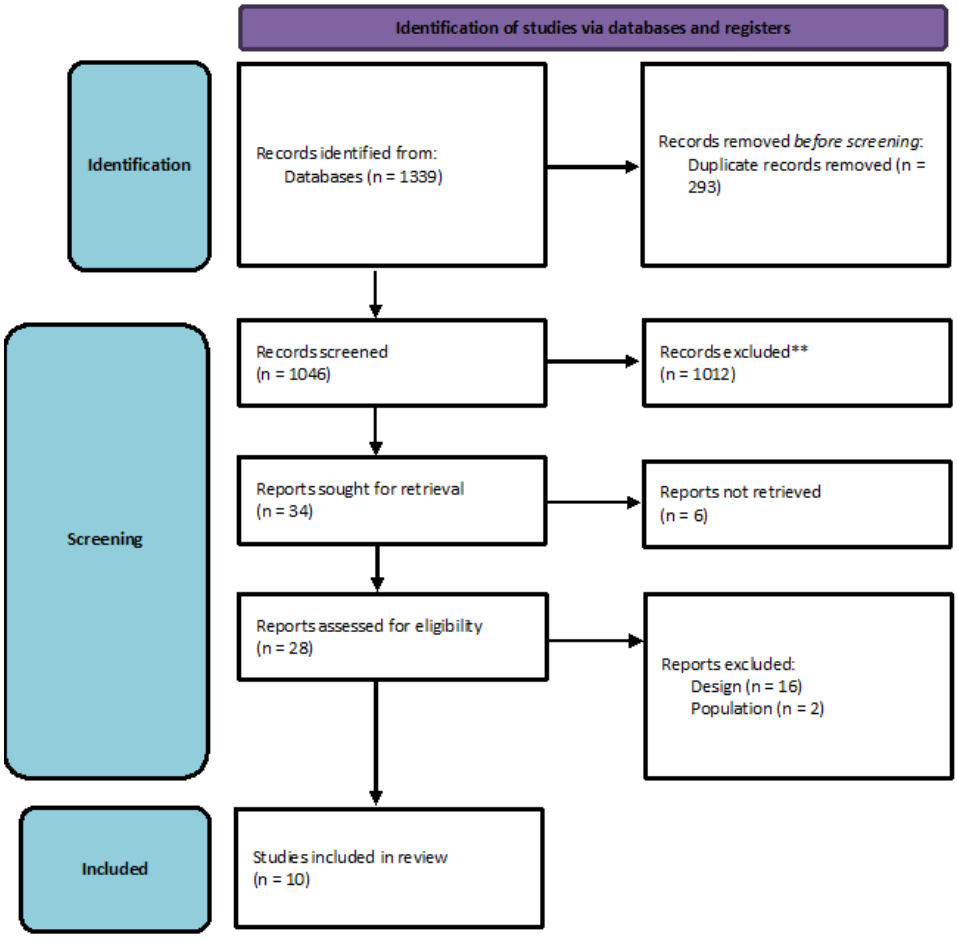

Figure 1: PRISMA flow diagram.

Table 1. Clinical Trials of JAK2 Inhibitors in Alopecia Areata (AA).

Study (Author, Year)	Design	Population	Interventions	Duration	Efficacy Outcomes	Adverse Events
King et al., [11], (BRAVE-AA1)	Phase III, randomized, double-blind, placebo-controlled	654 adults with severe AA (≥50% SCALD)	Baricitinib 4 mg, 2 mg vs placebo (3:2:2)	36 weeks	SALT ≤20 (≥80% regrowth) in 38.8% (4 mg) vs 6.2% (placebo); difference +32.6 pp (p<0.001)	Acne, ↑CK, ↑LDL/HDL cholesterol more frequent with baricitinib; no serious AEs reported
King et al., [11], (BRAVE-AA2)	Phase III, randomized, double-blind, placebo-controlled	546 adults with severe AA (≥50% SCALD)	Baricitinib 4 mg, 2 mg vs placebo (3:2:2)	36 weeks	SALT ≤20 in 35.9% (4 mg) vs 3.3% (placebo) (p<0.001); ~19% response with 2 mg	AE profile similar to BRAVE-AA1 (mild infections, acne, minor lab abnormalities)
Kwon et al., [12],	Open-label extension of Phase III (BRAVE-AA1/2)	855 adults (continuing from AA1/2)	Continuous baricitinib 4 mg or 2 mg	52 weeks	SALT ≤20 in 40.9% (4 mg) vs 21.2% (2 mg) in AA1; 36.8% vs 24.4% in AA2 (maintained/increased improvement)	No new safety signals; common AEs: nasopharyngitis, headache, acne, mild infections; no thrombosis or deaths
King et al., [14],	Phase III, randomized withdrawal after 52 weeks of baricitinib (BRAVE-AA1)	154 adult responders after 52 weeks baricitinib	Continue baricitinib vs placebo (withdrawal)	Additional 100 weeks (up to week 152)	Relapse after discontinuation: >80% lost benefit within ~1 year off treatment; only 7% lost response with continuation; re-treatment recaptured response in most cases	No new AEs in extension; cumulative incidences of mild infections and headache; need for long-term therapy highlighted for sustained efficacy/safety
Mackay-Wiggan et al., [15]	Phase II, open-label pilot case series	12 adults with moderate-to-severe AA	Oral ruxolitinib 20 mg every 12 h	3–6 months treatment + 3 months follow-up	75% of patients showed significant response; mean regrowth ~92%; rapid clinical improvement (from 4 weeks)	No serious AEs; mild AEs: transient upper respiratory infections; partial hair loss after discontinuation, without return to baseline
Olsen et al., [16]	Phase II, 2 parts (A: open-label; B: randomized controlled)	142 adults with AA (25–100% SCALD)	Topical ruxolitinib 1.5% cream vs vehicle	24 weeks	No significant difference vs placebo in ≥50% hair regrowth (Part B); Part A (open-label) suggested some efficacy	Good topical safety profile; no differences in local/ systemic AEs vs vehicle

Each study enrolled approximately 500–650 patients. At 36 weeks, baricitinib demonstrated significantly greater efficacy than placebo in promoting hair regrowth: approximately 35–39% of patients treated with 4 mg baricitinib achieved ≥80% scalp coverage (SALT ≤20), compared to only 3–6% in the placebo group (p<0.001) [11].The 2 mg dose yielded intermediate response rates (~19–23%), also superior to placebo. The absolute difference in responders between 4 mg baricitinib and placebo was approximately 32 percentage points. In secondary outcome analyses, 4 mg baricitinib significantly improved eyebrow/ eyelash regrowth and physician's global impression scores compared to placebo, while the 2 mg dose provided more modest benefits. These trials established the efficacy of baricitinib in inducing hair regrowth in severe AA in the short-to-medium term [11].

At 36 weeks, baricitinib's safety profile in AA was acceptable, with no serious adverse events attributed to the drug reported in these trials. The most common adverse events (AEs) with baricitinib included mild upper respiratory infections, acne, asymptomatic elevations of creatine kinase, and increased LDL/HDL cholesterol levels, all more frequent than in the placebo group but clinically manageable [11,12]. No thromboembolic events, malignancies, or serious opportunistic infections related to the treatment were observed during this period. A 52-week extension analysis (open-label continuation of BRAVE-AA1/2, Kwon et al., [12]) showed that the proportion of patients with sustained responses increased or remained stable with continued therapy [11].

After one year of continuous treatment, approximately 37–41% of patients on 4 mg baricitinib achieved ≤ 20% alopecic area (i.e., ≥80% regrowth), similar to or slightly higher than the 36-week rates, while ~21–24% achieved this response with 2 mg (a modest improvement compared to week 36). Importantly, no new safety signals emerged at one year: the most frequently reported adverse events remained nasopharyngitis, headache, mild infections (e.g., herpes simplex, influenza), and acne (12,13). No cases of deep vein thrombosis, embolism, or treatment-related deaths were reported during the 52-week follow-up [13]. These findings suggest that baricitinib maintains efficacy with continued treatment and has a stable safety profile over one year [12].

Nevertheless, evidence indicates that discontinuation of treatment leads to a high relapse rate. In a randomized withdrawal trial [14] , after 52 weeks of baricitinib, responders who discontinued the drug experienced progressive hair loss: within just 2 months post-discontinuation, up to 10–11% had lost their improvement, and by ~6–12 months, more than 80% had significantly relapsed [14]. Conversely, those who continued baricitinib maintained hair regrowth (only ~7% lost response in the same period) [14]. This study also showed that reintroducing the drug could recapture response in most relapsing patients: approximately 63% of those re-treated with 2 mg and 85% with 4 mg baricitinib regained their previous hair density. These data highlight the chronic, relapsing nature of severe AA and the potential need for long-term maintenance therapy to sustain hair regrowth.

Regarding systemic ruxolitinib in AA, controlled evidence is more limited. An open-label phase II pilot study [15], in 12 patients with moderate-to-severe AA evaluated oral ruxolitinib 20 mg every 12 hours for 3–6 months [15]. The results were promising: 9 of 12 patients (75%) achieved significant hair regrowth, with a mean of 92% hair regrowth at the end of treatment. Improvement was observed as early as 4–8 weeks in several patients. During the 3-month follow-up after ruxolitinib discontinuation, some patients experienced partial relapse, but none returned to baseline alopecia levels. No serious adverse events were reported in this small study, and safety parameters (laboratory results, vital signs) remained within normal limits [15]. Mild AEs included transient respiratory infections, with no significant hematologic toxicity observed in the short term. While these findings suggest that JAK1/2 blockade with ruxolitinib may induce clinical remission in AA, the small sample size and lack of a control group underscore the need for larger randomized trials. In fact, a phase II randomized trial of topical ruxolitinib cream (1.5%) in alopecia areata failed to demonstrate superior efficacy compared to vehicle; after 24 weeks of topical treatment, no significant differences were seen in the proportion of patients achieving ≥50% hair regrowth between ruxolitinib and placebo groups [16]. This suggests that, unlike in atopic dermatitis, systemic treatment may be necessary in AA to achieve a clinical effect, due to the depth of follicular involvement and the systemic nature of autoimmunity in extensive AA.

Table 2: Clinical Trials of JAK2 Inhibitors in Atopic Dermatitis (AD).

Study (Author, Year)	Design	Population	Interventions	Duration	Efficacy Outcomes	Adverse Events
Papp et al., [17], (TRuE-AD1 & AD2)	Two Phase III randomized, double-blind, vehicle-controlled trials	1,249 patients ≥12 years with mild-to-moderate AD (IGA 2–3)	Ruxolitinib cream 0.75% BID, 1.5% BID vs vehicle BID (2:2:1)	8 weeks	IGA 0/1 ("success") in ~50–54% (ruxo 1.5%) vs 7–15% (vehicle) (p<0.0001). Itch improvement from 12 hours	Application site reactions <1%, even fewer than with vehicle. No relevant systemic AEs at 8 weeks; well tolerated
Eichenfield et al., [18], (extension)	Open-label extension of TRuE-AD1/2 ("as-needed" use)	245 adolescents (12–17 years) with baseline mild-to-moderate AD	Ruxolitinib cream 1.5% (intermittent/continued use after 8-week initial treatment)	52 weeks	Disease control maintained: ≥75% achieved IGA 0/1 at some point; low average body surface area affected (<3% BSA) during maintenance	No serious AEs over 52 weeks. Local reactions in 1.8%. No serious infections, thrombotic events, or malignancies reported
Simpson et al., [19], (BREEZE-AD5)	Phase III, randomized, double-blind, placebo-controlled	440 adults with moderate-to-severe AD refractory to topicals (North America)	Baricitinib 2 mg, 1 mg vs placebo (1:1:1)	16 weeks	EASI-75 in 30% (2 mg) vs 8% (placebo); IGA 0/1 in 24% vs 5% (p<0.001 for 2 mg vs placebo)	AEs similar to previous studies; mild URTIs, headache. No new safety signals at 16 weeks
Reich et al., [21], (BREEZE-AD7)	Phase III, randomized, double-blind, controlled (JAMA Derm)	1,239 adults with moderate-to-severe AD (global)	Baricitinib 4 mg ± TCS vs placebo ± TCS (1:1)	16 weeks + extension	~20% achieved IGA 0/1 with baricitinib 4 mg vs 10% with placebo (p<0.01); significant EASI improvement. Response maintained up to week 52 in extensions	Class-related JAK AEs: URTIs, elevated CPK, acne. Some cases of mild herpes zoster. No difference in serious AEs vs placebo
Bieber et al., [20], (BREEZE-AD4)	Phase III, randomized, double-blind, placebo-controlled + TCS	463 adults with moderate-to-severe AD (cyclosporine intolerant)	Baricitinib 4 mg, 2 mg, 1 mg + topical corticosteroids vs placebo + TCS	16 weeks + 52-week extension	EASI-75 in 32% (baricitinib 4 mg + TCS) vs 17% (placebo+TCS) (p=0.031). Improvements in itch and sleep. Effects maintained at 1 year	Emergent AEs more frequent with baricitinib 4 mg (66%) vs placebo (51%); mostly mild. Common AEs: nasopharyngitis, herpes simplex, headache. No deaths or thromboses observed

No published clinical trials were identified evaluating fedratinib or pacritinib in alopecia areata. These selective JAK2 inhibitors are used in myeloproliferative neoplasms (e.g., myelofibrosis) and have specific safety profiles (such as risks of anemia, thrombocytopenia, or neurotoxicity in the case of fedratinib). Given the lack of evidence in AA, their use in this indication cannot currently be recommended outside experimental protocols.

Atopic dermatitis: Clinical trials evaluating ruxolitinib (topical) and baricitinib (systemic) in moderate-to-severe atopic dermatitis (AD) were identified. No studies were found involving fedratinib or pacritinib in AD. The key findings are presented below (Table 2).

Topical ruxolitinib: Two randomized phase III trials (TRuE-AD1 and AD2, Papp et al., 2021) evaluated ruxolitinib cream 0.75% or 1.5% versus vehicle in patients with mild to moderate AD (IGA 2–3) in adults and adolescents (≥12 years) [17]. In total, approximately 1,200 patients were randomized (2:2:1) to ruxolitinib 0.75%, ruxolitinib 1.5%, or vehicle cream, applied twice daily for 8 weeks. The results showed a rapid and significant clinical improvement with topical ruxolitinib. The Investigator's Global Assessment (IGA) "success" response rate (IGA 0/1, clear or almost clear skin with ≥2-grade improvement) at 8 weeks was ~50–54% with ruxolitinib 1.5% (and ~39–50% with 0.75%) versus only 8–15% with vehicle. These differences were statistically significant in both studies (p<0.0001) [17]. Additionally, ruxolitinib cream provided rapid itch relief, with significant reductions in pruritus reported within the first 12 hours of using the 1.5% cream compared to vehicle. Regarding safety, topical therapy was well tolerated: application site reactions were infrequent (<1% of patients) and actually occurred less often with ruxolitinib than with vehicle. No local reactions were clinically significant. No relevant systemic adverse effects attributable to ruxolitinib absorption were observed over 8 weeks (plasma concentrations with topical use are very low). The main limitation noted was the lack of data beyond 8 weeks at that time [17].

Long-term extension data are now available for ruxolitinib cream. In an extension study up to 52 weeks ("as-needed" use following the initial 8-week course, in adolescent patients), intermittent/prolonged use of ruxolitinib 1.5% cream was shown to maintain disease control in AD and remained safe [18]. Over the course of 1 year of treatment, no serious adverse events, severe infections, or major ardiovascular events related to topical therapy were reported. Only ~1.8% of patients experienced any application site reaction over the year [18]. No concerning laboratory findings were observed. These results suggest that ruxolitinib cream can be used long term to control mild-to-moderate AD with a very favorable safety profile, offering a new topical non-steroidal anti-inflammatory approach.

Systemic baricitinib: Baricitinib (oral JAK1/JAK2 inhibitor) was evaluated in several phase III trials for moderate-to-severe atopic dermatitis in adults with inadequate response to topical treatments. In a North American phase III trial (BREEZE-AD5, Simpson et al., 2021), 440 patients were randomized 1:1:1 to receive baricitinib 2 mg, baricitinib 1 mg, or placebo daily for 16 weeks [19]. At 16 weeks, baricitinib demonstrated modest but significant benefits compared to placebo. The proportion of patients achieving ≥ 75% improvement in the Eczema Area and Severity Index (EASI-75) was 30% with baricitinib 2 mg versus 8% with placebo (p < 0.001). Similarly, IGA 0/1 (clear or almost clear skin) was achieved in 24% with baricitinib 2 mg vs 5% with placebo. The 1 mg dose had lesser effects (EASI-75 ~13%). During these 4 months of treatment, no new safety findings beyond those already known for baricitinib emerged. Common adverse events included nasopharyngitis, mild infections, and mild elevations of CPK or transaminases, consistent with the safety profile observed in rheumatoid arthritis and other AD studies. No unexpected serious events were reported during this short-term [19].

Other international trials (BREEZE-AD1, AD2) yielded similar results, confirming that baricitinib monotherapy provides significant

Table 3: Risk of bias of included studies (RoB2).

Assessment Question	Bieber et al., [13] (BREEZE-AD4)	Eichenfield et al., [18]	King et al., [11] (BRAVE-AA1)	King et al., [14]	Kwon et al., [12]	Mackay-Wiggan et al., [15]	Olsen et al., [16]	Papp et al., [17] (TRuE-AD1 & AD2)	Reich et al., [21] (BREEZE-AD7)	Simpson et al., [5] (BREEZE-AD5)
Domain 1: Risk of bias arising from the randomization process	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Domain 3: Missing outcome data	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
Domain 4: Risk of bias in measurement of the outcome	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Domain 5: Risk of bias in selection of the reported result	Low	Low	Low	Low	Low	High	Low	Low	Low	Low
Overall risk of bias	Low	Low	Low	Low	Low	High	Low	Low	Low	Low

clinical improvements, though less pronounced than those seen with biologics like dupilumab or with more selective JAK1 inhibitors. Therefore, baricitinib was also explored in combination with standard treatments. The BREEZE-AD4 trial [20], evaluated baricitinib alongside topical corticosteroids (TCS) in moderate-to-severe AD in adults who were unresponsive or unable to use cyclosporine [20]. In this study (N=361; groups: placebo+TCS, baricitinib 1 mg+TCS, 2 mg+TCS, 4 mg+TCS), baricitinib 4 mg combined with TCS achieved an EASI-75 response at week 16 in 32% of patients, significantly greater than the 17% with placebo+TCS (p=0.031) [20]. It also improved symptomatic parameters such as pruritus (score reduction) and night-time awakenings due to itching [20]. Importantly, these clinical improvements were maintained with continued treatment up to 52 weeks, ndicating no tachyphylaxis. In terms of safety, emergent adverse events were slightly more frequent with baricitinib than placebo, but mostly mild to moderate in severity (similar to the known profile). The most common AEs with baricitinib 4 mg + TCS were nasopharyngitis, labial herpes simplex infection, influenza, and headache. No deaths or thromboembolic events were observed in this trial. The one-year safety profile was consistent with previous studies, with no new concerns emerging with prolonged therapy [20]. Additionally, a pediatric study (BREEZE-AD-Peds, 2023) demonstrated similar efficacy and safety in children, which has expanded baricitinib's indication in AD in certain territories.

Ris-of-bias assessment: Risk-of-bias assessment using the Cochrane RoB 2 tool showed that nine of the ten included trials were judged to have a uniformly low risk of bias across all five domains. Specifically, the phase III studies BREEZE-AD4 [20], the trial reported by Eichenfield et al. [18], BRAVE-AA1 by King et al. [14] , the study by King et al. [14], Kwon et al. [12], Olsen et al. [16], TRuE-AD1 & AD2 by Papp et al. [17], BREEZE-AD7 by Reich et al. [21], and BREEZE-AD5 by Simpson et al. [19], all demonstrated a low risk arising from the randomization process, minimal deviations from the intended interventions, complete outcome data, accurate outcome measurement, and transparent selection of reported results, resulting in an overall low risk of bias. By contrast, the earlier study by Mackay-Wiggan et al. [15], although it met criteria for low risk due to missing outcome data was judged to carry a high risk of bias in the processes of randomization, adherence to assigned interventions, outcome measurement, and selective reporting, yielding an overall high risk of bias (Table 3).

Discussion

This systematic review evaluated the long-term safety and efficacy of JAK2 inhibitors particularly baricitinib and ruxolitinib in the management of alopecia areata (AA) and atopic dermatitis (AD). The evidence shows that baricitinib maintains durable efficacy in severe AA over 52 weeks, with approximately 37–41% of patients achieving ≥ 80% scalp hair regrowth (SALT ≤ 20) after one year. Topical ruxolitinib provided significant and sustained control of mild-to-moderate AD with a favorable safety profile up to 52 weeks. Importantly, no new safety concerns emerged with prolonged use. However, relapse rates were high after discontinuation of therapy, particularly in AA, emphasizing the potential need for continuous treatment [11,12].

Our findings are consistent with prior pivotal trials evaluating the efficacy of baricitinib in severe alopecia areata (AA). In the BRAVE-AA1 and BRAVE-AA2 phase III trials, baricitinib 4 mg daily led to significant hair regrowth, with 40.9% and 36.8% of patients achieving a Severity of Alopecia Tool (SALT) score ≤ 20 at week 52, respectively. These results underscore the sustained efficacy of baricitinib over a one-year period [6].

Similarly, the efficacy of ruxolitinib cream in atopic dermatitis (AD) aligns with previous studies. In a phase III trial, patients applying 1.5% ruxolitinib cream twice daily achieved Investigator's Global Assessment (IGA) treatment success rates of 52.6% at week 8, compared to 11.5% in the vehicle group (p<0.0001). These findings confirm the rapid and significant improvement in AD severity with ruxolitinib cream [22,23].

Contrasting with the favorable safety profiles observed in dermatologic applications, long-term use of JAK inhibitors like tofacitinib in rheumatoid arthritis (RA) has raised safety concerns. Integrated analyses of tofacitinib in RA patients have reported increased risks of serious infections, malignancies, and cardiovascular events over extended treatment durations [24]. However, such adverse events have not been prominently reported in dermatologic trials of baricitinib and ruxolitinib, suggesting a potentially safer profile in skin diseases. This discrepancy may be attributed to differences in patient populations, dosing regimens, and disease pathophysiology.

Additionally, the relapse rates upon discontinuation of baricitinib in AA are notably high. A study reported that over 80% of patients

who responded to baricitinib experienced a loss of treatment benefit by week 152 after withdrawal [25]. In contrast, discontinuation of dupilumab in AD has been associated with more sustained disease control, with some patients maintaining remission for extended periods [25]. These observations highlight the need for continuous therapy in AA to maintain treatment benefits, whereas AD may allow for more flexible treatment approaches.

This review has several limitations. First, heterogeneity among studies regarding follow-up duration, outcome definitions, and patient populations precluded meta-analysis. Second, extension studies often lacked control arms, limiting definitive conclusions on long-term comparative effectiveness. Third, generalizability is limited, as most trials excluded children under 12, elderly patients, and those with significant comorbidities. However, key strengths include the rigorous methodology adhering to PRISMA standards, independent risk-of-bias assessment (with 90% of included trials rated at low risk), and a focus on clinically meaningful long-term outcomes essential for real-world applicability.

The results suggest that baricitinib is an effective long-term option for severe AA, but clinicians should counsel patients about the high risk of relapse upon treatment cessation. Maintenance therapy may be necessary for sustained benefits. Ruxolitinib cream offers a valuable non-steroidal alternative for mild-to-moderate AD with excellent tolerability over a year. Future research should prioritize head-to-head comparisons between JAK inhibitors and biologics, studies in pediatric and elderly populations, and real-world registries to better capture rare but serious adverse events over longer periods (beyond 2–5 years).

Conclusions

JAK2 inhibition with baricitinib and ruxolitinib offers sustained efficacy and acceptable safety over 52 weeks in the treatment of alopecia areata and atopic dermatitis. However, the high relapse rates after therapy discontinuation, especially in AA, underscore the chronic, relapsing nature of these conditions and the potential need for long-term maintenance strategies. Overall, these agents represent important therapeutic advances, but careful patient selection, monitoring, and informed discussions regarding long-term management plans are essential.

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