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Dear Drs. Khandpur and Bhat,

We are pleased to submit our manuscript entitled "Comparative Efficacy of Upadacitinib, Baricitinib, and Ritlecitinib in Adolescents With Severe Alopecia Areata: A Systematic Review and Bayesian Network Meta-Analysis" for consideration in the *Indian Journal of Dermatology, Venereology and Leprology*.

In the United States, ritlecitinib is currently the only JAK inhibitor approved for adolescents with severe alopecia areata (AA). Baricitinib has recently been authorized by the EMA for this population and remains under review by the FDA. Upadacitinib has been submitted to both agencies for the treatment of severe AA in adolescents and adults. As a result, three oral JAK inhibitors are expected to become commercially available in the US and EU for adolescents with severe AA within the next year.

Our systematic review and Bayesian network meta-analysis demonstrates that although all three agents increased the likelihood of achieving a SALT score ≤20 relative to placebo, upadacitinib 30 mg produced the most favorable, statistically stable and robust efficacy estimates, followed by upadacitinib 15 mg, baricitinib 4 mg, and baricitinib 2 mg. In contrast, ritlecitinib generated highly unstable and imprecise effect estimates**,** characterized by extremely large odds ratios and wide uncertainty intervals that limited interpretability.

Direct responder rates from individual trials further clarified comparative efficacy at Week 24. For ritlecitinib**,** 25% of adolescents achieved a SALT score ≤20, indicating that 75% did not achieve clinically meaningful scalp hair regrowth. For baricitinib 2 mg and 4 mg, 16.6% and 31.8% achieved a SALT score ≤20, corresponding to non-response rates of 83.4% and 68.2%**.** In contrast, 56.0% and 56.5% of adolescents receiving upadacitinib 15 mg, and 84.6% and 72.2% receiving upadacitinib 30 mg (Study 1 and Study 2, respectively) achieved a SALT score ≤20. These findings indicate that only approximately 44% and 43.5% of adolescents on upadacitinib 15 mg, and 15.4% and 27.8% on upadacitinib 30 mg failed to achieve clinically meaningful scalp hair regrowth at Week 24.

Collectively, these data challenge the assumption that all JAK inhibitors for severe AA have similar efficacy, with roughly half of patients failing to achieve SALT ≤20 even after prolonged treatment. The Week 24 responder rates achieved with upadacitinib substantially exceed those previously reported for baricitinib, ritlecitinib, and deuruxolitinib in adults, as well as baricitinib and ritlecitinib in adolescents. Upadacitinib therefore appears to occupy a distinct efficacy tier among JAK inhibitors**,** with the potential to reduce the need for successive therapeutic switching.

This manuscript is original, has not been published previously, and is not under consideration elsewhere. All authors meet ICMJE criteria and have approved the final version.

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Generative AI tools were used solely to assist with language refinement, structural clarity, and brevity. All intellectual content, study design, data analysis, interpretation, and final revisions were performed and verified by the authors, who take full responsibility for the accuracy and integrity of the work. AI-generated suggestions were critically reviewed and incorporated only with human oversight.

We appreciate your consideration of our manuscript and look forward to your response.

Sincerely,

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Comparative Efficacy of Upadacitinib, Baricitinib, and Ritlecitinib in Adolescents With Severe Alopecia Areata: A Systematic Review and Bayesian Network Meta-Analysis

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Running Title: JAK Inhibitor Efficacy in Adolescents

Comparative Efficacy of Upadacitinib, Baricitinib, and Ritlecitinib in Adolescents With Severe Alopecia Areata: A Systematic Review and Bayesian Network Meta-Analysis

This systematic review and network meta-analysis was conducted in accordance with PRISMA-NMA guidelines, in accordance with an a priori protocol.

Abstract

Background: Severe alopecia areata (AA) in adolescents carries substantial physical, psychological, social, and economic burden, yet only one Janus kinase (JAK) inhibitor, ritlecitinib, is currently approved in the United States (US) for this population. Baricitinib has recently been authorized by the European Medicines Agency and remains under FDA review, while upadacitinib has been submitted to both agencies for adolescents and adults. Three oral JAK inhibitors are therefore expected to become available for adolescents with severe AA within the next year. This study evaluated the comparative efficacy of ritlecitinib, baricitinib, and upadacitinib in adolescents with severe AA.

Methods: A systematic review and Bayesian network meta-analysis of randomized, placebo-controlled trials was conducted. Adolescent data (ages 12–17) were extracted from eligible studies evaluating ritlecitinib, baricitinib, or upadacitinib. The primary outcome was achievement of a Severity of Alopecia Tool (SALT) score ≤20 at Week 24. Odds ratios (ORs) with 95% credible intervals (CrIs) were estimated using a fixed-effect Bayesian model. Week 24 SALT ≤20 responder rates were compared across trials.

Results: Four placebo-controlled trials were included. Compared with placebo, upadacitinib 30 mg demonstrated the highest and most stable efficacy (OR 174.13, 95% CrI 21.17–4520.81), followed by upadacitinib 15 mg (OR 48.09, 95% CrI 6.40–1304.38), baricitinib 4 mg (OR 15.30, 95% CrI 4.73–68.45), and baricitinib 2 mg (OR 6.46, 95% CrI 1.85–29.90). Indirect comparisons showed clear dose-response relationships: upadacitinib 30 mg exceeded upadacitinib 15 mg (OR 3.42, 95% CrI 1.38–9.26), and baricitinib 4 mg exceeded baricitinib 2 mg (OR 2.37, 95% CrI 1.14–5.01). Week 24 responder rates were directionally consistent: 56%–57% and 72%–85% of adolescents achieved SALT ≤20 with upadacitinib 15 mg and 30 mg, respectively, compared with 17% and 32% with baricitinib 2 mg and 4 mg, and 25% with ritlecitinib 50 mg. Ritlecitinib

estimates were unstable because of sparse adolescent data and near-zero placebo response rates, resulting in wide CrIs and substantial uncertainty.

Conclusions: Oral JAK inhibitors improved outcomes in adolescents with severe AA. Upadacitinib demonstrated a distinctly superior efficacy profile, with Week 24 responder rates far exceeding those historically observed with currently approved JAK inhibitors and markedly higher than those seen with baricitinib or ritlecitinib in this analysis. Baricitinib and ritlecitinib produced more modest and broadly similar responder rates. These findings suggest that upadacitinib may represent a higher-efficacy tier within the JAK inhibitor class.

Keywords

Alopecia areata; Adolescents; Upadacitinib; Baricitinib; Ritlecitinib

Introduction

Alopecia areata (AA) is a chronic autoimmune disorder characterized by non-scarring hair loss affecting the scalp, eyebrows, eyelashes, and other hair-bearing areas. The disease results from immune-mediated destruction of hair follicles driven primarily by autoreactive T lymphocytes and inflammatory cytokine signaling pathways [1]. Although AA can occur at any age, onset during adolescence is often associated with more severe clinical manifestations, longer disease duration, and a greater psychosocial burden. Adolescents with severe AA experience increased risks of depression, anxiety, social stigma, bullying, school absenteeism, and reduced academic performance [2]. Conventional therapies, including topical corticosteroids, intralesional corticosteroids, topical immunotherapy, and systemic immunosuppressants, frequently demonstrate variable efficacy and high relapse rates [3].

The introduction of JAK inhibitors to treat AA has transformed the management of severe alopecia areata and ushered in a modern paradigm in clinical trials methodology, including optimized study design and outcomes assessment [4-12]. However, there is still a considerable unmet need for drugs that are more effective, safer, and durable. In pivotal trials of baricitinib in adults with severe AA (BRAVE-AA1 [NCT03570749] and BRAVE-AA2 [NCT03899259]), approximately 60% and 80% of patients, respectively, did not achieve clinically meaningful scalp hair regrowth, defined as a Severity of Alopecia Tool (SALT) score ≤20 at Weeks 36 and 52 on the 4 mg and 2

mg doses. In the ritlecitinib studies (ALLEGRO 2a [NCT02974868] and ALLEGRO 2b/3 [NCT03732807]), approximately 55% of adults at Week 52 and 40% at Week 104 did not reach a SALT score ≤20 [5, 9]. In the pivotal deuruxolitinib trials (THRIVE-AA1 [NCT04518995] and THRIVE-AA2 [NCT04797650]), which were not included in the present analysis, approximately 71% and 80% of adults with severe AA failed to achieve a SALT score ≤20 at Week 24 [4, 8, 13]. Among adolescents treated with ritlecitinib in ALLEGRO 2b/3 (N=105), depending on dose, approximately 70% to 80% and 50% to 75% did not achieve a SALT score ≤20 at Weeks 24 and 48, respectively [12].

Durability of response also remains a challenge. In patients with meaningful hair regrowth, discontinuation of baricitinib results in loss of benefit in approximately 10% of patients by Week 8 and in at least 80% by Week 152, with most but not all responders regaining response upon retreatment (2 mg, 63%; 4 mg, 85%) [7]. Discontinuation of ritlecitinib similarly leads to loss of benefit, with 53% of responders (≥30% improvement in SALT score from baseline) regaining response upon retreatment [6, 14]. Given these limitations, and in the absence of a new, mechanistically differentiated pharmacologic class with an approved indication for severe AA, suboptimal efficacy or tolerability will likely necessitate switching among available oral JAK inhibitors to leverage interindividual or intraclass differences, as suggested in recent reports [15-21].

Baricitinib, ritlecitinib, and deuruxolitinib were commercialized in the United States (US) for severe AA in 2022, 2023, and 2025, respectively [13, 22, 23]. Among these agents, only ritlecitinib is currently approved for use in both adolescents and adults, and dermatologists now have more than four years of clinical experience with its use in adolescents. Baricitinib has recently been approved by the European Medicines Agency (EMA) for adolescents with severe AA [24] and remains under review by the US Food and Drug Administration (FDA) [25]. Upadacitinib has been submitted to both the FDA and EMA for the treatment of severe AA in adolescents and adults [26].

Baricitinib is a selective JAK1 and JAK2 inhibitor that suppresses inflammatory cytokine signaling pathways implicated in AA pathogenesis, particularly interferon-gamma–mediated immune activation [11, 27]. Ritlecitinib is a selective JAK3 and TEC (tyrosine kinase expressed

in hepatocellular carcinoma) family kinase inhibitor that reduces lymphocyte activation and immune-mediated follicular inflammation [12, 14, 28, 29]. The selective JAK1 inhibitor upadacitinib has been approved for the treatment of several inflammatory conditions such as atopic dermatitis and rheumatoid arthritis, showing promising results in AA in terms of effective inhibition of proinflammatory cytokine signaling [30]. While still awaiting approval in the US and EU for the treatment of AA, upadacitinib shows promise of efficacy in adolescents, providing an avenue for indirect comparisons to approved JAK inhibitors [31, 32].

However, direct comparative randomized trials of JAK inhibitors in adolescents with severe AA are not available. Most existing studies evaluate individual agents against placebo, which limits the ability to determine the relative efficacy and safety of available and emerging therapies [11, 12, 14, 30, 33-36]. Evidence regarding eyebrow and eyelash regrowth in adolescents is also limited.

Recent real-world prescribing trends presented at the American Academy of Dermatology meeting indicate that clinicians often initiate JAK inhibitors at lower doses and are hesitant to escalate to higher doses due to multiple boxed warnings, the need for ongoing laboratory monitoring, adverse events such as acne, and patient reluctance [37]. Against this backdrop, given that approximately 75% of adolescents treated with ritlecitinib at the indicated 50 mg dose did not achieve clinically meaningful scalp hair regrowth at 24 weeks and approximately 50% had not done so by 48 weeks [12], dermatologists may be well-motivated to extend their clinical experience with baricitinib, already established in adults with severe AA, and with upadacitinib, already well-characterized in moderate-to-severe atopic dermatitis, to this adolescent population.

Network meta-analysis allows indirect comparison of multiple therapies when direct comparative trials are lacking. By integrating evidence from placebo-controlled trials, network meta-analysis enables estimation of comparative treatment effects within a connected evidence network. Therefore, the present study aimed to perform a systematic review and Bayesian network meta-analysis evaluating the comparative efficacy of oral JAK inhibitors, specifically baricitinib, ritlecitinib, and upadacitinib that are approved or under active regulatory review by the FDA or EMA for severe AA in adolescents. The primary outcome was achievement of a SALT score ≤ 20 at Week 24. Secondary outcomes included eyebrow response and eyelash response.

Methods

Study Design

An exploratory placebo-anchored indirect comparison and Bayesian network meta-analysis (BNMA) [38] was conducted to compare the efficacy and safety of JAK inhibitors in adolescents with severe AA. The study followed PRISMA-NMA recommendations [39] and was conducted in accordance with an a priori protocol. Only trials with extractable adolescent-specific outcomes were eligible.

Eligibility Criteria

Eligible studies met the following inclusion criteria; teenagers aged 12 to 17 years with severe AA; assessment of either ritlecitinib, baricitinib, or upadacitinib, and a placebo arm; data from randomized placebo-controlled clinical trials. In line with the FDA's guidelines, teenagers refer to children aged 12 to 17 years [40-43]. This age range is also applied in FDA-approved prescribing information to structure adolescent labeling and safety and efficacy analyses.

Treatment arms included baricitinib 2 mg and 4 mg, ritlecitinib 30 mg, 50 mg, 200/30 mg, and 200/50 mg, and upadacitinib 15 mg and 30 mg. The ritlecitinib 200 mg regimens consisted of a 4-week loading dose followed by daily maintenance dosing. Although only the 50 mg daily dose was eventually approved, the FDA review noted that all four ritlecitinib regimens demonstrated clinically meaningful achievement of SALT scores ≤20 [44]. The ritlecitinib 10 mg arm was excluded because it was designed primarily for pharmacokinetic evaluation and was not clinically relevant.

Outcomes

The primary endpoint was achievement of a SALT score ≤20 at Week 24, based on extractable binary efficacy outcomes. Secondary exploratory outcomes included eyebrow and eyelash responses at Week 24 or the nearest comparable time point. Because of heterogeneity in definitions, assessment methods, and across adolescent datasets, formal network meta-analysis for eyebrow and eyelash was not appropriate. eyebrow and eyelash outcomes were therefore summarized descriptively using reported responder proportions

Data Extraction

Responder counts and total sample sizes were extracted from each treatment arm. When only percentages were reported, event counts were calculated using the reported denominators. Extracted variables included study characteristics, intervention regimens, sample sizes, efficacy outcomes, and safety outcomes. Placebo arms served as the common comparator for the evidence network. Conference abstracts and subgroup analyses were considered when they provided sufficient extractable adolescent-specific data. Non-randomized studies, case reports, narrative reviews, and studies lacking adolescent-specific outcomes were excluded.

Statistical Analysis

A fixed-effect Bayesian NMA was performed because of the limited number of adolescent studies and small sample sizes. Odds ratios (ORs) with 95% credible intervals (CrIs) were calculated for all indirect pairwise comparisons [45]. The primary comparative analysis focused on Week 24 SALT score ≤20 response rates. For secondary outcomes for which there was an inconsistency in the timing of data collection in the various studies, descriptive analysis was carried out.

The analysis was done using R software. The results obtained were a league table of indirect comparisons and forest plots of the odds ratios relative to placebo. Heterogeneity of the studies was measured using I^2 test statistic and model fit measures such as residual deviance and DIC.

Risk of Bias and Publication Bias

Risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool [46]. Publication bias and small-study effects were explored visually using comparison-adjusted funnel plots, although interpretation was limited by the small number of included studies.

Results

Study Selection

The PRISMA-based systematic literature search (shown in Fig. 1) identified 82 records from PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov databases. After removal of 42 duplicate records, 40 studies underwent title and abstract screening, of which 29 were excluded.

Eleven reports were assessed for full-text eligibility, and eight were excluded because of non-randomized designs, non-alopecia areata populations, absence of placebo comparators, or conference-abstract-only publications. Ultimately, four randomized placebo-controlled clinical trials met the eligibility criteria and were included in the final Bayesian network meta-analysis. These comprised one ritlecitinib trial (ALLEGRO phase 2b/3), one baricitinib trial (BRAVE-AA-PEDS), and two upadacitinib phase 3 clinical trials (UP-AA) [12, 32, 47-49].

Study Characteristics

Detailed study characteristics are summarized in Table 1. All included studies were international, multicenter randomized placebo-controlled trials. Evaluated interventions included ritlecitinib 30 mg, 50 mg, 200/30 mg, and 200/50 mg; baricitinib 2 mg and 4 mg; and upadacitinib 15 mg and 30 mg. All treatments were dosed once daily. Sample sizes varied across treatment arms, with the largest adolescent population observed in BRAVE-AA-PEDS, a dedicated pediatric study [33, 50-53], whereas ritlecitinib ALLEGRO [12, 14, 23, 54] and upadacitinib UP-AA [32, 47-49] data were derived from predominantly adult trials that included smaller adolescent subgroups.

Network Geometry

The evidence network included placebo-controlled comparisons among baricitinib, ritlecitinib, and upadacitinib regimens evaluated for achievement of SALT score ≤20 in adolescents with severe AA (shown in Fig. 2). Network plots demonstrated adequate connectivity for indirect treatment comparisons, although several treatment arms were informed by sparse subgroup data.

Bayesian Network Meta-Analysis

A Bayesian fixed-effect network meta-analysis was conducted because statistical heterogeneity across the network was low ($I^2 = 6\%$). Model fit was acceptable, with residual deviance closely approximating the number of unconstrained data points (residual deviance ratio 0.99) (shown in Fig. 3).

Compared with placebo, all JAK inhibitor regimens increased the likelihood of achieving a SALT score ≤20. Upadacitinib 30 mg demonstrated the highest and most stable efficacy estimates versus placebo (OR 174.13, 95% CrI 21.17 to 4520.81), followed by upadacitinib 15 mg (OR 48.09, 95%

CrI 6.40 to 1304.38). Baricitinib 4 mg demonstrated greater efficacy compared with baricitinib 2 mg, with ORs versus placebo of 15.30 (95% CrI 4.73 to 68.45) and 6.46 (95% CrI 1.85 to 29.90), respectively.

Ritlecitinib regimens produced extremely large effect estimates with very wide CrIs. For example, ritlecitinib 50 mg demonstrated an OR versus placebo exceeding 10^{10}, reflecting the instability introduced by sparse adolescent data and near-zero placebo responses.

Indirect Comparisons

Indirect comparisons demonstrated a clear dose-response relationship for both baricitinib and upadacitinib regimens (Table 2). Upadacitinib 30 mg demonstrated greater efficacy than upadacitinib 15 mg (OR 3.42, 95 percent CrI 1.38 to 9.26 for 30 mg vs 15 mg). Baricitinib 4 mg demonstrated greater efficacy than baricitinib 2 mg (OR 2.37, 95 percent CrI 1.14 to 5.01 for 4 mg vs 2 mg).

Indirect comparisons involving ritlecitinib regimens were unstable, with wide CrIs crossing clinically implausible ranges, again reflecting sparse data and zero-event placebo arms.

Observed Week 24 SALT ≤20 Responder Rates Across Trials

Direct responder rates from the individual trials provided additional clarity regarding comparative efficacy at Week 24 (shown in Fig. 4). Among adolescents treated with ritlecitinib in the ALLEGRO 2b/3 study (NCT03732807), 25% of patients receiving the approved 50 mg dose achieved a SALT score ≤20, indicating that 75% did not achieve clinically meaningful scalp hair regrowth by Week 24 [12, 14, 23, 54]. In BRAVE-AA-PEDS (NCT05723198), 16.6% and 31.8% of adolescents treated with baricitinib 2 mg and 4 mg, respectively, achieved a SALT score ≤20, corresponding to non-response rates of 83.4% and 68.2% [33, 50-53].

By contrast, the two pivotal UP-AA trials (NCT06012240) demonstrated substantially higher responder rates with upadacitinib [32, 47-49]. At Week 24, 56.0% and 56.5% of adolescents receiving upadacitinib 15 mg achieved a SALT score ≤20 in Study 1 and Study 2, respectively. The 30 mg dose produced even more robust responses, with 84.6% and 72.2% achieving a SALT score ≤20, in the two studies. These findings indicate that only approximately 44% and 43.5% of

adolescents on upadacitinib 15 mg, and 15.4% and 27.8% on upadacitinib 30 mg, failed to achieve clinically meaningful scalp hair regrowth at Week 24.

The response rates seen among all the JAK inhibitors were consistently aligned with the Bayesian network meta-analysis and indirect comparisons. The best efficacy was seen for upadacitinib 15 and 30 mg, whereas the responses were more modest and comparable in case of baricitinib and ritlecitinib. However, even with the use of a 4-week loading dose of 200 mg followed by maintenance dose of 50 mg (200/50 mg), the response rate for ritlecitinib at week 24 was 27.8%, closely approximating the response observed with baricitinib 4 mg.

Eyelash and Eyebrow Response Outcomes

Numerical response rates in adolescents to eyelash and eyebrow outcomes were observed to be higher for all JAK inhibitor treatment groups in comparison with placebo (shown in Fig. 5). The highest numerical response rates were observed for upadacitinib 30 mg, as its eyelash response was about 80.8%, and eyebrow response approached 92.9%. Intermediate results were observed for upadacitinib 15 mg, with eyelash and eyebrow response at about 35.0% and 35.2%.

Regarding baricitinib treatment regimens, baricitinib 4 mg performed better than baricitinib 2 mg for both outcomes. Baricitinib 4 mg demonstrated an eyelash response of approximately 42.9% compared with 25.5% for baricitinib 2 mg. Similarly, eyebrow response rates were about 50.0% for baricitinib 4 mg and 24.1% for baricitinib 2 mg, indicating a dose-dependent effect.

Efficacy of ritlecitinib treatments was not constant. Ritlecitinib 200 mg initial treatment for 4 weeks, followed by 50 mg (200/50 mg) had the highest efficacy rates in ritlecitinib treatments, with eyelash and eyebrow efficacy rates of approximately 61.5% and 40.0%, respectively. Ritlecitinib efficacy at the approved dosage of 50 mg was approximately 20% and 40% for eyelashes and eyebrows, respectively.

Placebo groups exhibited no or low eyelash and eyebrow efficacy. In general, descriptive efficacy of eyelashes and eyebrows correlated well with primary efficacy results.

Publication Bias and Small-Study Effects

There was no significant asymmetry noted on visual inspection of the comparison-adjusted funnel plot (shown in Fig. 6). However, assessment using the funnel plot was hindered by the few studies included, the limited adolescent subgroup studies, and a few rare-event comparisons.

Risk of Bias Assessment

The risk of bias was assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. The majority of the trials included had low risk of bias with respect to the key domains, including randomization, deviation from the intended intervention, incomplete outcome data, and outcome measurements (shown in Fig. 7). There were some concerns in the adolescent subgroup due to lack of detailed reporting and being exploratory in nature.

Discussion

This exploratory Bayesian network meta-analysis evaluated the comparative efficacy of the JAK inhibitors ritlecitinib, baricitinib, and upadacitinib in adolescents with severe AA using placebo-anchored indirect comparisons. All three agents improved the likelihood of achieving a SALT score ≤20 relative to placebo, reinforcing the expanding role of targeted immunomodulatory therapy in this population. Among the evaluated regimens, upadacitinib 30 mg produced the most favorable and statistically stable efficacy estimates, followed by upadacitinib 15 mg, baricitinib 4 mg, and baricitinib 2 mg. In contrast, ritlecitinib regimens generated highly unstable and imprecise effect estimates, characterized by extremely large odds ratios and wide uncertainty ranges that limited interpretability. These features were driven by sparse adolescent subgroup data and near-zero placebo response rates, which collectively constrained the reliability of indirect comparisons involving ritlecitinib despite its numerically elevated point estimates.

Direct Week 24 responder rates from individual trials supported these findings, with 72%–85% of adolescents achieving a SALT score ≤20 on upadacitinib 30 mg and 56%–57% on upadacitinib 15 mg, compared with 32% and 17% on baricitinib 4 mg and 2 mg, and 25% on ritlecitinib 50 mg. These observed responder rates indicate that upadacitinib demonstrated the strongest efficacy profile, whereas baricitinib and ritlecitinib produced more modest and broadly similar responses. Together, these results highlight meaningful differences in therapeutic performance across available and emerging JAK inhibitors for adolescents with severe AA and underscore the

importance of comparative evidence in guiding treatment selection in the absence of head-to-head trials.

These findings are biologically plausible given the well-established role of the JAK-STAT signaling pathway in AA pathogenesis [55, 56]. Interferon-gamma and other pro-inflammatory cytokines drive immune-mediated follicular destruction, and selective inhibition of JAK-dependent signaling is thought to restore hair follicle immune privilege and facilitate hair regrowth. Prior pivotal clinical trials have demonstrated meaningful efficacy for both ritlecitinib and baricitinib in severe AA, leading to regulatory approval in adults (ritlecitinib and baricitinib) and adolescents (ritlecitinib) [10, 57-59]. Emerging evidence increasingly supports substantial clinical benefit of selective JAK1 inhibition with upadacitinib in adolescents and adults [60, 61]. The present analysis compares the relative efficacy of the three agents, ritlecitinib already approved, and baricitinib and upadacitinib pending regulatory approval in the US for severe AA in adolescents, to provide exploratory comparative guidance in anticipation of broader regulatory approval.

The indirect comparisons further supported a dose-response relationship for both upadacitinib and baricitinib, with higher-dose regimens demonstrating numerically greater efficacy consistent with adult randomized controlled trial data. For ritlecitinib, although the approved dose is 50 mg for both adolescents and adults with severe AA, the present network meta-analysis included the 30 mg, 200/30 mg, and 200/50 mg regimens. This decision was justified by the comparatively narrow evidence base underlying ritlecitinib's regulatory approval, which rested on the single pivotal Phase 2b/3 study enrolling both adults and adolescents, with a relatively limited adolescent sample size. 200/30 mg and 200/50 mg treatment regimens included an initial four-week course of daily loading dose of 200 mg, which was followed by 20-week courses of either 30 mg or 50 mg maintenance doses. Patients, who had received a loading dose, exhibited better Week 24 SALT $\leq$20 response rate compared with patients treated by 50 mg and 30 mg without a loading dose [62], which suggests that high-dose therapy in the first period can increase the therapeutic efficacy. However, regardless of such promising numerical results of using loading dose, the efficacy profile of ritlecitinib proved to be the least successful among all three tested JAK inhibitors; moreover, responder rates of ritlecitinib seemed comparable with baricitinib rates rather than approaching significantly higher rates of upadacitinib. There is a current clinical trial, which is comparing

efficacy of 100 mg ritlecitinib regimen with the approved 50 mg dose in adolescents and adult patients with severe AA through the use of external and synthetic placebo control groups [63, 64]. Results from this study are expected to provide more definitive efficacy and safety data at higher ritlecitinib doses in adolescents and adults.

These data are also at odds with the assumption, which has been around for a while now, that the efficacy of all the orally administered JAK inhibitors of severe AA is essentially the same, with about half of the patients not achieving a SALT score ≤20 even after prolonged treatment. The responder rates at week 24 achieved by upadacitinib, in particular the 72-85% response rates achieved by the 30 mg dose, significantly outperform those previously reported for baricitinib, ritlecitinib, and deuruxolitinib in adult subjects, as well as baricitinib and ritlecitinib in adolescents in this study. It appears that upadacitinib belongs to a different efficacy tier among the JAK inhibitors, with the ability to cut down on the need for successive switching.

On the other hand, the lower responder rates achieved with baricitinib and ritlecitinib further confirm the location of these drugs in the efficacy tier characteristic of currently available JAK inhibitors. If proved true in future trials, this finding will have an impact on the treatment paradigm for severe AA.

Descriptive analyses of eyebrow and eyelash outcomes were broadly consistent with the primary efficacy findings. JAK inhibitor regimens generally demonstrated higher response rates than placebo, with numerically greater improvements observed with upadacitinib 30 mg and higher dose baricitinib regimens [65, 66]. Despite the above-mentioned conclusions, care must be exercised when interpreting these data due to inconsistent definitions of the efficacy of eyebrow/eyelashes and variable presentation of results in relevant studies, thus not permitting a network meta-analysis of these parameters.

Methods of quantitative evidence synthesis such as conventional meta-analysis and network meta-analysis contribute greatly to decision making in clinical practice, guidelines formulation, issues related to reimbursement and priority setting of research. Nevertheless, the validity of these methods is critically dependent on the evaluation of several key assumptions, which include comparability of the population enrolled in the studies, independence of the treatment comparisons, transitivity of the effect modifier and consistency of the direct and indirect evidence.

These assumptions in conventional meta-analysis include compatibility of the clinical question, effect measure, and presence of small/minimal heterogeneity. In addition to the above-listed criteria, network meta-analysis assumes connectivity of the evidence network, clear definition of the intervention nodes and the presence of transitivity and consistency.

The above-listed assumptions are generally satisfied in big industry sponsored global registration studies conducted after consultation with regulatory agencies, according to international standards of good clinical practice, manufacturing, laboratory and statistical practice. These methodological strengths provide an appropriate framework for the indirect comparisons conducted in the present analysis, while also acknowledging the unique challenges posed by sparse adolescent subgroup data.

The anticipated regulatory approval of upadacitinib and baricitinib for severe AA in adolescents will meaningfully expand therapeutic options and provide evidence-based alternatives to ritlecitinib, which is currently the only JAK inhibitor approved for this indication in this age group. Several intersecting clinical realities underscore the importance of this expanded armamentarium.

A recent anonymous survey of 86 U.S.-based board-certified dermatologists found that more than half reported a preference for attempting alternative therapies, primarily intralesional or topical corticosteroids before initiating a JAK inhibitor [67], reflecting persistent prescriber caution around this drug class. Among the agents compared in this study, upadacitinib holds a distinct advantage for patients with comorbid atopic dermatitis, as it is the only JAK inhibitor in this analysis with an established indication for moderate to severe atopic dermatitis [26, 68, 69].

At a population level, more than 50% of adult patients with severe AA fail to achieve a SALT score $\leq$20 after 12 months of continuous therapy with all three currently available JAK inhibitors (baricitinib, ritlecitinib and deuruxolitinib) at the highest indicated JAK inhibitor doses, a sobering efficacy ceiling that is compounded by compelling indirect evidence of striking interindividual and intraclass variability in treatment response. When initial therapy proves inadequate in efficacy or tolerability, sequential switching among available JAK inhibitors may yield incremental clinical benefit, particularly in patients who demonstrate partial response to a first agent [15-21]. Until mechanistically differentiated and potentially safer alternatives, such as rezpegaldesleukin, a first-in-class biologic that is anticipated to carry no boxed warnings or require ongoing laboratory

monitoring [70] become available for the management of severe AA, strategic intraclass JAK inhibitor rotation will remain an important tool for optimizing outcomes in patients who do not achieve or sustain adequate responses.

The present study has several limitations that should inform the interpretation of its findings. First, in the absence of randomized trials comparing JAK inhibitors in adolescents with AA, all comparative estimates were derived from indirect, placebo-anchored network meta-analyses; accordingly, these findings should be regarded as exploratory and hypothesis-generating rather than as definitive evidence of superiority between agents. Second, the small adolescent subgroup sample sizes across included studies contributed to statistical instability and wide CrIs for several treatment comparisons, most notably those involving ritlecitinib. Third, heterogeneity in baseline measures, including identified factors such as SALT score, duration of AA and duration of current episode, as well as unmeasured influences, raised considerations for the transitivity assumption. Heterogeneity in efficacy assessment timepoints and inconsistent reporting of secondary outcomes further limited the scope of comparative analyses for eyebrow and eyelash endpoints.

Fourth, because clinical responses to JAK inhibitors often continue to evolve beyond the short placebo-controlled induction windows used in most trials, this analysis cannot fully assess differences in durability, continued deepening of response, relapse dynamics, or long-term safety, features that are highly relevant in a chronic, relapsing condition. Following discontinuation of placebo groups and randomization or conversion to active treatments for the rest of participants, there will be no longer a stable common comparator in the network making indirect comparison during maintenance less reliable. This methodological approach also assumes that all JAK inhibitors have a similar pattern of long-term responses which is not always the case. Fifth, even though the SUCRA criterion has been extensively employed for interpreting the hierarchy of treatments in a network meta-analysis, its use in a rare subgroup data where there are unstable effect estimates can produce misleading hierarchies. For this reason, treatment hierarchy was deliberately ignored in this study while the emphasis of the analysis was shifted to effect estimates and clinical plausibility. Lastly, even though the analysis focuses on comparing the efficacy of the available JAK inhibitors, a broader and more personalized evaluation is needed when choosing treatment in clinical practice since the safety profiles and patient-related factors are not included in a network meta-analytic approach. As a result, the comparative rankings presented here should

be interpreted as one component of a larger evidence-based decision process rather than a definitive guide to agent selection.

Despite these limitations, this study represents the first focused comparative evaluation of oral JAK inhibitors in adolescents with severe AA. The findings reinforce the therapeutic potential of JAK inhibition in younger patients while highlighting the substantial evidence gaps that persist in this population. Although adequately powered head-to-head randomized trials remain the gold standard for comparative efficacy assessment, such trials are unlikely in this therapeutic area due to considerable financial and operational constraints. Consequently, indirect comparison methods, including Bayesian network meta-analysis, provide a valuable framework for informing relative efficacy and supporting clinical decision-making in the absence of direct evidence.

Conclusion

This exploratory Bayesian network meta-analysis demonstrated that oral JAK inhibitors improved achievement of a SALT score ≤20 in adolescents with severe AA relative to placebo. Across the evaluated regimens, upadacitinib 30 mg showed the most favorable and statistically stable efficacy profile, with upadacitinib 15 mg also demonstrating substantially greater efficacy than either baricitinib or ritlecitinib. Week 24 responder rates from the individual trials reinforced this hierarchy, with markedly higher responses for upadacitinib, particularly the 72% to 85% responses seen with the 30 mg dose, compared with the more modest and broadly similar responses observed with baricitinib and ritlecitinib. These findings suggest that upadacitinib may represent a distinct therapeutic tier within the JAK inhibitor class and challenge the long-standing assumption that all oral JAK inhibitors for severe AA achieve comparable efficacy. Descriptive eyebrow and eyelash outcomes were directionally consistent with the primary findings.

These results should be interpreted with caution, as the analysis relied on indirect placebo-anchored comparisons, small adolescent subgroup sample sizes, and heterogeneous reporting of secondary and safety outcomes. Comparisons involving ritlecitinib were particularly affected by statistical instability due to sparse data and near-zero placebo response rates. To the authors' knowledge, this study represents the first focused comparative evaluation of oral JAK inhibitors in adolescents with severe AA. The findings underscore the need for adequately

powered, head-to-head randomized trials with standardized efficacy and safety reporting to define the optimal therapeutic approach in this population.

Ethics Statement

Ethical approval and patient consent were not required because this was a network meta-analysis of previously published studies.

Conflicts of Interest Statement

The authors declare no conflicts of interest.

Funding Sources

The authors have nothing to report.

Author Contributions

AB conceived and developed the study idea, acquired the data, performed the analyses with assistance from a statistician, and drafted the manuscript. All authors reviewed the draft versions, contributed important intellectual input regarding the structure, content, and interpretation of the data, and have reviewed and approved the final version to be published. All authors agree to be accountable for all aspects of the work.

Data Availability Statement

Upon reasonable request, including a clearly defined research question with valid scientific rationale and, where applicable, a robust statistical analysis plan, and subject to a Data Use Agreement, the lead author will provide additional data that support the findings of this report.

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Tables

Table 1. Characteristics of Included Randomized Placebo-Controlled Trials Evaluating Baricitinib, Ritlecitinib, and Upadacitinib in Adolescents With Severe Alopecia Areata

Author (Year)	Trial Name	Design	Setting	Intervention Arms	Sample Size (per arm)	Responders (n)	SALT score ≤ 20	SALT score ≤ 20 (w/o Placebo)
Hordinsky et al., 2023 (NCT03732807) [12, 14, 23, 54]	ALLEGRO phase 2b/3	International, randomized, double-blind, placebo-controlled, combined dose-ranging pivotal Phase 2b/3 trial	118 hospitals and clinics in Argentina, Australia, Canada, Chile, China, Colombia, Czech Republic, Germany, Hungary, Japan, Korea, Mexico, Poland, Russia, Spain, Taiwan, the UK, and the USA	Placebo	19		0.0	
				Ritlecitinib 200/50 mg	18	5	27.8	27.78
				Ritlecitinib 200/30 mg	17	3	17.6	17.65
				Ritlecitinib 50 mg	16	3	18.8	25
				Ritlecitinib 30 mg	18	3	16.7	16.67
Passeron et al., 2025 (NCT05723198) [50-53]	BRAVE-AA-PEDS	International, randomized, double-blind, placebo-controlled, combined dose-ranging phase 3 pivotal trial	140 sites across multiple countries, including: United States, Argentina, Australia, Canada, France, Germany, Hungary, Japan, Mexico, Poland, South Korea, Spain, and Taiwan	Placebo	88	3	3.4	
				Baricitinib 2 mg	84	14	16.7	13.26
				Baricitinib 4 mg	85	27	31.8	28.35
				Placebo;	13	0	0.0	

Gooderham et al., 2026 (NCT06012240) [32, 47-49]	UP-AA Phase 3 Clinical Program (Study 1 & Study 2)	International, randomized, double-blind, placebo-controlled, combined dose-ranging pivotal phase 3 replicate trials	Global multicenter phase 3 clinical trial conducted across 269 study locations/ sites in multiple countries.	Upadacitinib 15 mg QD (UPA15) (S1)	25	14	56.0	56
				Upadacitinib 30 mg QD (UPA30) (S1)	26	22	84.6	54.62
				Placebo;	10	1	10.0	
				Upadacitinib 15 mg QD (UPA15) (S2)	23	13	56.5	46.52
				Upadacitinib 30 mg QD (UPA30) (S2)	21	16	76.2	66.19

Footnote: SALT = Severity of Alopecia Tool; QD = once daily; S1 = Study 1; S2 = Study 2; responders (n) represent participants achieving **SALT ≤20** at Week 24; **SALT ≤20 (w/o placebo)** represents the placebo-adjusted response rate, calculated by subtracting the placebo response within the corresponding trial (or within the corresponding study for UP-AA Study 1 and Study 2) from the observed active treatment response; percentages are rounded and minor differences may occur due to rounding.

Table 2. Indirect Comparisons of Oral JAK Inhibitors for Achievement of SALT score ≤20 in Adolescents With Severe Alopecia Areata: Bayesian Network Meta-Analysis Results

Treatment	Baricitinib 2 mg	Baricitinib 4 mg	Ritlecitinib 30 mg	Ritlecitinib 50 mg	Ritlecitinib 200/30 mg	Ritlecitinib 200/50 mg	Upadacitinib 15 mg	Upadacitinib 30 mg
Baricitinib 2 mg	—							
Baricitinib 4 mg	2.37 (1.14–5.01)	—						
Ritlecitinib 30 mg	230946882.2 (1.44–3.18E+24)	99009900.99 (0.61–1.48E+24)	—					
Ritlecitinib 50 mg	392156862.8 (2.55–5.59E+24)	168350168.4 (1.04–2.26E+24)	1.72 (0.30–11.70)	—				
Ritlecitinib 200/30 mg	242130750.6 (1.57–3.57E+24)	104602510.5 (0.65–1.45E+24)	1.08 (0.16–7.29)	0.63 (0.10–3.62)	—			
Ritlecitinib 200/50 mg	469483568.1 (3.03–6.76E+24)	198807157.1 (1.28–2.79E+24)	2.02 (0.39–12.80)	1.17 (0.24–6.14)	1.88 (0.36–11.57)	—		
Upadacitinib 15 mg	6.76 (0.55–256.97)	2.85 (0.24–106.81)	0 (0–5.62)	0 (0–3.39)	0 (0–5.44)	0 (0–2.73)	—	
Upadacitinib 30 mg	23.38 (1.89–963.01)	9.90 (0.81–378.46)	0 (0–19.49)	0 (0–11.06)	0 (0–18.16)	0 (0–9.37)	3.42 (1.38–9.26)	—

Footnote: Data are presented as **odds ratios (ORs) with 95% credible intervals (CrIs)** from the Bayesian network meta-analysis. An OR >1 favors the treatment listed in the row over the treatment listed in the column. Comparisons with 95% CrIs excluding 1 are considered statistically significant. Extremely large ORs and very wide CrIs (or values reported as 0 due to rounding) reflect sparse-event data and should be interpreted with caution.

Figures

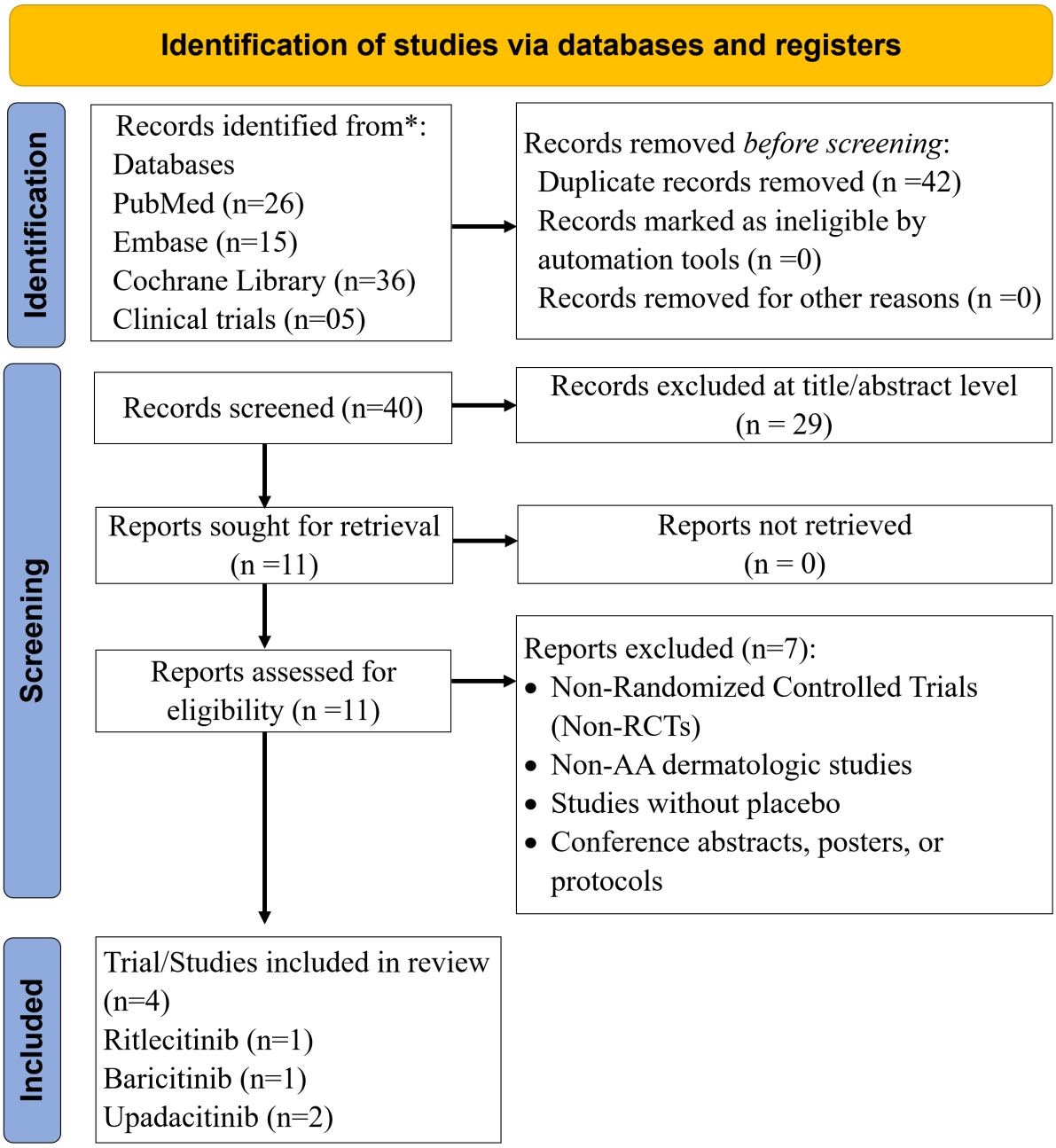

Fig. 1. PRISMA flow diagram of study selection.

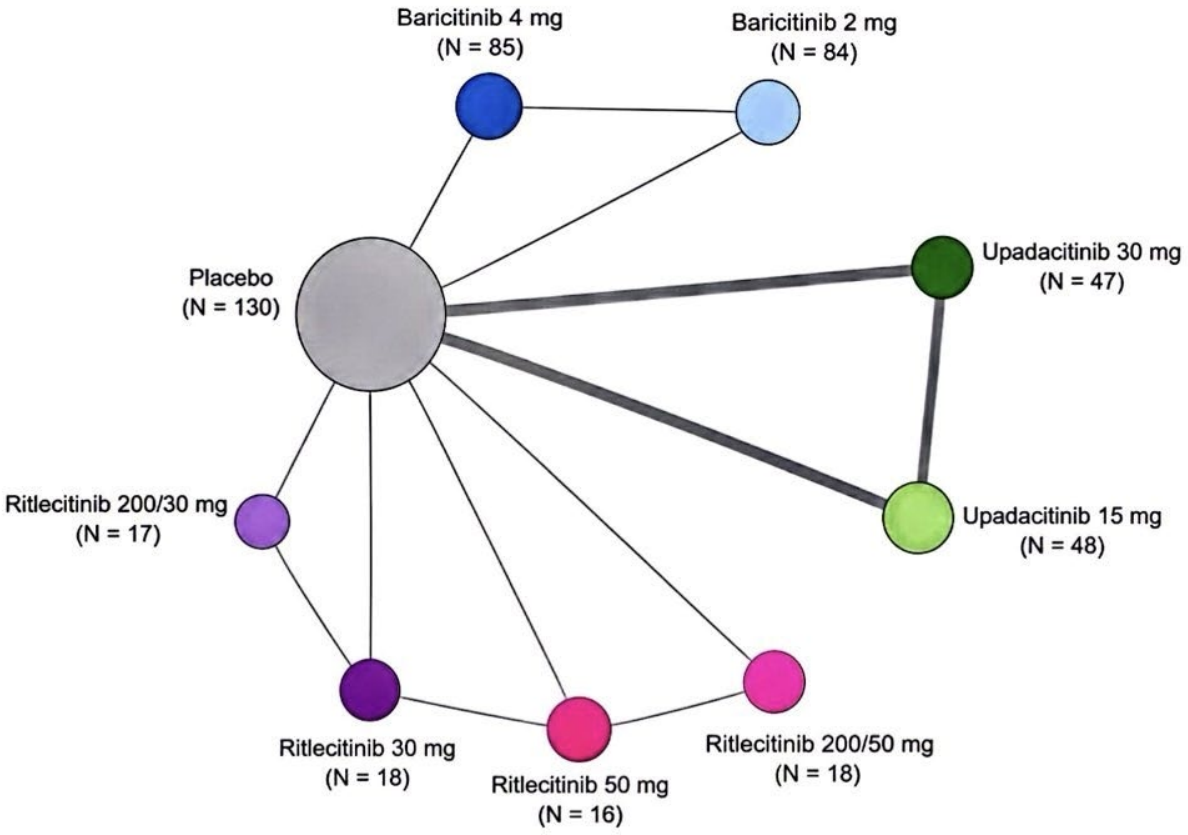

Fig. 2. Network geometry for the Bayesian network meta-analysis. Network plot showing the evidence structure for placebo-controlled comparisons of baricitinib, ritlecitinib, and upadacitinib regimens in adolescents with severe alopecia areata. Node size is proportional to the number of participants receiving each intervention, and line thickness reflects the number of direct comparisons available between treatments. Placebo served as the common comparator connecting all treatment nodes.

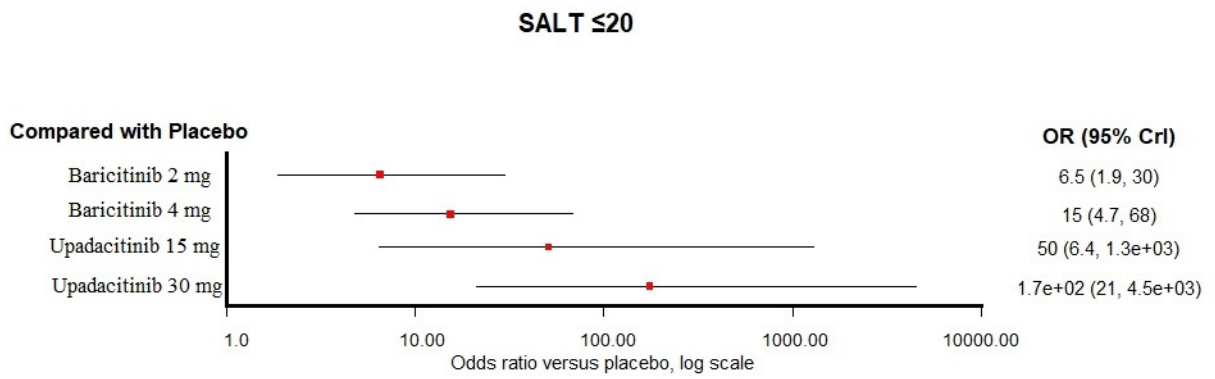

Fig. 3. Forest plot of treatment effects versus placebo for achievement of SALT score ≤20. Odds ratios (ORs) with 95% credible intervals (CrIs) derived from the fixed-effect Bayesian network meta-analysis. Values greater than 1 favor active treatment over placebo. Upadacitinib 30 mg demonstrated the highest and most stable efficacy estimate, whereas comparisons involving ritlecitinib exhibited substantial statistical uncertainty because of sparse adolescent subgroup data and near-zero placebo response rates. Ritlecitinib treatment arms were omitted from this figure for clarity because sparse-event data produced unstable and implausibly large estimates.

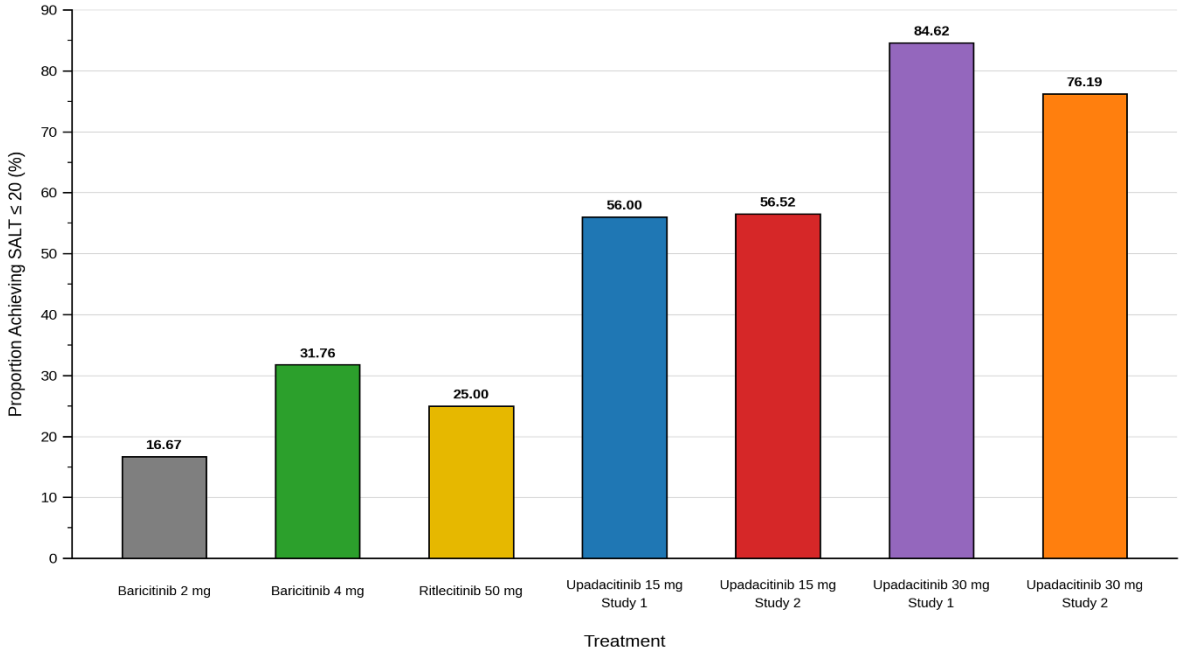

Fig. 4. Clinically meaningful scalp hair regrowth by Week 24 (SALT ≤20).

Proportions of adolescents with severe alopecia areata who achieved clinically meaningful scalp hair regrowth (SALT score ≤20) at Week 24 following treatment with baricitinib 2 mg, baricitinib 4 mg, ritlecitinib 50 mg (indicated dose), upadacitinib 15 mg and 30 mg (Study 1), and upadacitinib 15 mg and 30 mg (Study 2). On baricitinib 2 mg and 4 mg, 16.6% and 31.8% achieved a SALT score ≤20, corresponding to non-response rates of 83.4% and 68.2%. On ritlecitinib 50 mg, 25% achieved a SALT score ≤20, indicating that 75% did not achieve clinically meaningful scalp hair regrowth at Week 24. In the upadacitinib 15 mg groups, 56.0% (Study 1) and 56.5% (Study 2) achieved a SALT score ≤20, corresponding to non-response rates of 44% and 43.5%. In the upadacitinib 30 mg groups, 84.6% (Study 1) and 72.2% (Study 2) achieved a SALT score ≤20, corresponding to non-response rates of 15.4% and 27.8%. These data highlight the numerically higher Week 24 responder rates observed with upadacitinib, particularly at the 30 mg dose.

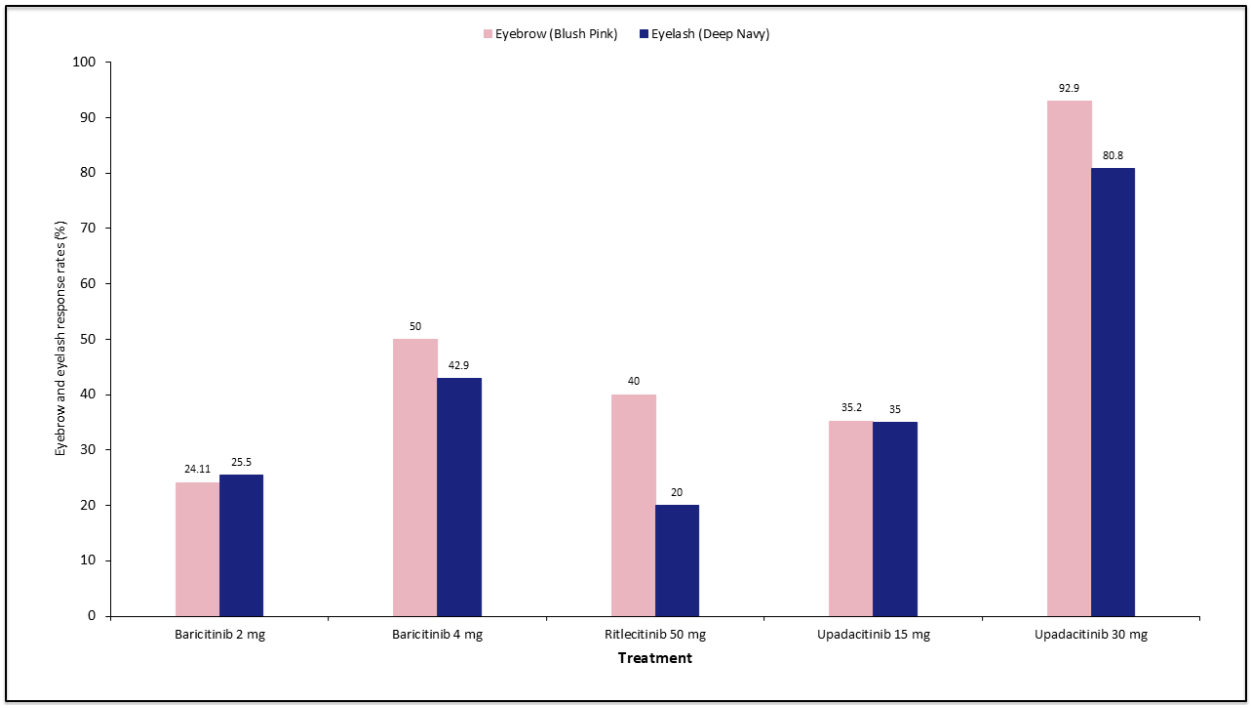

Fig. 5. Eyebrow and eyelash response rates among adolescents receiving JAK inhibitors.

This figure presents a descriptive comparison of eyebrow and eyelash response rates among adolescents with severe AA treated with baricitinib 2 mg, baricitinib 4 mg, ritlecitinib 50 mg, upadacitinib 15 mg, and upadacitinib 30 mg. Eyebrow response rates were 24.11%, 50%, 40%,

35.2%, and 92.9% for baricitinib 2 mg, baricitinib 4 mg, ritlecitinib 50 mg, upadacitinib 15 mg, and upadacitinib 30 mg, respectively. Corresponding eyelash response rates were 25.5%, 42.9%, 20%, 35%, and 80.8%. Upadacitinib data represent the aggregate of two studies. Treatment response was defined as achieving a clinician-reported outcome (ClinRO) score of 0 or 1 (absent or minimal hair loss) together with a ≥2-point improvement from baseline among participants with a baseline ClinRO score ≥2. The ClinRO eyebrow and eyelash scales are 4-point clinician-assessed measures ranging from 0 (no hair loss) to 3 (no notable eyebrow or eyelash hair loss). Upadacitinib 30 mg demonstrated the highest numerical response rates for both outcomes. A formal network meta-analysis was not performed because of heterogeneity in outcome definitions and reporting across studies.

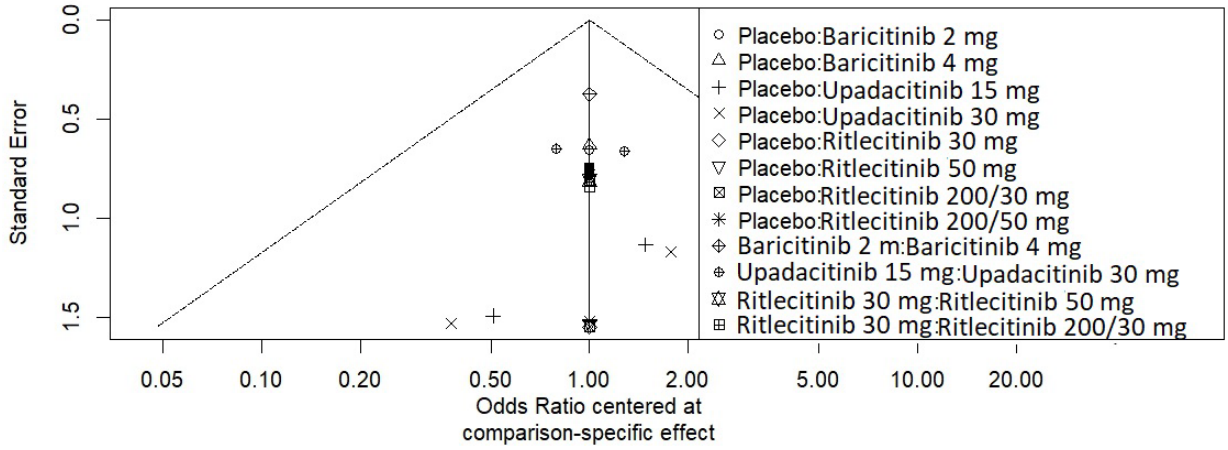

Fig 6. Comparison-adjusted funnel plot for assessment of publication bias and small-study effects. Comparison-adjusted funnel plot generated from the Bayesian network meta-analysis. Visual inspection did not suggest major asymmetry; however, interpretation is limited by the small number of included studies and sparse adolescent subgroup data.

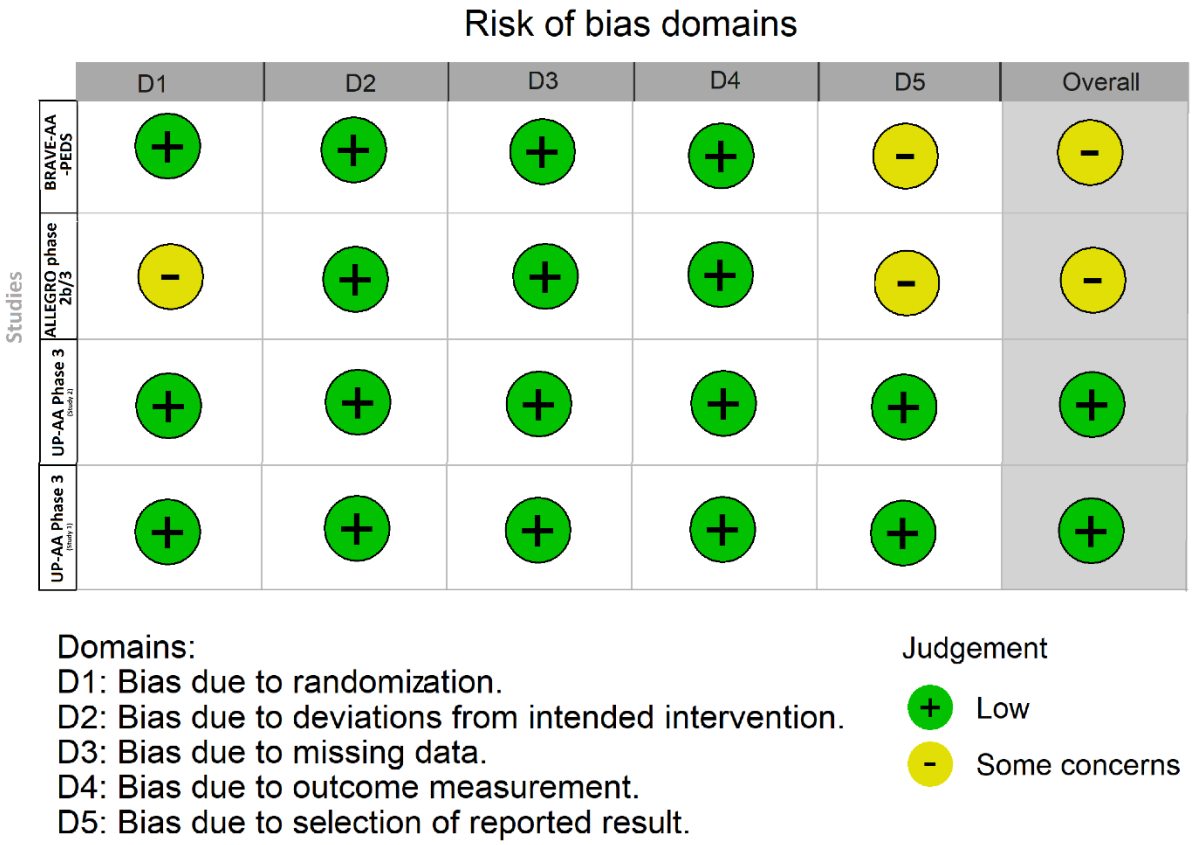

Fig. 7. Risk of bias assessment using the Cochrane Risk of Bias 2 (RoB 2) tool. Risk of bias summary across included studies. Most domains were judged as low risk of bias, including randomization, deviations from intended interventions, missing outcome data, and outcome measurement. Some concerns were identified in adolescent subgroup analyses because of limited reporting and exploratory subgroup design. No study was judged to be at high overall risk of bias.