

Treatment of alopecia areata with JAK inhibitors: a review of the literature

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Abstract

Alopecia areata (AA) is chronic autoimmune non-scarring hair loss, which can progress to alopecia totalis or universalis. Conventional treatments, such as corticosteroids and immunotherapies, often offer limited temporary benefits in moderate to severe cases. Recent advances have identified Janus kinase (JAK) inhibitors as a promising therapeutic option, targeting cytokine pathways involved in AA pathogenesis. This review explores the current evidence surrounding JAK inhibitors in the management of AA. Clinical trials and case series have demonstrated notable efficacy in promoting hair regrowth, even in extensive disease. Baricitinib and deuruxolitinib have shown particularly strong results, with significant scalp hair regrowth and acceptable safety profiles. Common adverse effects include acne, elevated lipid levels, and mild laboratory abnormalities, although long-term data remain limited. This review summarizes the mechanisms, efficacy outcomes, and safety data of various JAK inhibitors used in AA and highlights the need for further research to establish optimal dosing, treatment duration, and long-term safety.

Keywords: alopecia, alopecia areata, dermatology, hair disorder, JAK

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Introduction

Alopecia areata (AA) is a chronic autoimmune dermatologic condition characterized by non-scarring hair loss that typically presents as discrete, well-circumscribed patches on the scalp or beard; a rare variant is diffuse hair loss. In more extensive phenotypes, the disease may progress to alopecia totalis (complete scalp hair loss) or alopecia universalis (total body hair loss). Although AA is not physically debilitating, its impact on quality of life, particularly among pediatric and young adult populations, can be profound, contributing to significant psychological distress and psychiatric comorbidity (1).

The therapeutic landscape for AA has historically been limited to non-specific immunomodulatory strategies. Commonly employed treatments include topical and systemic corticosteroids, intralesional steroid injections, topical calcineurin inhibitors (e.g., tacrolimus and pimecrolimus), contact immunotherapy, phototherapy, and systemic immunosuppressants such as methotrexate or cyclosporin (2). Although combination regimens (e.g., corticosteroids with cyclosporin) may provide enhanced efficacy, outcomes remain variable, and relapse rates are high following cessation of therapy (3). For patients with extensive or treatment-refractory disease, durable regrowth remains elusive, underscoring the need for more targeted therapeutic modalities.

Recent advances in the understanding of AA pathophysiology have implicated the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathway as central drivers of disease. Cytotoxic CD8⁺NKG2D⁺ T cells targeting anagen hair follicles release interferon- γ and interleukin-15, perpetuating follicular inflammation via JAK-dependent signaling (4). Both pan-JAK and selective JAK3 inhibition have demonstrated efficacy in reversing AA in preclinical murine models, establishing proof of concept for JAK inhibition in this context (4, 5).

JAK inhibitors modulate inflammatory pathways by interfering with type I and II cytokine signaling, suppressing T cell and

natural killer cell activity, and attenuating the interferon-mediated response (5). Clinical data on JAK inhibitors in AA are rapidly accumulating, with multiple agents, most notably baricitinib, ritlecitinib, and deuruxolitinib, demonstrating significant efficacy in phase 2 and 3 trials (6). These agents offer a promising alternative for patients with moderate to severe disease, with emerging evidence supporting sustained hair regrowth in a substantial proportion of patients.

However, the therapeutic use of JAK inhibitors necessitates consideration of safety. Frequently reported adverse events include upper respiratory tract infections, acne, herpes simplex reactivation, nasopharyngitis, hyperlipidemia, elevated creatine kinase, and scalp folliculitis (6). Long-term safety data are still evolving, and the risks of immunosuppression and potential thromboembolic or malignancy-related sequelae warrant ongoing vigilance.

This review critically appraises the immunopathogenesis of AA, evaluates the current clinical evidence surrounding JAK inhibitor use, and considers the therapeutic potential and limitations of these agents within clinical dermatology.

Discussion

JAK inhibitors have emerged as the most promising systemic therapy for moderate to severe AA. These small molecules (e.g., baricitinib, ritlecitinib, deuruxolitinib, and tofacitinib) target the JAK-STAT pathway that drives the autoimmune attack on hair follicles. Recent phase 3 trials have demonstrated that oral JAK inhibitors produce significantly greater hair regrowth than placebo in adults (and adolescents) with $\geq 50\%$ scalp hair loss. For example, in the two pivotal BRAVE-AA trials of baricitinib (a JAK1/2 inhibitor) in severe AA (combined $n = 654$; 18–70 years old), 38.8% of patients on the 4 mg dose ($n = 219$) of baricitinib achieved a Severity of Alopecia Tool (SALT) score ≤ 20 ($\leq 20\%$ scalp hair loss) by week 36, versus only 6.2% on placebo ($n = 222$). The lower 2 mg dose ($n = 213$) also beat placebo (22.8% versus 6.2% responders) but was

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less effective than 4 mg (7). Similarly, a multinational trial of ritlecitinib (a selective JAK3/TEC inhibitor) in patients ≥ 12 years old ($n = 718$; 12–75 years old) reported that 50 mg once daily ($n = 239$) led to 36.5% achieving SALT ≤ 20 at week 24, compared to 7.4% of the placebo recipients ($n = 240$), or a difference of 29.1% (8). In the recent THRIVE-AA1 trial of deuruxolitinib (a JAK1/2 inhibitor), in adults ($n = 540$; 18–65 years old) 29.6% of patients on 8 mg twice daily ($n = 180$) and 41.5% on 12 mg twice daily ($n = 180$) reached SALT ≤ 20 at 24 weeks, compared to only 0.8% with placebo patients ($n = 180$) (9). In all these studies, secondary endpoints (e.g., higher SALT thresholds, quality-of-life scores, and patient satisfaction) also favored the active drug. Notably, extension data show that responders tend to maintain benefit over time; in the baricitinib trials, over 90% of responders ($n = 188$) still had SALT ≤ 20 at week 104 (10). In contrast, earlier off-label use of tofacitinib (a JAK1/3 inhibitor) in severe AA was supported only by case series, and pooled analyses suggest that 54% of such patients achieved substantial regrowth (11). However, no large placebo-controlled trials exist for tofacitinib in this setting (see Fig. 1).

These efficacy findings are reinforced by recent meta-analyses. A 2023 systematic review of randomized trials (12 studies; total $n = 2,134$) confirmed that JAK inhibitors significantly outperform placebo on all major outcomes. For instance, JAK-treated patients had a much greater mean reduction in SALT score (~ 34 points from baseline) and far higher odds of achieving SALT 50, SALT 90, or SALT ≤ 20 . The pooled odds ratio for SALT ≤ 20 with JAK therapy was on the order of 7 (roughly 277 per 1,000 treated achieved this outcome versus 66 per 1,000 on placebo) (12). A Bayesian network meta-analysis (15 trials; $n = 3,180$) also suggested that the highest-efficacy regimens are high-dose oral agents: deuruxolitinib 12 mg and ritlecitinib 50 mg ranked highest in reducing SALT scores (based on SUCRA analysis), whereas lower doses and topical JAKs were less effective (13). Deuruxolitinib 12 mg and brepocitinib, an investigational JAK1/tyrosine kinase 2 (TYK2) inhibitor had the best rankings for achieving SALT50/75/90 endpoints followed closely by ritlecitinib 50 mg and deuruxolitinib 8 mg. In practical terms, this evidence synthesis confirms that modern oral JAK inhibitors are currently the most potent drugs for inducing regrowth

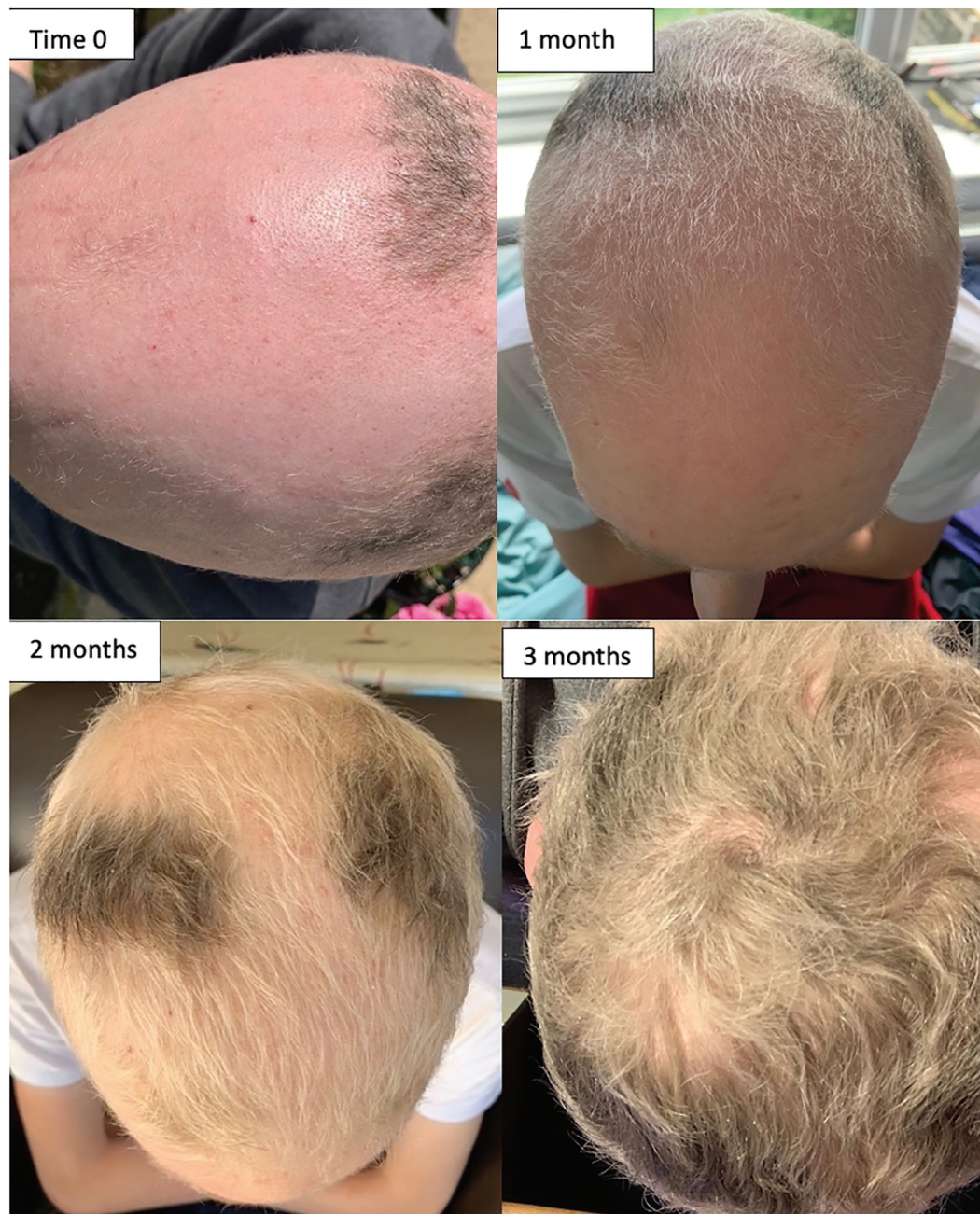


Figure 1 | Lateral view of a patient with alopecia totalis before baricitinib 4 mg once daily was commenced (Time 0) and 1, 2, and 3 months thereafter.

in moderate-to-severe AA (14). However, topical formulations are still in development or early trials, aiming to reduce systemic side effects while maintaining efficacy (15).

Safety data so far are reassuring but warrant caution. Across trials, most treatment-emergent adverse events were mild or moderate (upper respiratory infections, nasopharyngitis, headache, acne, etc.) and similar to known class effects (7, 8). In the BRAVE-AA studies, patients treated with baricitinib had higher rates of acne and transient creatine kinase and lipid elevations than placebo (7). However, no drug-related deaths or thromboembolic events were reported through 52 weeks. A meta-analysis of nine trials ($n = 1,780$) found no significant increase in severe adverse events or treatment discontinuations with JAK inhibitors compared with placebo, with a pooled relative risk of 0.77 for both outcomes. However, the overall rate of treatment-related events, mostly minor infections, was modestly higher with JAK inhibitors (pooled relative risk 1.25; 95% confidence interval 1.00–1.57) (12). Long-term extension studies support a stable safety profile; for baricitinib, 104-week data showed maintained efficacy with no new safety signals noted (10). Nonetheless, known risks of JAK inhibitors, such as serious infections, malignancy, and thrombosis, were seen in rheumatoid arthritis patients. Regulatory labels carry warnings about these rare events, although none were uniquely seen in the alopecia trials to date. Importantly, patient monitoring (labs and infection screening) is recommended in clinical use. The newer agents ritlecitinib and deuruxolitinib were approved partly based on favorable tolerability; ritlecitinib's approval (first in adolescents ≥ 12 years; ages 12 to 75 years in trial) reflects its novel selectivity and the absence of unexpected toxicities in its trial (14). No new safety signals specifically attributable to AA patients have emerged in trials, but clinicians should monitor patients closely (16).

Despite their promise, JAK inhibitors have limitations. A substantial fraction of patients do not achieve full regrowth; for example, only about one-third to one-half reach $SALT \leq 20$ even on the higher doses, and complete ($SALT \leq 10$) responses remain uncommon (7, 9). Crucially, AA is a relapsing disease, and regrowth typically diminishes after drug withdrawal, and so long-term or maintenance therapy may be required. Trial durations have generally been 24 to 52 weeks, and the durability of remission off-treatment is not established. Longer-term safety and optimal treatment duration are still under study (the BRAVE investigators explicitly call for multi-year data) (7). Patient heterogeneity is another challenge; trial participants were mostly adults without significant comorbidities, and so data in children < 12 years, the elderly, or those with severe systemic disease are sparse. Cost and access also affect real-world use of JAK inhibitors. In summary, high-quality evidence shows that oral JAK inhibitors can induce meaningful hair regrowth in moderate-to-severe AA (7, 19). Ongoing research, including head-to-head comparisons, combination strategies, and longer follow-up, will further define the place of JAK therapy in AA (17, 18, 20). Emerging combination approaches, such as JAK inhibitors administered alongside microneedling to enhance follicular penetration or combined with topical sensitizers (e.g., diphencyprone) have shown preliminary efficacy in small studies and may offer synergistic benefits, warranting formal investigation in controlled trials (21) (Table 1).

Table 1 | Comparison of JAK inhibitors used for the treatment of alopecia areata and those currently in the phase of investigation, and their efficacy, safety profiles, treatment outcomes, and side effects.

JAK inhibitor	Target	Key trials	Efficacy	Safety profile	Treatment outcome	Side effects
Baricitinib	JAK1/2	Phase 3 RCT	38.8% of patients receiving 4 mg of baricitinib achieved a SALT score ≤ 20 at week 36 (10)	Good tolerability, see above for specific	FDA approved (2022), EMA approved, high patient satisfaction	URT, nausea, headache, increased cholesterol levels, elevated liver enzymes
Ritlecitinib	JAK3 / TEC family kinase	Phase 2b/3	23% of patients achieved a SALT score ≤ 20 at week 24 and 31% by week 48 (9)	Good tolerability, nasopharyngitis, headache, URT, and nausea	FDA approved (2023), EMA approved, well suited for younger patients	Nasopharyngitis, headache, acne, diarrhea, fatigue, nausea
Brepocitinib	TYK2 / JAK1	Phase 2 trials completed	SALT score improvement in ~30% (preliminary)	Well tolerated in limited studies	Promising due to dual inhibition of TYK2/JAK1	Acne, upper respiratory infections, headache
Deuruxolitinib	JAK1/2	Phase 3 trials completed	~30% to 41% achieved SALT ≤ 20 at 24 weeks (higher dose)	Well tolerated, dose-dependent adverse effects	Promising alternative to baricitinib with similar response rate	Headache, acne, nasopharyngitis, elevated CPK, liver enzymes
ATI-502 (topical)	JAK1/3	Phase 2 trials completed	Modest regrowth in ~28% (based on investigator global assessment)	Excellent topical safety, minimal systemic absorption	Less effective than oral JAK; low risk makes it suitable for limited patches	Mild irritation at application site
ATI-1777 (topical)	JAK1/3	Phase 2a trials initiated	Early data not yet public	Designed for minimal systemic exposure	Still investigational; could suit patients with localized AA	Local skin effects only
SHR0302	Selective JAK1	Phase 2 trial completed	Moderate efficacy; ~25% to 30% regrowth in responders	Mild; JAK1 selectivity lowers systemic risk	Considered safe and moderately effective in Asian populations	Headache, mild GI symptoms, increased cholesterol levels, thrombocytopenia, raised liver enzymes
Delgocitinib	JAK1/2/3 and TYK2	Topically tested for dermatological diseases and AA early phase	Limited data in AA; effective in eczema	Safe topical use; no serious systemic events	Possibly helpful in scalp application; awaiting AA-specific results	Application site irritation

AA = alopecia areata, CPK = creatine phosphokinase, EMA = European Medical Agency, FDA = food and drug administration, GI = gastrointestinal, JAK = janus kinase, JAK = janus kinase, RCT = randomly controlled trial, SALT = Severity of Alopecia Tool, TEC = tyrosine kinase, URT = upper respiratory tract infection, URTI = urinary tract infection, TYK2 = tyrosine kinase 2.

Conclusions

JAK inhibitors have revolutionized the treatment of moderate-to-severe alopecia areata by consistently delivering superior hair regrowth compared to placebo, with approximately one-third to two-fifths of patients achieving near-complete scalp coverage by 6 months on agents such as baricitinib, ritlecitinib, or deuruxolitinib. Although short-term safety has been acceptable, most adverse events are mild-to-moderate infections, acneiform eruptions, or transient laboratory abnormalities. Long-term risks such as serious infection, thrombosis, and malignancy remain theoretical

and require ongoing surveillance. Key challenges include suboptimal response in up to half of treated patients, near-universal relapse upon discontinuation, and limited data beyond 1 year or in pediatric, elderly, and non-white populations. Clinicians should reserve JAK inhibitors for patients with extensive or refractory disease, perform rigorous baseline screening and periodic monitoring, and counsel patients on the necessity of sustained therapy. Future research must focus on long-term safety, optimal treatment duration, relapse prevention strategies, cost-effectiveness analyses, and development of standardized outcome measures to guide evidence-based practice.

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