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Predictors of Treatment Failure with JAK Inhibitors in Alopecia Areata: T-Cell Dynamics and Clinical Determinants of Inadequate Response

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ABSTRACT: The Janus kinase (JAK) inhibitors have been the first targeted treatments to be approved for Alopecia areata (AA), an autoimmune disease that affects T cells and results in non-scarring hair loss. Although baricitinib (2022), ritlecitinib (2023), and deuruxolitinib (2024) have been recently approved, there is still an important percentage of patients not achieving enough or any response (30-55% depending on the agent and endpoint). This review analyses in detail immunological and clinical factors that are involved in treatment failure in AA with JAK inhibitors, with a special emphasis on the dynamics of T cells, Treg dysfunction, Th2 skewing, AA phenotype and baseline disease burden. Mechanistic studies, real-world cohorts and phase 3 studies all support a

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multifactorial model of non-response, in which disease duration, alopecia totalis/alopecia universalis subtype, baseline atopy, high baseline Severity of Alopecia Tool (SALT) scores >75, and low Treg compartment size are all independent risk factors for failure. Single-cell transcriptomic evidence of emerging data indicates hyperactivation of $CD8^+$ effector memory T cells and JAK-STAT pathway redundancy as cellular substrates of resistance. The need for clinical translation to a biomarker-stratification framework is pressing. This review summarises the existing data and suggests further research in personalised JAK inhibitor treatment of AA.

Keywords: *Alopecia areata; JAK inhibitors; treatment failure; T-cell dynamics; regulatory T cells; baricitinib; ritlecitinib; biomarkers; SALT score; immune resistance.*

1. Introduction

Alopécie areata (AA) is one of the most common autoimmune conditions globally, impacting about 2% of the world's population in all age groups and ethnicities, in the form of non-scarring hair loss that is circular, diffuse or total, in the scalp and body.

The immunopathogenesis of AA is now recognized as being one in which the breakdown of hair follicle (HF) immune privilege allows the infiltration of peribulbar areas by autoreactive $CD8^+$ $NKG2D^+$ cytotoxic T lymphocytes, which secrete interferon-γ (IFN-γ) and signal through downstream Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathways to halt follicular cycling and trigger catagen. [1]

JAK–STAT signalling has emerged as a pivotal pathway that drives the pathogenesis of AA and has revolutionised the way the disease is treated. [2] In June of 2022, Baricitinib (JAK1/JAK2 inhibitor) was FDA-approved, followed by the FDA approval of ritlecitinib (JAK3/TEC family kinase inhibitor) in June 2023 and deuruxolitinib (JAK1/JAK2 inhibitor) in July 2024, marking the first approved therapies for AA solely based on the disease. [3,4,5].

The primary endpoint of SALT score ≤20 at week 24-36, however, shows a striking treatment gap at about 40-55% of participants not meeting that end point in pivotal phase 3 trials after using the most effective doses. This non-responder burden is even more evident

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in patients with long standing alopecia totalis (AT) or alopecia universalis (AU), ophiasis-pattern hair loss and significant comorbid atopic disease.

The lack of response of some patients is not only an interesting subject but a very relevant clinical question. High cost, high safety-monitoring burden of targeted therapies for which patients are unlikely to benefit is unnecessary harm, unnecessary cost and unnecessary delay to effective alternative strategies. This review is based on a combination of mechanistic and clinical findings and identifies the major findings for what are the main drivers of failure of JAK inhibitor therapy in AA, specifically focusing on T-cell biology.

2. Mechanisms of JAK Inhibitor Action in Alopecia Areata

2.1 JAK–STAT Signalling in AA Pathogenesis

The molecular mechanism linking AA with activation of the immune system is mediated by the JAK–STAT cascade. Infiltrating $CD8^+$ T cells produce IFN-γ, which binds to and signals through JAK1 and JAK2 to upregulate MHC class I expression on HF keratinocytes which continues antigen presentation. At the same time, common gamma-chain (γc) cytokines, including IL-2, IL-7 and IL-15, deliver essential homeostatic and activating signals to subsets of T cells via JAK1/JAK3 and TYK2. [6,7,8]

In particular, IL-15 is increased in lesional biopsies of AA scalp, activates CD8+NKG2D+ cytotoxic T lymphocytes and promotes their peribulbar persistence. The γc cytokine axis is the most important pathway, as has been confirmed by genome-wide association studies (GWAS) of the region of the IL2RA, IL2RB and HAVCR1 genes, all of which have functional links to this pathway. [9]

This cascade is interrupted by JAK inhibitors, which bind to the ATP-binding pocket of the kinase domain of the JAK enzymes, thus preventing further phosphorylation of STATs. However, this pathway is not a complete switch-off as compensatory kinases, upstream cytokine redundancy and non-JAK-dependent co-stimulatory pathways may keep the effector T-cell alive. [4,7]

2.2 Approved Agents and Respective Selectivity Profiles

Baricitinib is a once-daily oral JAK1/JAK2 preferential inhibitor which has shown proven efficacy in the pivotal phase 3 trials BRAVE-AA1 and BRAVE-AA2. The 4 mg dose

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resulted in SALT ≤20 in about 35–38% of patients at week 36. There is evidence of continued cumulative benefit in long-term data at 104 weeks, although about 25-30% of patients who are treated continuously are not responders. [10,11]

Ritlecitinib is a dual JAK3/TEC family inhibitor (ITK, BTK, BMX, TXK, TEC), which targets a complementary arm of immune signalling. Theoretically, ritlecitinib blocks T-cell activation upstream of cytokine release by blocking the activation of T-cell co-stimulatory pathways through ITK-mediated T-cell receptor (TCR). By the 24th month, 12.6% of the patients were relapsers and an additional 12.6% were strict non-responders, as identified by the analysis of individual SALT score trajectories from the ALLEGRO program. [12,13]

Deuruxolitinib (CTP-543) is a deuterium-derivatised JAK1/JAK2 inhibitor with prolonged half-life, which was shown to be superior to placebo in THRIVE-AA1 and THRIVE-AA2 and was approved by the FDA in July 2024. Even with this newcomer, the degree to which all approved agents respond differently makes it clear that there is a critical need to learn how to identify patient pretreatment features that predict outcome.

3. Immunological Mechanisms Underlying Treatment Failure

3.1 $CD8^+$ T-Cell Effector Memory Persistence

$CD8^+NKG2D^+$ effector memory T cells (T_em) are the major cells that mediate AA. These cells express high levels of cytotoxic granules (perforin, granzyme B) and produce IFN-γ and are activated constitutively in the presence of HF stress ligands (MICA, MICB, ULBP3) by the activation of their TCR-independent receptor, NKG2D. One of the important properties of these cells, which are associated with treatment failure, is their tissue-resident memory (T_RM) phenotype. [3]

In both mouse (C3H/HeJ) and human AA skin, single-cell RNA-sequencing (scRNAseq) has demonstrated that CD8+ T cells exist along a continuum of effector maturation, with the most terminally differentiated cells being found at the bottom of the HF, and the least being present on the surface. These terminally differentiated "residents" can remain in a latent state and be reactivated when treatment is stopped, as JAK inhibitors block the γc cytokine signalling pathway, rather than destroy the T-cell clone. [14]

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Dai et al. described a paradoxical effect after JAK1/3 inhibition, which resulted in a state of T-cell exhaustion characterised by increased PD-1 expression and decreased IFN-γ production and impaired function. This is an explanation of therapeutic efficacy in responders, but it is possible that therapeutic effect is absent in patients with a high pre-existing T_em burden if they are not completely exhausted [15]. Figure 1 presents the schematic of CD8⁺ T-cell effector memory persistence and JAK–STAT pathway redundancy in AA treatment failure.

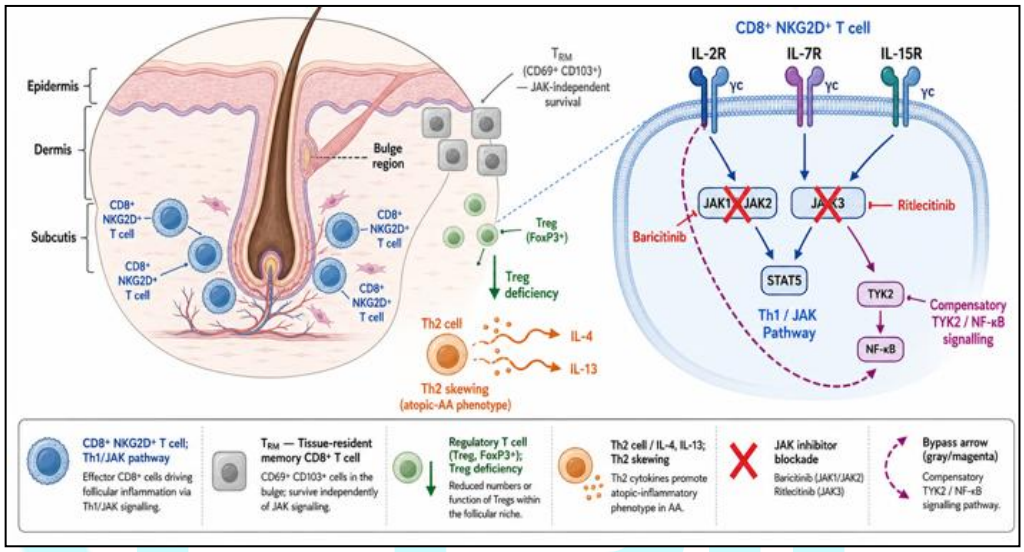

Figure 1. *Schematic of CD8⁺ T-cell effector memory persistence and JAK–STAT pathway redundancy in AA treatment failure.*

Caption: Arrows indicate signalling axes; cross-marks denote points of JAK inhibitor blockade. Residual signalling through compensatory pathways (TYK2, NF-κB) and T_RM retention contribute to non-response.

Sources: Adapted from references [3,14,15].

3.2 Regulatory T-Cell Deficiency and Functional Impairment

Quantitative and qualitative loss of CD4⁺FoxP3⁺ regulatory T cells (Tregs) is an underappreciated, but mechanistically important, cause of JAK inhibitor non-response. The density of Tregs is significantly lower in scalp with AA lesions than in non-AA lesional and normal control scalp. In patients with AA, circulating Tregs are defective in their suppressive actions, as evidenced by a decrease in both CTLA-4 and IL-10 expression and in contact-dependent inhibition of effector T cells. [16]

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Importantly, the inflammatory Th2 milieu of some AA patients, especially those with atopic dermatitis, further worsens the Treg deficit in AA. The suppression of FoxP3 expression in Tregs by IL-4 and IL-13 can lead to the polarisation of Tregs toward pathogenic Th2 and Th17 effector cells. In addition to its inhibitory effect on Treg production, IL-6 in active AA also inhibits TGF-β-mediated Treg production and induces differentiation into Th17. [16]

An important implication for the effect of JAK inhibitors is that they do not directly increase the number or function of Tregs. If a patient with severely depleted and dysfunctional Tregs enters treatment, the restoration of follicular cycling requires active Treg-mediated immunological tolerance at the level of the hair follicle stem cell niche, and may not be achieved even if the suppression of the JAK-STAT pathway is effective.

3.3 Th2 Immune Skewing and Atopic Comorbidity

The current view of AA as an exclusively Th1-mediated autoimmune disorder has been challenged by the mounting evidence for a complex and context-dependent inflammatory environment. The serum levels of Th2 cytokines (IL-4, IL-13, IL-31) are markedly up-regulated in AA lesions in patients with concurrent atopic dermatitis, elevated serum IgE and peripheral eosinophilia. This Th2 shift results in a qualitatively different inflammatory context, which is not fully covered by JAK1/JAK2 inhibition. [6,17,18]

Real-life observational studies suggest a lack of efficacy of baricitinib 4 mg in patients with diagnosed atopic dermatitis in this phase, whereas partial improvement was observed with dupilumab (IL-4Rα blockade), indicating that parallel signalling pathways sensitive to dupilumab are involved in the pathogenesis of hair loss in the atopic-AA phenotype. The underlying mechanism could be the up-regulation of IL-4-dependent thymic stromal lymphopoietin (TSLP) in the perifollicular microenvironment, which triggers mast cells and dendritic cells by an IL-4-independent mechanism. [6]

3.4 JAK-STAT Pathway Redundancy and Compensatory Signalling

One of the basic pharmacologic problems with selective JAK inhibitors is molecular pathway redundancy, by which upstream cytokines can sometimes send signals through other JAK isoforms (TYK2 and JAK3) that are not inhibited by the selective JAK being

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used. Further, non-JAK signalling of T-cell survival and proliferation via the OX40/OX40 ligand (CD134/CD252) family member can be sustained independently from γc cytokines.

Transcriptomic analysis of non-responders to baricitinib identified NF-κB target genes as being over-expressed, indicating that other inflammatory pathways may be engaged despite effective JAK inhibition. This is in line with clinical results that some patients who do not respond to one JAK inhibitor do respond to another JAK inhibitor with a different selectivity profile, but the number of patients who do achieve full responses after switching to another JAK inhibitor is not high. Table 1 shows the mechanisms underlying poor responses to JAK inhibitors in Alopecia Areata.

Table 1. Immunological Mechanisms Associated with Inadequate Response to JAK Inhibitors in Alopecia Areata.

Mechanism	Key Cellular Players	Evidence Source	Clinical Implication
$CD8^+$ T_em tissue-resident persistence	$CD8^+NKG2D^+$ TRM cells; granzyme B^+ $perforin^+$	scRNAseq (Christiano lab, 2023) [14]	Residual follicular T cells re-activate post-treatment
Incomplete T-cell exhaustion	Effector memory $CD8^+$ PD-1low	Dai et al. Front Immunol 2022 [15]	Insufficient induction of exhaustion state
Treg quantitative deficiency	$CD4^+FoxP3^+$ Tregs (circulating & lesional)	Wan et al. Front Immunol 2023 [16]	Impaired HF immune privilege restoration
Treg functional impairment	CTLA-$4^=$ $FoxP3^+$ Tregs; reduced IL-10	King BA, Craiglow BG 2023 [3]	Active suppression of effector T cells fails
Th2 immune skewing	Th2 cells; mast cells; eosinophils; ILC2s	Connell SJ, Jabbari A 2022 [4]	IL-4/IL-13 not suppressed by JAK1/2 inhibitors
JAK–STAT pathway redundancy	TYK2; JAK3; NF-κB signalling	Connell SJ, Jabbari A 2022 [4]	Residual pathway activation maintains disease
OX40/OX40L co-stimulation	Th2 cells; follicular dendritic cells	Expert Rev Clin Immunol 2025 [19]	JAK-independent T-cell survival

Abbreviations: *T_em, effector memory T cells; TRM, tissue-resident memory T cells; Treg, regulatory T cells; HF, hair follicle; ILC2, innate lymphoid cell type 2; scRNAseq, single-cell RNA sequencing.*

4. Clinical Predictors of Treatment Failure

4.1 Baseline Disease Severity and SALT Score

Baseline SALT score is the most stable clinical predictor of response to JAK inhibitors. Multivariate logistic regression analysis showed that baseline SALT score ≤60% was independently associated with early response ($p < 0.05$) and was optimised by receiver

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operating characteristic (ROC) analysis with an optimum threshold of SALT ≤60% to differentiate early responders from non-responders in this retrospective cohort of 44 patients treated with baricitinib. [20]

The results are consistent with the subgroup analyses from the phase 3 BRAVE-AA1 and BRAVE-AA2 trials, which showed that participants with a SALT = 100 (AT or AU) had lower rates of response at baseline than those with a SALT 50–75. The response rate is about 15–20 percentage points lower in patients with more than 90% baseline scalp hair loss compared to patients with 50–75% hair loss at the same time points. [11,21]

4.2 Disease Duration and the Window of Opportunity Concept

But disease duration has proved to be one particularly strong negative predictor, confirmed by several independent real-world datasets. Hayashi et al. performed a retrospective analysis that showed that disease duration <2 years was an independent predictor of response (SALT ≤20) at week 36 in baricitinib-treated patients ($p<0.05$). However, in another European cohort, disease duration of >7 years was a significant determinant of poor early response. [20,22]

The biological basis of this ‘therapeutic window of opportunity' is related to the progressive establishment of durable tissue-resident T-cell memory. Pathogenic T cells in early-stage AA are mainly circulating and recently recruited, requiring a strong reliance on γc cytokine survival signals that are vulnerable to JAK inhibition. In chronic disease, T_RM has become completely residential zed in the follicular niche, upregulating CD69 and CD103 and is largely independent of systemic cytokine support.

4.3 AA Subtype: Alopecia Totalis, Universalis, and Ophiasis

The more severe subtypes of AA (AT, AU, ophiasis) have significantly worse rates of response to JAK inhibitors than multifocal patchy AA. The baseline population of AT/AU patients was higher in the non-responder (29.3%) and partial-responder (12.6%) groups for the 191 patients who were receiving ritlecitinib treatment in the ALLEGRO rollover analysis. [13]

AA with ophiasis pattern is extremely difficult to treat. In ophiasis, the scalp follicles that are affected have a topographic separation from the hair follicle stem cell niche, may have different immunological microenvironments and are believed to have differential vascular

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perfusion that might lead to differences in effective JAK inhibitor drug reaching the target site.

4.4 Co morbid Atopic Disease

Atopic dermatitis and/or elevated IgE are known JAK inhibitor response modifiers in AA. Retrospective analyses and clinical experience show that in atopic-AA, treatment with baricitinib may result in hairline and eyebrow improvements without achieving full scalp coverage, which is seen in 'partial-responder' patients with atopic-AA with a JAK-susceptible phenotype and a persistent perifollicular inflammation driven by Th2 activity. [6,18]

The clinical implication has resulted in trials of exploratory combination therapies such as a combination of dupilumab (IL-4Rα) and baricitinib, which has been reported in small case series to provide a better hair regrowth response in atopic-AA than either drug alone. This therapeutic combination is representative of the concept of immunophenotype-matched treatment selection. [6,18]

4.5 Nail Involvement

Nail involvement (trachyonychia, pitting, onychorrhexis) in AA is a marker for severity and longitudinal persistence of the disease. In clinical trials, baricitinib and ritlecitinib improved nail manifestations (ClinRO-Nail assessments), although the presence of nail AA at baseline was associated with a more aggressive disease phenotype, higher baseline SALT scores, longer disease duration and higher likelihood of AT/AU classification, which are each independently associated with treatment failure. [22]

4.6 Erythrocyte Sedimentation Rate (ESR) as a Response Biomarker

A laboratory biomarker of early treatment response that is readily accessible has been identified: baseline ESR. Using a multivariate analysis of retrospective data, ESR ≥9 mm/h at treatment onset was found to be an independent predictor of early response to baricitinib (AUC 0.71 by ROC analysis, $p < 0.05$). An elevated ESR could suggest an acute-phase inflammatory state, in which the onset of the disease is recent and there is mainly the presence of T-cell activity, which is mainly circulating and cytokine-oriented, and is more responsive to JAK inhibition than the quiescent state of longstanding disease, in which

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T_RM predominates. [20]. Table 2 presents the clinical predictors of JAK inhibitor non-response in Alopecia Areata: Summary of evidence. Figure 2 shows the Forest plot of clinical predictors of JAK inhibitor non-response in alopecia areata.

Table 2. Clinical Predictors of JAK Inhibitor Non-Response in Alopecia Areata: Summary of Evidence

Predictor	Direction of Association	Threshold / Observation	Key Reference (DOI)
Baseline SALT score	Higher score → worse response	SALT >60% associated with non-response; ROC threshold ≤60% for early response	https://doi.org/10.3390/[PMCID: 12565575]
Disease duration	Longer → worse response	Duration ≤7 yr predicts response; duration ≥2 yr independently predicts non-response	https://doi.org/10.1111/1346-8138.70241
AA subtype (AT/AU/Ophiasis)	Severe subtype → worse response	Lower SALT ≤20 rates in AT/AU vs. patchy AA at 24–48 wks	https://doi.org/10.1111/jdv.20547
Comorbid atopic dermatitis	Present → partial or no response	Th2 skewing; JAK1/2 inhibitors do not suppress IL-4/13	https://doi.org/10.1016/j.autrev.2022.103061
Nail involvement at baseline	Present → indicator of severity	Associated with higher SALT, AT/AU subtype	https://doi.org/10.1111/1346-8138.70241
Baseline ESR	Low ESR (≤8 mm/h) → poor response	ESR ≥9 mm/h predicts early baricitinib response (AUC 0.71)	https://doi.org/10.3390/[PMCID: 12565575]
Prior JAK inhibitor failure	History of failure → lower response to next agent	42% SALT ≤20 with baricitinib; 41.7% with ritlecitinib switch	https://doi.org/10.1111/1346-8138.70241

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Abbreviations: *SALT, Severity of Alopecia Tool; AT, alopecia totalis; AU, alopecia universalis; ESR, erythrocyte sedimentation rate; ROC, receiver operating characteristic; AUC, area under the curve.*

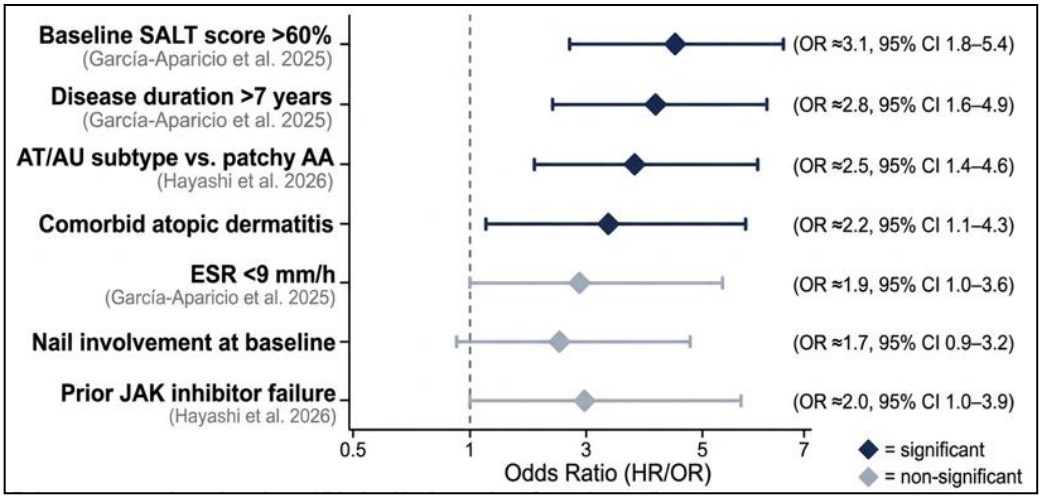

Figure 2. Forest plot of clinical predictors of JAK inhibitor non-response in alopecia areata.

Caption: *Odds ratios with 95% confidence intervals are presented for key multivariate predictors identified across published cohort studies and randomised trial subgroup analyses (2022–2025).*

Sources: Adapted from references [20, 22].

5. Evidence From Phase 3 Clinical Trials and Real-World Studies

5.1 BRAVE-AA Program (Baricitinib)

The phase 3 randomised controlled trials, BRAVE-AA1 (n=654) and BRAVE-AA2 (n=546), demonstrated that baricitinib 4 mg was the most effective dose of the therapeutic agent that has been approved for severe AA (SALT ≥50). Within the main period of the trial (Week 36), 38.8% of patients on baricitinib 4 mg achieved SALT ≤20 compared with 6.6% of patients on placebo and 35.9% of patients on baricitinib 2 mg achieved SALT ≤20 compared with 6.9% of patients on placebo. Cumulative responder proportions increased with 104-week continuous follow-up, and after 2 years of treatment, about 25-30% of the continuously treated patients had never reached SALT ≤20. [11,21]. Post- hoc stratification of BRAVE-AA data by baseline disease duration (dichotomised at 3.5 years) and AT/AU versus non-AT/AU subtype demonstrated that both these factors were independently associated with non-response, highlighting their potential as clinical decision-making variables for initiating baricitinib treatment. [21]

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5.2 ALLEGRO Program (Ritlecitinib)

A post-hoc analysis of ALLEGRO-2b/3 and ALLEGRO-LT studies classified patients into trajectory-based response groups following 24 months. Of 191 patients who were treated with ritlecitinib 50 mg, 45.5% were classified as responders (SALT ≤20), 12.6% as partial responders, 12.6% as relapsers and 29.3% as non-responders. Longer duration of disease and AT/AU subtype were the most independent risk factors for non-response in multivariable logistic regression. [13, 23]

5.3 Real-World Evidence: Switching and subsequent evidence

Hayashi et al. presented results of 65 real-world patients (50 baricitinib and 15 ritlecitinib) including 60% ritlecitinib patients who were previously treated with baricitinib without an adequate response. At Week 36, 42% of baricitinib-treated patients achieved SALT ≤20, with <2 years disease history and eyebrow loss at baseline (ClinRO score 3) as independent positive predictors. The percentage of patients achieving Ritlecitinib achievers (41.7%) reinforces the notion that, in certain patients, agent switching offers a small but clinically significant extra opportunity for response. [22, 24]

Kazmi et al. compared the efficacy and safety of tofacitinib and baricitinib in AA patients who failed the first-line JAK inhibitors. Around a third of patients responded meaningfully to switching, but rates were still significantly lower than in populations of patients who have never previously been treated with a JAK inhibitor, indicating that previous JAK inhibitor failure is another independent predictor of subsequent non-response. [25]

6. Emerging Biomarker Strategies for Response Prediction

6.1 Transcriptomic and scRNAseq Approaches

Recent single-cell RNA-sequencing of lesional scalp biopsies before and during treatment has started to define the immune landscape of treatment failure. A 2023 study from Christiano's group in PNAS showed that the heterogeneity of the $CD8^+$ T cell population, based on an ‘effectorness gradient', predicted the functional trajectory and the susceptibility to JAK inhibition. Responses were significantly lower in patients who had a high ratio of terminally differentiated effector $CD8^+$ T cells (Teff-high phenotype) vs a higher proportion of early-differentiated cells. [14]

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Although scRNA-seq is a laboratory technique and assayable classifiers derived from these data are still under development, they could be used as clinical assays (RT-PCR or NanoString) for pre-treatment immunophenotyping to inform selection of JAK inhibitors.

6.2 Serum Cytokine Profiling

The concentration of chemokines induced in AA serum by IFN-γ (CXCL9, CXCL10/IP-10, and CXCL11) is increased in AA patients compared to controls, and is associated with disease severity. Early data show that extremely high baseline CXCL10 is actually associated with response; this may represent more active JAK-STAT-dependent disease, whereas very low baseline IFN-γ signature scores (which may represent more Th2 or Th17 disease) are associated with non-response. Well-characterised cohorts must be used to urgently validate these cytokine-based response biomarkers in the future.

6.3 Trichoscopy-Based Predictors

Trichoscopic non-invasive features provide easy-to-acquire pre-treatment prognostic factors. The Presence of black dots, exclamation mark hairs and yellow dots was validated as predictors of treatment outcome in patchy AA by the Alopecia Areata Predictive Score. Interestingly, the density of the trichoscopy feature of dystrophic anagen hair, a surrogate for active follicular immune attack, may be useful as a marker for current activity of disease that can be controlled by JAK inhibitors. [26,27,28] Table 3 gives the Response Rates and Identified Non-Response Predictors by Approved JAK Inhibitor in AA Phase 3 and Real-World Studies.Figure 3 presents the proposed clinical algorithm for pre-treatment stratification of alopecia areata patients initiating JAK inhibitor therapy.

Table 3. Comparison of Response Rates and Identified Non-Response Predictors Across Approved JAK Inhibitors in AA Phase 3 and Real-World Studies.

Agent (Target)	Trial / Study	Primary Endpoint Response (%)	Key Non-Response Predictors	Reference
Baricitinib 4 mg (JAK1/2)	BRAVE-AA1 (n=654)	38.8% SALT ≤20 at Wk 36	AT/AU subtype; duration >3.5 yr; high SALT	King et al. NEJM 2022 [21]
Baricitinib 4 mg (JAK1/2)	BRAVE-AA1&2 104-wk	~60% cumulative responders	~25–30% persistent non-responders at 104 wks	Senna et al. JEADV 2024 [11]
Baricitinib 4 mg (JAK1/2)	Retrospective cohort (n=44)	34.1% early responders	SALT >60%, duration >7 yr, ESR <9 mm/h	García-Aparicio et al. 2025 [20]

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Agent (Target)	Trial / Study	Primary Endpoint Response (%)	Key Non-Response Predictors	Reference
Baricitinib 4 mg (JAK1/2)	Real-world (Hayashi, n=50)	42% SALT ≤20 at Wk 36	Duration ≥2 yr; absence of eyebrow loss	Hayashi et al. J Dermatol 2026 [22]
Ritlecitinib 50 mg (JAK3/TEC)	ALLEGRO-2b/3 rollover (n=191)	45.5% responders at Mo 24	AT/AU; long disease duration; non-response pattern	Piliang et al. BJD 2025 [13]
Ritlecitinib 50 mg (JAK3/TEC)	ALLEGRO SALT trajectories	29.3% strict non-responders	Older age at onset; higher SALT at baseline	Tziotzios et al. ALLEGRO-LT [29]
Baricitinib → Ritlecitinib switch	Real-world (Hayashi, n=15)	41.7% response after switch	Prior JAK inhibitor failure → reduced response rates	Hayashi et al. J Dermatol 2026 [22]

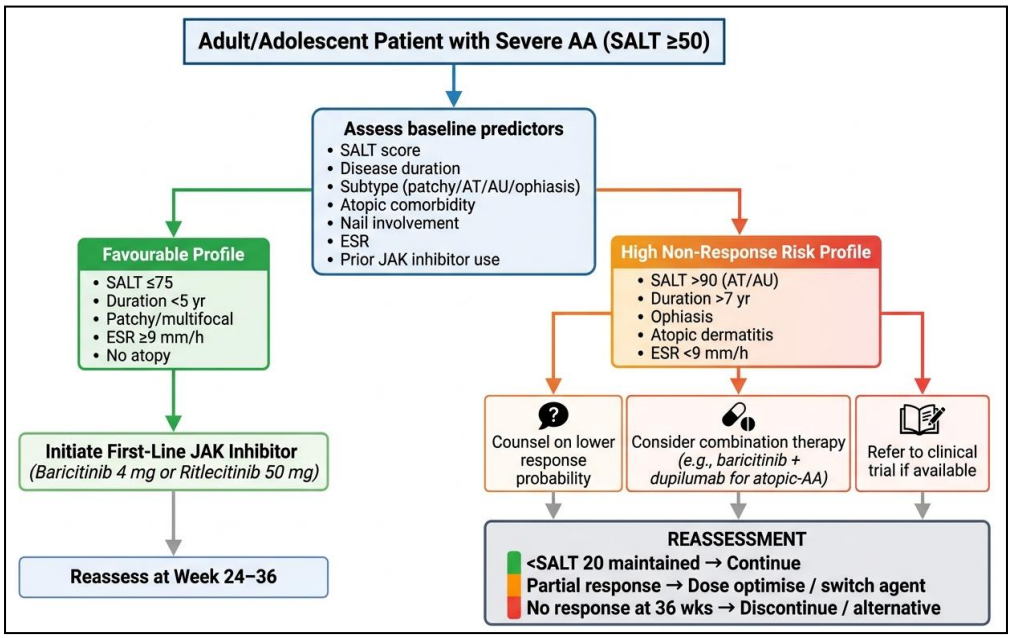

Figure 3. Proposed clinical algorithm for pre-treatment stratification of alopecia areata patients initiating JAK inhibitor therapy.

Caption: *Patients are stratified by baseline SALT score, disease duration, AA subtype, and atopic comorbidity. Green pathways represent favourable response prediction; red pathways represent high non-response risk warranting combination strategies or clinical trial enrolment.*

7. Management strategies after treatment failure

7.1 Dose Escalation and Extended Treatment Duration

Managing patients with longer treatment durations and higher doses. Treatment duration and dose escalation. Before declaring treatment failure, sufficient dose optimisation and

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treatment length should be provided. In partial responders, the dose–response relationship in AA is steeper than in RA; increasing baricitinib dose from 2 mg to 4 mg daily is warranted, and incremental benefit has been demonstrated. But, data from the 104-week BRAVE-AA trial suggest response accrual continues in a subpopulation of patients, particularly in patients who are late responders, as they have shown benefit from extended treatment beyond 24–36 weeks.

7.2 Switching Between JAK Inhibitors

The rational approach is to switch between JAK inhibitors with different selectivity profiles, on the basis of the pharmacologic rationale for different target coverage. Successful baricitinib treatment following tofacitinib therapy and vice versa have been reported by Kazmi et al. and Katamanin et al., respectively. The switch from baricitinib to ritlecitinib is especially relevant because ritlecitinib has been shown to possess structural, cellular and molecular characteristics that are different from those of JAK1/2-selective agents, with the former also demonstrating additional TEC kinase inhibition, which could impact TCR co-stimulatory signalling not targeted by JAK1/2-selective agents. [25,30,31]

7.3 Combination and Sequential Strategies

Some non-responder phenotypes have been shown to benefit from combination treatments, and evidence is emerging to support this. Combination therapy with dupilumab and baricitinib might be useful for the atopic-AA phenotype. Patients with extremely low Treg numbers in their blood and lymph nodes are theoretically good candidates for Treg augmentation treatment, which recently includes low-dose IL-2 therapy that has been found to selectively expand Tregs in the periphery and is successful in other autoimmune diseases. These combination strategies are still experimental and should be studied in larger, prospective, standardised trials. [32]

8. Future Research Directions

To understand and overcome JAK inhibitor treatment failure in AA, there is a need for convergent developments in immunology, translational pharmacology and clinical trial design. Multiple priority areas are identified.

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Standardised pre-treatment biopsy-based immunophenotyping, i.e., assessment of Treg:$CD8^+$ T-cell ratio and of the density of T_RM as well as of the expression of cytokines, such as Th1/Th2, should be integrated as exploratory endpoints in current JAK inhibitor trials. This is possible at academic dermatology centres with the availability of multiplex immunofluorescence panels and digital pathology pipelines.

Secondly, there is an urgent clinical need for the development of non-invasive biomarker surrogates. Circulating CXCL10, complete blood count-derived proxies for Tregs and serum IgE could provide easily obtainable, scalable markers for clinical application. Future validation with hard endpoints (SALT ≤20 at Week 36) in multicentre cohorts is needed.

Thirdly, the investigation of Treg augmentation regimens as add-on treatments to JAK inhibitors, such as low-dose IL-2, infusion of regulatory T cells, or abatacept (CTLA4-Ig), should be pursued in suitably designed proof-of-concept trials, especially in patients with documented Treg deficiency and/or those who have not achieved good clinical outcomes with JAK inhibitors alone.

The ultimate goal is finally the phenotypic and molecular classification of AA non-responders, similar to the ‘precision oncology' biomarker stratification. At least three or four clinically distinguishable AA immunophenotypes (Th1-enriched/high IFN-γ, Th2-enriched/atopic, Treg deficient/tolerogenic failure, T_RM-enriched/longstanding) could be identified, allowing for rational design of agents and combinations.

9. Conclusion

JAK inhibitors have been a breakthrough therapy in the treatment of alopecia areata, but the percentage of non-responders (30–55%), depending on the agent, dose, and endpoint, has clearly demonstrated that targeted immune suppression is not enough in a heterogeneous patient population. Multiple immunological factors and clinical characteristics converge to render drugs ineffective in known patient sub-groups: (1) persistence of tissue-resident memory CD8+ T cells, (2) depletion and dysfunction of Tregs, (3) Th2 immune skewing in the atopic-AA phenotype and (4) redundancy of the JAK-STAT pathway.

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Clinical predictors of non-response, such as high baseline SALT score (>60%), disease duration > 5–7 years, AT/AU or ophiasis subtype, comorbid atopic dermatitis, nail involvement, low baseline ESR and prior JAK inhibitor failure, have been demonstrated in phase 3 trials as well as in real-world cohorts and should be taken into consideration when counselling and shared decision-making for initial treatment.

The precision medicine framework for AA, based on pre-treatment immunophenotyping and available clinical biomarkers, is feasible and the most promising approach to bridging the treatment efficacy gap. It will take continued collaborative research between immunologists, dermatologists, and clinical trialists to reach this goal, and to enable AA patients to be completely free from a disease that is so disabling and psychologically devastating. [32]

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