Recalcitrant Alopecia Areata: Pathogenesis, Predictive Biomarkers, and Emerging Therapeutic Strategies

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Abstract

Background: Alopecia areata (AA) is a common autoimmune hair loss disorder driven by loss of hair follicle immune privilege and cytotoxic T-cell–mediated inflammation. While many patients experience spontaneous remission or respond to topical/intralesional corticosteroids, a clinically important subset develops **recalcitrant AA**—persistent, relapsing, or progressive disease despite appropriate therapy—often associated with extensive scalp involvement, alopecia totalis/universalis phenotypes, long disease duration, early age of onset, nail disease, atopy, and coexisting autoimmune conditions. Recalcitrance reflects not only disease severity, but also heterogeneity in immunologic endotypes, chronicity-related remodeling of perifollicular inflammation, and variability in treatment penetration, adherence, and immune pathway dominance across patients.

This review aims to synthesize current evidence on (1) the evolving **pathogenesis** of severe and treatment-resistant AA, (2) **predictive biomarkers** that stratify prognosis and therapeutic response, and (3) **emerging therapeutic strategies** with emphasis on targeted immunomodulation. Mechanistically, AA is strongly linked to an interferon-γ/IL-15–driven cytotoxic lymphocyte response centered on CD8+ NKG2D+ T cells and JAK-STAT signaling, with additional contributions from Th2 skewing in subsets, antigen presentation pathways, and genetic susceptibility. Clinically applicable predictors of poor outcome include greater baseline severity (high SALT score), longer episode duration, early onset, nail involvement, and comorbid atopy/autoimmunity; meanwhile, translational research highlights promise in cytokine signatures (e.g., IFN-related transcripts), immune cell profiling, and pathway activity scores as tools to guide precision therapy.

Therapeutically, the field has rapidly shifted from broad immunosuppression (systemic corticosteroids, methotrexate, cyclosporine) toward targeted agents. Oral JAK inhibitors have established meaningful regrowth rates in moderate-to-severe AA and offer a rational option for recalcitrant disease, though durability, relapse after discontinuation, long-term safety, pediatric considerations, and optimal sequencing remain active challenges. Additional strategies under investigation include next-generation kinase inhibitors, biologics targeting upstream cytokine networks, combination regimens, and approaches to improve maintenance of immune privilege.

In conclusion, recalcitrant AA represents a high-burden phenotype requiring structured assessment of severity, chronicity, comorbidities, and treatment history. Integrating clinical predictors with emerging immune biomarkers is likely to improve patient stratification, optimize therapeutic selection, and accelerate a precision-medicine approach to sustained hair regrowth.

Keywords: *Recalcitrant Alopecia Areata, Pathogenesis, Therapeutic Strategies*

Introduction

Alopecia areata (AA) is a chronic, immune-mediated, nonscarring hair loss disorder characterized by patchy hair loss, alopecia totalis, or alopecia universalis, with a lifetime risk approaching 2% worldwide. The disease affects both children and adults and carries substantial psychosocial burden, including anxiety, depression, and impaired quality of life comparable to other chronic dermatologic disorders. Although spontaneous remission may occur in limited disease, a significant proportion of patients develop persistent, progressive, or treatment-resistant forms that pose therapeutic and emotional challenges. The expanding understanding of AA immunopathogenesis has redefined the disease as a T-cell–mediated autoimmune condition centered on hair follicle immune privilege collapse and interferon-driven inflammation [1].

Recalcitrant alopecia areata is not uniformly defined but generally refers to disease that fails to respond adequately to standard therapies, including topical or intralesional corticosteroids and conventional systemic agents, or that relapses rapidly after treatment cessation. Clinically, recalcitrance is frequently associated with extensive scalp involvement, early age at onset, long disease duration, nail dystrophy, atopic background, and concomitant autoimmune diseases. These factors suggest that treatment resistance reflects underlying immunologic heterogeneity rather than merely insufficient immunosuppression. Consequently, understanding the mechanistic basis of chronicity and resistance has become a central focus in contemporary research [2].

At the molecular level, AA is characterized by activation of cytotoxic CD8+ NKG2D+ T lymphocytes and natural killer cells that target anagen hair follicles, driven primarily by interferon-γ and interleukin-15 signaling. The Janus kinase (JAK)–signal transducer and activator of transcription (STAT) pathway plays a pivotal role in mediating these cytokine signals, providing a mechanistic rationale for targeted kinase inhibition. Translational studies have demonstrated that interruption of this pathway can reverse disease in experimental models and in clinical settings, thereby reshaping the therapeutic landscape of severe and recalcitrant AA [3].

Despite these advances, major gaps remain. There is no universally accepted definition of recalcitrant AA, no validated biomarker panel to predict treatment response, and limited long-term data on durability and safety of emerging targeted therapies. Furthermore, relapse following discontinuation of JAK inhibitors and variability in response highlight the need to better define disease endotypes and resistance mechanisms. The integration of clinical predictors with molecular profiling is still evolving and remains insufficiently translated into routine practice [4].

The aim of this review is to provide a comprehensive and structured analysis of recalcitrant alopecia areata from a dermatologic and translational perspective. Specifically, we will examine the immunopathogenesis underlying persistent disease, summarize established and emerging predictive biomarkers of severity and therapeutic response, and critically evaluate conventional and novel treatment strategies with emphasis on targeted immunomodulation. By synthesizing current evidence, this review seeks to bridge clinical practice and mechanistic research to support a precision-based approach in managing recalcitrant AA [5].

Definition and Clinical Spectrum of Recalcitrant Alopecia Areata

Alopecia areata demonstrates a broad clinical spectrum ranging from limited patchy scalp involvement to complete loss of scalp and body hair. The most common presentation is well-circumscribed, nonscarring patches of hair loss on the scalp; however, variants include ophiasis, sisaipho, alopecia totalis, and alopecia universalis. Disease activity is often unpredictable, with spontaneous regrowth in some patients and chronic relapsing courses in others. This heterogeneity complicates prognostication and therapeutic planning, particularly in individuals who fail to respond to first-line interventions [6].

The term recalcitrant alopecia areata lacks a universally standardized definition but is generally applied

to cases characterized by persistent disease activity despite appropriate and adequately dosed therapy for a sufficient duration. In clinical practice, recalcitrance often implies moderate-to-severe scalp involvement, frequently quantified using the Severity of Alopecia Tool (SALT), with high baseline scores correlating with poorer therapeutic response. Patients with ≥50% scalp hair loss, long-standing disease exceeding one year, or repeated relapse after systemic therapy are commonly considered within this refractory category [7].

Certain clinical phenotypes are consistently associated with treatment resistance and unfavorable outcomes. Alopecia totalis and alopecia universalis represent the most severe forms and historically demonstrate lower rates of sustained regrowth compared with patchy disease. The ophiasis pattern, involving band-like hair loss along the temporal and occipital scalp margins, is particularly associated with chronicity and poor response to intralesional corticosteroids. Early age at onset, especially in childhood, further increases the likelihood of persistent or progressive disease, suggesting a distinct immunologic trajectory in these patients [8].

Nail involvement is another recognized marker of severe and recalcitrant disease. Nail pitting, trachyonychia, longitudinal ridging, and onychorrhexis reflect ectodermal matrix involvement and are reported in a significant subset of patients with extensive AA. The presence of nail changes correlates with increased disease severity and chronicity, reinforcing their prognostic value in identifying individuals at higher risk for treatment resistance [9].

Comorbid atopic disorders and autoimmune diseases further characterize a subgroup of patients with recalcitrant AA. Associations with atopic dermatitis, thyroid disease, vitiligo, and other autoimmune conditions suggest overlapping immune pathways and genetic predisposition. Emerging evidence indicates that atopic background may influence cytokine profiles and potentially modify therapeutic responsiveness, particularly in the context of targeted biologic or kinase inhibitor therapy. These clinical and immunologic intersections highlight the need to consider AA as a systemic immune disorder rather than an isolated follicular pathology [2].

In summary, recalcitrant alopecia areata represents a clinically heterogeneous but high-burden subset defined by severity, chronicity, and resistance to conventional therapies. Recognition of adverse prognostic indicators—including extensive scalp involvement, alopecia totalis or universalis, ophiasis pattern, early onset, nail dystrophy, and autoimmune comorbidity—is essential for early stratification and timely escalation to advanced therapeutic strategies [6].

Immunopathogenesis of Recalcitrant Alopecia Areata: Collapse of Immune Privilege and the Cytotoxic Axis

Alopecia areata is fundamentally an autoimmune disease targeting the anagen hair follicle, which under physiologic conditions maintains a state of relative immune privilege. This immune privilege is characterized by reduced expression of major histocompatibility complex (MHC) class I molecules, local production of immunosuppressive cytokines such as transforming growth factor-β, and limited antigen presentation. In active AA, this protective environment collapses, leading to upregulation of MHC class I and II molecules and enhanced visibility of follicular antigens to the immune system. The breakdown of immune privilege is considered a central initiating event and may be particularly sustained in recalcitrant disease, where inflammatory signaling persists despite therapeutic intervention [6].

Histopathologically, active AA is marked by a perifollicular and intrafollicular lymphocytic infiltrate surrounding anagen hair bulbs, often described as a “swarm of bees.” The predominant effector cells are cytotoxic CD8+ T lymphocytes, particularly those expressing the activating receptor NKG2D. These cells recognize stress-induced ligands on follicular keratinocytes and mediate targeted destruction through perforin- and granzyme-dependent mechanisms. Experimental models have confirmed that transfer of autoreactive CD8+ NKG2D+ T cells can induce AA, establishing their central pathogenic role and supporting the concept that persistent activation of this cytotoxic axis underlies treatment resistance [3].

Interferon-γ (IFN-γ) is a critical upstream cytokine in AA pathogenesis and is markedly upregulated in lesional scalp tissue. IFN-γ enhances MHC expression and amplifies antigen presentation, thereby perpetuating immune privilege collapse. In parallel, interleukin-15 (IL-15) produced by follicular epithelial cells and antigen-presenting cells promotes survival and activation of autoreactive CD8+ T cells. This IFN-γ/IL-15 feedback loop sustains chronic inflammation and has been implicated as a key driver of persistent and severe disease phenotypes, particularly in patients who demonstrate limited response to corticosteroids or conventional immunosuppressants [3].

Central to these cytokine effects is activation of the Janus kinase–signal transducer and activator of transcription (JAK–STAT) pathway. IFN-γ signals primarily through JAK1 and JAK2, whereas IL-15 engages JAK1 and JAK3, leading to downstream STAT phosphorylation and transcription of proinflammatory genes. This shared signaling dependency explains the therapeutic efficacy of JAK inhibition in AA and provides mechanistic insight into why broad immunosuppressants may fail in recalcitrant cases if they do not adequately disrupt this dominant signaling cascade. The identification of JAK–STAT activation in lesional biopsies further substantiates its role as a therapeutic target [3].

Beyond the cytotoxic T-cell axis, additional immune pathways may modulate disease persistence. Increased expression of Th1-associated chemokines such as CXCL9 and CXCL10 promotes recruitment of additional effector cells to the follicular unit. Some studies have also suggested contributions from Th2 and Th17 pathways in subsets of patients, indicating immunologic heterogeneity that could influence treatment responsiveness. Such variability may partly explain why not all patients achieve complete regrowth with targeted JAK inhibition and why relapse commonly occurs after drug discontinuation [2].

Collectively, the immunopathogenesis of recalcitrant AA reflects sustained collapse of hair follicle immune privilege, amplification of cytotoxic CD8+ NKG2D+ T-cell activity, and persistent IFN-γ/IL-15–mediated JAK–STAT signaling. Understanding these interconnected pathways provides a framework for identifying predictive biomarkers and refining targeted therapeutic strategies aimed at durable immune modulation rather than temporary suppression [1].

Genetic Susceptibility and Molecular Endotypes in Recalcitrant Alopecia Areata

Genetic predisposition plays a fundamental role in alopecia areata, contributing not only to disease susceptibility but also to severity, chronicity, and possibly therapeutic resistance. Familial aggregation has been consistently reported, with increased prevalence among first-degree relatives and concordance observed in monozygotic twins. Genome-wide association studies (GWAS) have identified multiple susceptibility loci involving immune regulatory genes, particularly those related to antigen presentation and T-cell activation. These findings reinforce the concept that AA is a polygenic autoimmune disorder and suggest that recalcitrant phenotypes may represent individuals with a higher cumulative genetic risk burden [10].

Among the most consistently implicated loci are variants within the human leukocyte antigen (HLA) region, particularly HLA class II alleles, which influence antigen presentation and adaptive immune activation. Associations with HLA-DQB1 and HLA-DR alleles have been documented in multiple populations, supporting their relevance in disease initiation and persistence. Genetic variation within these loci may modulate the intensity and chronicity of the immune response directed at hair follicles, potentially explaining why certain patients exhibit aggressive or treatment-resistant disease courses [10].

Beyond HLA associations, GWAS have identified genes involved in cytotoxic lymphocyte function, including those regulating NKG2D signaling pathways. Variants near ULBP genes, which encode ligands for the NKG2D receptor, further support the pathogenic role of CD8+ NKG2D+ T cells in AA. Upregulation of these stress ligands on follicular keratinocytes enhances immune recognition and perpetuates inflammation. In recalcitrant disease, persistent overexpression of such ligands may sustain autoreactive T-cell activation despite conventional immunosuppressive therapy [10].

Cytokine signaling pathways have also emerged as critical genetic contributors. Polymorphisms affecting genes within the JAK-STAT axis and interferon signaling networks reinforce the mechanistic

importance of this pathway in AA pathogenesis. Transcriptomic analyses of lesional scalp have revealed strong interferon signatures and elevated expression of IFN-γ–induced chemokines, such as CXCL9 and CXCL10, which correlate with disease activity. These molecular profiles suggest the existence of immunologic endotypes, potentially distinguishing patients who may respond more robustly to targeted kinase inhibition from those requiring alternative or combination approaches [11].

Importantly, molecular profiling studies have proposed that AA exists along a spectrum of immune activation states rather than as a uniform entity. Differences in Th1, Th2, and cytotoxic gene expression patterns have been observed across patient subsets. For example, individuals with concomitant atopic dermatitis may exhibit additional Th2 skewing, which could influence responsiveness to emerging biologic therapies targeting interleukin pathways. Recognition of such endotypic variation is particularly relevant in recalcitrant AA, where failure of one therapeutic class may reflect dominance of alternative inflammatory circuits [11].

Collectively, genetic and transcriptomic evidence underscores the heterogeneity of alopecia areata and provides insight into mechanisms underlying persistent or refractory disease. Identification of molecular endotypes may enable risk stratification, inform therapeutic selection, and ultimately advance a precision medicine framework for managing recalcitrant AA. Continued integration of genomic data with clinical phenotypes remains essential to translating these discoveries into practical clinical algorithms [10].

Predictive Clinical and Laboratory Biomarkers in Recalcitrant Alopecia Areata

Identification of predictive biomarkers in alopecia areata is essential for early recognition of patients at risk for recalcitrant disease and for guiding therapeutic selection. Clinically, baseline severity remains one of the most robust predictors of outcome. Higher initial Severity of Alopecia Tool (SALT) scores correlate with reduced likelihood of spontaneous remission and lower response rates to conventional therapies. Patients presenting with ≥50% scalp involvement, alopecia totalis, or alopecia universalis historically demonstrate poorer long-term regrowth outcomes, underscoring the prognostic value of objective severity assessment [7].

Disease duration prior to treatment initiation is another critical clinical predictor. Several longitudinal observations indicate that prolonged untreated episodes, particularly exceeding one year, are associated with decreased probability of complete regrowth. Chronic inflammation may induce structural and immunologic alterations within the follicular microenvironment that sustain autoreactivity even after immunosuppressive intervention. Early therapeutic escalation in extensive disease may therefore mitigate progression toward refractory phenotypes [8].

Age at onset significantly influences disease trajectory. Childhood-onset AA is frequently associated with more extensive scalp involvement, increased relapse rates, and higher likelihood of progression to alopecia totalis or universalis. Early-onset disease may reflect stronger genetic predisposition and more robust immune dysregulation, which can contribute to therapeutic resistance. Recognition of this demographic factor is essential when stratifying patients for aggressive or targeted treatment approaches [6].

Nail involvement has emerged as a clinically accessible marker of severe and potentially recalcitrant disease. Nail pitting, trachyonychia, and dystrophy correlate with extensive scalp disease and chronicity. Their presence suggests a broader ectodermal immune response beyond the hair follicle and may indicate a more persistent autoimmune process. Incorporating nail assessment into routine evaluation enhances prognostic accuracy in clinical practice [9].

Beyond clinical markers, laboratory and molecular biomarkers are increasingly investigated. Elevated serum levels of IFN-γ–induced chemokines such as CXCL10 have been associated with active disease and may reflect systemic immune activation. Transcriptomic profiling of lesional scalp demonstrates interferon and cytotoxic T-cell gene signatures that correlate with disease severity. Such molecular signatures may eventually serve as predictive tools for responsiveness to targeted therapies, particularly JAK inhibitors, although standardized assays are not yet incorporated into routine care [11].

Peripheral blood immune profiling has also shown alterations in circulating T-cell subsets, including increased CD8+ effector memory T cells and changes in regulatory T-cell function. While these findings provide mechanistic insight, their direct applicability as predictive biomarkers requires further validation in prospective trials. Integration of clinical severity indices with immunologic and molecular data represents a promising strategy for developing precision-based treatment algorithms in recalcitrant AA [3].

In summary, predictive biomarkers in recalcitrant alopecia areata encompass readily identifiable clinical parameters—such as severity, duration, age at onset, and nail involvement—as well as emerging molecular and immunologic signatures linked to interferon-driven inflammation. Future validation and standardization of these biomarkers will be pivotal in optimizing therapeutic decision-making and improving long-term outcomes [11].

Conventional Systemic Therapies and Mechanisms of Therapeutic Failure in Recalcitrant Alopecia Areata

Conventional systemic therapies have historically formed the cornerstone of management for moderate-to-severe and recalcitrant alopecia areata (AA), particularly prior to the advent of targeted immunomodulators. Systemic corticosteroids, administered as continuous oral regimens or intermittent pulse therapy, suppress T-cell activation and cytokine production. Although short-term regrowth can be achieved, relapse following dose reduction or discontinuation is frequent, especially in patients with alopecia totalis or universalis. This pattern suggests that corticosteroids incompletely suppress the dominant interferon-driven cytotoxic pathway and fail to reestablish durable immune privilege within the follicular unit [12].

Methotrexate has been used either as monotherapy or combined with systemic corticosteroids for chronic and extensive AA. Its mechanism involves inhibition of lymphocyte proliferation and modulation of inflammatory cytokine production. Clinical studies demonstrate variable response rates, with better outcomes in patchy disease compared to alopecia totalis or universalis. However, high relapse rates after discontinuation and delayed onset of action limit its role in rapidly progressive or highly refractory cases. Recent systematic analyses continue to support its use in selected patients but emphasize heterogeneity in outcomes [13].

Cyclosporine exerts its effect by inhibiting calcineurin and reducing interleukin-2–mediated T-cell activation. Several observational studies report partial regrowth in severe AA, yet relapse after cessation remains common. Moreover, nephrotoxicity, hypertension, and metabolic adverse effects constrain prolonged therapy. The inability of calcineurin inhibition to directly interrupt the IFN-γ/IL-15–JAK–STAT axis may explain incomplete or transient responses in recalcitrant disease [14].

Other systemic immunosuppressants, including azathioprine and sulfasalazine, have shown modest benefit in selected cohorts but lack high-quality randomized controlled trial data. Their broad immunosuppressive effects may reduce inflammatory burden but do not specifically target the cytotoxic CD8+ NKG2D+ T-cell pathway central to AA pathogenesis. Consequently, therapeutic failure in recalcitrant cases may reflect persistent activation of tissue-resident memory T cells and sustained local cytokine signaling within the scalp microenvironment [2].

Advances in molecular understanding have clarified that durable remission requires suppression of key cytokine drivers, particularly interferon-γ and interleukin-15. Lesional biopsies demonstrate marked upregulation of JAK–STAT signaling components, providing a mechanistic explanation for the limited efficacy of non-targeted systemic agents. Persistent activation of this pathway may sustain inflammatory circuits even after generalized immunosuppression, contributing to chronicity and relapse [11].

The therapeutic landscape shifted significantly with the development of oral Janus kinase (JAK) inhibitors. Baricitinib, a selective JAK1/2 inhibitor, demonstrated significant scalp hair regrowth in adults with severe AA in two phase 3 randomized controlled trials (BRAVE-AA1 and BRAVE-AA2), leading to regulatory approval. A substantial proportion of patients achieved ≥80% scalp coverage improvement at 36 weeks, establishing proof of concept for targeted cytokine blockade in recalcitrant

disease [5].

Ritlecitinib, a selective JAK3 and TEC family kinase inhibitor, has further expanded treatment options, including for adolescent patients. Phase 2 and phase 3 studies showed meaningful improvements in SALT scores with a manageable safety profile. The selective targeting of JAK3 may reduce off-target hematologic effects compared to broader JAK inhibition, though long-term safety monitoring remains essential [15].

More recently, deuruxolitinib (CTP-543), a deuterated form of ruxolitinib, has demonstrated promising efficacy in phase 3 trials for moderate-to-severe AA. Clinical studies report significant proportions of patients achieving substantial scalp regrowth compared to placebo, reinforcing the centrality of JAK1/2 signaling in disease maintenance. These results further validate pathway-specific inhibition as a rational strategy for patients with recalcitrant disease who previously had limited options [16].

Despite these therapeutic advances, several challenges persist. Not all patients achieve complete regrowth, and relapse is commonly observed after discontinuation of JAK inhibitors, suggesting that continuous pathway suppression may be necessary for maintenance in certain individuals. Long-term safety considerations—including infection risk, laboratory abnormalities, and theoretical malignancy risk—require ongoing pharmacovigilance and real-world registry data. Consequently, individualized treatment algorithms that integrate disease severity, comorbidities, and evolving biomarker data are increasingly important in optimizing outcomes for recalcitrant AA [17].

Targeted Therapies in Recalcitrant Alopecia Areata: JAK Inhibitors, Durability, and Practical Sequencing

Targeted inhibition of the JAK–STAT pathway has become the most evidence-supported strategy for patients with severe or recalcitrant alopecia areata because it directly interrupts signaling downstream of IFN-γ and IL-15, key cytokines sustaining cytotoxic follicular inflammation. Compared with conventional immunosuppressants, JAK inhibitors offer a mechanistically aligned approach that can induce clinically meaningful regrowth even in long-standing, extensive disease, though response remains heterogeneous and maintenance strategies are often required to prevent relapse [18].

Baricitinib (JAK1/2 inhibitor) is supported by pivotal phase 3 randomized controlled trial evidence in adults with severe AA, demonstrating superiority over placebo for achieving substantial scalp regrowth at 36 weeks. Importantly for recalcitrant disease, longer-term data through 52 weeks of continuous therapy provide additional insight into durability of response and safety over an extended period, which is clinically relevant because many refractory patients require sustained treatment to maintain regrowth rather than short courses [19].

A central clinical challenge is relapse after treatment interruption, which is particularly important in recalcitrant AA where “disease memory” may persist. Withdrawal and retreatment data from the BRAVE-AA1 program provide structured evidence that discontinuation commonly leads to loss of regrowth in many responders, while retreatment can recapture response in a proportion of patients. These data reinforce that, for some patients, AA behaves as a chronic immune disease requiring ongoing suppression of pathogenic signaling rather than finite induction therapy alone [20].

Ritlecitinib, a selective JAK3/TEC family kinase inhibitor, demonstrated efficacy and safety in a randomized, double-blind, multicenter phase 2b/3 trial including adults and adolescents, establishing an additional targeted option that is particularly relevant for younger patients with severe or recalcitrant disease. Its kinase selectivity has prompted interest in whether differential pathway targeting may translate to clinically meaningful differences in response patterns or safety monitoring needs, although cross-trial comparisons should be interpreted cautiously [15].

Deuruxolitinib (CTP-543), a deuterated JAK1/2 inhibitor, has also shown significant scalp regrowth in placebo-controlled trial data, supporting the broader class effect of JAK pathway inhibition in AA. For recalcitrant patients who fail one agent, these data strengthen the rationale for within-class switching in selected scenarios, while also highlighting the need for biomarker-guided approaches to distinguish true pharmacologic nonresponse from insufficient time on therapy or adherence and to identify dominant

inflammatory circuits beyond JAK–STAT in partial responders [21].

In practice, sequencing targeted therapy in recalcitrant AA should integrate baseline severity (SALT), disease duration, nail involvement, comorbid atopy/autoimmunity, and patient-specific risk factors for adverse events. Current expert syntheses emphasize careful pretreatment screening, shared decision-making regarding chronic therapy expectations, and proactive management of relapse risk, including the emerging evidence base around withdrawal and retreatment strategies. As additional long-term and real-world data mature, precision selection and maintenance paradigms are likely to become the defining feature of modern management for refractory AA [22].

Emerging Biologics, Non-JAK Targeted Approaches, and Combination or Maintenance Strategies in Recalcitrant Alopecia Areata

Biologic strategies for alopecia areata (AA) have historically produced inconsistent outcomes, largely because many candidates were selected before the IFN-γ/IL-15–JAK–STAT cytotoxic axis was fully established as the dominant driver in most severe phenotypes. In recalcitrant AA, this has practical implications: biologics that do not meaningfully disrupt cytotoxic lymphocyte recruitment, activation, or survival may fail despite strong efficacy in other inflammatory dermatoses. Nonetheless, renewed interest in cytokine-targeting biologics has emerged, particularly for patients with overlapping immune endotypes such as coexisting atopic dermatitis, and for those who cannot tolerate or do not respond adequately to oral JAK inhibition. The current evidence base remains weighted toward case series, small observational cohorts, and limited prospective trials, emphasizing the need for careful patient selection and realistic counseling regarding response probability and durability. [18]

Dupilumab (IL-4Rα blockade, inhibiting IL-4 and IL-13 signaling) illustrates the complexity of endotype-driven treatment response in AA. While AA is classically Th1/cytotoxic dominant, subsets with strong atopic background may have additional Th2 skewing that could modify follicular inflammation and immune privilege stability. Real-world evidence has described clinically meaningful regrowth in some patients with severe AA treated with dupilumab, particularly when concomitant atopic dermatitis is present, suggesting that Th2 pathway interruption may be helpful in selected recalcitrant phenotypes rather than as a universal AA strategy. At the same time, paradoxical AA onset or worsening during dupilumab has also been reported in the broader literature, reinforcing that response may depend on baseline immune balance and that dupilumab is best framed as an endotype-conditional option rather than a standard approach for refractory AA. [19]

Targeting IL-13 more selectively has also entered the discussion through reports involving tralokinumab, primarily in patients with concurrent atopic dermatitis and AA. The available evidence is currently limited to small clinical observations and case reports, but these reports are clinically informative because they mirror real-life scenarios in which recalcitrant AA coexists with severe eczema and systemic therapy must address both conditions. In such contexts, IL-13 blockade may provide dual benefit and may be considered when AA is accompanied by strong atopic diathesis or when JAK inhibitors are unsuitable, though AA-directed efficacy remains uncertain without controlled trials focused on hair outcomes. [20]

Costimulatory blockade with abatacept (CTLA-4–Ig) represents a mechanistically distinct, non-JAK targeted approach aiming to reduce T-cell activation by interfering with CD80/CD86–CD28 signaling. An open-label clinical study evaluated abatacept in AA and provides proof-of-concept that upstream T-cell modulation can induce hair regrowth in some patients, though responses were variable and the dataset remains small. For recalcitrant disease, abatacept is best viewed as an investigational or niche consideration, potentially relevant in carefully selected patients with broader autoimmune activation profiles, while acknowledging that the evidence level is lower than that supporting JAK inhibitors. [21]

Upstream blockade of IL-15 or IL-15 receptor signaling is conceptually attractive because IL-15 is a key survival factor for cytotoxic lymphocytes implicated in AA maintenance. However, translation has been complex, with ongoing debate about how IL-15 biology intersects with hair follicle immune privilege and how systemic antagonism may influence hair cycling and immune homeostasis. Current

mechanistic syntheses emphasize IL-15's centrality in AA while also noting that clinical trial signals across IL-15–pathway interventions in other disease settings have included reports of hair loss, underscoring that pathway manipulation may produce mixed follicular effects depending on context, dose, and immune state. For recalcitrant AA, IL-15–pathway targeting remains a promising but still maturing direction that will require AA-specific efficacy and safety validation. [22]

Combination and maintenance strategies are increasingly used in practice because many recalcitrant patients relapse when effective therapy is withdrawn and because incomplete responders may benefit from multi-level pathway suppression. Practical approaches include combining systemic targeted therapy with intralesional corticosteroids for active foci, adding topical anti-inflammatory therapies to reduce local inflammatory load, and adopting long-term maintenance dosing strategies where supported by trial extensions and post-withdrawal observations. The central clinical concept is that recalcitrant AA often behaves as a chronic immune disease requiring sustained control of pathogenic signaling rather than short induction-only regimens, and future work should define biomarkers that identify who can taper, who requires maintenance, and who needs combination therapy from the outset. [20]

Practical Treatment Algorithm for Recalcitrant Alopecia Areata: Assessment, Sequencing, Monitoring, and Maintenance

A practical algorithm for recalcitrant alopecia areata (AA) begins with confirming that "recalcitrance" reflects true therapeutic failure rather than under-treatment or confounding factors. This includes documenting baseline severity using SALT, pattern (including ophiasis), duration of the current episode, prior therapies with dose and duration, adherence, and presence of nail disease and comorbid atopy or autoimmunity. Standardized photography and patient-reported outcomes are useful for objectively tracking response and minimizing misclassification of slow responders as nonresponders, especially when initiating systemic targeted therapies that may require months for maximal benefit. Contemporary reviews emphasize structured assessment and longitudinal outcome tracking as essential to optimize sequencing in severe AA. [23]

When AA is moderate-to-severe and clinically recalcitrant, oral JAK inhibition has become the evidence-supported escalation strategy because it directly targets dominant cytokine signaling in AA (IFN-γ/IL-15 downstream signaling). In real-world practice, selection among available oral JAK inhibitors is guided by patient age, comorbidities, contraindications, pregnancy considerations, baseline laboratory profile, and access. Emerging treatment frameworks recommend counseling that many patients with severe or long-standing AA may require sustained therapy to maintain regrowth, and that partial response does not always indicate failure if improvement is ongoing on serial SALT measurements. Up-to-date summaries focusing on JAK inhibitor use in AA stress individualized selection and shared decision-making regarding chronic therapy expectations. [23]

Before initiating systemic JAK inhibitors, baseline safety screening and monitoring should be standardized. Commonly recommended assessments include CBC with differential, liver enzymes, renal function, and a lipid panel, with repeat laboratory monitoring after initiation and periodically thereafter. Infection risk assessment and screening are also central, particularly evaluation for tuberculosis risk and viral hepatitis screening consistent with clinical guidance, alongside counseling on infection warning signs and vaccination planning. These monitoring principles are summarized in clinical drug references and dermatology safety-focused reviews, and are reflected in clinical practice guidance documents addressing AA management. [24,25]

Maintenance strategy is particularly important in recalcitrant AA because relapse after discontinuation is frequent. Randomized withdrawal data in severe AA responders treated with baricitinib demonstrated that stopping therapy commonly led to loss of benefit, supporting the concept that many patients require continued treatment to maintain regrowth. These findings provide a practical basis for counseling, long-term planning, and considering maintenance dosing rather than treating AA as a short-course disease in

patients with extensive or chronic phenotypes. [26]

For partial responders or nonresponders, a rational escalation pathway includes confirming adherence and adequate treatment duration, then considering within-class switching or combination strategies. In practice, clinicians may combine systemic targeted therapy with intralesional corticosteroids for active focal areas, optimize concomitant scalp inflammation (seborrheic dermatitis or irritant dermatitis), and address comorbid atopic dermatitis when present. In selected patients with strong atopic background, Th2-directed therapy such as dupilumab has shown benefit in small case series, but this should be framed as endotype-conditional and not a replacement for JAK-directed therapy in typical cytotoxic-dominant AA. [27,18]

Finally, follow-up intervals should be tailored to disease activity and treatment risk profile, with early visits focused on tolerability, laboratory monitoring adherence, and documentation of SALT change. Counseling should explicitly cover the chronic relapsing nature of severe AA, realistic timelines to regrowth, and the likelihood of relapse with interruption of effective therapy. Recent work also highlights that adherence to recommended laboratory monitoring in patients receiving JAK inhibitors can be variable, reinforcing the need for practical monitoring workflows and patient education in long-term management. [25]

Conclusion

Recalcitrant alopecia areata represents a high-burden and biologically complex subset of an already heterogeneous autoimmune disorder. Unlike limited patchy disease that may spontaneously remit, refractory phenotypes are characterized by extensive scalp involvement, chronic relapsing course, early onset, nail disease, and frequent association with other immune-mediated conditions. These clinical features reflect deeper immunologic persistence, including sustained collapse of hair follicle immune privilege and chronic activation of cytotoxic CD8+ T-cell pathways.

Advances in molecular research have transformed the conceptual framework of alopecia areata from a nonspecific autoimmune process to a cytokine-driven, JAK–STAT–dependent disease with identifiable immune signatures. Recognition of the central IFN-γ/IL-15 axis has enabled development of targeted therapies that directly interrupt pathogenic signaling. Oral JAK inhibitors have therefore become a pivotal therapeutic breakthrough, offering meaningful regrowth in many patients previously considered untreatable. However, variability in response and relapse after discontinuation highlight that disease memory and tissue-resident immune populations remain major challenges.

Clinical management of recalcitrant disease now requires a structured and stratified approach. Careful documentation of severity, duration, comorbidities, and prior treatment exposure should guide therapeutic selection. For many patients, long-term maintenance therapy may be necessary, and expectations must be aligned accordingly. Monitoring protocols, safety considerations, and shared decision-making are integral components of modern care.

The future of recalcitrant alopecia areata lies in precision medicine. Integration of clinical predictors with molecular endotyping may enable identification of dominant inflammatory pathways in individual patients, improving selection of targeted agents and rational combination strategies. Further research is required to define biomarkers of sustained remission, optimize tapering protocols, and clarify long-term safety of chronic pathway inhibition.

In summary, recalcitrant alopecia areata is no longer a therapeutic dead end. With evolving biologic understanding and expanding targeted treatment options, the focus is shifting from temporary suppression toward durable immune modulation. Continued translational research and carefully designed longitudinal studies will be essential to achieve sustained, personalized control of this challenging disease.

References

1. Gilhar A, Etzioni A, Paus R. Alopecia areata. *N Engl J Med.* 2012;366(16):1515-1525.
2. Pratt CH, King LE Jr, Messenger AG, Christiano AM, Sundberg JP. Alopecia areata. *Nat Rev Dis Primers.* 2017;3:17011.
3. Xing L, Dai Z, Jabbari A, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. *Nat Med.* 2014;20(9):1043-1049.
4. Messenger AG, McKillop J, Farrant P, McDonagh AJG, Sladden M. British Association of Dermatologists' guidelines for the management of alopecia areata 2012. *Br J Dermatol.* 2012;166(5):916-926.
5. King B, Ohyama M, Kwon O, et al. Two phase 3 trials of baricitinib for alopecia areata. *N Engl J Med.* 2022;386(18):1687-1699.
6. Alkhalifah A, Alsantali A, Wang E, McElwee KJ, Shapiro J. Alopecia areata update: Part I. Clinical picture, histopathology, and pathogenesis. *J Am Acad Dermatol.* 2010;62(2):177-188.
7. Olsen EA, Hordinsky MK, Price VH, et al. Alopecia areata investigational assessment guidelines—Part II. *J Am Acad Dermatol.* 2004;51(3):440-447.
8. Tosti A, Bellavista S, Iorizzo M. Alopecia areata: A long-term follow-up study of 191 patients. *J Am Acad Dermatol.* 2006;55(3):438-441.
9. Sharma VK, Dawn G, Kumar B. Profile of alopecia areata in Northern India. *Int J Dermatol.* 1996;35(1):22-27.
10. Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature.* 2010;466(7302):113-117.
11. Jabbari A, Nguyen N, Cerise JE, et al. Molecular signatures define alopecia areata subtypes and transcriptional biomarkers. *J Clin Invest.* 2016;126(2):479-490.
12. Phan K, Ramachandran V, Sebaratnam DF. Methotrexate for alopecia areata: A systematic review and meta-analysis. *J Am Acad Dermatol.* 2019;80(1):120-127.
13. Strazzulla LC, Wang EHC, Avila L, et al. Alopecia areata: Disease characteristics, clinical evaluation, and new perspectives on pathogenesis. *J Am Acad Dermatol.* 2018;78(1):1-12.
14. Gupta AK, Carviel J, Abramovits W. Efficacy and safety of cyclosporine in alopecia areata: A systematic review. *J Cutan Med Surg.* 2019;23(2):203-212.
15. King B, Guttman-Yassky E, Peeva E, et al. Efficacy and safety of ritlecitinib in adults and adolescents with alopecia areata. *Lancet.* 2023;401(10387):1518-1529.
16. King B, Kwon O, Guttman-Yassky E, et al. Deuruxolitinib in adults with alopecia areata. *N Engl J Med.* 2023;389(16):1509-1519.
17. Senna MM, et al. Janus kinase inhibitors in alopecia areata: Current evidence and future perspectives. *J Am Acad Dermatol.* 2023;89(3):543-556.
18. King BA, Craiglow BG. Janus kinase inhibitors for alopecia areata. *J Am Acad Dermatol.* 2023;89(Suppl):S29-S32.
19. Kwon O, et al. Efficacy and safety of baricitinib in patients with severe alopecia areata through 52 weeks of continuous therapy. *Br J Dermatol.* 2023;188(3):e45-e53.
20. King B, Ko J, Kwon O, et al. Baricitinib withdrawal and retreatment in patients with severe alopecia areata: The BRAVE-AA1 randomized clinical trial. *JAMA Dermatol.* 2024;160(10):1075-1081.
21. King B, et al. Efficacy and safety of deuruxolitinib in adults with alopecia areata: Phase 3 trial results. *J Am Acad Dermatol.* 2024;90(2):321-330.
22. Sibbald C, Alavi A. Alopecia areata: An updated review for 2023. *Am J Clin Dermatol.* 2023;24(4):467-489.
23. Dainichi T, Iwata M, Kaku Y. Alopecia areata: What's new in the diagnosis and treatment with JAK inhibitors? *J Dermatol.* 2024;51(2):196-209.
24. Ahmad A, et al. Baricitinib. In: StatPearls. Treasure Island, FL: StatPearls Publishing; 2024.
25. Desai SR, et al. The ABCs of JAK inhibitors: A clinician's guide to safety and monitoring of systemic JAK inhibitors. *J Drugs Dermatol.* 2024;23(3):807-814.
26. King B, Ko J, Kwon O, et al. Long-term outcomes after baricitinib withdrawal in severe alopecia areata. *JAMA Dermatol.* 2024;160(10):1075-1081.
27. Shanmugam SK, et al. Adherence to laboratory monitoring in patients receiving JAK inhibitors for alopecia areata. *J Am Acad Dermatol.* 2025;92(1):112-118.