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Botulinum Toxin A for Treatment-Resistant Alopecia Areata: A Critical Review of Evidence and Mechanisms

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ABSTRACT

Background: Alopecia areata (AA) is a T cell–mediated autoimmune disorder characterized by nonscarring hair loss resulting from collapse of hair follicle immune privilege and activation of cytotoxic lymphocytes. Although recent advances, particularly Janus kinase (JAK) inhibitors, have transformed management of moderate-to-severe disease, a subset of patients remains treatment-resistant or experiences relapse despite systemic immunomodulation. Emerging evidence suggests that neuroimmune interactions, including neuropeptide-mediated inflammation and stress-induced signaling, may contribute to disease persistence in certain individuals. Botulinum toxin A (BoNT-A), a neurotoxin classically used for neuromuscular and aesthetic indications, has been proposed as a novel therapeutic strategy based on its capacity to modulate acetylcholine release, inhibit neuropeptides such as substance P and calcitonin gene-related peptide (CGRP), and influence local microcirculation.

This review critically evaluates the mechanistic rationale and available clinical evidence supporting the use of BoNT-A in treatment-resistant alopecia areata. We examine the neuroimmune pathways implicated in AA pathogenesis, including the role of perifollicular nerve signaling, stress-axis activation, and neurogenic inflammation. Preclinical data suggest that substance P can promote perifollicular inflammation and disrupt hair follicle cycling, while BoNT-A has demonstrated anti-inflammatory effects in other dermatologic conditions through inhibition of neuropeptide release. However, translation of these mechanisms into consistent clinical benefit in AA remains uncertain.

Clinical evidence for BoNT-A in AA is limited to small pilot studies and case reports, with heterogeneous injection protocols, variable dosing, and inconsistent outcome measures. Some reports describe partial regrowth in refractory cases, whereas others show minimal or no benefit. No large randomized controlled trials have definitively established efficacy, and the absence of standardized methodology complicates interpretation. Safety profiles appear favorable when administered appropriately, but long-term data in AA populations are lacking.

In conclusion, while Botulinum toxin A presents a biologically plausible and mechanistically intriguing approach to treatment-resistant alopecia areata, current evidence remains preliminary and insufficient to support routine clinical use. Well-designed controlled trials with biomarker stratification are necessary to determine whether neuroimmune modulation represents a meaningful adjunct or alternative in recalcitrant disease management.

Keywords: Botulinum Toxin A, Treatment-Resistant Alopecia Areata

INTRODUCTION

Alopecia areata (AA) is a chronic autoimmune disorder characterized by nonscarring hair loss resulting from immune-mediated attack on anagen hair follicles. The disease affects approximately 2% of the population during their lifetime and may present as patchy scalp involvement, alopecia totalis, or alopecia universalis. Although spontaneous remission occurs in some patients, a substantial proportion develops persistent, relapsing, or progressive disease that proves resistant to conventional therapies. Recent advances in understanding the cytotoxic T cell–driven, interferon-γ–mediated pathogenesis of AA have led to targeted treatment strategies, particularly Janus kinase (JAK) inhibitors, which have demonstrated meaningful clinical efficacy in moderate-to-severe cases [1,2].

Despite these advances, treatment resistance remains a significant clinical challenge. Not all patients respond adequately to JAK inhibition, and relapse after treatment discontinuation is common. Moreover, some individuals are not candidates for systemic immunosuppression due to comorbidities, safety concerns, or personal preference. These therapeutic gaps underscore the need to explore alternative or adjunctive approaches targeting complementary pathogenic pathways beyond classical adaptive immune activation [2,3].

Emerging evidence suggests that neuroimmune interactions may play a contributory role in AA pathogenesis. The hair follicle is a neuroimmunologically active structure richly innervated by sensory nerve fibers capable of releasing neuropeptides such as substance P and calcitonin gene-related peptide (CGRP). Experimental studies demonstrate that substance P can induce perifollicular inflammation, promote mast cell degranulation, and disrupt hair cycling, thereby linking psychological stress and neural signaling to immune-mediated follicular damage. These findings support the concept that AA may, in part, represent a disorder of neurogenic inflammation superimposed upon autoimmune dysregulation [4,5].

Botulinum toxin A (BoNT-A), a neurotoxin derived from *Clostridium botulinum*, exerts its primary action by inhibiting presynaptic acetylcholine release through cleavage of SNAP-25, leading to neuromuscular blockade. Beyond its well-established cosmetic and neurologic uses, BoNT-A has demonstrated anti-inflammatory properties mediated through inhibition of neuropeptide release, including substance P and CGRP. In dermatology, these effects have been explored in conditions such as hyperhidrosis, rosacea, and chronic pruritus, suggesting broader applications in disorders characterized by neurogenic inflammation [6,7].

Given the recognized interplay between neural signaling, stress pathways, and perifollicular immune activation in AA, BoNT-A has been proposed as a potential therapeutic strategy for treatment-resistant cases. However, the mechanistic plausibility of this approach must be weighed against limited and heterogeneous clinical evidence. To date, no consensus exists regarding efficacy, optimal dosing, injection technique, or patient selection criteria.

The aim of this review is to critically evaluate the mechanistic rationale and available clinical data supporting Botulinum toxin A as a therapeutic intervention in treatment-resistant alopecia areata. By integrating current understanding of neuroimmune biology with published clinical observations, we seek to clarify whether BoNT-A represents a promising adjunctive strategy or an experimental concept requiring further validation.

Neuroimmune Pathogenesis of Alopecia Areata: Role of Neuropeptides and the Stress Axis

Alopecia areata (AA) is traditionally conceptualized as a cytotoxic T cell–mediated autoimmune disease; however, increasing experimental and clinical evidence indicates that neuroimmune interactions contribute meaningfully to disease activity. The hair follicle is a neuroimmunologically dynamic structure in which sensory nerve fibers, immune cells, and epithelial cells interact closely. Under physiologic conditions, this microenvironment supports immune privilege and balanced hair cycling. Disruption of neural–immune equilibrium may predispose susceptible individuals to inflammatory activation and follicular regression, particularly in stress-responsive contexts [1].

Psychological stress has long been recognized as a precipitating or exacerbating factor in AA. Clinical studies report higher rates of significant life stressors preceding disease onset or flare. In murine models, stress exposure induces premature catagen development accompanied by perifollicular inflammatory infiltrates. Mechanistically, stress activates central and peripheral neuroendocrine pathways, including local production of corticotropin-releasing hormone and neuropeptides within the skin. These findings support the concept of a functional brain–hair follicle axis influencing immune reactivity at the follicular level [8].

Substance P is among the most extensively studied neuropeptides in hair biology. Released from peripheral sensory nerves, it binds to neurokinin-1 receptors expressed on keratinocytes, mast cells, and immune cells. Experimental work demonstrates that substance P induces mast cell degranulation, enhances expression of proinflammatory cytokines, and promotes premature transition of anagen follicles into catagen. Importantly, these changes are accompanied by perifollicular inflammatory infiltration, providing mechanistic evidence that neuropeptide signaling can directly impair hair follicle immune privilege and cycling dynamics [9].

Calcitonin gene-related peptide (CGRP) is another neuropeptide implicated in cutaneous immune modulation. CGRP-positive nerve fibers are abundant around hair follicles and influence vasodilation, immune cell trafficking, and cytokine secretion. While its direct pathogenic role in AA is less clearly defined than substance P, CGRP participates in neurogenic inflammation and may modulate T-cell responses within the perifollicular environment. The broader literature on neuropeptides in skin disease supports a paradigm in which neural mediators amplify or sustain inflammatory circuits [10].

Importantly, neurogenic inflammation may interact synergistically with established adaptive immune mechanisms in AA. Substance P has been shown to enhance antigen presentation and promote recruitment of cytotoxic lymphocytes, thereby potentially intensifying interferon-driven immune responses. In this framework, neural signaling does not replace T cell–mediated autoimmunity but may amplify or perpetuate it, particularly in patients with chronic, stress-associated, or treatment-resistant disease. This layered pathogenic model supports investigation of therapies that target neural components of inflammation alongside immune-directed treatments [4].

Collectively, the evidence suggests that alopecia areata exists at the intersection of immune dysregulation and neurogenic signaling. In treatment-resistant cases, persistent neuropeptide-mediated inflammation may represent an underrecognized contributor to disease maintenance. This neuroimmune context provides the theoretical basis for exploring Botulinum toxin A, which modulates neurotransmitter and neuropeptide release, as a potential adjunctive therapeutic strategy in refractory AA [6].

Mechanistic Rationale for Botulinum Toxin A in Treatment-Resistant Alopecia Areata

Botulinum toxin A (BoNT-A) is a purified neurotoxin derived from *Clostridium botulinum* that exerts its primary biologic effect through cleavage of synaptosomal-associated protein 25 (SNAP-25), thereby inhibiting presynaptic acetylcholine release at neuromuscular junctions. Beyond its neuromuscular applications, accumulating evidence demonstrates that BoNT-A also modulates sensory neurotransmission and neuropeptide release, including substance P and calcitonin gene-related peptide (CGRP). These broader neuromodulatory properties provide a biologically plausible rationale for its exploration in inflammatory dermatologic disorders characterized by neurogenic components [11].

Substance P plays a key role in stress-induced perifollicular inflammation and premature catagen induction. Experimental studies have shown that inhibition of substance P signaling attenuates inflammatory cell recruitment and mast cell activation in cutaneous tissues. BoNT-A has been demonstrated to reduce substance P release from peripheral nerve endings, thereby decreasing neurogenic inflammation in several dermatologic conditions. By limiting neuropeptide-driven amplification of local immune responses, BoNT-A could theoretically mitigate persistent perifollicular inflammation in treatment-resistant alopecia areata [12].

In addition to neuropeptide inhibition, BoNT-A may influence cutaneous microcirculation. Acetylcholine and neuropeptide-mediated vasodilation contribute to vascular dynamics within inflamed skin. By reducing cholinergic signaling, BoNT-A may alter local blood flow and tissue oxygenation, potentially affecting inflammatory cell trafficking. Although the direct relevance of these vascular effects to alopecia areata remains incompletely defined, modulation of perifollicular microenvironmental conditions may influence immune cell infiltration and follicular cycling [13].

BoNT-A has also been shown to exert anti-inflammatory effects independent of neuromuscular blockade. Studies suggest that it may downregulate expression of proinflammatory cytokines and reduce mast cell degranulation. Given that mast cells are enriched around hair follicles and contribute to immune privilege collapse in alopecia areata, attenuation of mast cell–mediated signaling may represent another mechanism through which BoNT-A could exert therapeutic benefit in recalcitrant disease [12].

Importantly, neuroimmune modulation may be particularly relevant in patients whose disease is strongly associated with stress triggers or chronic neurogenic inflammation. In such individuals, persistent neural activation may sustain perifollicular immune responses even when systemic immunosuppression partially controls adaptive immune pathways. Targeting the neural component with BoNT-A may therefore function as an adjunctive strategy rather than a replacement for immune-directed

therapies, potentially offering benefit in select refractory cases [4].

However, mechanistic plausibility does not equate to clinical efficacy. The extent to which inhibition of neuropeptide release meaningfully alters the dominant cytotoxic T-cell–driven pathogenesis of alopecia areata remains uncertain. Given that interferon-γ and interleukin-15–mediated pathways are central to disease persistence, the relative contribution of neurogenic amplification versus primary autoimmune activation must be carefully considered when evaluating BoNT-A as a therapeutic candidate. Thus, critical appraisal of available clinical evidence is essential before drawing conclusions regarding its role in treatment-resistant alopecia areata [2].

Preclinical and Experimental Evidence Supporting Neurotoxin-Based Modulation in Alopecia Areata

Preclinical investigation into the role of neural mediators in alopecia areata has largely focused on stress-induced models and neuropeptide-driven inflammation rather than direct application of Botulinum toxin A (BoNT-A) in autoimmune hair loss. Murine studies have demonstrated that stress exposure induces perifollicular accumulation of inflammatory cells and premature catagen transition, effects that correlate with increased expression of substance P and other neurogenic mediators. Importantly, pharmacologic blockade of neurokinin-1 receptor signaling has been shown to attenuate inflammation and partially restore hair cycling in experimental systems, reinforcing the concept that neuropeptide pathways may contribute to follicular immune dysregulation [8].

Further mechanistic studies indicate that substance P promotes mast cell degranulation and enhances local cytokine production within the perifollicular environment. Mast cells, in turn, can amplify inflammatory signaling and contribute to immune privilege collapse. Experimental interruption of mast cell activation reduces inflammatory changes in hair follicle models, suggesting that targeting upstream neural triggers may indirectly modulate immune activation. Although BoNT-A has not been extensively evaluated in autoimmune alopecia animal models, its capacity to inhibit substance P release offers indirect mechanistic relevance in this context [9].

Evidence from other inflammatory dermatologic conditions provides additional biologic plausibility. In models of psoriasis and atopic dermatitis, neural mediators including substance P and CGRP have been implicated in perpetuating inflammation. BoNT-A has demonstrated anti-inflammatory effects in certain cutaneous disorders characterized by neurogenic inflammation, including reduction of pruritus and inflammatory erythema. These findings suggest that modulation of peripheral nerve signaling can alter local immune responses, though extrapolation to alopecia areata requires caution due to distinct pathogenic drivers [11].

Experimental data also support the broader concept of cutaneous neuroimmune crosstalk. Sensory nerves regulate immune cell recruitment, vascular permeability, and cytokine production through neuropeptide release. Disruption of this signaling can alter inflammatory thresholds within the skin. In alopecia areata, where cytotoxic lymphocyte activity predominates, neural inputs may function as amplifiers rather than primary initiators. Therefore, the theoretical impact of BoNT-A in recalcitrant disease may be more pronounced in subsets with strong stress associations or heightened neurogenic activation [10].

Notably, no robust controlled animal studies have definitively demonstrated that BoNT-A alone can reverse established autoimmune hair loss. The absence of direct preclinical efficacy data specific to alopecia areata represents a significant limitation in the mechanistic evidence chain. Current rationale relies primarily on extrapolation from neuropeptide biology and indirect observations in other inflammatory conditions. This gap underscores the need for targeted experimental models assessing whether inhibition of neurogenic signaling meaningfully attenuates cytotoxic T-cell–mediated follicular damage [2].

Collectively, available preclinical data support a contributory role of neurogenic inflammation in hair follicle immune dynamics but do not yet establish BoNT-A as a proven disease-modifying intervention in alopecia areata. The transition from theoretical plausibility to clinical validation therefore depends heavily on critical evaluation of human studies, which remain limited in number and methodological rigor.

Clinical Evidence of Botulinum Toxin A in Treatment-Resistant Alopecia Areata

The human evidence base for Botulinum toxin A (BoNT-A) in alopecia areata is small and is dominated by negative or neutral outcomes in recalcitrant disease, with a minority of positive signals mainly confined to the cephalalgic alopecia areata phenotype. This distinction is clinically important because cephalalgic AA is characterized by neuralgiform head pain with localized alopecia and may represent a neurogenic-dominant endotype rather than the classic interferon-driven cytotoxic phenotype. As a result, aggregating cephalalgic AA with alopecia totalis/universalis (AT/AU) can overestimate expected benefit in treatment-resistant

autoimmune AA. [15]

The best-cited early prospective clinical experience in scalp AA was reported by Cho and colleagues, who examined intradermal BoNT-A injections in a small cohort (n=7) with varying severity, including patients with totalis/universalis disease. The protocol used repeated intradermal injections (10 units per site across treated areas over three sessions). Outcomes were largely negative: most patients showed no clinical change, one patient reported worsening, and one patient experienced spontaneous recovery unrelated to treatment. The authors concluded BoNT-A was not supported as an alternative therapy for recalcitrant AA, while noting that future work in mild-to-moderate AA would be needed to fully exclude benefit in less severe disease. [14]

In contrast, the best-known positive clinical signal comes from the case report describing cephalalgic alopecia areata. Cutrer and Pittelkow reported remission of neuralgiform head pain with concomitant hair regrowth after botulinum toxin A injections, suggesting a mechanistic link between neural signaling and localized follicular dysfunction in this syndrome. While this observation is compelling for hypothesis generation, it is a single-patient report and cannot establish efficacy for conventional AA, particularly severe or treatment-resistant variants. Nonetheless, it provides a key clinical anchor for the neuroimmune rationale that underpins BoNT-A interest in alopecia. [15]

Follow-up mechanistic work by Cutrer and colleagues further complicated the simplistic assumption that BoNT-A benefits would correlate with reduced neuropeptide activity. In cephalalgia alopecia, botulinum toxin treatment was associated with increased substance P and CGRP-containing cutaneous nerves in the scalp on histologic assessment, an observation that raises questions about compensatory neural changes after neuromodulator therapy. For alopecia researchers, this finding is important because it suggests that BoNT-A effects on neuropeptide biology may be context-dependent and not uniformly anti-neurogenic in all settings, which may help explain inconsistent results when extrapolated to autoimmune AA. [16]

A more rigorous evaluation relevant to recalcitrant AT/AU was published by Thuangtong in a randomized, double-blind, placebo-controlled split-scalp trial in which 20 patients with refractory AT or AU received intradermal botulinum toxin A (50 units in 2.5 mL) on one half of the scalp and saline on the other half. Using SALT scoring, scalp mapping, and serial photography across four months, the study found no terminal hair regrowth benefit on the treated side compared with placebo. This trial is particularly influential because it directly targets the most treatment-resistant phenotypes and uses an internal control design, strengthening confidence that BoNT-A monotherapy is unlikely to be effective for classic recalcitrant AT/AU. [17]

Systematic syntheses of botulinum toxin for hair loss similarly conclude that evidence for AA is sparse and inconsistent, with most available data addressing androgenetic alopecia rather than autoimmune alopecia. Hussein's systematic review (search through September 2022) highlights the limited number of AA-related reports and the major methodological weaknesses across studies, including heterogeneous protocols, lack of standardized endpoints, and small sample sizes. From a critical appraisal standpoint, the current AA evidence supports, at most, investigational use in narrowly selected contexts rather than routine clinical adoption. [18]

A more recent broad review of botulinum toxin in hair and scalp disorders likewise emphasizes that data for autoimmune alopecia remain limited and that the most consistent evidence for BoNT in scalp practice relates to non-alopecia indications such as craniofacial hyperhidrosis, with hair-growth outcomes in alopecia studies showing high variability. For AA specifically, this reinforces that any future progress will require appropriately powered randomized trials, careful phenotyping (including identification of neurogenic-predominant subsets), and incorporation of mechanistic biomarkers to avoid repeating negative results seen in recalcitrant AT/AU. [19]

Mechanistic Interpretation of Variable Outcomes and Why Recalcitrant AT/AU Often Fails to Respond

The most consistent negative signal for Botulinum toxin A (BoNT-A) in alopecia areata comes from studies enriched for alopecia totalis and alopecia universalis, where the dominant pathology is sustained cytotoxic immune activation at the follicular unit. In these phenotypes, interferon-driven signaling and IL-15–dependent survival of autoreactive lymphocytes are central, meaning that neuromodulation alone may be insufficient to interrupt the core autoimmune circuit. Consequently, even if BoNT-A reduces neurogenic amplification, the principal drivers of follicular immune privilege collapse may remain active and capable of maintaining disease. [2]

A second explanation for weak efficacy in recalcitrant disease is chronicity-related "immune memory" within the scalp. Chronic inflammatory dermatoses are increasingly understood to persist through tissue-resident memory T cells that remain in previously

affected skin and rapidly reinitiate inflammation upon triggers. Recent work in alopecia areata suggests that treatment-refractory chronic cases may show increased infiltration of skin-resident memory T-cell populations, supporting a biologic basis for persistent or rapidly relapsing disease. If BoNT-A does not meaningfully reduce these pathogenic resident compartments, clinical benefit would be expected to be limited in long-standing refractory AA. [20]

Third, modern high-resolution immune profiling indicates that persistent AA is driven by clonally expanded cytotoxic T cells that can maintain pathogenic activity across time. Single-cell and T-cell receptor sequencing in experimental AA models supports a causal role for clonally expanded CD8+ T cells in disease maintenance. This concept strengthens the interpretation that interventions must either directly suppress these clones, interrupt their survival signals, or restore immune privilege robustly; BoNT-A's mechanism is indirect and may not sufficiently affect the clonal immune architecture underpinning recalcitrant disease. [21]

Fourth, while neuropeptides such as substance P can amplify perifollicular inflammation, their role may be more prominent in early lesions or in neurogenic-predominant variants such as cephalalgic alopecia. In AA mouse models, exogenous substance P worsened immune features including mast cell degranulation, accelerated catagen, and increased cytotoxic CD8+ granzyme B–positive infiltrates, supporting neuropeptides as amplifiers rather than primary initiators. This framing helps reconcile why BoNT-A may show occasional benefit in pain-associated or stress-linked phenotypes yet fail in classic refractory AT/AU dominated by sustained cytotoxic autoimmunity. [22]

Fifth, the directionality of neuropeptide changes after BoNT-A may not be uniformly suppressive across all tissues or disease states. The observation that BoNT-A treatment in cephalalgia alopecia was associated with increased substance P and CGRP-containing cutaneous nerves suggests complex compensatory neural remodeling after chemodenervation. If similar compensatory changes occur in some AA patients, BoNT-A could produce variable or even paradoxical outcomes, contributing to heterogeneous clinical results across small studies and case reports. [16]

Finally, methodological issues likely contribute substantially to inconsistent outcomes. Trials and reports vary in dilution, injection depth (intradermal vs subcutaneous), scalp mapping, total dose, treatment intervals, and outcome measures. In addition, AA is biologically heterogeneous; without stratification by stress association, pain phenotype, inflammatory biomarkers, or disease duration, any true signal confined to a neurogenic endotype may be diluted within broader recalcitrant cohorts. Contemporary mechanistic reviews of AA emphasize that immune-pathway dominance and tissue-level inflammatory architecture differ across patients, reinforcing the need for phenotype- and biomarker-guided trial design if BoNT-A is to be evaluated fairly. [23]

Safety, Injection Protocol Considerations, and Practical Limitations of Botulinum Toxin A in Alopecia Areata

Botulinum toxin A has an extensive safety record across neurologic and dermatologic indications, but safety considerations in alopecia areata must be framed within the context of off-label scalp use and the typically large treatment surface area required for AA. All botulinum toxin products carry warnings regarding distant spread of toxin effect, with potential systemic symptoms (eg, generalized weakness, dysphagia, dysphonia, breathing difficulties) reported hours to weeks after injection, particularly when higher total doses are used or in susceptible individuals. While these severe outcomes are uncommon in dermatologic practice at typical doses, they remain essential elements of patient counseling, informed consent, and risk stratification when considering investigational use for AA. [24]

Local adverse effects are the most common practical limitation and include injection-site pain, bruising, transient edema, headache, localized tightness, and unintended weakness of adjacent muscles depending on injection depth and anatomic placement. Data from scalp-focused botulinum toxin literature (across scalp conditions rather than AA exclusively) indicate that adverse effects are generally mild and self-limited, but they also highlight variability in reporting and the absence of standardized safety endpoints. In AA trials and pilot studies, heterogeneity in adverse-event capture makes cross-study comparison difficult, reinforcing the need for consistent monitoring frameworks in future AA-specific trials. [25]

Injection technique is a major determinant of both safety and interpretability of outcomes. Most AA studies have used intradermal injections with relatively dilute toxin to target superficial neural and cholinergic structures, conceptually aligning with the goal of neurogenic modulation rather than deep muscle paralysis. However, defining "intradermal" on the scalp is technically challenging due to variable dermal thickness and operator technique, and shallow vs deeper placement can shift the adverse-event profile toward pain and wheals or toward unwanted frontalis/occipitalis effects. Lack of standardized scalp mapping and

depth confirmation is therefore a recurring limitation in the AA BoNT-A literature. [14]

Total dose and surface coverage also constrain feasibility in extensive AA. Recalcitrant alopecia totalis/universalis would theoretically require broad scalp coverage, increasing cost, visit burden, and cumulative dosing relative to focal cosmetic patterns. In the split-scalp randomized trial design used for refractory AT/AU, a moderate dose was distributed across one half of the scalp, yet no regrowth benefit was detected, raising the question of whether higher dosing would be needed for efficacy and, if so, whether that would compromise safety, tolerability, or practicality. This dose–coverage dilemma is a central translational barrier for BoNT-A in classic treatment-resistant AT/AU. [17]

Coexisting scalp disorders may alter tolerability and confound interpretation. For example, seborrheic dermatitis, irritant dermatitis, and scalp dysesthesia can increase injection discomfort and may drive symptom improvement that is misinterpreted as AA improvement. Conversely, studies exploring intradermal botulinum toxin for scalp sebum reduction suggest that the scalp can tolerate intradermal dosing with favorable short-term safety, but these populations differ fundamentally from AA cohorts in immune biology and outcome expectations. From a trial-design perspective, controlling concomitant scalp inflammation and using objective regrowth endpoints (SALT-based measures and standardized photography) are essential to avoid false-positive interpretations. [26]

Finally, practical limitations include the absence of validated patient-selection criteria and the uncertainty of the mechanism in autoimmune-dominant AA. If BoNT-A benefit is confined to neurogenic-predominant phenotypes (eg, pain-associated cephalalgic AA), broad application to treatment-resistant classic AA will produce high nonresponse rates, undermining cost-effectiveness and increasing exposure without clear benefit. This reinforces that future studies should predefine phenotypes, incorporate neuroimmune biomarkers where feasible, and explicitly evaluate BoNT-A as adjunctive therapy rather than monotherapy in severe recalcitrant disease. [15]

Comparison With Established Evidence-Based Therapies and Where Botulinum Toxin A Fits in Recalcitrant Alopecia Areata

When Botulinum toxin A (BoNT-A) is evaluated against established alopecia areata (AA) therapies, the most striking difference is the level of evidence and the magnitude of expected benefit in severe, treatment-resistant disease. For moderate-to-severe AA, randomized phase 3 data support clinically meaningful scalp regrowth with oral JAK inhibition, and these trials have reshaped the therapeutic standard for many patients with extensive disease. In contrast, the best-controlled BoNT-A data in refractory alopecia totalis/universalis have shown no meaningful regrowth benefit, suggesting that BoNT-A monotherapy is unlikely to compete with immune-targeted systemic therapy in classic recalcitrant AA phenotypes. [3][17]

Conventional first-line and second-line approaches for AA (topical corticosteroids, intralesional triamcinolone, topical immunotherapy with diphenylcyclopropenone, and selected systemic immunosuppressants) remain clinically relevant, but they are limited by relapse, variable response in extensive disease, and tolerability or monitoring burdens. Topical immunotherapy continues to be used in severe AA, including AT/AU, with ongoing contemporary reports describing potential benefit in selected patients, though response rates and durability remain heterogeneous across studies and protocols. In refractory disease, these modalities are often considered either as adjuncts or as alternatives when systemic targeted therapy is not feasible. [1][27]

By comparison, JAK inhibitors offer pathway-level suppression aligned with dominant AA immunobiology. Baricitinib demonstrated superiority over placebo in severe AA in two pivotal phase 3 trials, establishing an evidence-based systemic option for patients with extensive or refractory disease. More recently, ritlecitinib expanded the landscape with randomized trial evidence including adolescents, supporting its use in severe disease across a broader age range. Deuruxolitinib has also shown efficacy in phase 3 data in adults with moderate-to-severe AA, further validating the class and broadening therapeutic choice where approved and accessible. [3][28][29]

Given this context, a rational position for BoNT-A is not as a replacement for immune-directed therapy in treatment-resistant AA, but as a potential adjunct in narrowly selected scenarios where neurogenic inflammation plausibly contributes to disease activity. The most defensible niche is a neurogenic-predominant presentation (such as cephalalgic alopecia) or patients with prominent scalp pain/dysesthesia and stress-linked flares, where symptom improvement could be clinically meaningful even if hair regrowth benefit is uncertain. Even then, the current evidence is insufficient to recommend routine use, and its role should be framed as investigational or individualized off-label care rather than guideline-based AA therapy. [15][17]

In practical terms, BoNT-A could be considered only after confirming true refractoriness, optimizing evidence-based therapies, and discussing realistic goals and uncertainty. If used, it should ideally be combined with standard AA management (for example, intralesional corticosteroids for focal activity or systemic therapy in severe disease when appropriate), while carefully separating symptomatic improvement (pain/pruritus/dysesthesia) from objective regrowth endpoints (SALT-based response and standardized photography). This approach aligns with the broader direction of AA care toward phenotype-aware management and structured outcome measurement. [22][23]

Limitations of Current Evidence

The most important limitation is that the clinical evidence for Botulinum toxin A in alopecia areata is extremely small and concentrated in small cohorts, single-center experiences, and individual case reports, with only limited controlled data in classic refractory phenotypes. Even the better-designed split-scalp randomized trial in alopecia totalis/universalis evaluated a short follow-up horizon for a chronic relapsing autoimmune condition, which restricts inference about delayed responders, maintenance effects, or relapse dynamics. Taken together, the current literature does not provide a sufficiently robust evidentiary foundation to justify routine clinical use in treatment-resistant AA. [17]

A second limitation is biological and phenotypic heterogeneity that is rarely addressed in study design. Evidence suggests that neural mechanisms may be most relevant in neurogenic-predominant presentations such as cephalalgic alopecia areata, while classic recalcitrant AT/AU is dominated by persistent cytotoxic immune circuits. Pooling these distinct phenotypes risks diluting any true neurogenic signal and overgeneralizing findings from a rare syndrome to common autoimmune AA. This is a core reason that "mixed-results" literature may reflect patient selection rather than inconsistent pharmacology. [15]

Third, modern immune profiling indicates that chronic and treatment-resistant AA can be maintained by skin-resident memory T-cell populations and persistent lesional immune architecture that supports rapid reactivation. If these resident populations remain intact, neuromodulation alone would be expected to have limited impact on sustained autoimmune targeting of the follicle. This provides a mechanistic explanation for the repeated observation that BoNT-A monotherapy fails to induce terminal regrowth in long-standing refractory AT/AU. [30]

Fourth, clonal immune persistence adds another layer of resistance biology. High-throughput T-cell receptor sequencing has identified clonally expanded CD8+ T-cell populations in alopecia areata, supporting the concept that durable control may require direct suppression or elimination of pathogenic clones or their survival signals. This framework favors immune-targeted therapy as the backbone of treatment in recalcitrant disease and suggests that BoNT-A, at best, would function as an adjunct modulating triggers or amplifiers rather than reversing the autoimmune core. [32]

Fifth, protocol heterogeneity across BoNT-A studies is substantial and impairs interpretability. Variability in toxin formulation, dilution, injection depth, scalp mapping, total dose, treatment interval, and outcome measurement makes it difficult to compare results across reports or to replicate protocols in practice. Systematic reviews of BoNT-A for hair loss repeatedly emphasize these methodological weaknesses and the dominance of non-AA indications in the broader scalp literature, reinforcing that AA-specific conclusions remain limited. [18]

Future Research Directions

Future trials should begin with rigorous phenotyping and stratification. At minimum, studies should distinguish patchy AA from AT/AU, identify pain or dysesthesia features, assess stress-associated flares, and document disease duration and prior treatment exposure in a standardized manner. The strongest hypothesis for BoNT-A is that it benefits a neurogenic-predominant endotype, so enrichment strategies that select for neural symptoms or stress-linked activity are likely essential to avoid repeating negative outcomes seen in unselected refractory cohorts. [15]

Biomarker integration is also essential. Contemporary understanding of AA emphasizes multiple interacting immune pathways and the likely role of tissue-resident memory T cells in relapse and persistence. Trials that incorporate scalp biopsies or minimally invasive molecular profiling could test whether BoNT-A meaningfully alters neuropeptide signaling, perifollicular mast cell activation, or downstream immune recruitment, and whether any such changes correlate with objective regrowth. This would shift the field from anecdotal response toward mechanism-linked efficacy. [33]

Randomized designs should prioritize objective hair endpoints and clinically meaningful time horizons. Split-scalp designs can reduce interpatient variability, but they should include longer follow-up and predefined maintenance phases to determine whether

BoNT-A affects relapse frequency, symptom burden, or the durability of regrowth when used with standard therapies. Because BoNT-A effects are time-limited, studies should also test repeat-cycle protocols that reflect real-world administration rather than single short courses. [17]

Finally, the most realistic future role for BoNT-A is as an adjunct rather than monotherapy in recalcitrant AA. Trials should evaluate add-on BoNT-A to an evidence-based backbone (for example, JAK inhibition or topical immunotherapy) in patients with prominent neurogenic symptoms, with outcomes that separate symptom improvement from true follicular recovery. If BoNT-A reduces stress-linked flares, scalp dysesthesia, or neurogenic inflammation, it may still provide clinically meaningful benefit even if regrowth effects are modest, but this must be demonstrated with controlled methodology. [33]

Conclusion

Botulinum toxin A has a biologically plausible neuroimmune rationale in alopecia areata through modulation of neurotransmission and neuropeptide-associated inflammation, yet the current clinical evidence does not support its use as an effective monotherapy for classic treatment-resistant alopecia totalis or universalis. The most credible potential niche is a neurogenic-predominant phenotype, where symptoms such as scalp pain or dysesthesia and stress-associated activity suggest a stronger neural contribution. Moving forward, well-designed trials with phenotype enrichment, biomarker integration, standardized protocols, and adjunctive-study designs are required to determine whether BoNT-A has a meaningful and reproducible role in recalcitrant alopecia areata.

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