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ALOPECIA AREATA: CURRENT INSIGHTS INTO IMMUNOPATHOGENESIS, DIAGNOSIS, AND EVOLVING THERAPEUTIC STRATEGIES

Tushar Tapadiya¹, Deepa S. Mandlik², Ravindra Kulkarni³ and Vaibhav M. Shinde^{*1}

Department of Pharmacognosy¹, Department of Pharmacology², Department of Pharmaceutical Chemistry³, Bharati Vidyapeeth (Deemed to be University), Poona College of Pharmacy, Pune - 411038, Maharashtra, India.

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Correspondence to Author:

Dr. Vaibhav Shinde

Assistant Professor & HOD
Department of Pharmacognosy,
Poona College of Pharmacy, Bharati
Vidyapeeth (Deemed to be
University), Pune - 411038, India.

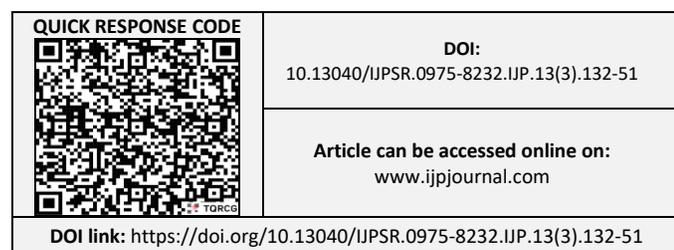
E-mail: vaibhavshinde847@gmail.com

ABSTRACT: Alopecia areata (AA) is a chronic autoimmune disorder leading to non-scarring hair loss and affecting millions worldwide across all age groups. Despite extensive research, the precise molecular mechanisms remain incompletely understood, arising from complex interactions among immune dysregulation, genetic susceptibility, and environmental triggers. Emerging evidence also implicates lifestyle factors, psychological stress, gut microbiome imbalance, and drug exposures in disease onset and progression. This review synthesizes current knowledge on the immunopathogenesis of AA, integrating insights from T-cell mediated autoimmunity, genetic variations, and epigenetic regulation. Advances in diagnostic strategies, including trichoscopy, histopathology, and severity assessment tools, are critically evaluated with attention to their clinical applicability and limitations. Importantly, the therapeutic landscape of AA is rapidly evolving: beyond traditional approaches such as corticosteroids and minoxidil, recent progress in biologics, JAK inhibitors, regenerative strategies including stem cell and exosome-based therapies, nanotechnology, and microneedle-assisted delivery systems is reshaping treatment paradigms. By bridging mechanistic understanding with therapeutic innovation, this review highlights unmet clinical needs, emphasizes opportunities for precision and regenerative medicine, and outlines future directions toward achieving durable and patient-centered outcomes in AA.

INTRODUCTION: Alopecia areata (AA) is an autoimmune disorder in which the immune system mistakenly attacks hair follicles, leading to non-scarring, patchy hair loss on the scalp and other hair-covered areas. AA shows a wide clinical spectrum from small, clearly demarcated bald patches to widespread hair loss that may involve the entire scalp or body¹.

This long-term disorder primarily affects hair follicles and nails, and in certain instances, it may also influence the retinal pigment epithelium². AA can appear in many forms, like complete scalp hair loss (alopecia totalis) or total body hair loss (alopecia universalis)³.

This condition affects people irrespective of their age, gender, or origin. On a worldwide scale, there are approximately 20.9 cases in every 100,000 person-years, with an estimated lifetime risk of about 2% among the general population, with estimates globally ranging from 0.57% to 3.8%⁴. Approximately 20% of cases are seen in children, while nearly 60% of adults experience their initial



hair loss patches before age 30⁵. Multiple research studies have established that AA is associated not only with autoimmune diseases but also it is also linked with several chronic diseases, including thyroiditis and vitiligo. Furthermore, AA may also have connections to chromosomal disorders, notably Down syndrome, as well as polyglandular autoimmune syndrome type 1⁶. This condition is closely influenced by immune system activity, with CD8+ T lymphocytes specifically attacking hair follicles⁷. Environmental and psychological stresses like tobacco use, poor sleep quality, obesity, and dietary elements like fatty acids and gluten may play a role in triggering AA⁸. AA is mostly diagnosed by its common clinical signs, and examinations like trichoscopy and histopathology are useful in patients with AA⁹. Treatments for AA may include corticosteroids injected, applied topically, or taken orally as well as minoxidil and specific light-based treatments. However, these approaches may bring about side effects such as unwanted hair growth in certain areas or skin irritation, and there is no guarantee that the hair that regrows during treatment will remain after the therapy is stopped¹⁰. Although this condition is not deadly, it often carries a significant emotional impact. Hair plays a crucial role in human identity, particularly for women, and its loss can profoundly influence self-esteem and body image¹¹.

This review identifies key gaps in both academic and clinical research surrounding AA by exploring its pathogenesis, diagnostic techniques, and treatment approaches. It first examines the immunologic mechanisms behind AA, along with environmental and epigenetic factors influencing the condition. Next, it outlines current diagnostic tools and severity assessment methods. Additionally, it highlights emerging therapies, including small-molecules, Biologics, and combination therapies. Finally, the review discusses upcoming research directions, accenting the importance of investigating AA pathogenesis and advancing targeted therapies to assist clinicians and dermatologists in developing clear management guidelines.

Pathophysiology: The development of AA is a complex process heavily influenced by the human immune system. A key factor is the involvement of Type IV hypersensitivity reactions driven by T

cells which contribute to the disease. Beyond autoimmunity, genetic predisposition and environmental influences, such as stress and viral infections, significantly influence the development and advancement of AA¹².

Immunity: Hair follicles possess a form of specialized immunity, but this is limited to the anagen phase 3. In AA, the immune system attacks hair follicles through two separate pathways. First, it directly attacks the follicles, an action triggered by autoantigens produced by melanocytes within the follicles. Second, it weakens the follicle's natural protection by increasing MHC class I levels, which makes it easier for CD8+ T cells to spot and attack the hair follicle when autoantigens are present. Upon stimulation, these cells release perforin and granzymes, which work together to damage follicular keratinocytes and Perforin creates pores in target cell membranes, while granzymes trigger apoptosis. This process leads to hair follicle destruction and subsequent hair loss. Some CD8+ T cells later transition into memory T cells, persisting within the body and potentially causing repeated instances of AA³.

The Th1 and Th17 arms of CD4+ T cells modulate immune activity via IFN- γ and IL-17 release, contributing to inflammatory signalling¹³. Macrophage activation by IFN- γ production boosts MHC expression in dendritic cells, aiding T-cell antigen recognition. Likewise, IL-17 from Th17 cells extends and amplifies inflammation. Additionally, AA sees an increase in IL-2 and IL-6 levels, with IL-2 promoting T-cell proliferation and IL-6 playing a key role in B-cell activation and overall inflammatory processes¹⁴. TNF- α is an essential cytokine that stimulates immune cell activation and migration, heightens inflammation, and exacerbates hair follicle damage. The cooperation among cytokines sustains the inflammation in AA. IFN- γ strengthens TNF- α 's activity, further aggravating inflammation. Such disturbances affect the hair cycle by delaying the normal switch from the growing to the resting phase, resulting in early hair loss¹⁵. In AA, regulatory T-cell dysfunction diminishes their ability to control effector T-cell activity, leading to immune dysregulation and an excessive autoimmune response¹³. Histological analysis of the affected tissue revealed a dense infiltration

belonging to CD8+ T lymphocytes, compromising the structural integrity of hair follicles¹⁴. A visual

summary of the immune dysregulation and follicular destruction in AA is illustrated in **Fig. 1**.

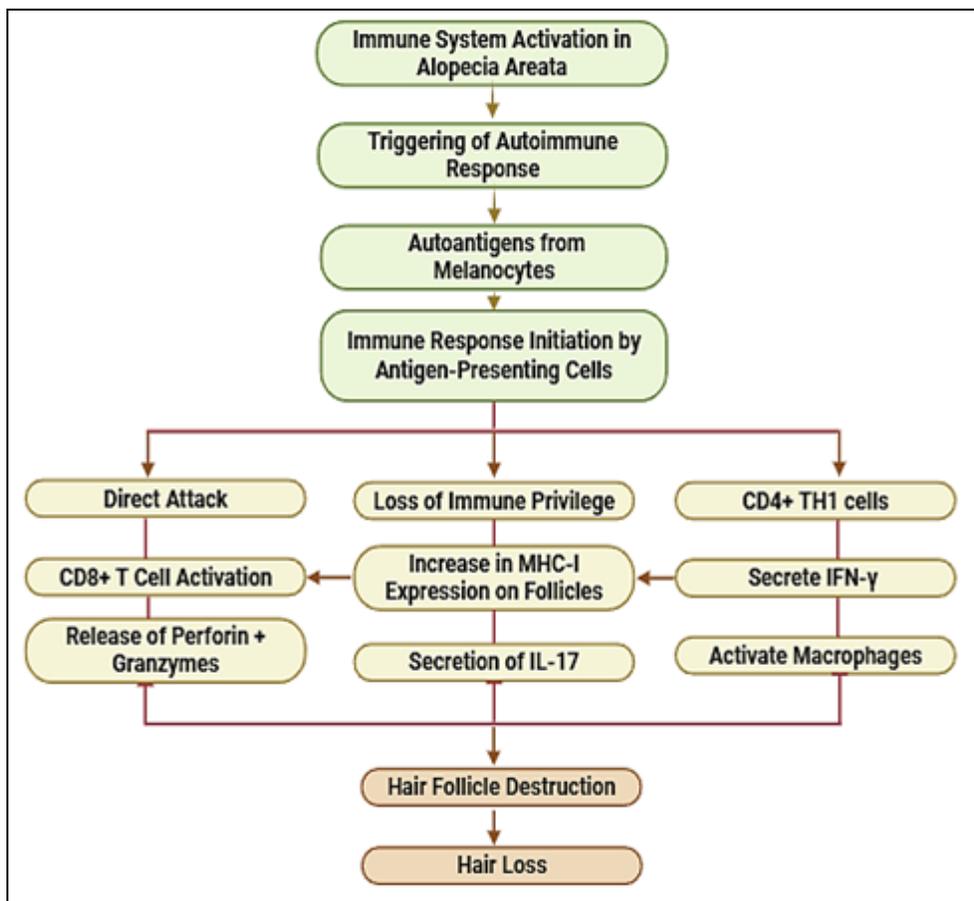


FIG. 1: MECHANISTIC OVERVIEW OF IMMUNE-MEDIATED HAIR FOLLICLE DESTRUCTION IN AA

Genetic Factors: AA has a recognized genetic component in its pathophysiology, with incidence rates being notably higher among individuals with a family history of the condition¹⁶. Genome-wide association studies (GWAS) have identified several genetic loci associated with susceptibility. A total of 14 genetic risk loci were found, with HLA-DR emerging as a key etiological factor, showing the strongest correlation with MHC¹⁷. Genome-Wide Association Studies (GWAS) have identified genomic regions linked to AA, including NKG2D, which is connected with natural killer (NK) cell receptors, ULBP3/6, and MICA, which are involved in activating ligands, and CTLA4, which serves as a regulator of T-cell function¹⁸.

MicroRNAs contribute to AA diagnosis by their expression patterns in affected tissues. Recent studies indicate that miR-101 could serve as a potential indicator of disease presence¹⁹. In addition, lesional skin in AA patients exhibits a significant increase in the expression levels of

miRNA-155, 146a, and 203. Furthermore, individuals presenting with numerous lesions demonstrate considerably higher miRNA-146a levels than those with just a single lesion²⁰. A study analysed the association between interleukin-related genes and AA, identifying IL2RA, IL17A, IL12B, and IL23R as key contributors. The study examined various single-nucleotide polymorphisms (SNPs) and found that rs3118470 within IL2RA posed a significant risk factor under dominant and homozygous models. However, SNPs associated with IL17A, IL12B, and IL23R did not exhibit statistically meaningful correlations. The findings suggest that genetic susceptibility to AA may differ across populations, highlighting the importance of further research tailored to various ethnic groups to enhance the accuracy of meta-analyses and improve genetic insights²¹.

A whole-exome sequencing and genome-based collapsing study examined 849 AA cases against 15,640 controls. The analysis pinpointed KRT82, a

gene responsible for encoding hair-specific type II keratin, as the sole genome-wide significant gene enriched in AA cases, with its expression notably diminished within the follicular and skin of affected individuals. Another AA-related gene, KRTCAP3, is linked to hair keratin, whereas DECR2 plays a role in beta-oxidation and is also strongly associated with the disease²². Next-generation sequencing has identified CCHCR1 within an AA-linked region of the HLA class I gene cluster. The protein it encodes plays a role in hair shaft structure, suggesting that disrupted keratinization may contribute to AA pathogenesis²³.

JAK-STAT Signalling Pathway: In recent studies, the JAK-STAT pathway has gained attention for its role in AA. This pathway controls immune signalling through cytokine receptors and the JAK-STAT protein family. JAK1 and JAK3 are mainly linked to inflammatory and autoimmune responses, while JAK2 is more involved in red blood cell and platelet production²⁴. The STAT protein family acts as key transcription factors in the JAK-STAT pathway, binding to DNA and transmitting signals downstream of JAKs. This group includes STAT1 to STAT6, each involved in processes like immune balance, cell growth, and tissue development²⁵. Cytokines such as IFN- γ , IL-2, and IL-15 bind to their receptors on immune or follicular cells, activating JAK1, JAK3, and TYK2 kinases. These kinases then phosphorylate STAT1 and STAT3, which translocate into the nucleus and initiate pro-inflammatory gene expression. This cascade results in CD8⁺ T cell activation, driving follicular inflammation and leading to hair follicle destruction²⁶.

Environmental Factors:

Smoking and Alcohol: Research has confirmed that smoking elevates the risk of developing AA, with long-term smokers and those who smoke more than five cigarettes daily showing a significantly higher likelihood. Some studies indicate a slight but statistically relevant connection between smoking and the development of AA. The harmful effects of smoking, including free radical formation and elevated pro-inflammatory cytokines, may lead to hair follicle damage and IP. At the same time, immune mechanisms, including Th1, Th2, and Th17, play a critical role in AA's development²⁷.

Alcohol has been shown to elevate the levels of inflammatory cytokines, with TGF- α , IFN- γ , and IL-6, that may worsen inflammatory diseases such as psoriasis and possibly AA. Researchers propose that alcohol consumption may intensify TH17-driven inflammation, potentially triggering AA. Furthermore, moderate alcohol intake can disrupt the body's stress response by altering ACTH and cortisol levels, which may contribute to AA progression²⁸.

Microbial Imbalance: Research suggests that people with AA tend to have higher levels of *Cutibacterium acnes* on the scalp, while *Staphylococcus epidermidis* and *S. aureus* are present in lower concentrations. This altered microbial composition may contribute to inflammation and autoimmune responses associated with AA²⁹. A study found that people with severe AA had much lower levels of *S. caprae* and a sharp rise in the *Cutibacterium/S. caprae* ratio, suggesting a possible link between bacterial imbalance and disease severity. While the exact role of *C. acnes* in AA remains uncertain, its presence could be linked to disease progression³⁰. Another study explored gut microbiota differences between AA universalis patients and healthy individuals. Results showed that a 25% elevation in Parabacteroides distasonis and the Clostridialesvadin BB60 group showed around a 9–11% higher likelihood of developing AU, implying that these bacterial changes could act as predictive markers for the disorder³¹.

Role of Psychological Stress in Immune Dysregulation:

Emotional stress is widely recognized as a significant factor in the development and progression of AA, with approximately 23% of affected individuals experiencing a major psychological stressor or distressing life events before symptoms initiate or worsen. Stress in AA activates the HPA axis, leading to the release of neuropeptides such as CRH and substance P. These messengers disrupt the hair follicle's immune privilege, making it easier for the immune system to target it³². Hair follicle cells accumulate intracellular reactive oxygen species (ROS) under environmental stress and insufficient antioxidant defences, promoting the upregulation of stress-related ligands like MICA. Natural killer cells detect such molecules

and respond by releasing IFN- γ ³³. Stress triggers both autoimmune responses and programmed cell death in hair follicles. Corticotropin-releasing hormone and substance P promote keratinocyte apoptosis through pathways involving tumour necrosis factor-alpha (TNF- α), while simultaneously causing mast cells to release their contents, which leads to neurogenic inflammation. This inflammation speeds up the transition of hair follicles to the catagen stage, leading to premature shedding, causing early hair shedding. Furthermore, substance P worsens the inhibition of hair growth by decreasing activation of the TrkA receptor and increasing signals that promote apoptosis, thereby connecting stress with the development of telogen effluvium and progression of AA³⁴. A comprehensive Systematic review of 73 studies involving approximately 414,319 participants highlights a significant association between AA and psychological distress. Findings reveal that people with AA are more prone to emotional challenges such as anxiety and depression, often triggered by prior stressful experiences. Many report that the condition negatively affects their quality of life, especially in terms of social engagement and self-esteem. Over time, a significant number may also experience psychiatric issues linked to the psychological burden of the disease³⁵.

Diet and Obesity: The Mediterranean diet, known for its high levels of omega-3 fatty acids and antioxidants, has been shown to lower systemic inflammation and enhance recovery in conditions such as AA. Vitamin D plays a significant role in immune regulation by inhibiting Th17 cell proliferation, reducing Th1 cell presence, and strengthening T-reg cell function. As an essential immunomodulator, a deficiency in vitamin D has been linked to a higher risk of autoimmune disorders³⁶. Studies have shown that individuals with AA often have reduced vitamin D levels, which tend to decrease further with increasing disease severity. Recent findings indicate that link between vitamin D deficiency and high CRP, with a greater chance of progression to alopecia universalis³⁷.

Obesity promotes systemic inflammation, possibly through pathways mediated by interleukin-17, which enhance the probability of Perifollicular

inflammation and disrupt immune privilege, ultimately causing hair loss. Research has demonstrated a strong link between high BMI and more severe AA, suggesting that obesity may accelerate disease progression and reduce treatment effectiveness³⁸. Patients with AA were found to have lower serum adiponectin levels compared to healthy controls, a hormone involved in fat metabolism. Additionally, a reduction in adiponectin levels correlated with increased disease severity, suggesting that adiponectin could represent a potential indicator for assessing AA progression in obese individuals³⁹.

Sleep: Patients with AA tend to have worsened sleep quality, often linked to greater anxiety, emotional distress, and reduced overall well-being. Additionally, AA is closely connected to sleep disorders, as those affected are more likely to develop obstructive sleep apnea and non-apnea insomnia. At the same time, these conditions may also contribute to AA progression⁴⁰. Poor sleep quality, assessed through metrics like the Pittsburgh Sleep Quality Index, correlates with higher stress levels and worsening AA symptoms. Inadequate sleep interferes with immune function, promoting inflammation and autoimmune activity. Although the exact pathways are not fully understood, conflicts in the HPA axis, a key stress regulator, appear to contribute⁴¹.

Virus and Immunization: The association between viral illnesses and AA has received increased attention in recent years, particularly in the context of the COVID-19 pandemic. Reports from systematic evaluations have highlighted cases of AA appearing after vaccination, especially following administration of mRNA-based platforms such as those developed by Pfizer and Moderna. Both the viral infection and the immunological response to vaccination can stimulate the secretion of pro-inflammatory mediators like IFN- γ , which is instrumental in damaging hair follicles and disrupting their immune privilege. The elevated levels of IFN- γ and related cytokines post-COVID-19 infection or immunization may accelerate AA progression in individuals with underlying susceptibility⁴². AA has also been linked to infections caused by HPV, EBV, HIV, and hepatitis B and C. Additionally,

research has documented cases of AA emerging following hepatitis B immunization⁴³.

Drugs Triggering AA: The data from the FDA's adverse event reports suggest that monoclonal antibodies, especially adalimumab and dupilumab, are commonly linked to cases of AA⁴⁴. A variety of medications, including immunosuppressants (like sulfasalazine), enzyme inducers (such as rifampicin and phenobarbital), retinoids, tyrosine kinase inhibitors, and certain proton pump inhibitors like lansoprazole, have been implicated in the possible induction of AA⁴⁵. A documented case of AU developed following treatment with sacubitril/azilsartan, an angiotensin receptor-

neprilysin inhibitor prescribed for cardiovascular conditions. The findings indicate that certain cardiovascular therapies might induce alopecia through immune system alterations⁴⁶. Another case documented AU following treatment with the B-cell targeting agent rituximab, reinforcing those immunomodulatory drugs, particularly those designed to target specific immune cells, can trigger alopecia in susceptible individuals⁴⁷. Chemotherapeutic agents like Docetaxel and capecitabine are also associated with drug-induced alopecia⁴⁸. These multifactorial contributors interact with immune mechanisms to initiate and sustain follicular damage, as illustrated in **Fig. 2**.

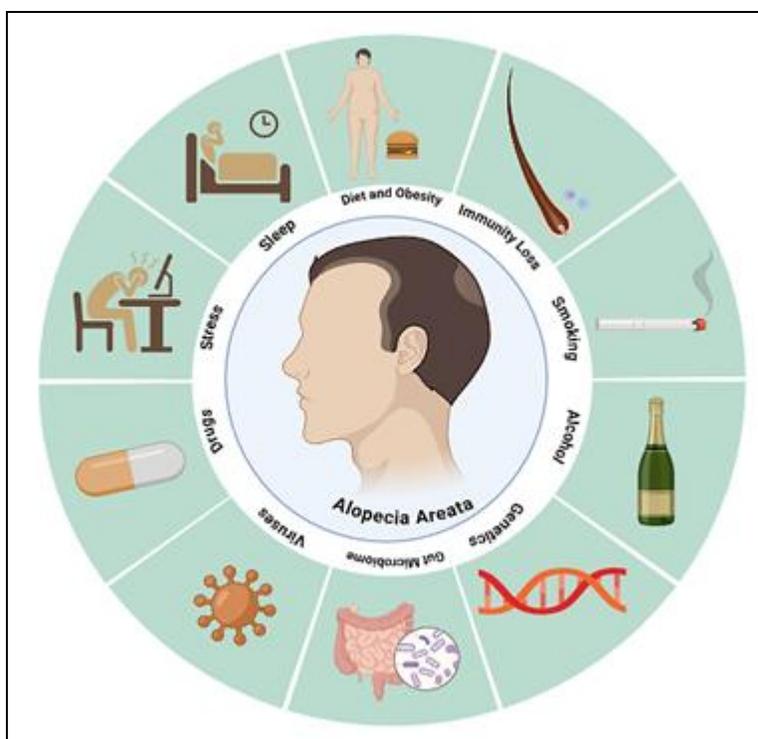


FIG. 2: VISUAL SUMMARY OF THE MULTIFACTORIAL TRIGGERS CONTRIBUTING TO THE PATHOGENESIS OF AA

Diagnostic Framework for AA: AA is mostly diagnosed according to clinical findings, supported by additional tools like the hair pull test, dermoscopic evaluation, laboratory investigations, and histological analysis of skin biopsies. However, in the majority of cases, advanced diagnostic techniques are not required.

Clinical Manifestations of AA: In AA, the skin remains unchanged, but affected individuals experience one or more well-defined hair loss patches, typically round or oval, across the scalp; these patches usually range from 1 to 2 centimetres

in diameter, though their size may differ. Hair loss may also extend beyond the scalp, affecting periocular hair such as the brows and lashes⁴⁹. Sites involved are typically devoid of redness, flaking, or permanent skin damage. The margins of these patches often contain fragile hairs that shed easily, some of which may be broken. The proximal ends of these hairs tend to be thinner and show reduced pigmentation in their lower segments. As AA progresses, patches may enlarge, merge into irregular formations, and potentially develop into AT or AU⁵⁰.

Nail involvement is a common issue in AA, affecting around 6–10% of patients as a recognized complication⁵¹. Several nail abnormalities are also seen in AA patients, most notably small punctate depressions (nail pitting) and a coarse, sandpaper-like surface texture. Nail pitting tends to be more common, whereas rough nails are less frequently documented⁵². Furthermore, AA patients may exhibit atopic tendencies, autoimmune thyroid disease, or concurrent vitiligo, along with an increased risk of conditions such as diabetes and Down syndrome⁵³.

Adjunctive Diagnosis of AA:

Hair Pull Test Evaluation: The hair pull test serves as a straightforward and dependable method for identifying AA. Patients are typically advised to avoid washing their hair for 3 to 5 days before the procedure. During the test, a small cluster of approximately 50 to 60 hairs is gently tugged from the scalp using the thumb and forefinger. If more than six hairs are dislodged, the test is deemed positive, indicating a potential diagnosis of patchy AA⁵⁴.

Dermoscopy: Dermoscopy is a valuable non-invasive technique used for diagnosing, identifying, and assessing AA. This is marked by distinct features, including “exclamation mark” hairs, where the mid-section narrows while the ends thicken, black dots, and follicular opening irregularities within hair-loss regions. When dermoscopy identifies patterns such as yellow dots, black dots, broken or dystrophic hairs, conical hairs, exclamation point-shaped strands, or short vellus hairs, AA can be diagnosed. Moreover, dermoscopy is useful in differentiating other forms of scalp hair reduction⁵⁵.

Histopathological Analysis: Histopathological analysis plays a key role when diagnosing AA is difficult. It typically shows inflammatory infiltration around the hair bulb, mainly composed of lymphocytes, with some eosinophils and mast cells. Moreover, follicular reduction and dystrophic anagen follicles are evident, particularly in patients undergoing AA progression or recovery. Recognizing these structural follicular features helps establish the diagnosis⁵⁶.

Genetic Tests: As genomic research progresses, scientists are exploring the use of genetic testing to support AA diagnosis. Certain genes, such as HLA, CTLA-4, and ULBP1, are linked with immune regulation, hair follicle health, and inflammatory responses, indicating their relevance to AA⁵⁷. Examining genetic variations could improve the precision of AA diagnosis and assist in predicting patient responses to treatment. Despite advancements, genetic testing has not yet become a standard part of clinical evaluation. Still, it enhances traditional diagnostic approaches by offering valuable insights into AA's genetic predisposition and underlying etiology⁵⁸.

Evaluation of AA:

SALT Scores: The Severity of Alopecia Tool (SALT) is a vital clinical metric for assessing the extent of hair loss and tracking disease progression in individuals with AA. The SALT scoring method categorizes the scalp into four regions, each with a defined area percentage⁵⁹. It assesses severity by estimating the extent of hair loss in these regions and calculating a cumulative score. Below is a summary of AA severity staging based on the percentage of hair loss and associated scalp region involvement, as shown in **Table 1**.

TABLE 1: SALT SCALP DISTRIBUTION AND AA SEVERITY

Scalp Region	Percentage of Total Scalp Area	AA Severity Stage	Percentage of Scalp Hair Loss
Top	40%	S0	No hair loss
Back	24%	S1	Less than 25%
Left Side	18%	S2	25–49%
Right Side	18%	S3	50–74%
—	—	S4	75–99%
—	—	S5	Complete hair loss

Under this classification, AA is considered mild when it involves less than 25% of the scalp, intermediate when the extent falls between 25% and 49%, and pronounced when hair loss surpasses 50%⁶⁰. The SALT scoring system now

incorporates body hair loss (B) and nail involvement (N) assessments to improve diagnostic accuracy. Body hair is categorized as B0 (no loss), B1 (partial loss), and B2 (total loss), while nail involvement is classified as N0 (no changes), N1

(partial changes), and N1a (abnormalities in all 20 nails). These additional classifications improve the assessment process, providing a more comprehensive understanding of the patient's condition to aid in more effective treatment planning⁶¹.

Other Evaluation Tools: The SALT score is a widely adopted clinical instrument for assessing the severity of AA. In addition to SALT, various other evaluation tools are employed to provide a more comprehensive assessment. Assessment measures include several validated indices that evaluate disease severity, patch visibility, and quality-of-life outcomes in AA. Offer further insights into the disease's impact⁶². However, assessment of AA involves considering various dimensions, such as the scope of hair loss, its impact on daily life, treatment progress, disease status, emotional effects, and necessary interventions. By incorporating these aspects, healthcare providers can develop a comprehensive understanding of the patient's condition, ultimately enabling more targeted and effective treatment strategies.

Treatment Modalities for AA: Hair re-growth is possible in AA, with patchy cases often resolving on their own. Still, recurrence is frequent, and available treatments vary according to the condition's clinical characteristics. While these therapeutic options help control hair loss and encourage re-growth, they do not address the root cause, and there is no certainty of lasting recovery, as relapses can happen unexpectedly⁶³. The prolonged persistence of AA increases the likelihood of disease progression, with up to 20% of cases advancing to complete scalp hair loss⁶⁴.

Traditional Treatments: Traditional treatment strategies for AA primarily rely on pharmacological methods that regulate immune activity and encourage hair growth. Therapeutic options such as intralesional corticosteroids, systemic and topical steroid preparations, and contact immunotherapy are frequently used, though clinical responses can be highly variable. Furthermore, the potential side effects and risks associated with these treatments can limit their clinical utility. Consequently, while conventional approaches may provide relief, they come with certain drawbacks.

Topical Corticosteroids: The approach involves suppressing local inflammation *via* topical agents to enhance follicular activity. In early stages, topical steroids effectively address localized bald spots, with their skin absorption enhanced by wrapping the treated area. Class 3 and 4 glucocorticosteroids are commonly used in topical therapy due to their potent intracellular effects. Their action involves genomic and non-genomic processes, with cortisol binding to the glucocorticoid receptor (GR), a widely present cytoplasmic receptor. Once bound, the cortisol-GR complex moves into the nucleus and regulates immune responses by suppressing inflammation and promoting anti-inflammatory cytokine expression through interaction with glucocorticoid responsive elements (GRE). Lower cortisol levels further influence immune regulation by repressing NF-kappa B activity. NF-kappa B is typically activated by IL-1 alongside TNF, playing a crucial role in chronic inflammation⁶⁵.

The recurrence rate for topical therapy ranges between 37% and 63%, indicating variability in treatment effectiveness⁶⁵. While topical treatments are generally less effective for AT and AU, they can still be considered for patients who do not respond to other therapies, particularly when applied under occlusion to enhance absorption⁶⁶.

Topical Minoxidil: A popular topical solution, minoxidil helps stimulate hair growth, though it requires consistent application over an extended period to produce noticeable effects. However, studies indicate that its effectiveness in treating AA is limited⁶⁷.

This treatment does not target immune-related issues at the local level but instead improves circulation at the hair follicle by promoting angiogenesis, widening blood vessels, stimulating cell proliferation, and regulating potassium channels⁶⁸. Therapy has shown effectiveness for AGA in both women and men, but its impact on AA remains uncertain⁶⁹. Furthermore, skin sensitivity may occur as a side effect of this drug. Due to its vasodilation properties, caution is advised for patients with heart conditions. Common adverse reactions include mild scalp irritation, often accompanied by itching⁷⁰.

Anthralin: Anthralin has been utilized as a therapeutic option for AA, including in paediatric cases⁷¹. The standard approach for anthralin therapy in AA involves short-contact treatment using 0.5–1% anthralin, with application durations varying from a few minutes to overnight⁷². The precise mechanism of anthralin in AA remains uncertain. However, researchers suggest that its anti-inflammatory effect may result from the free radicals it produces, which help eliminate infiltrated lymphocytes⁷³. Anthralin can lead to skin staining and regional lymphadenopathy (LAD), though these effects generally resolve after discontinuation. Patients frequently report itching, burning, or oozing, with some instances involving bullous eruptions. Although these reactions occur frequently, adverse systemic manifestations are rare, rendering anthralin a largely tolerable therapeutic agent⁷⁴.

Prostaglandin-Based Topical Agents:

Prostaglandins like latanoprost and bimatoprost, commonly used to treat glaucoma, have been associated with eyelash hypertrichosis. As prostaglandin F₂- α (PGF₂ α) analogues, they aid in improving eyelash and eyebrow hypotrichosis and alopecia, likely by prolonging the anagen phase of hair follicles⁷⁵. Research indicates that nightly application of 0.005% latanoprost eye formulation to the lid borders resulted in moderate to complete eyelash re-growth for 45% of individuals with eyelash AA, without reported adverse effects⁷⁶. In a clinical study, AA patients treated with bimatoprost formulation (0.03%) showed notable hair regrowth, with results surpassing those of mometasone furoate cream (0.1%)⁷⁷. Topical latanoprost has proven effective for treating localized patchy AA as a monotherapy or alongside other topical treatments. Additionally, prostaglandin analogues demonstrate a strong safety profile in paediatric and adult AA patients⁷⁸.

Contact Immunotherapy: In contact immunotherapy, topical sensitizers such as DPCP and SADBE are used to elicit allergic dermatitis at bald patches, aiming to trigger follicular regeneration⁷⁹. When more than 50% of the scalp is affected, but AT is not present, CI is often the preferred treatment due to its minimal side effects⁸⁰. To begin contact immunotherapy, patients undergo initial sensitization using a specific agent.

Once sensitization is established, the treatment is extended to a broader area, with incremental increases in drug concentration to trigger a manageable allergic reaction. After reaching this stage, the therapy is maintained through weekly sessions⁸¹. Although the exact process behind contact immunotherapy is still uncertain, researchers suggest that hair regrowth may be linked to a shift in inflammatory cells surrounding hair follicles, which relocate to the dermatitis site⁸². Research shows that contact immunotherapy leads to an average hair regrowth rate of 65.5%, with higher success in patchy AA (74.6%) than in AT/AU (54.5%). Complete regrowth occurs in 32.3% of cases, but relapse rates reach 38.3% during treatment and 49.0% after stopping therapy⁸³. This therapy is contraindicated for pregnant individuals and those with a history of atopic eczema⁸⁴. Potential side effects encompass cervical and occipital lymphadenopathy, disseminated or generalized eczema, along with hypo- or hyperpigmentation⁸⁵.

Phototherapy: Phototherapy for AA includes ultraviolet light therapy, ultraviolet B (UVB) laser excimer, and psoralen plus ultraviolet A (PUVA) treatment. UVB therapy at a 308 nm wavelength is more effective than polychromatic narrowband UVB in stimulating T-cell apoptosis in vitro. By inducing apoptosis at the epidermal and dermo epidermal levels, it suppresses T-lymphocyte expansion and downregulates cytokine release⁸⁶. UVB therapy has shown a 50% hair regrowth rate, along with a measurable increase in hair diameter⁸⁷.

UVA therapy, in contrast, penetrates deeper into the dermis, contributing to tanning but being less absorbed by the epidermis. To enhance the effectiveness of UVA treatment, psoralens compounds that increase skin sensitivity to the light, can be administered either orally (0.1% 8-methoxypsoralen) before UV exposure or deliver topically in an attenuated solution (0.001% 8-methoxypsoralen) 20 minutes before exposure, a method known as PUVA Turban, which helps bypass systemic effects⁸⁸. UVA therapy has demonstrated an efficacy rate of 84% in promoting hair regrowth in AA patients. Phototherapy offers promising results, but it is not without risks. Prolonged UV exposure may lead to photoaging,

keratotic changes, and a higher incidence of skin cancers⁸⁹.

Systemic Therapeutic Approaches:

Systemic Corticosteroids: Oral corticosteroids effectively help control rapidly advancing and widespread AA. However, treatment discontinuation often leads to relapse, and long-term use is associated with significant systemic side effects. A systematic review from 2016 evaluated pulsed corticoid therapy (PCT), a short-term corticosteroid treatment given for a few days each month. Covering 41 studies primarily on intravenous administration, the review found that full recovery was uncommon, but those who responded had a relatively low relapse rate of 17%. As a result, PCT may be a useful option for patients with specific positive prognostic indicators, including multifocal AA, a first occurrence of AA, or cases lasting under two years⁹⁰. Combining systemic glucocorticoids with minoxidil therapy has been found to help lower relapse rates, improving treatment outcomes⁹¹.

Methotrexate: Methotrexate has been suggested as a potential treatment for AA. It is recognized for its effectiveness in managing various inflammatory and autoimmune disorders⁹². The precise mechanism by which methotrexate manage AA remains unclear. However, evidence suggests that it works by inhibiting the enzyme dihydrofolate reductase, leading to increased adenosine levels and its release into the extracellular space. This process suppresses the accumulation of white blood cells and regulates the activities of monocytes, macrophages, and T cells. Additionally, methotrexate is associated with a reduction in the synthesis of TNF-alpha and interferon-gamma⁹³. Methotrexate commonly causes digestive-related side effects, such as nausea, vomiting, ulcers in the mouth, and reduced appetite. However, its most severe risk is potential liver damage⁹⁴.

Cyclosporine: Cyclosporine functions by inhibiting calcineurin phosphatase, which in turn suppresses the expression of interleukin-2, a key cytokine that contributes to the activation of T-cell-mediated immune responses. While cyclosporine can be administered as a single-agent therapy, its effectiveness is notably enhanced when used in combination with corticosteroids.

Studies report a treatment success rate of 69% for the combination approach, compared to 57% when used alone. Moreover, the likelihood of disease recurrence is considerably lower with combination therapy (36%) than with cyclosporine monotherapy, which shows a relapse rate of 74%⁹⁵. Common adverse reactions to the treatment involve digestive discomfort and an increased risk of high blood pressure⁹⁶. Due to the limited research, the therapeutic value of cyclosporine in AA remains uncertain, with no strong clinical evidence to confirm or dismiss its efficacy.

Phosphodiesterase Inhibitors: Apremilast, a phosphodiesterase 4 (PDE4) inhibitor, is FDA-approved for use in the therapeutic management of psoriatic arthritis and extensive plaque psoriasis. Emerging clinical evidence supports its potential in managing AA. A retrospective analysis reported substantial hair regrowth in patients with chronic AA who did not respond to conventional treatment options. These individuals exhibited favourable results after receiving oral apremilast therapy⁹⁷.

Apremilast functions by increasing intracellular cAMP levels, which boosts IL-10 expression while reducing critical proinflammatory mediators, such as TNF- α , IFN- γ , and IL-17, among others⁹⁸. Apremilast is generally associated with gastrointestinal symptoms, mild infections of the upper respiratory tract, and occasional headaches⁹⁹. While initial research suggests apremilast may be beneficial for AA, more extensive clinical trials are required to establish its effectiveness with greater certainty.

Biological Therapies:

Inhibitors of Th17-Driven Inflammation: As a human monoclonal antibody, secukinumab is designed to selectively inhibit IL-17A, thereby disrupting the Th17 inflammatory signalling pathway to modulate immune responses. Research indicates that secukinumab led to hair regeneration in individuals affected by both psoriasis and total AA. Yet, once the medication was stopped, hair loss recurred, suggesting that secukinumab could be a promising therapy for AA through its effects on Th17 cytokines¹⁰⁰. Although secukinumab shows theoretical promise in treating AA, its effectiveness has yet to be definitively established.

Since IL-17 is integral to the development of AA, Th17 inhibitors like ixekizumab and brodalumab are also considered promising therapeutic options for managing the condition¹⁰¹.

Th2 Inflammatory Signalling Pathway

Inhibitors: AA is often linked to atopic dermatitis (AD), which is predominantly Th2-skewed. Both conditions share a similar genetic foundation¹⁰². Additionally, AA exhibits phenotypic similarities with atopic dermatitis (AD), including symptoms like pruritus, increased IgE levels, filaggrin mutations, and molecular activity involving Th2, IL-23, and Th1 activation¹⁰³.

Dupilumab specifically inhibits the Th2 inflammatory signalling pathway. By attaching to the IL-4 receptor's α -subunit, it inhibits IL-4 and IL-13 signalling, thereby mitigating Th2-driven inflammation and modulating cytokine activity¹⁰⁴. Clinical findings suggest that dupilumab may mitigate the progression of AA in individuals with preexisting atopic dermatitis while simultaneously addressing their AD symptoms¹⁰⁵.

IL-12/IL-23 Inhibitors: Ustekinumab is a fully human IgG1 monoclonal antibody that targets the p40 subunit common to IL-12 and IL-23, thereby modulating Th1 and Th17 cell differentiation¹⁰⁶. Research indicates that ustekinumab therapy resulted in noticeable hair regrowth among patients. The treatment was well tolerated, demonstrating a safety profile comparable to that seen in adults. Common adverse effects observed included respiratory infections, headaches, and localized injection site reactions¹⁰⁷.

Tildrakizumab is a humanized monoclonal antibody targeting the IL-23 pathway by selectively preventing the interaction between its p19 subunit and its receptor, thereby suppressing the secretion of inflammatory mediators¹⁰⁸. A clinical pilot study examined the effects of tildrakizumab on nine adults with AA, including seven cases of AT or AU. Results showed that two participants experienced a modest reduction in SALT scores (11–18 points), whereas the remaining individuals exhibited no noticeable therapeutic response¹⁰⁹. While this study does not offer definitive proof, it indicates that tildrakizumab may hold potential as a therapeutic strategy for AA.

Low-Dose IL-2: IL-2 is a crucial cytokine that regulates Treg homeostasis, significantly contributing to immune balance. A reduction in Treg levels may disrupt hair follicular immune privilege (IP), potentially involved in AA development¹¹⁰. An open pilot study demonstrated that subcutaneous administration following low-intensity IL-2 resulted in a notable elevation in Treg levels at affected skin sites in severe AA cases. This increase correlated with partial hair regrowth and marked clinical improvement in AA¹¹¹. Although large-scale, multi-center trials are lacking, current encouraging findings emphasize the need for further investigation into the beneficial potential and underlying mode of action of low-intensity IL-2 in the treatment of AA, given the presently limited data.

Platelet-Rich Plasma: Platelet-rich plasma, a biologically active concentrate rich in platelets, is abundant in bioactive mediators. Its effectiveness in treating AA is attributed to its role in enhancing matrix restoration and stimulating hair structure recovery, primarily via reducing MCP-1 expression and elevating TGF- β levels¹¹². A review primarily focused on studies examining platelet-rich plasma (PRP) in androgenetic alopecia (AGA), along with three studies on AA. The findings suggest PRP has a generally beneficial effect when administering a minimum of three treatment sessions¹¹³. Another Comparative research indicates that PRP therapy outperforms 5% minoxidil in treating AA¹¹⁴. Several clinical studies have examined PRP's effectiveness in treating both AGA and AA, highlighting increasing attention and investigation in this area.

Advanced and Adjunctive Therapies:

Combination Drug Therapy: This approach aims to maximize therapeutic benefits in the shortest possible time while minimizing toxicity and drug resistance risks. An optimal drug combination minimizes toxicity and adverse effects while enhancing synergistic interactions between medications to maximize therapeutic benefits and prevent drug resistance. Low-dose prednisone adjunct to methotrexate improves both efficacy and patient tolerance in treating AT and AU. Additionally, this approach offers a more economical option for managing AA¹¹⁵.

Another combination of latanoprost with betamethasone and minoxidil shows potential as an effective supplementary therapeutic option. A study of 108 AA patients, both male and female, found that topical latanoprost enhances the efficacy of betamethasone and minoxidil while preserving a favorable safety profile. This combination treatment has been shown to effectively manage patchy alopecia without triggering negative side effects ¹¹⁶.

Role of Exosomes: Extracellular vesicles, including exosomes, are tiny vesicular bodies released by cells into various biofluids, with dimensions generally between 30–150 nm. Laden with bioactive molecules, they are gaining attention for their potential therapeutic uses ¹¹⁷. Exosomes, a specialized type of extracellular vesicle (EVs), can efficiently cross cell membranes and exhibit a reduced likelihood of provoking immune reactions ¹¹⁸. Recent studies highlight the promising role of stem cell-derived exosomes in hair follicle repair and regeneration. Specifically, mesenchymal stem cell-derived exosomes enhance DPC activity by promoting their proliferation and movement in mice. This process triggers the release of essential growth factors like IGF-1 and VEGF, aiding hair restoration ¹¹⁹. Furthermore, integrating exosomes with microneedling (MN) has gained attention as a novel approach for enhancing hair growth. In particular, Microneedle systems with PVA tips and HA bases, enriched with chitosan lactate and ADSC-derived exosomes, show promising therapeutic effects ¹²⁰. Exosomes show promise as a potential therapeutic modality, indicating their future role in advanced treatment approaches.

Nanotechnology: Nanoparticles (NPs) are artificially engineered microscopic structures designed for various applications. Their distinctive composition grants them a large surface area while ensuring excellent biocompatibility and biodegradability ¹²¹. Additionally, NPs improve drug stability, solubility, and concentration, extend drug release, and reduce adverse effects on cellular function and metabolism ¹²². Interestingly, NPs show an affinity for hair follicle cells, clustering around them, which highlights nanotechnology's potential in addressing follicle-related conditions such as AA ¹²³. Nanoparticles composed of certain metals effectively reach deep dermal structures and

exhibit extended localization ¹²⁴. Furthermore, NP gels formulated PLGA-based system improve the transport of tofacitinib citrate, leading to greater drug absorption and efficacy ¹²⁵. Ultimately, nanotechnology emerges as a viable and secure strategy for effectively treating AA.

Microneedle-Based Therapy: Microneedles (MN) provide an innovative way to enhance drug delivery by forming microscopic channels in the stratum corneum, improving the penetration and effectiveness of topical treatments ¹²⁶. Microneedling has been shown to promote hair regrowth in alopecia by stimulating the wound healing response, leading to the release of platelet-derived growth factor and epidermal growth factors, as well as activating the hair bulge ¹²⁷. Additionally, microneedling increases the expression of Wnt proteins, which are known to stimulate dermal papilla stem cells and support hair growth ¹²⁸. Research highlights the positive effects of microneedling (MN) when paired with betamethasone, suggesting its potential as an effective treatment approach ¹²⁹. While microneedling has been extensively studied for AGA treatment, its potential role in addressing AA remains less explored.

Alternative and Future Therapies:

JAK Inhibitors: JAK inhibitors recently gained attention as a promising therapeutic strategy for managing AA. Several JAK inhibitors are already approved for various inflammatory conditions. Tofacitinib, which targets JAK1 and JAK3, is used for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. Baricitinib and Ruxolitinib, both acting on JAK1 and JAK2, are indicated for diseases like rheumatoid arthritis, myelofibrosis, polycythemia vera, and graft-versus-host disease ¹³⁰. A case report described almost full hair regrowth in three AA patients treated with oral Ruxolitinib. Post-treatment biopsies showed reduced T-cell infiltration around follicles and lower HLA class I and II expression ¹³¹. A retrospective study in 11 children with severe AA (aged 6–12) reported that 73% exhibited visible hair regrowth and 64% achieved $\geq 50\%$ SALT improvement after 6 months of tofacitinib treatment. Most adverse effects were mild. The findings align with a broader literature review covering 31 paediatric AA cases, where 87% of

patients responded positively to tofacitinib therapy. These outcomes highlight the drug's potential as a viable and relatively safe option in treatment-resistant paediatric AA¹³². Most patients who respond to JAK inhibitors tend to relapse after stopping treatment, typically within 2 to 3 months¹³³. Studies show that JAK inhibitors have demonstrated therapeutic promise in AA and may play a key role in future treatment strategies.

Stem Cell Therapy: Recent research suggests that Mesenchymal Stem Cells (MSCs) could serve as an effective treatment for AA, primarily because of their immunosuppressive functions. They work by reducing pro-inflammatory T cell proliferation and enhancing the presence of controlling T cells¹³⁴. Research on IFN- γ -induced AA in mice revealed an increase in the presence of CD4+ and CD8+ T cells. MSC treatment effectively decreased several inflammatory factors and minimized T cell infiltration, suggesting its therapeutic potential in managing AA¹³⁵. Using MSC therapy could be an effective strategy for managing and potentially preventing AA.

Gut Microbiota: Recent studies highlight the role of gut microbiota in modulating immune responses and its involvement in AA pathogenesis¹³⁶. Research comparing the scalp microbiota between AA patients and healthy individuals shows distinct variations in bacterial populations, particularly Actinobacteria and Firmicutes, suggesting microbial influences on AA¹³⁷. Short-chain fatty acids (SCFAs) provide essential energy to gut bacteria and intestinal lining cells while modulating T lymphocyte chromatin structure, thereby enhancing gene expression¹³⁸. Their interaction with G protein-coupled receptor 43 (GPR43) is crucial in mitigating inflammation¹³⁹. While SCFAs have systemic effects upon absorption, their topical application may be particularly beneficial for AA¹⁴⁰. Moreover, studies suggest topical SCFAs induce tissue plasminogen activator expression, reduce fibrin deposition, and help alleviate chronic sinusitis¹⁴¹. These findings indicate that applying short-chain fatty acids (SCFAs) directly to scalp hair follicles could be a promising therapeutic approach for treating AA.

Statins: Statins not only help reduce lipid levels but also play a role in suppressing inflammation

and modulating immune responses¹⁴². Research suggests that simvastatin may help reduce inflammation by suppressing NF- κ B and JAK/STAT pathways, limiting ROS production, and stimulating the Wnt/ β -catenin pathway. Its immune-regulating properties could be further strengthened with ezetimibe¹⁴³. A pilot study reported that 12 out of 19 patients with AA, involving 40–70% of the scalp, achieved more than 50% hair regrowth, with no adverse effects observed during the treatment¹⁴⁴. These findings suggest that statins hold promise, but randomized controlled trials (RCTs) with larger sample sizes are needed to confirm their effectiveness.

Antihistamines: Clinical studies suggest that fexofenadine may serve as a suitable adjunct to Diphenylcyclopropenone (DPCP) or Squaric Acid Dibutyl Ester (SADBE) topical immunotherapy for atopic AA by alleviating itching and improving treatment effectiveness¹⁴⁵. Additionally, hair regrowth has been observed following the administration of ebastine¹⁴⁶. Another study suggests that combining antihistamines with topical corticosteroids and superficial cryotherapy enhances hair regrowth in patients compared to those not using antihistamines. Additionally, no serious side effects requiring discontinuation have been observed¹⁴⁷.

Gene Therapy: Alopecia and many other diseases are being explored for treatment through the innovative field of gene therapy¹⁴⁸. Gene therapies typically involve delivering genetic material using modified vectors, either directly into a subject's epidermal tissue (*in-vivo*) or indirectly (*ex-vivo*). In *ex-vivo* approaches, cells are extracted from the host, genetically modified, and subsequently administered back into the skin¹⁴⁹.

RNA interference-based gene therapy is considered a revolutionary method in individualized treatment. The rapid development of topical siRNA for gene silencing has positioned it as an appealing strategy for drug discovery and therapeutic applications¹⁵⁰. Through the use of siRNA, RNA interference enables highly targeted gene suppression with exceptional specificity¹⁵¹. A study conducted an *in-vivo* model of AA explored the use of gelatine microspheres for delivering siRNA to treat AA, demonstrating its effectiveness in suppressing Th1-

related genes and promoting hair regrowth. It was observed that Th1 cells were highly present in alopecic regions, with CD4 T lymphocytes predominantly expressing CCR5. Further analysis of cytokine therapy revealed that IL-4 and anti-interferon antibody injections reduced CD8 T cell accumulation and interferon mRNA levels, aiding recovery. The siRNA specifically targeted T-box21 to minimize Th1 cytokine production, while gelatine conjugation enhanced therapeutic efficiency¹⁵².

Herbal Extracts: Herbal remedies have been traditionally used for centuries to promote hair growth and prevent hair loss. Although their safety and efficacy remain uncertain, they are generally believed to cause fewer side effects than conventional treatments¹⁵³. Onion has been explored for its therapeutic role in AA. In a clinical trial with 62 participants, 87% of those using topical onion juice showed complete hair regrowth within 8 weeks, compared to only 13% in the

control group using plain water¹⁵⁴. These findings suggest that raw onion juice could be beneficial in AA treatment. Similarly, garlic's antibacterial and vasodilatory effects may support hair regrowth. In a double-blind randomized controlled trial of 40 patients, a 5% garlic gel with 0.1% betamethasone showed greater improvement in hair density and patch size than corticosteroid alone, with no reported side effects. This supports garlic as a potential adjunct in AA therapy¹⁵⁵. Glycyrrhizin, a plant-based glycoside, exhibits immunomodulatory activity and may influence T cell function, including Th17 differentiation. Clinical studies combining it with vitamin B2, with or without peony glucosides, have shown promising regrowth outcomes in both adult and paediatric alopecia areata patients, with comparable efficacy across groups¹⁵⁶.

A visual overview of advanced and future-directed therapeutic approaches in AA is presented in **Fig. 3**.

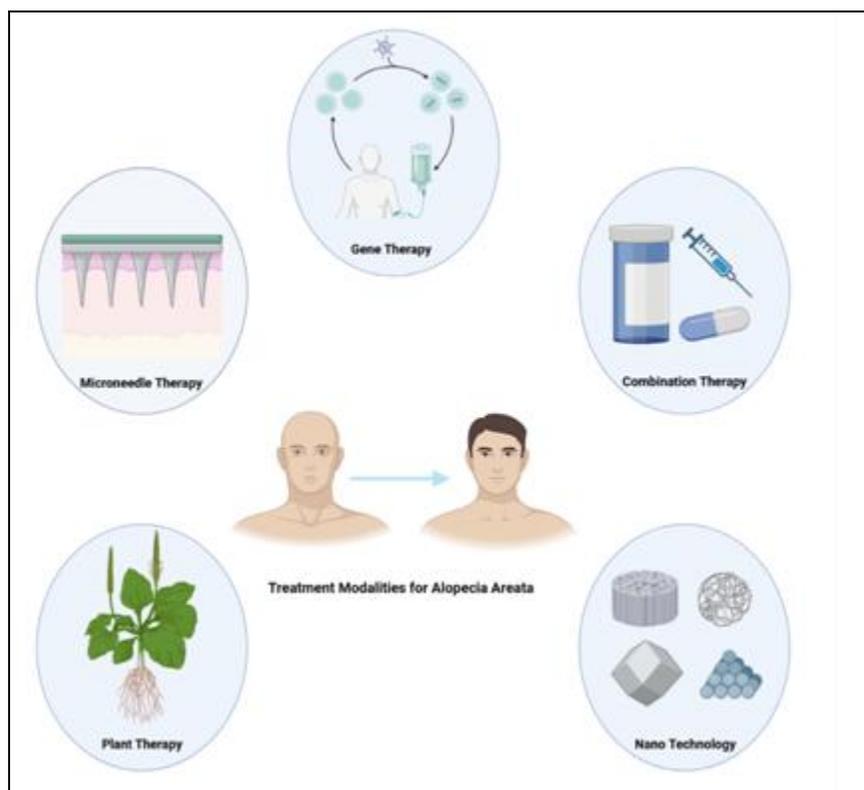


FIG. 3: THIS FIGURE ILLUSTRATES EMERGING TREATMENT STRATEGIES FOR AA. THESE APPROACHES AIM TO RESTORE IMMUNE BALANCE, STIMULATE FOLLICULAR REGENERATION, AND ENHANCE THERAPEUTIC EFFICACY

Final Insights and Emerging Opportunities: Alopecia areata is a common autoimmune disorder characterized by the abrupt onset of localized hair

loss, typically affecting distinct regions of the scalp or body. Even though research on its pathophysiology and available treatments has

progressed, several uncertainties remain challenging for effective management. A deeper understanding of AA's underlying mechanisms could enhance clinical treatments, support precision therapy, and facilitate timely detection with more targeted therapies. These developments could have profound medical and social impacts, enhance patient outcomes, and alleviate the overall disease burden. However, current data highlight a considerable gap in the availability of drugs designed specifically for AA, both in development and clinical application, with no definitive cure yet established. Traditional treatments like glucocorticoids, minoxidil, and light therapy face limitations, including inconsistent efficacy, possible side effects, and frequent relapse. Recently, interest in small-molecule drugs and biologic agents has grown due to their promising safety and effectiveness in skin disease management. Among them, Immunotherapeutics such as JAK inhibitors have demonstrated significant potential in AA treatment. However, existing data from small-scale trials and case reports require larger studies to confirm their reliability and safety. Additionally, while key molecular targets associated with AA have been identified, many findings stem from animal models, which may not fully replicate human disease complexity. As a result, further validation is required before these approaches can be translated into viable human treatments.

Emerging therapies for AA, such as stem cell therapy and follicle engineering, offer promising regenerative solutions. Meanwhile, AI-driven drug design incorporating nano-enzymes is opening new doors in treatment innovation. Though these methods remain experimental, they could transform care for patients with difficult-to-treat or severe forms of the condition as research and technology advance. Detecting AA in its early stages is challenging due to dependence on clinical evaluation and the need to identify other causes of the hair loss. The absence of reliable biomarkers makes monitoring even more difficult. While scalp biopsies and dermoscopy can aid diagnosis, their invasive nature restricts widespread use. This underscores the growing demand for non-invasive diagnostic approaches, such as serum biomarkers and advanced imaging methods, to enhance early detection of AA. Progress in gene expression

profiling and proteomic technologies has identified potential biomarkers that may aid in predicting disease progression and personalizing treatment strategies. Furthermore, the integration of artificial intelligence, particularly machine learning algorithms for dermoscopic image analysis, holds significant promise for improving the precision and efficiency of AA diagnosis. The progress of advanced diagnostic tools and targeted therapies holds potential for enhanced disease management in the future. Moreover, Major hurdles include identifying immune triggers, evaluating the chronic safety of treatments, and tailoring therapies to individual genetic and environmental profiles. Ongoing research in these domains is essential to enhance the quality of life for those affected by AA by enabling the development of safer and more effective therapeutic options.

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