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Research Article

ARCHIVES OF INTERNAL MEDICINE RESEARCH

ISSN: 2688-5654



Unlocking the Immune Mechanisms of Alopecia: Clinical Realities and Epidemiology

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Abstract

Alopecia areata (AA) is an autoimmune disease that causes patterned, nonscarring hair loss. This disease can onset in the early 20s and continues to progress throughout a person's life. AA may cause significant psychological stress including feelings of insecurity, body dysmorphia, and anxiety. The purpose of this literature review is to analyze the underlying immune mechanism responsible for the pathophysiology associated with AA. Furthermore, we investigate current treatment and therapeutic modalities. Database such as Google Scholar and PubMed were used to source articles surrounding alopecia areata. Key terms such as alopecia areata, immune privilege, and immune mechanism of alopecia, were used to find relevant articles on this topic. Compromising immune privilege is the primary driver for the development of AA. This can occur due to genetic predisposition, viral infection, or prolonged oxidative stress. The immune system activates various responses including cytotoxic CD8 T-cell proliferation, CD4+ Helper T Cell modulation, and NK chemotaxis toward hair follicles. As a result, there is persistent inflammation from cytokine factors such as IFN-α, IFN-γ, IL-2, IL-15, and IL-17 which leads to destruction and the balding pattern. Currently, the most widely used treatment options include immunosuppressants such as methotrexate, cyclosporine, and glucocorticoids to reduce system-wide immune response. Additionally, there have been developments in more specific monoclonal antibodies that can target certain activation or proliferative pathways, such as JAK-STAT, as well as inflammatory cytokines IL-4, IL-13, or IL-17A. This review demonstrates how alopecia areata is a multi-facet disease that has various components contributing to pathophysiology and treatment.

Keywords: Alopecia areata; Hair follicle pathology; Hair follicle physiology; Immune cells; Immune mechanism of alopecia areata; Inflammation; Treatment of alopecia areata

Introduction

Alopecia is a nonspecific term for hair loss that is evaluated based on the pattern of hair loss and, when indicated, histological analysis of scalp biopsies. The term encompasses multiple subtypes, including both nonscarring and scarring forms, with immune-mediated alopecia representing common and clinically significant variants [1,2,3]. Alopecia represents a significant area of study due to its prevalence and impact on affected individuals. Globally, alopecia affects approximately 2% of the population, and in the United States alone, nearly 80 million individuals experience some form of hair loss. Onset frequently occurs early in life, with approximately 40% of cases beginning by age 20 and nearly 80% by age 40 [3,4,5].

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Citation: Angelie Pathak, Andrew Abou Jaoude, Hina Patel, Jason Zar, Devendra K. Agrawal. Unlocking the Immune Mechanisms of Alopecia: Clinical Realities and Epidemiology. Archives of Internal Medicine Research. 9 (2026): 331-340.

Received: October 21, 2026
Accepted: October 29, 2026
Published: October 31, 2026

Pathak A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0260

Psychosocial Burden and Clinical Significance

Beyond its physical manifestations, alopecia carries substantial long-term clinical and psychosocial consequences. Patients often experience anxiety, depression, increased stress, and reduced quality-of-life scores compared to the general population [5,6]. Furthermore, these psychological burdens may decreased daily productivity and contribute to comorbidities that develop from chronic stress. The lack of consistently effective long-term treatment, alongside the unpredictable nature of disease onset and progression, further compound these mental and emotional challenges [5,7].

Scope of the Review

This review focuses on the immune mechanisms underlying alopecia, particularly alopecia areata (AA), which is fundamentally an autoimmune condition. The disease is characterized by T-cell– mediated injury to hair follicles following the collapse of immune privilege within the follicular environment. Cytotoxic $CD8^+$ T cells infiltrate the follicle and drive inflammatory signaling through cytokine networks, including interferon-gamma (IFN-γ) and activation of the JAK-STAT pathway [8]. Understanding these immune mechanisms provides a foundation for the development of more targeted and effective therapeutic strategies.

II. Hair Follicle Biology

Hair Follicle Anatomy

The hair follicle is an organ-like structure composed of several anatomically distinct regions that each play specialized roles in hair development and cycling. These regions include the hair bulb, suprabulbar zone, isthmus, infundibulum, and dermal papilla. The hair bulb contains rapidly proliferating matrix cells responsible for generating the hair shaft and inner root sheath [9,10]. Adjacent to the bulb, the dermal papilla provides regulatory signaling and is associated with a vascular supply that supports follicular growth and differentiation. The suprabulbar region lies just above the bulb and contributes to early hair shaft formation as keratinization begins [11]. More superficially, the isthmus and infundibulum represent the upper segments of the follicle, which connect the follicle to the epidermal surface and interact with surrounding skin structures such as sebaceous glands [12].

The Hair Growth Cycle

Hair follicles undergo a cyclical growth process consisting of three primary phases: anagen, catagen, and telogen, with a subsequent exogen phase associated with hair shedding (Figure 1) [13]. The anagen phase represents the active growth stage during which matrix cells within the hair bulb rapidly proliferate, producing the hair shaft [14]. This phase determines hair length and typically encompasses most hair follicles at any given time.

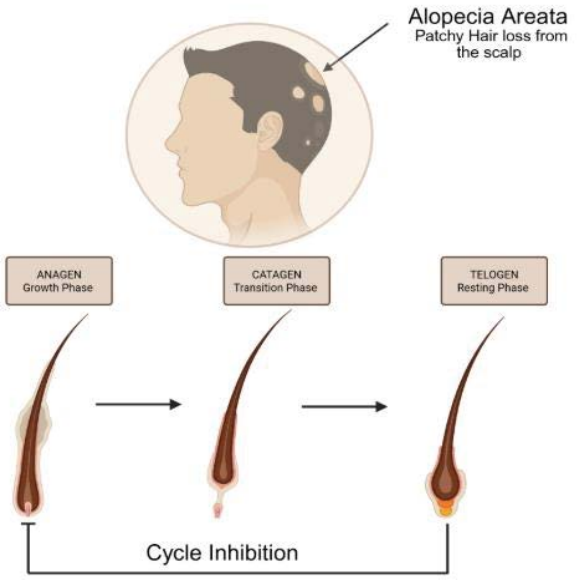


Figure 1: Normal Hair Follicle Cycle and Its Disruption in Alopecia Areata. Illustration depicting the three primary phases of the natural hair follicle cycle: anagen (active growth), catagen (regression and transition), and telogen (resting phase). Under normal physiological conditions, hair follicles undergo continuous cycling between these phases to maintain hair growth and renewal. In alopecia areata, autoimmune-mediated inflammation targets anagen hair follicles, inhibiting normal follicular cycling, and contributing to hair loss.

The catagen phase is a short transitional period characterized by regression of the follicle and cessation of active hair production. During this stage, structural changes occur, including condensation of the dermal papilla and thickening of the vitreous layer as the follicle shortens [15].

The telogen phase represents the resting stage of the hair cycle. During this phase, the fully keratinized club hair remains anchored within the follicle, however, no longer grows [16,17]. The follicle remains in a quiescent state until the exogen phase occurs. The exogen phase is characterized by the club hair shedding and the follicle re-entering the anagen phase to initiate a new cycle of hair growth [18].

III. Immune Privilege of the Hair Follicle

Immune privilege, as it relates to the hair follicle, is described as a protection from the anagenic growth phase; it protects the follicle and autoantigens. However, the disruption of this immune privilege is essential for the formation of AA [19]. In those who experience some level of genetic susceptibility, which can include viral infection, oxidative stressors, and HLA-DR susceptible individuals, the follicle experiences stress, causing an upregulation of MHC class I polypeptide– related sequence A (MICA). MICA plays a role as NKG2D ligands, functioning to activate immune receptor NKG2D that is expressed on CD8+ T and NK cells [20,21]. This is further enforced via IFN-gamma, allowing for MHC

Pathak A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0260

overexpression and downregulating immune privilege (Figure 2). This leads to the classic presentation of the swarm of bees' effect with granzyme, perforin, and apoptosis [4,22].

Reduced MHC Expression

One main feature for passive hair follicle immune privilege is via MHC I and II downregulation. Upregulation of the MHC molecules can trigger T-cell attack, as seen in AA. Therefore, maintaining a low.

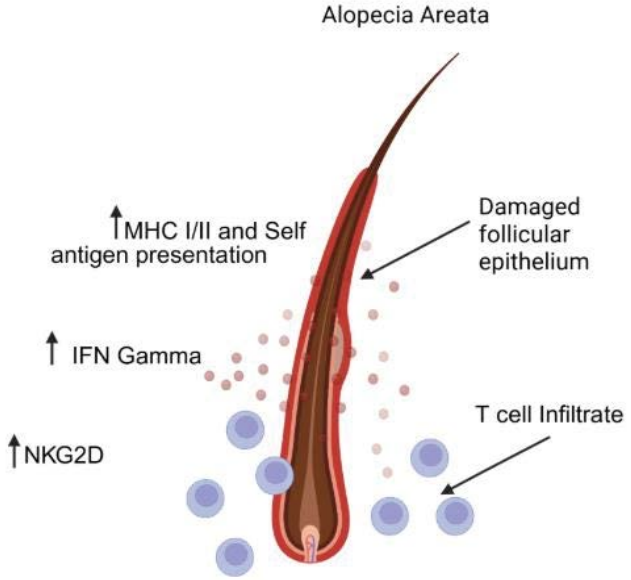


Figure 2: Overview for collapse of hair follicle immune privilege. Schematic illustration depicting the autoimmune mechanisms underlying alopecia areata. Loss of hair follicle immune privilege is characterized by increased major histocompatibility complex (MHC) class I and II expression and elevated interferon-gamma (IFN-γ) signaling. Recruitment and activation of cytotoxic T cells, particularly NKG2D-expressing CD8+ T cells, promote inflammatory infiltration and damage to the follicular epithelium, disrupting normal hair growth and contributing to hair loss.

baseline level is fundamental for preserving follicle protection. MHC is present on all nucleated cells; however, the bulge of the follicle is responsible for MHC downregulation in combination with beta-2 microglobulin [23]. This is central because with low MHC I, fewer CD8 T cells and autoantigens are being activated. The autoantigens activity and excitement are primarily formulated in times of active growth of the hair pigment [24].

Comparatively, MHC II is usually seen on antigen-presenting cells (APCs,) and the lack of MHC II on follicle-based epithelium explains diminished CD4 activation. These autoantigen targets are mainly expressed during the growth-phase anagen activation of pigmented follicles, which suggests AA prefers attacking pigmented anagen hairs. Correspondingly, the bulge and nonpigmented (white) hair compartments of the follicle are spared due to lack of melanocyte autoantigens [25,26].

IV. Breakdown of Immune Privilege in Alopecia Areata

Loss of Immune Privilege

In alopecia areata, immune privilege is lost within the hair follicle during the active growth phase (Figure 2). Under normal conditions, hair follicles are protected from immune attack through low expression of MHC class I and II molecules, allowing limited presentation of follicular antigens to T cells [27,28]. This protection is further supported by TGF-β, IL-10, and α-MSH.

MHC Upregulation and Initiation of the Autoimmune Response

Some individuals may be genetically susceptible, making them particularly sensitive to potential triggers such as infections and oxidative stress [29]. Increased IFN-γ signaling activates the JAKSTAT pathway and ultimately increases MHC class I and II expression on follicular cells, allowing immune recognition of previously protected follicular antigens [30,31].

Additionally, IFN-γ increases the expression of NKG2D ligands and inflammatory chemokines, further promoting inflammation and the accumulation of $CD8^+NKG2D^+$ cytotoxic T cells around the hair bulb. This contributes to a perifollicular lymphocytic infiltrate [32].

V. Immune Cells Involved in Alopecia Areata

$CD8^+$ Cytotoxic T Lymphocytes

$CD8^+$ cytotoxic T cells are considered the primary drivers of alopecia areata pathogenesis. Evidence from mouse model experiments demonstrates that $CD8^+$ T cells alone have the potential to induce alopecia-like disease, highlighting their central role in follicular destruction [33]. These cells exert their effects through NKG2D receptor–mediated recognition of hair follicle structures, leading to immune-mediated attack of the follicle (Figure 3).

The autoimmune response is initiated when the immune privilege of the hair follicle collapses, resulting in increased susceptibility to immune recognition. Inflammatory signaling, particularly through interferon-gamma (IFN-γ), leads to upregulation of major histocompatibility complex class I (MHC I) molecules on follicular cells. This enhanced antigen presentation facilitates recognition by $CD8^+$ cytotoxic T cells [28].

In addition, stressed or damaged hair follicles express MHC class I–related chain A (MICA), a ligand for the NKG2D receptor, which further activates $CD8^+$ T cells. Once activated, these cytotoxic cells target follicular structures through several mechanisms, including the release of granzymes and perforin, as well as the secretion of inflammatory cytokines such as IFN-γ. These mechanisms

ultimately promote follicular cell apoptosis and contribute to hair follicle injury [34].

CD4⁺ T Helper Cells

CD4⁺ T helper cells appear to play a supportive rather than primary role in alopecia areata pathogenesis (Figure 3). While these cells are not sufficient alone to initiate disease, CD4+ T helper cells contribute to the amplification of immune responses when acting in conjunction with CD8⁺ cytotoxic T cells [35].

CD4⁺ T cells promote the activation of T helper cell subsets, including Th1, Th2, and Th17 cells, which contribute to inflammatory signaling within the follicular microenvironment. These cells stimulate the production of cytokines such as IFN-γ, interleukin-12 (IL-12), and interleukin-17 (IL-17), which further enhance immune activation and promote the recruitment of additional inflammatory cells to the follicle [36,37].

Natural Killer Cells

Natural killer (NK) cells have also been observed within perifollicular inflammatory infiltrates in alopecia areata (Figure 3). These cells express NKG2D and may be identified by markers such as CD56; they can contribute to immune activation and contribute to inflammatory aggregation around the hair follicle [38,39]. However, experimental studies suggest that elimination of NK cells alone does not fully prevent disease development, suggesting that NK cells have a contributory role rather than essential.

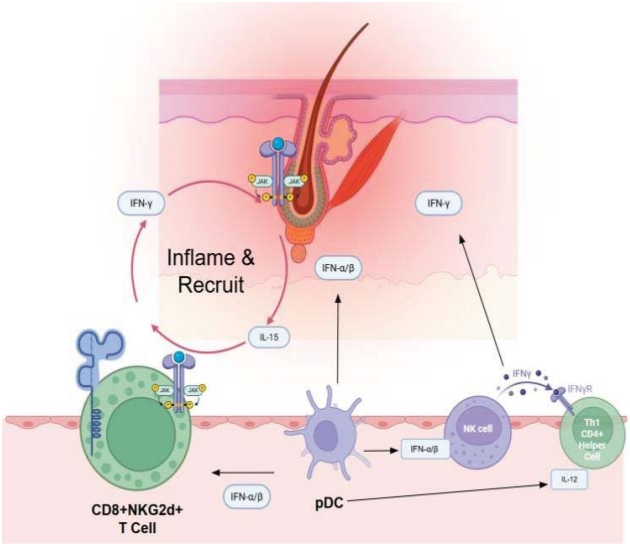


Figure 3: Simplified illustration of Type 1 immune cascade seen in alopecia areata pathophysiology. Plasmacytoid dendritic cells (pDC) act as the upstream initiator, releasing type I interferon (IFN-α/β) that activates the CD8⁺NKG2D⁺ cytotoxic T cell, natural killer (NK) cells, and the follicular epithelium itself. The CD8⁺NKG2D⁺ T cell is the principal effector: its IFN-γ signals through JAK1/JAK2–STAT1, which upregulates MHC class I (exposing follicular autoantigen) and induces keratinocyte-derived IL-15. IL-15 then signals back through JAK1/JAK3 on the CD8⁺NKG2D⁺ cell to sustain IFN-γ output, establishing the positive feedback loop. NK-cell produce IFN-γ as a secondary, reinforcing signal (via IFN-γR) rather than a primary Th1-inducing cytokine. The resulting Th1 cells contribute additional IFN-γ to the inflammatory cascade.

Dendritic Cells

Dendritic cells, particularly plasmacytoid dendritic cells (pDC), play an important role in initiating and sustaining autoimmune responses in alopecia areata (Figure 3). These cells produce interferon-alpha (IFN-α), which is associated with the expression of the antiviral protein MxA, a marker of interferon signaling. Experimental mouse models have demonstrated that injection of plasmacytoid dendritic cells can induce alopecia-like lesions and increase the expression of MHC class I molecules and the chemokine CXCL10 [40,41]. This process further promotes recruitment of immune cells and amplifies inflammatory signaling within the follicular environment. Additionally, activation of dendritic cell signaling pathways contributes to increased expression of inflammatory mediators, including IL-15 and components of the JAKSTAT signaling pathway, such as JAK2, JAK3, and STAT1, further driving immune-mediated follicular damage [42,43].

VI. Cytokine Networks and Intracellular Signaling

IFN-γ and IL-15: The Central Feedback Loop

Interferon-gamma (IFN-γ) and cytokines such as IL-2, IL-15, and IL-17 are key components of the inflammatory network, creating feedback loops that allow follicular attack to continue (Figure 3). CD8⁺ T-cell infiltration and activation increase IFN-γ production within the inflammatory environment. IFN-γ activates JAK-STAT signaling and upregulates MHC class I expression and IL-15 production. IL-15, in turn, supports cytotoxic T-cell activation and further IFN-γ production [30,36]. The IFN-γ /IL-15 interaction represents a central inflammatory feedback loop that can be seen in AA.

JAK-STAT Pathway Activation

Inflammatory cytokine signaling in alopecia areata occurs primarily via the Janus kinase (JAK)signal transducer and activator of transcription (STAT) pathway through type II interferons, including IFN-γ and IL-15, allowing for translation of receptor-specific programs. These cytokines then promote the phosphorylation of tyrosine residues and cytoplasmic STAT monomers, inducing STAT dimerization, nuclear translocation, and binding to DNA GAS sites, thereby causing downstream gene program activation [44].

A separate but related pathway involves the CXCR3 ligands CXCL9, CXCL10, and CXCL11, which recruit

Pathak A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0260

CXCR3-expressing immune cells and further promote follicular inflammation. Additionally, an inflammasome-driven pathway may contribute through NLRP3 activation and the release of IL-1β and IL-18, exacerbating inflammation [45].

VII. The Gut–Skin–Hair Axis

Microbial Metabolites and Barrier Regulation

The gut–skin–hair axis represents a proposed bidirectional relationship linking immune, metabolic, and neuroendocrine pathways (Figure 4). The overview of this relationship starts with alterations in the natural gut biome, followed by invasion of bacterial toxins and cytokines leaking into the blood. These molecules then travel toward the skin and hair follicle, eliciting an immune response (Figure 4C).

Gut bacteria produce short-chain fatty acids (SCFAs), which can activate G-protein-coupled receptors (GPR) such as GPR43 and GPR109A to support epithelial barrier function. Additionally, the microbiota converts tryptophan into indole derivatives, which activate aryl hydrocarbon receptor for further epithelial support. Inflammatory signaling is also regulated through FXR and TGR5, whose activity is influenced by bile acids modified by the gut microbiota. When gut microbiota dysbiosis occurs, SCFA production may be altered, a finding that has been described in inflammatory skin conditions [46]. Furthermore, dysbiosis may compromise tight junction integrity, disrupt the mechanisms and signaling of inflammatory regulation [47,48].

Microbiota Dysbiosis in Alopecia Areata

In relation to alopecia areata, alterations in the microbiota have been reported alongside increased Th17 and Th1/17 $CD4^+$ T-cell populations. Ruminococcaceae, Holdemania filiformis, Parabacteroides distasonis, P. johnsonii, Bacteroides eggerthii, and Clostridiales vadin have been investigated for associations with disease severity and hair loss. Ruminococcaceae is a family within Firmicutes, and some of its members produce SCFAs [49]. Specific taxa, including Ruminococcaceae UCG-003 and UCG-004/UCG-010, have also been associated with alopecia areata [50].

VIII. Clinical Correlations

Histopathologic Findings

The classic histological finding in AA is described as a "swarm of bees." This presents as a lymphocytic infiltrate during the acute phase. Terminal anagen follicles are seen with dense infiltrates that extend into the suprabulbar zone while sparing telogen follicles. This ultimately leads to apoptosis of keratinocytes, resulting in disruption of hair shaft production. The infiltrate is composed primarily of $CD4^+$ and $CD8^+$ T cells, in combination with eosinophils around the bulb, as well as chemokines and APCs [51].

IX. Therapeutic Implications

Conventional Immunosuppressive Therapies

The nature of AA is an autoimmune disorder characterized by T-cell–mediated injury to hair follicles, and current therapeutic strategies largely aim to suppress or modulate this aberrant immune response. Traditional immunosuppressive therapies have historically been used to mitigate disease activity, although many remain off label for the treatment of AA. These therapies primarily function by inhibiting $CD8^+$ T-cell autoreactivity and reducing the cytokine-driven inflammatory cascade responsible for follicular damage. Mechanistically, interferon-γ (IFN-γ) and interleukin-15 (IL-15) play a central role in disease pathogenesis by inducing ectopic expression of major histocompatibility complex class I (MHC I) molecules on hair follicle epithelial cells

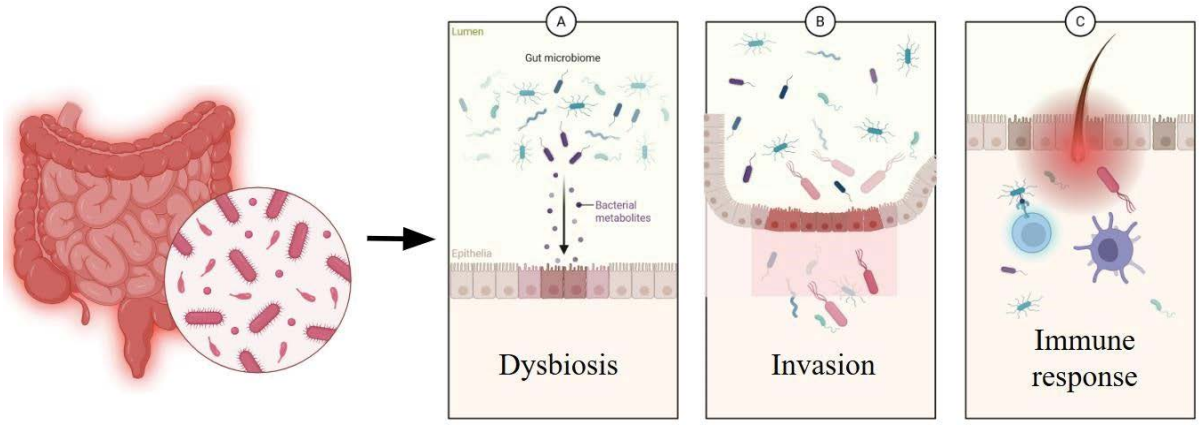


Figure 4: A summary illustrating the proposed mechanism of the gut-skin-hair axis. The visual schema shows changes in gut microbiome (either from viral infection, or oxidative stress) can lead to dysbiosis. (A) Visualizes the gut microbe dysbiosis that can disrupt the integrity of gut epithelia. (B) The gut bacteria invade into the blood stream alongside cytokines and toxins found in the gut biome. (C) The proposed molecules migrate toward the skin and hair follicle, eliciting an immune response that causes inflammation.

Pathak A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0260

[52,53]. This process exposes previously immune-privileged follicular autoantigens to $CD8^+NKG2D^+$ cytotoxic T cells, resulting in targeted immune attack and disruption of the hair growth cycle. By suppressing these immune pathways, immunosuppressive therapies attempt to restore follicular immune privilege and reduce further T-cell–mediated injury [54].

Among conventional treatments, intralesional triamcinolone acetonide remains one of the most widely used first-line therapies for localized disease. Clinical studies have reported hair regrowth in approximately 60–67% of treated patients, with the greatest therapeutic response observed in individuals with less than 50% scalp involvement. Despite its efficacy, intralesional corticosteroid therapy is associated with potential adverse effects, including injection-site pain, localized skin atrophy, and frequent relapse following cessation of treatment [55-57]. Additional systemic immunosuppressive agents—including glucocorticoids, cyclosporine, methotrexate, and azathioprine—have also been utilized in more severe or refractory cases. However, their long-term use is often limited by systemic toxicity and inconsistent therapeutic responses. Some immunosuppressive agents, particularly methotrexate, have the potential to cause hair thinning as an adverse effect, but their greater ability to suppress autoimmune T-cell activity can reduce follicular inflammation and promote hair regrowth in alopecia areata.

Targeted Immune Therapies: JAK Inhibitors

In recent years, targeted immunotherapies have significantly advanced the therapeutic landscape for alopecia areata, particularly through the development of Janus kinase (JAK) inhibitors. These agents specifically inhibit the JAK-STAT signaling pathway, which mediates downstream signaling of several cytokines implicated in AA pathogenesis, including IFN-□ and IL-15. Inhibition of this pathway effectively disrupts the inflammatory signaling cascade responsible for activating cytotoxic T cells and sustaining autoimmune attack on hair follicles [58,59]. As a result, JAK inhibitors suppress immune-mediated follicular damage, allowing hair follicles to recover and re-enter the anagen phase, thereby promoting hair regrowth.

Several agents have demonstrated promising clinical outcomes, including baricitinib, a JAK1/2 inhibitor, and ritlecitinib, a JAK3/TEC family kinase inhibitor [60]. Clinical trials have shown that oral JAK inhibitors can produce substantial hair regrowth in patients with moderate to severe alopecia areata. In contrast, topical JAK inhibitors appear to demonstrate reduced efficacy, likely due to limited drug penetration and insufficient inhibition of systemic immune signaling.

Emerging Immune-Modulating Treatments

Beyond JAK-STAT pathway inhibition, biologic therapies represent another emerging therapeutic approach that targets extracellular cytokine signaling. Biologics are monoclonal antibodies designed to selectively bind cytokines or cytokine receptors in the extracellular environment, thereby preventing activation of downstream inflammatory pathways [61]. This targeted mechanism allows for selective modulation of specific immune pathways rather than broadly suppressing all immune pathways. For example, dupilumab targets IL-4Rα to inhibit both interleukin-4 (IL-4) and interleukin-13 (IL-13) signaling, which are involved in type 2 immune responses, while secukinumab functions by neutralizing interleukin-17A (IL-17A) [62,63]. Although biologic therapies have shown considerable efficacy in other immune-mediated dermatologic conditions such as atopic dermatitis and psoriasis, their role in alopecia areata remains an active area of investigation. Ongoing studies aim to determine whether targeting these cytokine pathways can provide durable therapeutic benefit in AA while maintaining favorable safety profiles [64].

Collectively, these evolving therapeutic strategies highlight the growing shift from broad immunosuppression toward targeted immune modulation in the treatment of alopecia areata. Advances in understanding the immunologic mechanisms underlying AA have facilitated the development of therapies that specifically disrupt pathogenic signaling pathways, offering the potential for improved efficacy and reduced systemic toxicity.

X. Conclusion

Summary of Immune Mechanisms

This review highlights the complexity of alopecia areata development and the multitude of factors that may contribute to disease pathogenesis, particularly autoimmune mechanisms and Tcell–mediated injury during the anagen phase. Under homeostatic conditions, reduced expression of MHC molecules contributes to maintenance of hair follicle immune privilege. This protection is further supported by immunosuppressive factors such as TGF-β, IL-10, and α-MSH. Disruption of these protective mechanisms may result in diminished immune protection of the hair follicle. In combination with genetic susceptibility, environmental triggers, infections, and oxidative stress, these changes may contribute to follicular damage. Inflammation is further amplified through the IL-15/ IFN-γ and JAK-STAT pathways, with APCs and $CD4^+$ T cells also contributing to the inflammatory response. Together, these factors demonstrate the complex interaction between dysregulated inflammatory signaling, impaired immune protection, and potential targets for future therapies [65,66].

Current studies have focused on the central mechanisms of pathogenesis involving IFN-γ and IL15. A major strength of this area in AA research is translation into targeted therapies,

Pathak A, et al., Arch Intern Med Res 2026
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particularly JAK inhibitors, which have demonstrated clinical benefit by disrupting inflammatory signaling. Current research has substantially advanced the understanding of alopecia areata by identifying the collapse of hair follicle immune privilege, $CD8^+$ T-cell–mediated injury, and the IFN-γ/IL-15 feedback loop as central mechanisms underlying disease pathogenesis. Furthermore, advances in molecular and cellular research have expanded the understanding of additional immune populations and cytokine pathways that may contribute to disease progression [67,68,69].

Despite these advances, several limitations remain. Although the inflammatory mechanisms responsible for sustaining follicular injury have been extensively investigated, the initial events that trigger immune privilege collapse are not fully understood. Additionally, variability in therapeutic response and recurrence of hair loss following treatment highlight gaps in understanding the mechanisms responsible for persistent autoimmune activity and long-term immune regulation. Emerging research into the gut–skin–hair axis has identified potential associations between microbial dysbiosis, altered microbial metabolites, and immune dysfunction; however, much of this evidence remains associative, limiting conclusions regarding causality. Further limitations include the need for validated biomarkers of disease activity, and a clearer understanding of how findings from experimental models translate to human disease. Addressing these gaps through integrated molecular, immunologic, and clinical research may facilitate the development of individualized therapies aimed at restoring follicular immune privilege and achieving sustained remission.

Importance of Immune-Targeted Research and Future Directions

In the future, deeper investigation into the gut–skin–hair axis and how specific components of the microbiome may play a fundamental role in the development of alopecia areata could be important for preventive strategies and therapeutic development. Focus should be placed on metagenomic sequencing and microbial profiling to determine whether these microbial changes precede disease development or occur secondarily because of inflammation. Additionally, further investigation into butyrate and tryptophan-derived metabolites may help clarify their influence on T-cell regulation and inflammatory signaling [70,71].

Furthermore, longitudinal prospective studies could evaluate the microbiome before and after treatment with JAK inhibitors to better understand how therapy affects microbial composition and whether specific microbial pathways could serve as additional therapeutic targets. These future studies may provide deeper insight into whether and how microbial changes precede disease, influence immune function, and potentially predict relapse and hair follicle damage [72].

Key Points

1. Alopecia areata is a hair loss disease that is characterized as patterned, non-scaring balding with underlying immune mediated pathophysiology.
2. The hair follicle consists of three phases in its life cycle including anagen (active growth), catagen (regression and vascularization of the follicle), and telogen phase (resting and anchoring follicle).
3. Hair follicles naturally have a protective phenomenon, referred to as immune privilege, which allows hair to be shielded from systemic disease or unrelated stressors within the body.
4. Alopecia areata etiology is attributed to a multitude of factors; however, the primary driver is suppressing immune privilege by disrupting levels of TGF-β, IL-10, and MHC class I and II molecules.
5. The immunological cells involved in developing alopecia areata include Cytotoxic CD8 T cells, CD4+ T Helper Cells, plasmacytoid dendritic cells, and NK cells.
6. Overactivation of cytokines such as IFN-α, IFN-γ, IL-2, IL-15, and IL-17 and intracellular JAK-STAT signaling pathways further contribute to inflammation and destruction of hair follicles.
7. The gut-skin-hair axis is an immune, metabolic, and neuroendocrine network that explains another underlying mechanism for alopecia areata pathophysiology.
8. Current therapeutic modalities for alopecia areata include immunosuppressive modulators, monoclonal antibodies targeting immune cells, and corticosteroids to reduce inflammatory stress on hair follicles.

Abbreviations

AA: Alopecia Are; **APC:** Antigen presenting cell; **GPCR**: G-protein coupled receptor; **HLA-DR**: Human Leukocyte Antigen-DR; **IFN-γ:** Interferon- gamma; **IL**: Interleukin; **JAK-STAT**: Janus Kinase and Signal Transducer and Activator of Transcription; **MHC**: Major Histocompatibility Complex; **α-MSH**: Alpha-melanocyte stimulating hormone; **MxA**: Matrix protein; **NK**: Natural Killer; **NKG2D**: Natural Killer Group 2, member D; **pDC:** Plasmacytoid dendritic cells; **SCFA**: Short-chain fatty acids; **TGF-β**: Transformation growth factor – beta

Data Availability

No new pre-clinical or clinical studies were performed, and all findings were gathered from the published articles and critically reviewed. All collected findings and their analyses are deposited in the Cloud provided by WesternU and are also available with the corresponding author upon request through the proper channel.

Ethics Approval Declaration

No new pre-clinical or clinical studies were performed, and all findings were gathered from the published articles and critically reviewed. Hence, an approval from the Institutional Review Board or any other Approval Committee for Ethics Approval is not applicable.

Ethics and Consent to Participate Declarations

Not Applicable

Funding

The research work of DKA is supported by the R25AI179582 grant from the National Institutes of Health, USA. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Competing interests

All authors have read the manuscript and declare no conflict of interest. No writing assistance was utilized in the production of this manuscript.

Consent for publication

All authors have read the manuscript and consented for publication.

References

1. Walter K. Common Causes of Hair Loss. JAMA. 328 (2022): 686.
2. Mirmirani P, Fu J. Diagnosis and Treatment of Nonscarring Hair Loss in Primary Care in 2021. JAMA. 325 (2021): 878-879.
3. Heidari K, Shojaei S, Matin AA, Agrawal DK. Hair follicles as immune targets: unraveling cellular players, cytokine crosstalk, and precision pathways for future therapy of alopecia areata. Expert Rev Clin Immunol 22 (2026): 789-808.
4. Aabedi A, Agrawal DK. Convergent Regenerative Strategies in PM&R for Musculoskeletal and Hair Restoration: Integration of PRP, Exosomes, and Physical Modalities. Arch Intern Med Res 9 (2026): 26-33.
5. Ungar B, Renert-Yuval Y, Dlova NC, et al. Alopecia areata. Nat Rev Dis Primers 11 (2025): 77.
6. Okhovat JP, Marks DH, Manatis-Lornell A, et al. Association between alopecia areata, anxiety, and depression: A systematic review and meta-analysis. J Am Acad Dermatol. 2023 May; 88 (2023): 1040-1050.
7. Christou E, Lalagianni N, McSweeney SM, et al. Psychosocial burden and the impact of illness perceptions and stigma on quality of life, anxiety and depression in alopecia areata: results from the Alopecia + Me study. Br J Dermatol 193 (2025): 458467.
8. Lensing M, Jabbari A. An overview of JAK/STAT pathways and JAK inhibition in alopecia areata. Front Immunol 13 (2022): 955035.
9. Paus R, Cotsarelis G. The biology of hair follicles. N Engl J Med 341 (1999): 491-497.
10. Sperling LC. Hair anatomy for the clinician. J Am Acad Dermatol 25 (1991): 1-17.
11. Zeng Y, Abe A, Takashima S, et al. Preferential crosstalk between perifollicular capillary vessels and dermal papilla cells during hair cycling homeostasis. Sci Rep 16 (2026):15328.
12. Shamloul G, Khachemoune A. An updated review of the sebaceous gland and its role in health and diseases Part 1: Embryology, evolution, structure, and function of sebaceous glands. Dermatol Ther 34 (2021): e14695.
13. Tamura Y, Takata K, Eguchi A, Kataoka Y. In vivo monitoring of hair cycle stages via bioluminescence imaging of hair follicle NG2 cells. Sci Rep 8 (2018): 393.
14. Wang ECE, Higgins CA. Immune cell regulation of the hair cycle. Exp Dermatol 29 (2020): 322-333.
15. De Weert J, Kint A, Geerts ML. Morphological changes in the proximal area of the rat's hair follicle during early catagen. An electron-microscopic study. Arch Dermatol Res 272 (1982): 79-92.
16. Lee JH, Choi S. Deciphering the molecular mechanisms of stem cell dynamics in hair follicle regeneration. Exp Mol Med 56 (2024): 110-117.
17. Piérard-Franchimont C, Piérard GE. Alterations in hair follicle dynamics in women. Biomed Res Int (2013): 957432.
18. Wu P, Zhang Y, Xing Y, et al. The balance of Bmp6 and Wnt10b regulates the telogen-anagen transition of hair follicles. Cell Commun Signal 17 (2019): 16. Erratum in: Cell Commun Signal 18 (2020): 4.
19. Zhou C, Li X, Wang C, Zhang J. Alopecia Areata: an Update on Etiopathogenesis, Diagnosis, and Management. Clin Rev Allergy Immunol 61 (2021): 403-423.
20. Betz RC, Petukhova L, Ripke S, et al. Genome-wide meta-analysis in alopecia areata resolves HLA associations and reveals two new susceptibility loci. Nat Commun. Jan 22;6:5966. doi: 10.1038/ncomms6966. PMID: 25608926; PMCID: PMC4451186.
21. Peterle L, Sanfilippo S, Borgia F, et al. Alopecia Areata: A Review of the Role of Oxidative Stress, Possible

Pathak A, et al., Arch Intern Med Res 2026
DOI:10.26502/aimr.0260

Biomarkers, and Potential Novel Therapeutic Approaches. Antioxidants (Basel) 12 (2023): 135.

22. Seok J, Cho SD, Lee J, et al. A virtual memory CD8+ T cell-originated subset causes alopecia areata through innate-like cytotoxicity. Nat Immunol 24 (2023): 1308-1317. Erratum in: Nat Immunol 27 (2026): 166.

23. Ito T, Ito N, Bettermann A, et al. Collapse and restoration of MHC class-I-dependent immune privilege: exploiting the human hair follicle as a model. Am J Pathol 164 (2004): 623-634.

24. Bertolini M, McElwee K, Gilhar A, et al. Hair follicle immune privilege and its collapse in alopecia areata. Exp Dermatol 29 (2020): 703-725.

25. Rieger-Molitor L, Maj C, Redler S, et al. Do Alopecia Areata and Hair Colour Have a Shared Genetic Component? Exp Dermatol 35 (2026): e70299.

26. Ito T, Kageyama R, Nakazawa S, Honda T. Understanding the significance of cytokines and chemokines in the pathogenesis of alopecia areata. Exp Dermatol 29 (2020): 726-732.

27. Wang Y, Li Y, Feng Y, et al. Immunopathogenesis and Experimental Models of Alopecia Areata: From Mechanistic Insights to Translational Platforms. Clin Rev Allergy Immunol 69 (2026): 47.

28. Ungar B, Renert-Yuval Y, Dlova NC, et al. Alopecia areata. Nat Rev Dis Primers 11 (2025): 77.

29. Gil-Quiñones SR, Sepúlveda-Pachón IT, Sánchez Vanegas G, et al. Effect of PTPN22, FAS/FASL, IL2RA and CTLA4 genetic polymorphisms on the risk of developing alopecia areata: A systematic review of the literature and meta-analysis. PLoS One 16 (2021): e0258499.

30. Pourang A, Mesinkovska NA. New and Emerging Therapies for Alopecia Areata. Drugs 80 (2020): 635-646.

31. Betz RC, Petukhova L, Ripke S, et al. Genome-wide meta-analysis in alopecia areata resolves HLA associations and reveals two new susceptibility loci. Nat Commun 6 (2015):5966.

32. Dai Z, Xing L, Cerise J, et al. CXCR3 Blockade Inhibits T Cell Migration into the Skin and Prevents Development of Alopecia Areata. J Immunol 197 (2016): 1089-1099.

33. Lee EY, Dai Z, Jaiswal A, et al. Functional interrogation of lymphocyte subsets in alopecia areata using single-cell RNA sequencing. Proc Natl Acad Sci U S A. 120 (2023): e2305764120.

34. Wang Y, Li Y, Feng Y, et al. Immunopathogenesis and Experimental Models of Alopecia Areata: From Mechanistic Insights to Translational Platforms. Clin Rev Allergy Immunol 69 (2026): 47.

35. Lee EY, Dai Z, Jaiswal A, et al. Functional interrogation of lymphocyte subsets in alopecia areata using single-cell RNA sequencing. Proc Natl Acad Sci U S A. 120 (2023): e2305764120.

36. Yang X, Zhang W, Zhao X, et al. Changes and significance of Th1/Th2 and Treg/Th17 cells and their cytokines in patients with alopecia areata. Exp Cell Res 442 (2024): 114259.

37. Zhao HB, Zhang YN, Qiang Y, et al. From mechanisms to therapies: current advances breakthroughs in alopecia areata immunopathology. Front Immunol 16 (2025): 1621492.

38. Wang Y, Li Y, Feng Y, et al. Immunopathogenesis and Experimental Models of Alopecia Areata: From Mechanistic Insights to Translational Platforms. Clin Rev Allergy Immunol 69 (2026):47.

39. Lee EY, Dai Z, Jaiswal A, et al. Functional interrogation of lymphocyte subsets in alopecia areata using single-cell RNA sequencing. Proc Natl Acad Sci U S A. 120 (2023): e2305764120.

40. Abou Rahal J, Kurban M, Kibbi AG, Abbas O. Plasmacytoid dendritic cells in alopecia areata: missing link? J Eur Acad Dermatol Venereol 30 (2016): 119-123.

41. Ito T, Suzuki T, Sakabe JI, et al. Plasmacytoid dendritic cells as a possible key player to initiate alopecia areata in the C3H/HeJ mouse. Allergol Int 69 (2020): 121-131.

42. Fan J, Luo Y, Gao C, Wang Y. IL-15 in alopecia areata: the immune tolerance mechanistic insights and translational perspectives. Front Med (Lausanne) 13 (2026): 1815855.

43. Hu BD, He H, Bose S, et al. Comprehensive single-cell transcriptomic profiling of the scalp from patients with moderate-to-severe alopecia areata. J Allergy Clin Immunol 157 (2026): 1099-1113.

44. Xing L, Dai Z, Jabbari A, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med 20 (2014): 1043-1049.

45. Hashimoto K, Yamada Y, Sekiguchi K, et al. NLRP3 inflammasome activation contributes to development of alopecia areata in C3H/HeJ mice. Exp Dermatol 31 (2022): 133-142.

46. Liu Z, Liu X. Gut microbiome, metabolome and alopecia areata. Front Microbiol 14 (2023): 1281660.

47. Guo Z, Yang J, Zang R, et al. The brain-gut-skin axis in inflammatory and disfiguring skin diseases: mechanistic insights, clinical correlations, and therapeutic strategies. Front Immunol. 17 (2026): 1737303.

48. Mann ER, Lam YK, Uhlig HH. Short-chain fatty acids:

linking diet, the microbiome and immunity. Nat Rev Immunol 24 (2024): 577-595.

49. Moreno-Arrones OM, Serrano-Villar S, Perez-Brocal V, et al. Analysis of the gut microbiota in alopecia areata: identification of bacterial biomarkers. J Eur Acad Dermatol Venereol 34 (2020): 400-405.

50. Bi D, Tey JT, Yao D, et al. The causal relationship between gut microbiota and alopecia areata: a Mendelian randomization analysis. Front Microbiol 15: (2024) 1431646.

51. Van Caelenberg E, Belpaire A, van Geel N, Speeckaert R. A meta-analysis of chemokines in alopecia areata: recruiting immune cells toward the hair follicle. Front Immunol 16 (2025): 1648868.

52. Gupta AK, Wang T, Polla Ravi S, et al. Systematic review of newer agents for the management of alopecia areata in adults: Janus kinase inhibitors, biologics and phosphodiesterase-4 inhibitors. J Eur Acad Dermatol Venereol 37 (2023): 666-679.

53. Cui J, Wu P, Chang Y, et al. A two-hit mechanism triggers autoimmune hair loss. Nature 30 (2026).

54. Mateos-Haro M, Novoa-Candia M, Sánchez Vanegas G, et al. Treatments for alopecia areata: a network meta-analysis. Cochrane Database Syst Rev 10 (2023): CD013719.

55. Bansal, B., Bansal, S., Sushama, S. et al. Step-down approach to concentration of intralesional triamcinolone acetonide in treatment of scalp patchy alopecia areata: insights from an open-label randomized trial. Arch Dermatol Res 317, 938 (2025).

56. Chaudhary F, Lee W, Escander T, Agrawal DK. Exploring the Complexities of Atopic Dermatitis: Pathophysiological Mechanisms and Therapeutic Approaches. J Biotechnol Biomed 7 (2024): 314-328.

57. Najafi N, Maatouk H, Vardanyan KG, et al. A Systematic Review of the Mechanisms and Therapeutic Applications of GHK-Cu (Glycyl-L-Histidyl-L-Lysine-Copper Complex) in Topical Microneedle Delivery: A Case for Expanded Clinical Trials. Arch Intern Med Res 9 (2026): 269-293.

58. Morriss S, Foo CH, Lin E, et al. Efficacy and Safety of Oral Janus Kinase Inhibitors in Adults and Adolescents with Alopecia Areata: A Systematic Review and Meta-Analysis of Randomised Controlled Trials. Am J Clin Dermatol 27 (2026): 925-943.

59. Aceituno D, Fawsitt CG, Power GM, et al. Systematic review and indirect treatment comparisons of ritlecitinib against baricitinib in alopecia areata. J Eur Acad Dermatol Venereol 39 (6): 1134-1142.

60. Freitas E, Guttman-Yassky E, Torres T. Baricitinib for the Treatment of Alopecia Areata. Drugs 83 (2023): 761-770.

61. Husein-ElAhmed H, Husein-ElAhmed S. Comparative efficacy of oral Janus kinase inhibitors and biologics in adult alopecia areata: A systematic review and Bayesian network meta-analysis. J Eur Acad Dermatol Venereol 38 (2024): 835-843.

62. Dahabreh D, Jung S, Renert-Yuval Y, et al. Alopecia Areata: Current Treatments and New Directions. Am J Clin Dermatol 24 (2023): 895-912.

63. Guttman-Yassky E, Renert-Yuval Y, Bares J, et al. Phase 2a randomized clinical trial of dupilumab (anti-IL-4Rα) for alopecia areata patients. Allergy 77 (2022): 897-906.

64. Anderer S. New Guidance for Common Hair Loss Disorder. JAMA. 25 (2026).

65. Hu BD, He H, Bose S, et al. Comprehensive single-cell transcriptomic profiling of the scalp from patients with moderate-to-severe alopecia areata. J Allergy Clin Immunol 157 (2026): 1099-1113.

66. Bertolini M, McElwee K, Gilhar A, et al. Hair follicle immune privilege and its collapse in alopecia areata. Exp Dermatol 29 (2020): 703-725.

67. Shin JM, Choi DK, Sohn KC, et al. Induction of alopecia areata in C3H/HeJ mice using polyinosinic-polycytidylic acid (poly[I:C]) and interferon-gamma. Sci Rep 8 (2018): 12518.

68. Ding H, Yu Z, Yao H, et al. Global burden of alopecia areata from 1990 to 2019 and emerging treatment trends analyzed through GBD 2019 and bibliometric data. Sci Rep 15 (2025): 25869.

69. King B, Ohyama M, Kwon O, et al.; BRAVE-AA Investigators. Two Phase 3 Trials of Baricitinib for Alopecia Areata. N Engl J Med 386 (2022): 1687-1699.

70. Pinto D, Sorbellini E, Marzani B, et al. Scalp bacterial shift in Alopecia areata. PLoS One 14 (2019): e0215206.

71. Saadh MJ, Allela OQB, Ballal S, et al. The effects of microbiota-derived short-chain fatty acids on T lymphocytes: From autoimmune diseases to cancer. Semin Oncol. 2025 Oct; 52 (2025): 152398.

72. Liu K, Deng S, Zhou Y, et al. Crosstalk Between the Skin Environment and Microbial Community in Immune-Related Skin Diseases. Clin Rev Allergy Immunol 68 (2025): 16.

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Citation: Angelie Pathak, Andrew Abou Jaoude, Hina Patel, Jason Zar, Devendra K. Agrawal. Unlocking the Immune Mechanisms of Alopecia: Clinical Realities and Epidemiology. Archives of Internal Medicine Research. 9 (2026): 331-340.