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# Alopecia Areata: Pathogenesis, current treatments, and future perspectives

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**Abstract**

**Introduction and purpose:**

Alopecia areata (AA) is a chronic autoimmune disorder characterized by non-scarring hair loss, often presenting as round patches. The disease is thought to result from an immune dysregulation. Current research suggests that the loss of immune privilege in hair follicles plays a key role, leading to their destruction by autoreactive T-cells. This review, based on scientific articles retrieved from PubMed and Google Scholar, aims to examine available treatment options and summarize the current state of understanding alopecia areata pathogenesis.

**State of knowledge:**

The treatment approach depends on disease severity. The severity of the disease is graded according to the SALT scale. For limited hair loss, topical therapies such as glucocorticosteroids, minoxidil, anthralin, diphenylcyclopropenone (DPCP), and phototherapy are commonly employed. In severe cases, systemic therapies like oral corticosteroids, methotrexate, and other immunosuppressants are used. Recent advancements highlight Janus kinase (JAK) inhibitors as promising therapies, with clinical trials showing their effectiveness in refractory AA cases. Additionally, emerging treatments like stem cell-based therapies are under investigation, offering hope for the future.

**Conclusions:**

Despite progress in therapeutic options, AA remains a condition with significant unmet medical needs. The exact mechanisms driving the disease are not fully understood, and no universally effective treatment exists. Further research is essential to better understand the pathogenesis of AA and develop more effective and targeted therapies. This review emphasizes the need for continued exploration of innovative treatment strategies and a deeper understanding of the disease's ethological factors to improve patients' outcomes.

Key words: alopecia areata; autoimmune diseases; dermatology

## Introduction

Alopecia areata is an autoimmune disease characterized by non-scaring hair loss resulting from damage of follicle by T cells. Usually it occurs as a small round bald lesion (patchy alopecia arata), usually on the scalp. However, the disease may progress to total loss of hair of the scalp (alopecia totalis) or all body hair (alopecia universalis)[i]. It's not life threating, but is connected with a reduced quality of life. It also has a negative impact on patients economic status[ii]. A hair loss causes low self-esteem and problems with social interactions[ iii ]. Research demonstrates that individuals with alopecia areata have an elevated risk of developing anxiety and depression, with this association being particularly pronounced in adults experiencing more extensive hair loss[iv].

Alopecia areata affects 2% of the global population, but positive family history increases risk to 48%[v]. It is the second-most frequent non-scarring alopecia, after male and female pattern alopecia. AA prevalence is lower in adults than children, is increasing over time, and

significantly differs by region. Alopecia areata is more prevalent among Asian, Black, and Hispanic populations[vi].

The diagnosis of alopecia areata is made based on clinical examination and trichoscopy. The most characteristic trichoscopic feature of alopecia areata is the presence of exclamation mark hairs. These are short hair shafts with a thickened, pigmented distal end, resulting from the dystrophic mechanism of hair loss. The presence of exclamation mark hairs at the periphery of alopecia patches is indicative of active disease. Additional trichoscopic markers associated with alopecia areata activity include black dots, triangular hairs, broken hairs, tapered hairs, and Pohl-Pincus constrictions. Trichoscopic findings commonly associated with alopecia areata include yellow dots, but they are not specific to this condition. These dots represent empty follicular openings filled with keratin and sebum[vii]. In cases of alopecia areata, they often appear in clusters, corresponding to the number of hairs within follicular units. Vellus hairs, characterized as unpigmented shafts less than 10 mm in length and 0.03 mm in thickness, are 10% of healthy human scalp, but increased proportion of them may occur in alopecia areata [viii]. The histological features of the active acute phase of AA are characterized by dense lymphocytic infiltrates surrounding the lower portions of anagen and/or catagen hair follicles, with peribulbar infiltrates often described as resembling a "swarm of bees." In chronic alopecia areata, inflammation may not occur [ix].

To standardize and simplify the assessment of alopecia areata severity in clinical trials, the Severity of Alopecia Tool (SALT) score has been created. The SALT score is widely regarded as an adequate method for evaluating the extent of patchy AA on the scalp in clinical settings. The scalp is divided into four quadrants: left profile (18% of the surface), right profile (18%), top (40%), and back (24%). The percentage of hair loss in each quadrant is estimated and then summed to obtain the total SALT score. The score ranges from 0% (indicating no hair loss) to 100% (indicating complete hair loss). In its original framework, the severity of hair loss was categorized as follows: S0 = no hair loss, S1 = 1–24% hair loss, S2 = 25–49% hair loss, S3 = 50–74% hair loss, S4 = 75–99% hair loss, and S5 = 100% hair loss [x]. Other sources propose the following classification: SALT <20 was classified as mild, 20 ≤ SALT <50 as moderate, and SALT ≥50 as severe. Moderate AA was further categorized as severe if any of the following criteria were met: a dermatology life quality index (DLQI) score exceeding 10, loss of eyebrows or eyelashes, active hair loss, or AA that was resistant to treatment[xi].

Studies reveal that dermatologic and systemic conditions associated with alopecia areata include vitiligo, lupus erythematosus, psoriasis, atopic dermatitis and allergic rhinitis [xii]. Autoimmune thyroid disorders are the most commonly occurring condition in individuals with AA [xiii]. Patients with Down syndrome and polyglandular autoimmune syndrome type 1 have an increased risk of developing alopecia areata [xiv]. The scalp is main place of occurrence of AA, nails can also be affected, which is connected with a worse outcome [xv]. Study of patients biomarkers reveal dysregulation of cardiovascular and atherosclerosis biomarkers, which suggests a possible systematic approach [xvi].

**Ethiopatogenesis**

The exact pathobiology of alopecia areata has still remained elusive. Historically, AA was connected with infections, trauma responses, hormonal fluctuations or thallium acetate

poisoning. Inflammation as a cause of alopecia areata was described over 100 years ago, but a big groundbreak in understanding of ethiopatogenesis was identifying several immune-related and several key pathogenetic effector cells in 1950 [1]. Today the common theory is the collapse of the immune privilege of the hair follicle caused by immunological mechanism. Multiple genetic and environment factors contribute to the pathogenesis of AA. Viral infections, such as Epstein–Barr virus (EBV), hepatitis B and C, and swine flu, have been linked to both the initial onset and recurrence of the condition. Additionally, certain vaccines, including those for influenza, hepatitis, and COVID-19, have been reported as possible triggers for AA flare-ups [10].

A major risk factors in AA are HLA ( human leukocyte antigen) genes. The most significant risks in HLA-DQB1*03, HLA- DQB1*04, HLA-DQB1*16, HLA-C*04-01, and HLA-DR.

Initial studies on candidate genes detected the human leukocyte antigen (HLA) class I and II genes as major risk factors in AA pathogenesis, identifying HLA-DQB1*03, HLA- DQB1*04, HLA-DQB1*16, HLA-C*04-01, and HLA-DR as the most significant risk geno- types [4,38]. These genes are closely linked to the effector functions of CD4+ and CD8+ T cells.

Further studies with using genome-wide association studies (GWASs) made possible to identify AA associated genomic regions, in which a large number of genes was immune-related such as genes associated with autophagy, regulatory T lymphocytes, cytomegalovirus infection, and most importantly γ-chain cytokines which are known to promote the activation and survival of IFN-γ autoreactive NKG2D+ CD8+ T lymphocytes. Studies showed that CD8+NKG2D+ T cells are sufficient for the induction of AA [xvii]. IFN-γ activates the Janus kinase (JAK) and signal transducers and activators of transcription (STAT) pathway, which leads to the activation of genes that support a CD8+ T cell response. Those cells causing inflammation, disturb and disrupt hair growth cycle. Autoimmune response leads to collapse anagen, the first stage of hair cycle, without destroying the hair follicle, what results a hair loss [xviii]. Genes associated with AA also include peroxiredoxin 5 (PRDX5) and syntaxin 17 (STX17). They are involved in hair follicle regulation based on co-localization with keratin 31, expressed in the hair shaft and inner root sheath. This suggests dysfunction of the hair follicle takes part in the pathogenesis of AA [xix].

Monogenic cause of alopecia areata has not been detected, but an identification of one is expected to happen, which may help to gain a better understanding of the causes of the disease and develop more effective treatment strategies.

**Treatment**

Individuals affected by alopecia areata retain the capacity for hair regrowth, with 34% to 50% of those experiencing patchy hair loss achieving spontaneous regrowth within a year. Nevertheless, the majority of patients are likely to experience episodes of recurrence [xx].

There are many treatment options available, depending on the clinical presentation of the disease. Unfortunately, none of these treatments address the root cause of AA. All therapeutic approaches focus on suppressing hair loss and promoting regrowth. However, regrowth is not guaranteed, and relapses can occur at any time [xxi]. The longer the condition persists, the more likely it is to progress. Up to 20% of AA cases evolve into total loss of scalp hair [xxii].

## Topical treatment

### Corticosteroids

Steroids, such as clobetasol, triamcinolone can be administered in various forms, including lotions, foams, shampoos, or through intralesional injections. These injections are delivered into the upper subcutaneous tissue using a fine needle or a needle-free device. Among corticosteroid treatments, intralesional administration has shown superior efficacy compared to topical applications [xxiii]. Intralesional corticosteroids, usually triamcinolone acetonide are first line therapy for patients with lost less than 50% of scalp hair [xxiv]. Due to their relatively low incidence of side effects, topical steroids are the first choice for treating AA in children [ xxv ]. Lotions, foams are choice for patients who either prefer to avoid intralesional corticosteroids or cannot endure the pain associated with the procedure. Glucocorticosteroids exert their effects at the cellular level, which can be genomic or non-genomic. On the genomic level, cortisol binds to the glucocorticoid receptor (GR) typically in the cytoplasm of nearly every cell in the body.

This cortisol-GR complex then translocates to the nucleus, where it interacts with glucocorticoid response elements (GRE), resulting in the inhibition of pro-inflammatory cytokines and the promotion of anti-inflammatory cytokine expression. This process typically takes between 30 to 60 minutes. Lower cortisol levels can lead to transrepression of NF-kappa B, mediated by the cortisol-GR complex. NF-kappa B is a family of transcription factor protein complexes and has a key role in chronic inflammation [xxvi]. The non-genomic mechanism involves membrane receptors and second messengers, facilitating a swift response that impacts monocytes, T cells, and platelets, occurring in just a few minutes [xxvii]. A clinical trials with using clobetasol showed hair regrowth in 80% patients after 12 weeks treatment [xxviii]. The relapse rate for this treatment method is between 37% and 63% [xxix]. If the treatment does not show results after 6 months, it should be changed. Studies showed that using corticosteroids causes downregulation of inflammatory cytokines genes and upregulation of genes encoding several hair keratins (KRT35, KRT75 and KRT86), which seems to be the most responsive to treatment and could be the best biomarker for the treatment response [25]. Folliculitis is a frequent side effect of topical corticosteroids. In rare cases, telangiectasia and atrophy may develop. One of the potential side effects of injections is skin atrophy, but it typically reverses after a few months [25].

### Anthralin

Anthralin, also known as dithranol, is an anthracene derivative commonly used as an ingredient in psoriasis treatment. The exact mechanism of action of anthralin in alopecia areata is still unknown. Anthralin may work by altering the local immune response in the skin. When applied to the scalp, anthralin causes mild irritation, leading to pruritus, erythema, and scaling. Patients who exhibit only a weak inflammatory reaction to anthralin might not experience substantial therapeutic benefits [xxx]. While targeted irritation is the goal, it can also limit treatment, leading to discontinuation in up to 11% of patients. The use of anthralin might be associated with a reduced immediate response but one that is more persistent [xxxi]. Studies showed that using anthralin, the complete response rate was below 50% (between 30 and 35%). Effectiveness can be increased by combining dithranol with diphenylcyclopropenone (DPCP).

Moreover, a reported case highlights the successful and effective use of a combination of anthralin and calcipotriol but further investigation is encouraged to evaluate this approach [xxxii]. Commonly reported reactions include skin staining and regional lymphadenopathy (LAD), both of which typically resolve upon discontinuation of treatment. Other frequently observed side effects are itching, burning sensations, oozing, and in some cases, bullous eruptions. While these local effects are relatively common, systemic adverse effects are rare, making anthralin a generally safe treatment option when used appropriately [xxxiii].

**Contact immunotherapy**

Contact immunotherapy is preferred method in patients with more than 50% loss of scalp hair due to few side effects. Diphenylcyclopropenone (DPCP) is used the most often sensitizer. Other sensitizers- squaric acid dibutyl ester (SADBE) and dinitrochlorobenzene (DNCB) are not often used anymore because the first is unstable in acetone, in which have to be solved and expensive. The second may have mutagenic and carcinogenic potential [xxxiv].

Mechanism of action is based on inducing an allergic reaction leading to a local eczematous reaction causing some mild redness. This theory suggests that the immune system may redirect its focus from the hair follicles to the irritation caused by drug allowing the follicles to recover [xxxv]. Contraindication to treatment are pregnancy, atopic egzema. The common side effects of using DPCP are cervical/occipital lymphadenopathy, eczema, hyperpigmentation, itching.xxxvi The average response rate of DCPC treatment was 53,7% [xxxvii].

**Minoxidil**

Minoxidil, initially developed as an antihypertensive drug, was observed to cause hypertrichosis as a side effect, which led to its widespread use in the treatment of various types of alopecia. The mechanism of action of minoxidil is believed to involve multiple pathways. Minoxidil acts as a vasodilator by opening ATP-sensitive potassium (KATP) channels, causing membrane hyperpolarization. This improves the delivery of nutrient-rich, oxygenated blood to hair follicles. It also reduces inflammation by suppressing T lymphocyte activity and inhibiting cytokines such as interleukin-1α and prostacyclin. Additionally, minoxidil is thought to influence vascular endothelial growth factors (VEGF) in dermal papilla cells and activate the VEGF-related β-catenin signaling pathway. β-catenin is a transcription factor involved in hair follicle regeneration. Minoxidil also enhances DNA synthesis within the anagen bulb, promoting hair growth [xxxviii].

Minoxidil may also influence the duration of the anagen and telogen phases of the hair growth cycle. Temporary increases in hair growth and allergic skin reactions are potential side effects. While it is effective as monotherapy in androgenetic alopecia, studies suggest that it is not significantly effective in the treatment of alopecia areata. However, combining minoxidil with other topical or systemic treatments has been shown to enhance its effectiveness.

**Ultraviolet therapy**

Phototherapy is regarded as a secondary treatment option due to its potential for serious side effects and a high relapse rate. This method utilizes ultraviolet (UV) light at various

wavelengths to treat a range of dermatological disorders. Current phototherapy techniques include broadband UVB (290–320 nm), narrowband UVB (311–313 nm), the 308 nm excimer laser, UVA 1 (340–400 nm), UVA combined with psoralen (PUVA), and extracorporeal photochemotherapy (photopheresis).

UVB radiation primarily targets cells within the epidermis and the epidermal-dermal junction, whereas UVA radiation penetrates deeper, affecting both the epidermis and dermis, with a particular impact on blood vessels. UV radiation induces both immediate and delayed biological effects. Immediate effects include the formation of DNA photoproducts and DNA damage, leading to apoptosis in keratinocytes, Langerhans cells, activated T-lymphocytes, neutrophils, macrophages, natural killer (NK) cells, fibroblasts, endothelial cells, and mast cells. Additionally, UV radiation triggers lipid peroxidation, resulting in cell membrane damage, and causes the isomerization of chromophores, such as urocanic acid.

Delayed effects include the production of prostaglandins and cytokines, which are essential for immune suppression. These effects lead to both systemic and local immune modulation, resulting in changes in cytokine expression, such as the induction of the interleukin-1 receptor antagonist, reductions in interleukin-2, and increases in interleukin-10 and interleukin-15. Additionally, delayed effects can cause cell cycle arrest. Collectively, these mechanisms contribute to the reduction of disease activity [xxxix].

The effectiveness of UVB therapy demonstrated a 50% regrowth of hair, with an increase in hair diameter. The efficacy of UVA therapy was reported to be 84% [xl, xli]. The long-term effects of high cumulative UV exposure include skin photoaging and photocarcinogenesis. Insufficient eye protection during irradiation can lead to acute keratitis or conjunctivitis. However, these side effects can be prevented by consistently using proper eye protection [xlii].

**Other:**

Other topical treatments for alopecia areata include prostaglandin analogs and tacrolimus. The proposed mechanism of action involves the stimulation of prostaglandin E2 (PGE2) synthesis. Prostaglandin analogs promote the anagen phase, increase hair density, and facilitate the transition from the telogen to the anagen phase [xliii]. Clinical trials in animals have shown that bimatoprost was effective in treating alopecia areata, but its efficacy in humans remains debatable. It is important to study a larger sample size, extend the study duration, and test higher drug concentrations to confirm whether bimatoprost is effective in treating alopecia areata.[xliv] The case of tacrolimus research is similar. While animal studies showed promising results, these findings could not be replicated in human trials [xlv].

Systemic treatment

**Corticosteroids**

Indications for oral corticosteroids include rapidly progressing and extensive alopecia areata. While they are effective, their use is limited due to serious side effects and a high relapse rate. Clinical trials have shown a complete response in 43% of the overall study population, and in 51% of studies focusing exclusively on pediatric patients. The relapse rate was higher in the pediatric population. Factors contributing to a lower relapse rate included multifocal alopecia

areata, a first occurrence of AA, and a duration of AA lasting less than 24 months [xlvi]. Combining systemic glucocorticoids with minoxidil therapy can also help lower relapse rates [xlvii]. Systemic glucocorticoids often cause side effects related to adrenal suppression, including long-term impacts on bone growth and integrity, ocular complications, and worsening of hypertension or diabetes. Prolonged use increases the severity and risks of these side effects. When used for less than six months, more common side effects include weight gain and mood swings. Steroids can be administered orally, intravenously, or intramuscularly. Most studies show no significant difference between these routes of administration [1].

**Methotrexate**

Methotrexate (MTX), one of an immmunosuppressive agents (ISA) used in chronic diseases was originally intended as a cancer-fighting medication for leukemia.

The mechanism of action of MTX involves blocking a dihydrofolate reductases which stops purine production. This causes a buildup of adenosine, leading to a reduction in TNF-α and IFN-γ synthesis [xlviii]. MTX has been used both as a standalone treatment and in combination with corticosteroids. Studies involving patients treated with both of these medications revealed that 36% experienced complete regrowth, while 63.2% had regrowth ranging from 50% to 100%. The average time for regrowth was 3 months, with full regrowth occurring within an average of 9.9 months. The use of MTX as monotherapy requires further studies [xlix]. MTX tends to affect rapidly dividing cells, such as those in the skin and gastrointestinal system. Therefore, the most common side effects of methotrexate are gastrointestinal issues, such as nausea, vomiting, mouth sores, and a loss of appetite. The most severe side effect is liver damage. These adverse effects are similar to those caused by a lack of folate and can be mitigated by taking folic acid in conjunction with methotrexate [l].

**Azathioprine**

Azathioprine is a steroid-sparing immunosuppressive agent that reduces the immune response against hair follicles. Its mechanism of action involves inhibiting DNA synthesis, which leads to the suppression of T-cell proliferation and cytokine release. Azathioprine is primarily used in steroid-dependent patients who experience relapses upon dose reduction and require maintenance therapy to sustain remission. In a clinical trial, 73 patients were prescribed azathioprine. A total of 80.8% (59 out of 73) of patients continued azathioprine therapy for at least six months, while 75.3% (55 out of 73) remained on azathioprine for at least 12 months. At the six-month mark, 78.0% (46 out of 59) of azathioprine users required concurrent prednisolone at an average daily dose of 8.65 mg, and 67.3% (37 out of 55) of azathioprine users at 12 months required a daily dose reduced to 5.62 mg [li]. The most common side effects are nausea, vomiting, and diarrhea. Nausea appears to be less common in patients who receive prednisolone simultaneously. Other adverse effects include leukopenia, macrocytosis, and increased susceptibility to herpes [lii].

**Cyclosporine**

Cyclosporine is an immunosuppressive drug primarily used to prevent the rejection of transplanted organs. The mechanism of action of cyclosporine involves inhibiting the activity

of calcineurin phosphatase, which leads to the inhibition of interleukin-2 gene transcription, a process necessary for the full activation of the T-cell pathway [liii]. Cyclosporine can be used in monotherapy, but its combination with corticosteroids is associated with greater treatment efficacy (69% in combination with corticosteroids, 57% in monotherapy) and a lower risk of recurrence (36% in combination with corticosteroids, 74% in monotherapy). The most common adverse effects were gastrointestinal problems, hypertrichosis, and hypertension [liv].

**Jak Inhibitors**

The Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway is a cellular signaling system triggered by various cytokine receptors, playing a key role in controlling the production of different inflammatory mediators. Inhibiting Janus kinase has been identified as a treatment option for several chronic inflammatory skin disorders, including alopecia areata. Type I and type II cytokine receptors activate signaling pathways involving non-receptor tyrosine kinases known as Janus kinases (JAKs) and transcription factors called signal transducers and activators of transcription (STATs). There are four known JAKs—JAK1, JAK2, JAK3, and TYK2—and seven STATs: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. When cytokine molecules bind to the receptor molecules, they activate the JAK/STAT pathway, leading to phosphorylation of tyrosine residues. These active residues then activate the STAT proteins. The activated STAT proteins dimerize and translocate into the cell nucleus, where they bind to specific DNA sequences in the promoter regions of cytokine-responsive genes, thereby initiating transcription. The JAK receptors regulate immune cell functions, influencing the activity of key CD4+ T cells: T helper 1 (Th1), Th2, Th17, and T regulatory (Treg) cells. Consequently, they govern the actions of immune-mediated cells involved in the autoimmune mechanisms underlying various skin disorders [lv]. JAKibs are divided into two generations. The first generation consists of non-selective JAK inhibitors such as baricitinib and tofacitinib. Second-generation JAK inhibitors, including abrocitinib, filgotinib, upadacitinib, brepocitinib, and ritlecitinib, target specific members of the JAK family with greater selectivity. This more selective spectrum of inhibitory activity may help minimize the risk of adverse effects. Despite their broad range of action, JAK inhibitors can cause a variety of side effects. The most common relatively minor side effects include nausea, urinary tract infections, anemia, and elevated HDL, LDL, and creatinine concentrations. Fungal infections may also occur, though rarely. The most common major side effect is varicella zoster infection. Less frequent, but more severe, major side effects include non-melanoma skin cancer, tuberculosis, and Pneumocystis jirovecii pneumonia [lvi].

Tofacinib: Tofacitinib is the first orally administered JAK inhibitor to be tested and approved. This drug is approved for the treatment of psoriasis, psoriatic arthritis, juvenile idiopathic arthritis, keratoconjunctivitis sicca, and transplant rejection [21]. Tofacitinib is commonly regarded as a JAK inhibitor with a particular affinity for JAK1 and JAK3. It reduces signaling from γc family cytokines (JAK1/JAK3) and IFN-γ (JAK1/JAK2), suggesting it can influence both immune cells and hair follicles [lvii].

In a clinical trial involving 66 patients treated for 3 months, 32% of them experienced 50% or greater hair regrowth. However, 8.5 weeks after discontinuation of the medication, relapse of

AA was observed. A shorter disease duration and the presence of histological peribulbar inflammation in pretreatment scalp biopsies were associated with better treatment efficacy [lviii].

Ruxolitinib: Ruxolitinib: is an inhibitor of JAK1 and JAK2, approved for the treatment of myelofibrosis and psoriasis, and is the first JAKib used to treat alopecia areata. Ruxolitinib has the ability to attenuate γc family cytokine signaling (via JAK1/JAK3) as well as IFN-γ signaling (via JAK1/JAK2). As a result, it is likely to exert effects on immune cells sensitive to γc family cytokine signaling and directly target hair follicles, which are influenced by IFN-γ signaling [lix]. A clinical trial on 12 adult patients treated with ruxolitinib showed that 9 of them experienced a 92% regrowth of hair. However, three months after discontinuing treatment, all nine responders reported hair shedding, with three individuals experiencing significant hair loss [lx].

Baricitinib: Baricitinib, a Janus kinase (JAK) inhibitor, has been approved for the treatment of alopecia areata (AA) in multiple countries, supported by evidence from two pivotal studies, BRAVE-AA1 and BRAVE-AA2. These clinical trials evaluated the efficacy and safety of baricitinib in adults presenting with ≥50% scalp hair loss. Participants were treated with baricitinib over a 36-week period, 38.8% of participants who reviewed 4 mg of baricitinib, 22.8% with 2 mg baricitinib reached a SALT score< 20% [lxi].

Deuruxolitynib: Deuruxolitinib selectively inhibits the JAK1 and JAK2 pathways. In the clinical trial THRIVE-AA1, 706 patients were divided into three groups receiving either 8 mg, 12 mg, or a placebo. Both doses of deuruxolitinib led to significantly higher percentages of patients achieving a SALT score of ≤20 at 24 weeks compared to the placebo group. Specifically, 29.6% of patients receiving 8 mg and 41.5% of those receiving 12 mg twice daily reached a SALT score ≤20 after 24 weeks. However, the sustainability of hair regrowth was not assessed in this study [lxii].

Ritlecinib: Ritlecinib is an inhibitor of JAK3 and TEC kinase family approved by FDA to treat AA. Ex vivo experimental data regarding alopecia areata have shown that JAK3 appears to be a dominant factor determining AA, what makes ritlecinib it an ideal target drug the disease. Preliminary data indicate that the inhibition of JAK3 is effective and exerts a favorable impact on the suppression of cytokines, JAK receptors, and Th cell subtypes in AA. There was a clinical trial with 191 patients. They received ritlecitinib at a dose of 50 milligrams. After one year, 74 out of 164 participants (45%) demonstrated scalp hair regrowth, defined as a reduction in scalp hair loss to 20% or less. This rate increased to 61% after two years. Additionally, the scalp hair regrowth observed in 8 out of 10 individuals was sustained between the one- and two-year mark [lxiii].

I**fidancitinib:** Current data suggest that achieving dual inhibition of JAK1 and JAK3 can effectively block downstream signaling pathways in alopecia areata. Furthermore, the benefit

of minimizing unwanted JAK2-related side effects would make it an optimal treatment for AA. Ifidancitinib is a selective, next-generation inhibitor of JAK1/3 that is expected to interfere with γc cytokine and IFN-γ signaling pathways. Furthermore, the drug suppressed the in vitro differentiation of naive CD8+ T cells into NKG2D+CD8+ T cells, which play a pivotal role in the pathogenesis of AA, and also modulated memory T cells implicated in the disease.
Resident memory T cells persist in peripheral tissues for long periods and play an important role in host defense against infections and tumors. In the skin, these cells have been noted in psoriasis, vitiligo, and atopic dermatitis [54]. While these cells have been noted in AA, their role remains undefined. It has been shown that treatment with JAK1ibs or JAK3ibs significantly decreased the frequency of these cells, but the same was not noted with JAK2ibs treatment [55].

Apremilast

Apremilast is an oral selective phosphodiesterase 4 (PDE4) inhibitor. PDE4 is highly expressed by cells involved in immune response regulation, it prevents the degradation of cAMP. Increased level of cAMP leads to decreased synthesis of pro-inflammatory factors as TNF-α, IFN-γ, IL-23, IL-12 and chemokines CXCL9, CXCL 10, and CCL4. Additionally, cAMP promotes the increase of anti-inflammatory markers, such as IL-10 [lxiv]. Study with 15 patients who had not responded to standard therapies. They received 30 mg of apremilast for once or twice a day, for 4-8 weeks, what depended on tolerance. Treating was effective in all 15 patients, four of them demonstrated a good response (>75% hair regrowth), nine had moderate response (50-74%), and two ha mild response (25-49%). Digestive system side effects were exacerbated in the majority of individuals (11 of 15), necessitating a reduction in the drug dosage [lxv]. The recurrence rate was not investigated. Other adverse events of using apremilast were abdominal pain, headache, and nasopharyngitis [lxvi].

Dupilumab

Dupilumab, a human anti–IL-4Rα antibody. By targeting IL-4Rα, dupilumab interferes with the signaling pathways mediated by both IL-4 and IL-13. Additionally, dupilumab inhibits IL-4 signaling. Dupilumab was found to be effective treatment in atopic dermatitis (AD) [lxvii]. Studies on suffering on both AD and AA showed hair regrowth. 16 patients received 300 mg subcutaneous injections of dupilumab every 2 weeks. Primarly, four of them worsened SALT in first 2 months, but those with follow-up improved with time. After 4 months of treating, 6 patients experienced improvement in AA. 4 patients with SALT 0, treated tofacitinib for AA, simultaneously treated with dupilumab did not experience hair loss during decreasing doses of tofacitinib [lxviii]. A few case reports showed efficacy of dupilumab in AA. A 16-old male with AT and atopic dermatitis was treated dupilumab. The patient received a loading dose of 600 mg dupilumab and then 300 mg injections every 2 weeks and experienced total hair regrowth after 8 months. After 3 years of treatment no evidence of AA collapse was noticed [lxix]. This drug appears to be a promising option for patients who are currently suffering from other immunological condition. The results from few case reports are promising; however, further studies are necessary to validate these findings [lxx].

**Mesenchymal Stem Cell Therapy**

Recent research has emphasized the promising role of Mesenchymal Stem Cells (MSCs) as a potential alternative therapy for Alopecia Areata (AA), owing to their immunosuppressive effects. Sources of MSCS aree skin fibroblasts, peripheral blood, bone marrow, adipose tissue, and tonsils. Owing to their distinctive properties, stem cells hold significant potential for application in preventing graft rejection and managing a wide range of autoimmune disorders such as rheumatoid arthritis. Mechanism of action is based on inhibition of pro-inflammatory T cells proliferation. Additionally, MSCc causes upregulation of regulatory T cells [lxxi]. There was a clinical trial on mice, in which AA was induced via IFN-γ. A successful induction was confirmed by histological examining, what revealed enhanced infiltration of CD4+CD8+ T cells within the dermis and the perifollicular region of the subcutaneous tissue. Then miles was divided into two groups- control group, which received saline (CTL), and experimental, which received MSC (MSC) administration. After 49 days, hair regrowth was in both groups, but in the next hair cycle, hair loss was observed again. Then expression patterns of inflammatory factors in the skin was analyzed. In mice with AA-induced CTL, the levels of JAK1, JAK2, STAT1, STAT3, IFN-γR, IL-1β, IL-10, and IL-17α were significantly elevated in comparison to the HC group. On the other hand, MSC treatment in the AA group led to a substantial reduction in the expression of JAK1, JAK2, STAT1, STAT3, IFN-γR, IL-1β, IL-10, IL-18, IL-17α, IL-15, and IL-6 relative to the saline-treated CTL-AA group. Notably, IL-10 expression was markedly upregulated alongside IFN-γ but was effectively downregulated following MSC administration. A noticeable decrease in T cell infiltration was evident in the dermis and subcutaneous adipose tissue of the MSC-treated group compared to the CTL group. These results indicate that MSCT played a role in mitigating the symptoms of AA [lxxii]. Studies show that MSC can the administration of stem cells may represent a promising option for both the treatment and prevention of AA.

In human applications, intravenous delivery of MSCs necessitates a higher number of cells and raises concerns regarding efficiency and safety. Clinical trials have identified thromboembolism and fibrosis as the most frequently observed adverse effects associated with MSC therapy. The major adverse events were believed to be linked to systemic intravascular administration [lxxiii]. Studies conducted on rats with brain injuries have demonstrated that only a small amount of the drug reaches the site of injury, while the majority accumulates in the lungs [lxxiv]. As a result, intralesional MSC injection is believed to be a better option for future AA treatments in humans. Administering MSCs locally may potentially be more effective than systemic delivery, due to addressing localized inflammation.

**Complementary and Alternative Medicines**

Various complementary and alternative therapies have been suggested as potential monotherapies or adjuncts in the treatment of alopecia areata. Among these, the most robust evidence supports the use of specific combinations of essential oils, topical garlic preparations, and oral formulations containing peony glucosides alongside compound glycyrrhizin [lxxv].

Essential oils may be utilized in the treatment of alopecia areata due to their anti-inflammatory properties, their influence on skin barrier function, and their potential to induce dermatitis. Notably, lavender oil has been shown to promote hair growth in mice, highlighting its potential

therapeutic application [lxxvi]. In a double-blind randomized controlled trial, Hay et al. evaluated the effectiveness of daily scalp massage using a blend of essential oils (thyme, rosemary, lavender, and cedarwood in a carrier oil) compared to massage with carrier oil alone in 84 participants. After seven months, 44% of those in the aromatherapy group experienced significant improvement, defined as more than 10% hair regrowth, whereas only 15% of the control group showed similar results. Importantly, no adverse effects were reported during the study [lxxvii].

The mechanism of action of garlic in the treatment of alopecia areata is not fully understood, but it may act by inducing mild contact dermatitis [lxxviii]. Additionally, garlic is believed to possess antimicrobial and vasodilatory properties, which could contribute to its therapeutic effects [lxxix]. Hajheydari et al. conducted a double-blind RCT comparing 5% garlic gel combined with 0.1% betamethasone to betamethasone alone in 40 patients with alopecia areata. Treatments were applied twice daily for three months. The garlic group showed a higher number of total and terminal hairs, along with reduced patch size, compared to the control group. No adverse effects were reported, supporting the use of garlic as an adjunct to topical corticosteroids to enhance hair regrowth in alopecia areata [lxxx]. Compound glycyrrhizin, a glycoside extract derived from plants, possesses immunoregulatory effects and has been reported to activate T cells, potentially influencing Th17 cell differentiation [lxxxi]. Two RCTs investigated the use of compound glycyrrhizin with vitamin B2, with and without glucosides of peony, in patients with alopecia areata. One study included adults with >75% hair loss, and the other included pediatric patients with >50% loss. After three months, marked hair regrowth was observed in 68.2% of adults in the combination group and 71.4% in the group with peony glucosides, with no significant difference in outcomes [lxxxii].

Discussion :

Alopecia Areatais an autoimmune condition that results in non-scarring hair loss and affects approximately 2% of the global population. AA can be classified based on the extent of hair loss into three main forms: patchy alopecia areata (localized bald patches on the scalp), alopecia totalis (complete scalp hair loss), and alopecia universalis (total loss of body hair). This classification is useful for determining appropriate treatment strategies, as different forms of AA may require tailored therapeutic approaches. For instance, localized cases might respond well to topical corticosteroids, while more severe forms such as alopecia totalis or universalis often necessitate systemic treatments like immunomodulatory therapies. Alopecia Areata arises from the loss of immune privilege in hair follicles, predominantly due to the activity of CD8+ T cells and pro-inflammatory cytokines like IFN-γ, which trigger the JAK/STAT signaling pathway. Both genetic factors, including HLA gene variations, and external influences, such as infections and stress, play a role in the development of the disease. Individuals with AA frequently have comorbid autoimmune diseases, with studies indicating that thyroid disorders are the most commonly associated conditions.

Diagnosis is based on clinical examination and trichoscopy, identifying features like exclamation mark hairs and yellow dots. The Severity of Alopecia Tool (SALT) quantifies hair loss to guide treatment.

There is no definitive cure for AA. Current treatments focus on controlling symptoms and promoting hair regrowth, though relapse is common.

According to current studies, topical corticosteroids are the first-line treatment for patients with a low SALT score. These corticosteroids can be administered in various forms, with intralesional injections demonstrating the highest efficacy. However, corticosteroids are associated with numerous side effects. A reduction in the severity of these side effects, as well as an improvement in treatment efficacy, can be achieved by combining corticosteroids with other topical medications. Combining steroid therapies with treatments like anthralin, minoxidil, or DPCP can be beneficial in managing alopecia areata, , depending on individual patient factors and disease severity, patient adherence and their ability to administer the treatment correctly. Ultraviolet therapy, including UVB and UVA radiation, is used as a secondary treatment for alopecia areata due to its potential side effects and high relapse rates. However, long-term UV exposure can lead to skin aging and an increased risk of skin cancer, and eye protection is essential to prevent keratitis or conjunctivitis.

In patients with extensive alopecia areata, systemic therapy is often recommended. These treatments primarily include immunosuppressive medications. It's important to note that while these systemic therapies can be effective, they also carry risks due to their immunosuppressive nature. Potential side effects include increased susceptibility to infections, liver enzyme abnormalities, and gastrointestinal disturbances. Therefore, careful monitoring and consultation with a healthcare professional are essential when considering these treatments. Systemic treatments for alopecia areata include corticosteroids, methotrexate, azathioprine, and cyclosporine. Oral corticosteroids are effective in rapidly progressing and extensive AA but have high relapse rates and serious side effects, including weight gain, mood swings, and potential long-term impacts on bone health and blood pressure. Methotrexate, an immunosuppressive agent, is used in combination with corticosteroids and has shown significant regrowth results, though it can cause gastrointestinal issues and liver damage. Azathioprine is a steroid-sparing drug that is often used for steroid-dependent patients, with side effects like nausea and increased susceptibility to infections. Cyclosporine is effective when combined with corticosteroids but carries side effects such as gastrointestinal problems and hypertension. JAK inhibitors target the JAK-STAT pathway, playing a key role in controlling inflammation and immune responses, making them a promising treatment for alopecia areata. First-generation JAKi, like tofacitinib and ruxolitinib, have shown positive results in clinical trials, with up to 92% hair regrowth in some patients. Second-generation JAKi, such as abrocitinib, baricitinib, and ritlecitinib, offer more selective targeting of specific JAK enzymes, potentially reducing side effects while achieving similar or better results. Baricitinib, approved for AA treatment, showed that 38.8% of patients had significant regrowth after 36 weeks of treatment. Newer drugs, like deuruxolitinib and ifindacitinib, selectively inhibit JAK1/3 and offer promising results in early trials, with enhanced targeting of key immune pathways involved in AA.

Biologic treatments, such as apremilast and dupilumab, have shown promising results in alopecia areata. Apremilast, a selective PDE4 inhibitor, demonstrated effectiveness in a small study, with most patients showing some degree of hair regrowth, although gastrointestinal side effects were common. Dupilumab, an anti-IL-4Rα antibody, has also shown potential,

particularly in patients with co-existing atopic dermatitis, leading to significant hair regrowth in some cases. Despite positive outcomes in case reports and small trials, further large-scale studies are needed to confirm the efficacy and safety of these biologics for AA. Recent studies suggest that mesenchymal stem cell (MSC) therapy holds promise for treating alopecia areata due to its immunosuppressive effects. MSCs, which can be sourced from various tissues, inhibit pro-inflammatory T-cell proliferation and promote regulatory T-cell activation, reducing inflammatory markers associated with AA. Clinical trials in mice demonstrated MSC treatment led to reduced T-cell infiltration and lowered expression of inflammatory cytokines, alleviating AA symptoms. However, human applications require careful consideration, as intravenous MSC delivery may lead to adverse effects such as thromboembolism and fibrosis, with intralesional injection offering a potentially safer alternative. Complementary therapies like essential oils, garlic, and glycyrrhizin compounds have also shown potential benefits, with some studies indicating improved hair regrowth when combined with conventional treatments.

## Conclusion

The exact and direct cause of alopecia areata remains unknown, making effective treatment challenging. However, numerous recent studies have significantly enhanced our understanding of the disease's etiology and progression, paving the way for new therapeutic approaches. Many experiments are currently underway, leading to the development of innovative treatment methods. In addition to addressing hair loss itself, patients often require management of other conditions arising from AA. Therapeutic support is frequently essential for those affected. Living with this condition also imposes financial burdens. Given the widespread prevalence of AA in the general population and its significant effects on quality of life, further research is essential to establish the most effective strategies for evaluating and managing individuals impacted by this condition.

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