

Alopecia Areata: An Overview of Current and Emerging Treatment Modalities

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Abstract:

Background: Alopecia areata (AA) is an autoimmune, non-scarring hair loss disorder characterized by an unpredictable clinical course and variable treatment responses. The primary goals of treatment are to arrest disease progression, promote hair regrowth, and prevent recurrence. Therapeutic approaches vary according to disease severity, extent, duration, and patient characteristics. Topical and intralesional corticosteroids are commonly used for localized disease, while topical immunotherapy, minoxidil, vitamin D analogues, and other topical agents may provide additional benefits. Extensive or rapidly progressive disease may require systemic treatments, including corticosteroids, methotrexate, cyclosporine, and azathioprine. Recent advances in understanding the immunopathogenesis of AA have introduced Janus kinase (JAK) inhibitors as targeted therapeutic options that interrupt inflammatory signaling pathways responsible for hair follicle damage. Additional therapeutic modalities include platelet-rich plasma, phototherapy, and microneedling, which may promote hair regrowth through immunomodulation, growth factor release, and stimulation of follicular activity. However, treatment selection remains challenging because of variable efficacy, potential adverse effects, and disease recurrence. Understanding the mechanisms, clinical applications, benefits, and limitations of available therapies is essential for developing individualized treatment strategies and improving clinical outcomes and patients' quality of life.

Keywords: Alopecia areata; Corticosteroids; Topical immunotherapy; JAK inhibitors; Platelet-rich plasma; Microneedling; Hair regrowth.

Introduction:

Alopecia areata (AA) is an immunologically mediated disease characterized by non-scarring hair loss. AA is presented by rapid and complete hair loss in one or more round or oval patches, usually on the scalp, beard area, eyebrows, eyelashes, and less commonly, on other hairy areas of the body (1)

The aim of treatment of AA is to arrest disease progression and to reverse hair loss (2).

A) Topical Treatment:

1- Topical corticosteroids

The first-line treatment for most patients with patchy AA is a topical corticosteroid (3).

Corticosteroids are synthetic derivatives of naturally occurring glucocorticoids from the adrenal gland, at the cellular level, glucocorticoids form a complex with the cytoplasmic glucocorticoid receptor (GR), which is translocated to the nucleus. Then it modulates the expression thousands of genes both directly, through binding of the glucocorticoid response element of DNA, and indirectly, through transrepression (4).

The major anti-inflammatory effects of glucocorticoids result from inhibition of nuclear factor- κ B (NF- κ B) and activator protein-1 (AP1) resulting in interference with inflammatory response genes and down-regulation of pro inflammatory cytokines (5).

In AA, therapeutic benefit of corticosteroids is postulated to result from reduction of interleukin (IL)-2-, IL-15-, and interferon-gamma (IFN- γ)-mediated peribulbar CD8⁺ T-lymphocyte inflammation, allowing for restoration of hair growth (6).

Very high potency topical steroids (Clobetasol Propionate 0.05%) are recommended as a first-line treatment for patients with scalp AA who cannot tolerate injections (7).

Side effects include folliculitis (more with ointment compared with foam formulations), rarely skin atrophy and telangiectasia (8).

2- Intralesional corticosteroids

Intralesional corticosteroids are widely used in the treatment of AA. In fact, they are the first-line treatment in localized conditions involving <50% of the scalp (9).

Triamcinolone acetonide (5–10 mg/ml) are commonly use. It is injected locally every 4–6 weeks. It results in localized hair growth in about 60% of treated sites. Lower concentrations of 2.5 mg/ml are used for eyebrows and face (9).

Repeated injections at the same site or the use of higher concentrations of triamcinolone should be avoided as this may lead to prolonged skin atrophy (10).

3- Topical immunotherapy

The mechanism of action of topical sensitizers is poorly understood. Many theories have been suggested, including antigenic competition, perifollicular lymphocytes apoptosis, changes in the peribulbar CD4/CD8 lymphocyte ratio, and IL10 secretion after diphenylcyclopropenone (DPCP) application (8).

- **Dinitrochlorobenzene** was the first topical sensitizer to be used in the treatment of extensive AA since 1976 (8) . It induces contact dermatitis, and it has been discontinued because it has been shown to be mutagenic (11) .

- **Squaric acid dibutylester (SADBE)** is a commonly used contact sensitizer in immunotherapy for AA. contact dermatitis is induced by the currently high recommended sensitization dose of 1%–2% SADBE, often decreasing patient compliance (12).

The starting concentration of 0.01% without sensitization. After one or two weeks of initial 0.01% SADBE application, the concentration of SADBE increased gradually to 0.025%, 0.05%, 0.1%, 0.25%, 0.5%, 1% and 2% until the patients felt itching or erythema at the AA lesion site (12).

- **Diphenylcyclopropenone (DPCP)** is based on the concept of antigenic competition, inducing the formation of CD8 lymphocytes, which inhibits the active perifollicular immune response, allowing hair growth (13).

It is preferred because it is cheaper and is more stable in acetone. The exact mechanisms involved in immunomodulation therapy for alopecia are poorly understood (13).

A vesicular or bullous reaction is one of the undesired adverse effects of topical sensitizers. If this reaction develops, the patient should wash off the contact sensitizer, and a topical corticosteroid should be applied to the affected area (8).

Other adverse effects include cervical and occipital lymphadenopathy, facial and scalp edema, contact urticaria, flu-like symptoms, erythema multiforme-like reactions, and pigmentary disturbances (hyperpigmentation, hypopigmentation, dyschromia inconfetti, and even vitiligo) (8).

4- Minoxidil

Minoxidil induces opening of ATP-dependent potassium channels in vascular smooth muscle cells, which results in their relaxation and vasodilation which leads to an increased cutaneous blood flow, resulting in enhanced oxygen and growth factor delivery to the hair follicle. It also stimulates prostaglandin E2 (PGE2) and leukotriene B4 (LTB4) production, which enable hair follicles to grow by maintaining the anagen phase, and shorten the telogen phase (8).

Minoxidil also has an immunomodulatory effect by acting as a proliferative and anti-apoptotic agent on dermal papilla cells by triggering the activation of ERK and Akt pathways. It also prevents cell death by elevating the Bcl-2/Bax ratio and causes significant down regulation of IL-1 α gene expression which is a direct growth inhibitory agent in hair follicles and plays an important role in the pathogenesis of alopecia areata (8).

Minoxidil 5% solution twice daily is used as adjuvant treatment to conventional AA therapy (with mainly topical or intralesional corticosteroids). Contact dermatitis and hypertrichosis are the most common side effects. Contact dermatitis can be minimized by using minoxidil foam which does not contain propylene glycol (8).

5- Lactic Acid

Lactic acid is a member of alpha-hydroxy acids. It is a colorless or slightly yellow liquid that is odorless or has a light but not unpleasant odor and a mildly acidic taste (14).

Topical 15% lactic acid was used to treat AA. It was used twice and thrice weekly in different groups. The response of AA to topical 15% lactic acid solution was good achieving 82% complete hair growth of the patches treated thrice weekly and 53% complete hair growth of the treated patches in patients treated twice weekly during the period of therapy (14).

Lactic acid has been used in treatment of many skin diseases like topical treatment of AA and vitiligo, in these diseases gave high recovery rate and the mechanisms could be suggested by spontaneous secretion of vascular endothelial growth factor (VEGF) by human reconstructed epidermis (8). VEGF is a multifunctional angiogenic cytokine involved in angiogenesis and wound healing. Also, this cytokine will enhance and stimulate the growth of hair follicles so recovery of AA (14).

It is difficult to define the precise mode of action of lactic acid in treating AA; lactic acid may act through its irritant effect (14).

The two major side effects of alphahydroxy Acids are irritation and sun sensitivity. Symptoms of irritation include redness, burning, itching, pain and possibly scarring (15).

6- Vitamin D3

Calcipotriol is a vitamin D analogue and a potent immunomodulatory molecule. Low serum vitamin D levels have been observed in patients with AA and various autoimmune diseases (16).

Topical calcipotriol has been reported to be used successfully in treating AA. It regulates keratinocytes proliferation and differentiation. It can induce hair regrowth in AA lesions by regulation of the differentiation of B cells, T cells, dendritic cells, and Toll-like receptor (TLRs) expression (17).

It helps in maintaining the immune privilege of HF by decreasing the production of IFN- γ . It attenuates or prevents the autoimmune response that drives AA by regulating the autoreactive effector T cells and mast cells; also, by down-regulating the cytokine (CXCL-10) and the intercellular TLRs (18).

It contributes to prevent (NKG2D) and CD8 T cell activation and trafficking in AA by down-regulating both NKG2D-activating and chemokine receptor activating ligands (CXCR3) and inhibits JAK/STAT pathway and in turn block the effects of key cytokines in the pathogenesis of AA (18).

Also, it controls the overactive self-effector T cells by enhancing the inhibitory function of T cells, and increases the expression of CTLA-4 (an inhibitory receptor induced in effector T cells upon activation and constitutively expressed by Tregs) and PD-1 (an immune-inhibitory receptor expressed in T cells, B cells, NK cells and APCs). It contributes to restoring the hair growth cycle by attenuating the oxidative stress in AA (19).

Side effects such as burning, itching, rash, irritation, redness, dry skin, or peeling at the application site may occur and hypercalcemia (20).

7- Prostaglandin analogue (PG)

Clinically known prostaglandin analogs include bimatoprost, latanoprost, and cetirizine. The topical application of bimatoprost 0.03% lotion daily from 12 to 16 weeks has been found to significantly increase the diameter and number of vellus hairs (21).

8- JAK inhibitors

Topical application of JAK inhibitors may be a desirable treatment option for AA, since it will localize the effect of JAK inhibition to the site of application (22).

Topical formulations of JAK inhibitors have not shown satisfactory results for regrowing scalp hair in humans but have shown some efficacy in regrowing eyebrow and eyelash hair. Tofacitinib was the most common monotherapy, followed by ruxolitinib, and delgocitinib (23).

B) Systemic Treatment:

1- Systemic Corticosteroids

Systemic corticosteroids are one of the most common methods used in the treatment of extensive alopecia, especially acute progressive ones, it is used in autoimmune diseases and have demonstrated a significant benefit in most clinical variants of AA, with reduced efficacy in ophiasis and AU types. Oral and intravenous corticosteroid pulse therapy have been used in the treatment of AA (24).

Dosing strategies include a higher dose of oral prednisolone (0.5–0.75 mg/kg) with subsequent tapering from 6 to 12 weeks, maintaining a static dose of prednisolone (0.25 mg/kg) for 6–12 weeks or commencing a lower dose (0.1–0.2 mg/kg) and increasing the dose over time according to response and tolerance. There is no expert consensus on the optimal use of oral prednisolone in AA (25).

Side effects include general weakness, acneiform eruption, weight gain, gastrointestinal upset, facial mooning and oligomenorrhea. Others include osteoporosis, diabetes, and suppression of adrenocorticotrophic axis (26).

2- Methotrexate (MTX)

Methotrexate (15–25 mg per week) alone or in conjunction with prednisone 10–20 mg daily. Using the same regimens, complete hair regrowth was achieved in 64% of alopecia totalis/AU patients (27).

It is known to inhibit enzyme dihydrofolate reductase, which leads to a decrease in intracellular folate concentrations. This decrease inhibits purine and pyrimidine metabolism and, consequently, nucleic acid synthesis, thus resulting in antineoplastic effects when administered at high doses (28).

It also inhibits 5-aminoimidazole-4-carboxamide ribo-nucleotide formyl-transferase enzyme, which is involved in purine synthesis, which leads to a buildup of adenosine, that is a mediator of many of the anti-inflammatory effects of MTX. Also, it inhibits white blood cell accumulation, leads to a reduction in TNF- α and IFN- γ synthesis, and inhibits monocyte, macrophage, and T-cell activities. This action might explain the effect of MTX in AA (29).

The main short-term adverse effect of MTX is pancytopenia. Other adverse effects include mucositis, oral and/or gastrointestinal ulcers, rash, photosensitivity, acne, alopecia, anorexia, diarrhea, nausea, and interstitial pneumonitis. Other long-term effects are pulmonary fibrosis, malignancy, increased risk of occlusive vascular disease, and myelosuppression (29).

3- Cyclosporine

Cyclosporine is an immunosuppressant agent that inhibits helper T-cell activation and suppresses IFN- γ . Cyclosporine alone or in conjunction with systemic steroids was tried with variable results. The success rate ranges from 25 to 76.7% (8). Side effects include nephrotoxicity, immune suppression, hypertension, and hypertrichosis of body hair (8).

4- Azathioprine

Azathioprine has been shown to be effective in the treatment of AA (30). It has been used at a dosage of 2–2.5 mg/kg/day (27).

Azathioprine interferes with DNA synthesis by inhibition of enzymes of purine synthesis, thereby affecting proliferation of cytotoxic T-cells and also by suppression of cytokines release by helper T-cells which dampens

the immune response, with reduction in colonization of T-cells around follicles, normal follicular growth phase resumes and clinical response is seen in the form of hair growth (31).

Side effects of long-term azathioprine account for monitoring of hematological parameters and dipping of leukocyte, especially lymphocyte count, are considered an alarming feature for stopping the drug (31).

5- Janus kinase (JAK) inhibitors:

In AA, CD8 T cells produce IFN- γ , which signals via JAK1 and JAK2 to enhance production of IL-15. In combination with the IL-15 receptor- α , IL-15 binds to the surface of CD8 T cells leading to signaling through JAK1 and JAK3 to produce more IFN- γ (32). Both the IFN- γ and IL-15 pathways are targeted by JAK inhibitors including tofacitinib (JAKi 1/3), ruxolitinib (JAKi 3), baricitinib (JAKi TyK2), Ritlecitinib (JAKi 1/2) and Deuruxolitinib (JAKi 1/2) (32).

Janus kinase inhibitors act by inhibition of JAK phosphorylation by blocking the downstream regulatory signaling pathway that involves STAT activation (33).

They help stimulate and restore hair growth through several means which involve, terminating the T-cell mediated immune response on hair follicle by blocking the downstream signaling of inflammatory mediators IFN- γ and γ_c cytokines, inhibiting the production of inflammatory T helper cells and restoring the anagen phase of the hair follicle by promoting activation and/or stimulation of hair follicle stem cells (34).

The most frequently reported adverse events for all JAKi were infections, particularly infections of the upper respiratory tract, with the highest rate reported for baricitinib followed by tofacitinib then ruxolitinib (35). Nasopharyngitis has been associated with treatment with all types of JAKi except tofacitinib. Other infections reported with all types of JAK-I included urinary tract infections and herpes zoster (36).

Besides infections, the most frequent adverse effect was headache, Gastrointestinal perforation has been described in patients treated with tofacitinib mainly patients with inflammatory bowel disease. The most significant abnormality was hypercholesterinemia (35). Baricitinib have been suspected to be associated with a higher risk of malignancy (37).

Tofacitinib

Tofacitinib inhibits the effects of many cytokines including IL-2, IL-4, IL-7, IL-15, IL-21 and IFN- γ , by blocking the STAT phosphorylation induced by these inflammatory mediators, thereby disrupting the downstream signaling pathway of JAK 1/3 dependent γ_c receptors (38).

Administering oral tofacitinib ≥ 10 mg daily for 6–12 months resulted in $\geq 90\%$ hair regrowth. Patients were first given tofacitinib 5mg twice daily for 1 month and if $\geq 50\%$ regrowth from baseline was not achieved during this time, the dosage gradually increased to 15mg then 20 mg daily (39).

Baricitinib

Baricitinib 4 mg and 2 mg daily for 8 months of treatment resulted in regrowth on the scalp as well as regrowth on eyebrows and eyelashes. After 13 months of treatment, regrowth had been maintained, and no adverse effects were noted (22).

Ritlecitinib

Treatment with ritlecitinib 50 mg and 30 mg daily has been shown to induce hair regrowth with a significant proportion of patients reaching $\leq 20\%$ scalp hair loss (40). It doesn't have JAK1/JAK2 inhibitor's side effects such as increased cholesterol and liver enzymes, thrombocytopenia, anemia (40).

Deuruxolitinib

Deuruxolitinib inhibits JAK1/JAK2 and higher proportion of patients with severe AA were treated with deuruxolitinib 12mg and 8mg daily (41).

Other treatments for alopecia areata:

A- Platelet-rich plasma (PRP) monotherapy for AA:

Platelet-rich plasma is an autologous plasma preparation of concentrated platelets. Growth factors contained in α granules within the platelets are released when PRP is activated. These growth factors have been shown to stimulate angiogenesis, proliferation and differentiation in HFs leading to an increase in duration of anagen phase and promotion of hair growth (26).

It is believed to be a potent anti-inflammatory agent capable of limiting local tissue inflammation. The PRP growth factor including TGF- β is a known immunosuppressant leading to restoring follicular immune privilege (26).

B- Phototherapy:

a- Excimer

Excimer laser/light 308 nm is described as a source of narrow-band monochromatic ultraviolet B radiation. It has cutaneous immunomodulation and prompts T-cell apoptosis, making it a potential and hopeful method for treating AA (42).

Although the phototherapeutic mechanism of action of excimer light in terms of AA treatment remains unclear, this is thought to be similar to that in play when psoriasis, vitiligo, and atopic dermatitis are treated; the cutaneous immunosuppression by UVB would be the principal mechanism of action. In addition, it induces T-cell apoptosis (43).

b- Ultraviolet B (UVB) light

Ultraviolet B-light may directly affect the β -catenin pathway of hair follicle cycling. A study showed that UVB light-induced repigmentation of vitiligo patches by activating the 5-catenin pathway of hair follicle bulge stem cells (44). As Wnt/ β -catenin signaling in dermal papilla cells is the canonical pathway inducing anagen phase and stimulating hair growth, activation of the β -catenin pathway by UVB light may stimulate hair regrowth of AA lesions (45).

Microneedling

Microneedling (MN) is a therapeutic modality in dermatology. MN offers a relatively low cost and minimally invasive tool for the treatment of multiple cosmetic and dermatologic conditions (46).

Mechanism of action

The basis of MN relies on physical trauma. It has been proposed that the trauma generated by needle penetration in the skin induces regeneration of the dermis (47).

The needles penetrate the stratum corneum and create small holes known as micro-conduits with minimal damage to the epidermis. This sequentially leads to the generation of growth factors which stimulate the production of collagen and elastin in the papillary layer of the dermis (46).

The natural wound healing cascade is induced as platelets and neutrophils are recruited to release growth factors such as TGF- α , TGF- β , and platelet-derived growth factor (PDGF). This ultimately results in the deposition of collagen by fibroblasts (46).

Additionally, the role of MN in the treatment of hair pathology has become a field of focus as it is thought to stimulate stem cells in the dermal papilla, increase blood flow to hair follicles, and recruit growth factors and signaling pathways which induce hair restoration. They also act as drug delivery (48).

Microneedles act as an advanced approach to enhance dermatological pathology management. It explores the complex dermis structure and highlights the limitations of traditional transdermal methods, emphasizing MNs' advantage in bypassing the stratum corneum to deliver drugs directly to the subdermal matrix (46).

Types of devices

Currently, there are many mechanical MN devices registered with the Food and Drug Administration (FDA), with the majority being a variation of either the Dermaroller or the Dermapen (49).

The Dermaroller is a hand-held device with a cylindrical roller of 24 circular arrays. Each array is equipped with eight medical grade solid steel microneedles, totaling 192 needles on one Dermaroller device (49).

The Dermapen is a spring-loaded MN device which acts as an electrically powered pen, delivering stamp-like motions across the skin. Several commercial variations of this device exist based on the same principles (50).

These MN modalities include fractional radiofrequency microneedling (FRFM), light emitting diode (LED) MN devices (49).

Fractional radiofrequency microneedling (FRFM) is differentiated from manual MN due to the method of each insulate needle releasing a radiofrequency current from the needle tip producing changes in dermal structural components. LED MN rollers combine solely LED light and MN (51).

Side effects

Transient erythema is the most common adverse effect, Granulomatous reaction in response to unauthorized use of topical products not approved for intradermal injection has been reported in some patients receiving MN therapy Otherwise, adverse events are rare and never result in systemic toxicity (46).

Although microneedling may provide some benefit to patients with AA, the size of the area requiring treatment should be considered as some patients find this treatment modality to be very painful. It may be tolerable for small lesions in patchy AA but impractical for patients with alopecia totalis or universalis (52).

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