

Alopecia Areata Updated Management: Minoxidil Solution 5% and Microneedling with Anthralin Cream 1% .

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Abstract

Background: Alopecia Areata (AA) is an autoimmune disease of the hair follicle that presents as non-scarring alopecia both in the scalp and non-scalp areas. The etiology of this disease remains unknown ;however, a current hypothesis implicates T-cell-mediated autoimmunity that affects hair follicles, as well as the up- regulation of inflammatory cytokines ,in the pathogenesis of disease .The severity ranges from focal (patch-type AA) to total scalp hair loss (alopecia totalis) to entire body hair loss (alopecia universalis).Microneedling (MN), also known as collagen induction therapy, is a process involving repetitive puncturing of the skin with sterilized microneedles. Its original conception can be traced back to 2012, when Orentreich and Orentreich developed the concept of “subcision” or using hypodermic needles to induce wound healing in depressed cutaneous scars. Anthralin is used in alopecia areata at concentrations ranging from 0.5 to 1 % for 20-30 minutes after which the scalp should be washed with shampoos in order to avoid excessive irritation.Minoxidil stimulates hair growth only in cases of mild AA, but slight to no effects were observed in patients with extensive AA. Only mild side effects of minoxidil were reported with no evidence of systemic effects

Keywords: Alopecia Areata (A.A),Microneedling, Minoxidil, Anthralin.

Alopecia Areata:

Alopecia areata occurs worldwide. The estimated prevalence is approximately 1 in 1000 people, with a lifetime risk of approximately 2 %(1). Both children and adults may develop alopecia areata, and the disorder occurs at similar rates in males and females. An analysis of clinical data collected from the population of Olmsted County, Minnesota between 2012 and 2017 revealed a mean age for diagnosis of alopecia areata of 32 years in males and 36 years in females (2).

Whether there is a seasonal pattern for flares of alopecia areata is unclear. A retrospective study of approximately 450 children with AA suggested a predilection for disease flares during cold months of the year. Additional study is necessary to confirm this finding (3).

PATHOGENESIS

Alopecia areata is an autoimmune disease in which hair follicles in the growth phase (anagen) prematurely undergo transition to the non-proliferative involution (catagen) and resting (telogen)

phases, leading to sudden hair shedding and inhibition of hair regrowth (figure 1). Unlike cicatricial alopecias, the inflammatory process in alopecia areata does not lead to permanent destruction of the hair follicle (4).

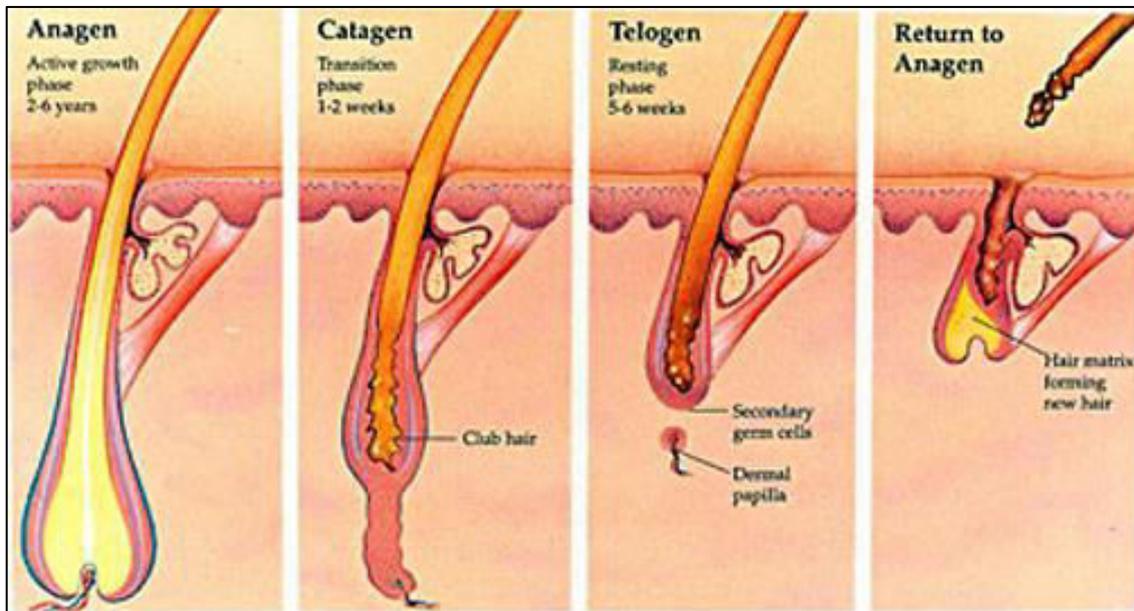


Figure (1): The normal human hair cycle (4).

The mechanisms leading to alopecia areata are not fully understood. Key events may include the loss of follicular immune privilege and the development of an associated T cell-mediated immune attack on cells within the hair bulb. Genetic susceptibility to alopecia areata also plays a role (5).

Loss of immune privilege and immune dysregulation

The combination of loss of immune privilege at the hair follicle and other immunologic events is likely necessary for the development of alopecia areata. The loss of immune privilege is postulated to involve unknown local stressors or events that inhibit the expression of hair follicle immune privilege "guardians" (eg, transforming growth factor [TGF]-beta and alpha-melanocyte-stimulating hormone [MSH]) and stimulate the expression of major histocompatibility complex class I polypeptide-related sequence A (MICA) on hair follicle cells. These events can lead to activation of natural killer cells and local secretion of interferon (IFN)-gamma and interleukin (IL)-15. IFN-gamma stimulates the expression of major histocompatibility complex (MHC)-I protein on hair follicle cells, which may allow the presentation of previously hidden antigens to T cells. IL-15 inhibits suppressive function of regulatory T cells and promotes proliferation of natural killer cells and T cells (6).

IFN-gamma and IL-15 activate target immune cells via the Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling pathway. The importance of this pathway is illustrated by the efficacy of Janus kinase (JAK) inhibitors for alopecia areata (7).

A mouse study suggests that a defect in hair follicle immune privilege may not always be necessary, supporting a role for broader immune system dysfunction in the pathogenesis (8).

Genetic predisposition

Familial and twin studies support a genetic predisposition to alopecia areata. In one study of 206 patients with alopecia areata, 20 percent had a first-degree relative with the disease (**Blaumeiser et al., 2016**). In a twin study, among 19 pairs of monozygotic twins, both twins had alopecia areata in 42 percent of twin pairs. In contrast, among 31 pairs of dizygotic twins, both twins had alopecia areata in only 10 percent of twin pairs (**9**).

Genome-wide association studies have confirmed association of AA with human leukocyte antigen (HLA) genes (**9**). The HLA-DQB1*03 allele, among others, may be an important marker for susceptibility to alopecia areata. Several susceptibility loci that have been associated with other autoimmune diseases (eg, cytotoxic T lymphocyte-associated antigen 4 [CTLA-4], IL-2/IL-21, interleukin-2 receptor-alpha [IL-2RA]) have also been identified, indicating that alopecia areata may share a common pathway with other autoimmune diseases, such as type 1 diabetes mellitus and rheumatoid arthritis (**10**).

Other factors, such as infections, drugs, and vaccinations, have been proposed as contributors to episodes of alopecia areata. Some patients report severe stress, especially emotional stress, as a precipitating event, although many patients have no such history. Remote events, such as childhood trauma, have also been associated with the development of alopecia areata in adults (**11**).

A role for vitamin D has been proposed based upon a study that found significantly lower serum levels of 25-hydroxyvitamin D in patients with alopecia areata compared with healthy controls and an inverse correlation between serum vitamin D levels and alopecia areata severity. Additional studies are necessary to determine the relevance of this finding (**11**).

CLINICAL FEATURES

Key clinical features of alopecia areata include the pattern and speed of hair loss, exclamation mark hairs, and associated nail dystrophy (**12**).

Hair loss

Alopecia areata most commonly occurs on the scalp but may occur on any hair-bearing area, such as the eyelashes, eyebrows, beard, extremities, or other areas (figure 2). Patchy alopecia, which manifests as smooth, circular, discrete areas of complete hair loss that develop over a period of a few weeks, is the most common clinical variant. The patches may remain discrete or enlarge and coalesce into bizarre patterns (**13**).



Figure (2): Alopecia areata; the hair loss is a round patch. Note the absence of scales or inflammation (12).

In a subset of patients, patchy alopecia progresses to alopecia totalis (total loss of scalp hair) or alopecia universalis (loss of all hair over the entire skin surface). In our experience, alopecia totalis or universalis also occasionally develop rapidly after the onset of diffuse hair loss (12).

Less common patterns of hair loss include the ophiasis pattern, that is a band-like area of alopecia extending across the occipital scalp, The rare sisaipho pattern that involves the frontal, temporal, and parietal scalp but sparing hair along the scalp periphery, resembling male pattern hair loss (14).

MANAGEMENT

The management of alopecia areata involves both addressing the psychological needs of the patient and offering treatment to patients who desire intervention. A variety of topical, intralesional, and systemic agents, as well as devices, have been used for alopecia areata, but the response to treatment varies widely, and few well-designed clinical trials have evaluated these therapies (15).

FIRST-LINE THERAPIES

Based upon the relative safety and the available, although limited, evidence for the efficacy of these agents, intralesional or topical corticosteroids are the initial treatment for most patients with patchy alopecia areata. Topical immunotherapy can be used as first-line treatment for patients with extensive disease (greater than 50 percent scalp hair loss) (16).

A. Contact immunotherapy

Contact immunotherapy using diphenylcyclopropenone (DPCP) and squaric acid dibutylester

(SADBE) is one of the most commonly used therapies in AA and is the mainstay of treatment for recalcitrant AA/AT/AU. However, the recent reports showed the comparable therapeutic and adverse effects in children compared with adults. Therefore, age would not be a limitation when considering contact immunotherapy as a treatment. (17)

B. Topical corticosteroids.

Corticosteroids reduce inflammation around the hair follicle and allow it to return to the normal growth cycle. Desoximetasone cream and clobetasol propionate foam showed significantly more hair regrowth effect compared with placebo in double-blind, randomized, placebo-controlled trials (DB-RPCT), respectively. Comparing the topical treatments, topical steroids were superior to Anthralin and tretinoin. Clobetasol propionate cream was more efficacious than hydrocortisone cream and betamethasone valerate was more effective as foam than lotion. The regrowth was more pronounced when applied occlusively. (18).

C. Intralesional corticosteroids

Intralesional triamcinolone injection (TA-ILI) is one of the most prevalent ways to treat AA. TA-ILI yielded a better response compared with topical betamethasone valerate and topical betamethasone valerate foam in RCT. Among the multiple triamcinolone concentrations, 2.5, 5 and 10 mg/dL were all found to be equally effective. Moreover, patients with exclamation mark hairs and positive hair pull test showed measurable improvement with TA-ILI. TA-ILI is sometimes chosen as a primary treatment, but its use is limited from pain, especially in children or patients with extensive scalp involvement. It may be selectively indicated for refractory patches that are resistant to other treatments. (19).

D. Minoxidil

Minoxidil has been used to induce hypertrichosis via vasodilation. One percent minoxidil resulted in more cosmetically acceptable growth compared with placebo in a DB-R-PCT. However, when 3% minoxidil or a placebo was applied to 15 subjects; neither group showed moderate regrowth. Minoxidil 1% therapy or placebo for 19 and 16 weeks did not result in any significant differences in DB-R-PCT. Minoxidil is one of the most widely used treatment modalities, yet its effect in severe cases seem to be variable. Thus, its recommended use is for mild to moderate disease. (20).

❖ SECOND-LINE THERAPIES

A. Anthralin

Anthralin is thought to affect hair regrowth through irritant contact dermatitis. In an uncontrolled study, 25% showed cosmetically acceptable hair growth however, it failed to show any therapeutic benefits in 11 AT cases. In a recent half-head study of pediatric patients, Anthralin showed a better therapeutic effect on the treated side than the untreated side. In a RCT comparing Anthralin and azelaic acid, both showed the comparable effect. While Anthralin is one of the most widely used AA treatment modalities, evidence supporting it as a monotherapy is more needed. (21).

B. Prostaglandin analogs.

The use of latanoprost in the treatment of AA has frequently been reported in ophthalmological publications. In the active controlled study, the treatment group used both TA-ILI and latanoprost on the scalp and eyebrows, while the control group used TA-ILI alone. The control group showed

no response; however, 45% of the treatment group exhibited cosmetically acceptable regrowth. The bimatoprost displayed significantly more rapid and better regrowth than mometasone furoate in a RCT. However, neither latanoprost nor bimatoprost produced an appreciable therapeutic effect in another RCT. (22).

C. Systemic corticosteroids.

Systemic corticosteroids are sometimes considered for severe AA or acute phase of the disease. Pulse corticosteroid therapy was found to be better in the clinical effect and side-effect profile than an oral daily steroid (OD). According to a systematic review of 41 studies including a total of 1078 cases, complete regrowth was achieved in 43%. The treatment group in the only R-PCT study available showed significant improvement. In a recently published study, AT/AU patients were treated with a combination of pulse corticosteroid therapy and OD, 80.6% of whom responded favorably, with 71% showing complete regrowth. Side-effects were noted in 32% of patients, especially with combination therapy use. Physicians should choose systemic corticosteroids as a therapeutic modality after taking into account relevant comorbidities and the likelihood of adverse effects on an individual basis. It is advisable to use them as short-term as possible and long-term use should be avoided. (23).

D. Superficial Cryotherapy.

Superficial cryotherapy using liquid nitrogen is a treatment modality for various neoplastic and inflammatory diseases. In a comparative study of superficial cryotherapy and clobetasol lotion, the response rates were 80% and 91.5%, respectively, and were not significantly different. When jet cryotherapy was performed on 11 recalcitrant AA patients who were non responders to conventional therapies, five showed excellent responses and three satisfactory responses (24).

The treatment was most effective when performed at the interval of 2 weeks or less. In a recent half-head study, superficial cryotherapy was reported to significantly increase hair thickness and density of eyebrows compared with control. The effects of this treatment are expected to be comparable with the treatments above without severe complications. (24).

E. Excimer laser.

Therapy with 308-nm excimer laser is used for AA. In a pilot study, more than half showed moderate to excellent response. Excimer laser therapy applied to 42 recalcitrant patches in 18 patients yielded an excellent response in 13 of 17 scalp lesions. Among nine children with recalcitrant AA, hair growth was seen in 60%. A therapeutic effect was achieved upon increasing the radiation dose to the point of generating marked erythema. Care should be given to the patients with darker skin because of post inflammatory hyperpigmentation. A few studies have also reported symptom improvement with the use of a pulsed infrared diode laser (904 nm) and a fractional photothermolysis laser. However, this was not the case for fractional carbon dioxide laser therapy. (25).

F. Simvastatin/ezetimibe.

In a pilot study, greater than 20% hair growth was demonstrated in 73.7% of the 29 patients without notable side effects. On the other hand, 82.4% of 20 AA/AT/AU cases showed no treatment response in another pilot study. Simvastatin/ ezetimibe seems to have an

immunomodulatory effect on AA, but it has been difficult to accurately determine the treatment effect from an insufficient number of well-designed studies. One study randomized the subjects who had a beneficial effect with simvastatin/ezetimibe into two groups. The group that continued the simvastatin/ezetimibe treatment had a better outcome than the other that stopped. (26).

G. Platelet-rich plasma (PRP)

Platelet-rich plasma has been found to encourage hair survival and growth. The PRP-treated hemipatches showed significantly more hair growth than the placebo or triamcinolone ILI in a DB-R-placebo- and active-controlled half-head study. PRP showed superior efficacy to minoxidil 5% or placebo in the recent comparative study. PRP is a new therapy that seems to have a significant therapeutic effect in AA, but robust data is lacking on long-term side-effects as well as on its therapeutic effects. (27).

H. Tretinoin

In a comparative study, the combination of topical tretinoin and triamcinolone ILI were used to treat 28 patients, while 30 patients treated with triamcinolone alone served as a control. The combination group showed a better response after 4 months than the control group. In all, 80 AA patients randomized to receive topical steroids, topical tretinoin, Anthralin or a placebo treatment showed response rates of 70%, 55%, 35% and 20%, respectively. More treatment data of this medication is needed to clarify its effect. (28).

I. Antidepressants

As AA can be accompanied by various psychosocial problems, counselling and management of these issues must be integrated into the treatment plan. In addition, these problems can contribute to the development of AA itself. (29).

J. Calcipotriol

As decreases in vitamin D level and vitamin D receptor expression in AA are not uncommon, topical calcipotriol is the subject of new research. (30).

K. Psoralen plus ultraviolet A therapy (PUVA)

Psoralen plus ultraviolet (UV)-A therapy resulted in complete regrowth in 40% and partial regrowth in 17% of AA patient . patients with severe AA were treated with a combination of PUVA and topical cyclosporin, 9.4% showed an excellent response and 9.4% a good response. (31).

THIRD-LINE THERAPIES

A. Janus kinase (JAK)/signal transducer and activator of transcription (STAT) inhibitors

Janus kinase/signal transducer and activator of transcription inhibitors are one of the most recently introduced treatment modalities for AA. Tofacitinib, baricitinib and ruxolitinib showed hair regrowth effect for AA in several case series. (32).

B. Cyclosporin

The combined therapeutic effect of cyclosporin and systemic steroids has been studied extensively. The efficacy rates of this combination vary widely (25–76.7%). Still, few robust studies of cyclosporin as a monotherapy have been conducted. (33).

C. Methotrexate (MTX)

In a comparative study of the combination of MTX and prednisolone versus MTX monotherapy in

severe AA patients, the rate of total recovery was higher in the combination group. Care should be taken when choosing this treatment modality. (34).

D. Sulfasalazine

In some retrospective studies and case series, hair growth greater than 50–60% was reported in 25.6–50% of patients using sulfasalazine. Careful monitoring is required because of its significant risk of side-effects. (35)

E. Azathioprine

This is another systemic therapy that can be considered for recalcitrant AA. However, the risk of systemic side-effects should be considered. (36).

F. Interleukin (IL)-12/IL-23p40 blocker.

Recently, ustekinumab has come as a potential treatment for AA. Treatment with ustekinumab yielded excellent outcomes in two AA patients and measurable changes in the pre- and post-treatment cytokine levels were detected. (37).

Microneedling

Microneedling (MN), also known as collagen induction therapy, is a process involving repetitive puncturing of the skin with sterilized microneedles. Its original conception can be traced back to 2012, when Orentreich and Orentreich developed the concept of “subcision” or using hypodermic needles to induce wound healing in depressed cutaneous scars (38).

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 (20).

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 (39).

Anthralin in Alopecia Areata

It is used at concentrations ranging from 0.5 to 1 % for 20-30 minutes after which the scalp should be washed with shampoos in order to avoid excessive irritant effects. The applications are made initially every other day and later on daily. Adverse effects include pruritus, erythema, scaling, staining of treated skin and fabrics, folliculitis, and regional lymphadenopathy (Nelson et al.,2010).

In an open study, 25% patients with severe alopecia areata were shown to respond positively to local applications of 0.5-1% anthralin. More placebo control studies are needed to justify the use of anthralin in alopecia areata (40).

The mechanism of anthralin's therapeutic effects in AA can only be speculated. Anthralin is unstable when exposed to air and the oxygen radicals generated from it are central to its anti-inflammatory and anti-proliferative effects in psoriasis. In AA therapy, free radicals generated from anthralin might be the mechanism of anti-inflammatory action for clearing the infiltrated lymphocytes. In this case, free radicals generated from anthralin within the skin should selectively suppress infiltrated lymphocytes and leave the follicular cells unhindered in affected skin; however, our preliminary studies showed that lymphocytes and different follicular cells were equally affected by anthralin in vitro, indicating that the mechanism is not simply a selective

cytotoxicity against lymphocytes. This was further supported by the data of immunostaining using CD4 and CD8 antibodies (41).

Histologic examination revealed no reduction in the total number of infiltrated lymphocytes; however, there was a general shift in the location of the CD8⁺ cells from perifollicular and intrafollicular regions in untreated skin to a uniform presence in the dermis upon successful anthralin treatment. This pattern of CD8⁺ redistribution was consistent between all the rats tested. It would be interesting to study what drives relocation of the CD8⁺ cells (41).

Minoxidil in Alopecia areata

Monotherapy with topical minoxidil stimulate hair growth only in cases of mild AA, but slight to no effects were observed in patients with extensive AA. Only mild side effects of minoxidil were reported with no evidence of systemic effects (42).

A higher concentration of topical minoxidil was preferable in AA treatment because of its dose-response effect. In extensive AA (more than 75% scalp involvement), 5% MS demonstrated 81% terminal hair regrowth versus 38% in 1% MS group (40).

The use of oral minoxidil 5 mg twice daily in 65 recalcitrant AA patients was studied. Better hair regrowth rate was noted in patients treated with oral minoxidil than in patients treated with 5% MS. However, only 18% of patients showed an improved cosmetic response at 34.8 weeks with a prominent increase in terminal hairs. Systemic symptoms of sodium and water retention developed in patients who did not adhere to the sodium restriction protocol. Other side effects included headache, palpitation, and facial hypertrichosis (40).

Conflict of Interest: No conflict of interest.

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