Alopecia Areata: Treatment Options

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Abstract

Alopecia areata (AA) is a common cause of reversible hair loss affecting approximately 1-2% of the general population. It commonly presents as round patches of hair loss which can be the first manifestation of a more severe alopecia totalis or universalis. The etiology of AA is unknown but is characterized by hair cycle dysfunction and the presence of peribulbar and perifollicular mononuclear cell infiltrates. Much evidence suggests that AA is a tissue restricted autoimmune disease. Current traditional therapies are predominantly immunomodulating modalities, including corticosteroids, topical immunotherapy, anthralin, and photochemotherapy (PUVA). These treatments stimulate hair growth

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but do not prevent hair loss and probably do not influence the course of the disease.

A nonspecific modality is topical minoxidil, which prolongs anagen and promotes growth of longer and wider hair. Improved future treatments may be immunosuppressive or immunomodulatory or they may otherwise protect hair follicles from the injurious effects of inflammation. Biologic therapies target specific immunologic responses and offer new strategies for treating pathogenic T cells and the cytokines they produce. The choice of therapy depends primarily on the patient’s age and the extent of the hair loss. The aim of this article is to review available data on current and potential agents for the treatment of alopecia areata.

**Keywords:** alopecia areata, therapy

## Introduction

Alopecia areata (AA) is a common cause of reversible hair loss afflicting approximately 1-2% of the general population [1] and it is also expressed in several non-human mammals [2]. It ranges in severity from small, round patches of hair loss that regrow spontaneously to persistent, extensive patchy involvement to the loss of all scalp hair (alopecia totalis) or all scalp and body hair (alopecia universalis). Characteristic nail changes may also accompany hair loss. AA affects both sexes equally and occurs at all ages, although children and young adults are affected most often.

The etiology of AA is unknown but is characterized by hair cycle dysfunction and the presence of peribulbar and perifollicular mononuclear cell infiltrates. Scalp biopsies from patients show a heavy presence of type 1 cytokines, including interleukin-2 (IL-2), interferon-γ (IFN-γ) and tumor necrosis factor α [3]. The most widely accepted hypothesis is that AA is a T-cell mediated autoimmune condition that is most likely to occur in genetically predisposed individuals. Although acute phases of hair loss are followed by spontaneous hair regrowth in most patients, the disorder may persist for many years or even for life when severe. But even in these cases hair loss is potentially reversible, because the disease usually does not result in destruction of hair follicles or scarring [4]. The prognosis of AA is influenced by several factors in particular by the type and extent of AA [5].
We aimed to review evidence for the management of alopecia areata and discuss which treatments may help patients. We also discuss potentially interesting new treatments that require further investigation.

Treatment of Alopecia Areata

Treatment of AA is still a difficult task for every dermatologist. Current traditional therapies are predominantly immunomodulating modalities, including corticosteroids, anthralin, topical sensitizers, and photochemotherapy (PUVA). A non-specific modality is minoxidil, which prolongs anagen and promotes growth of longer and wider hair. These treatments stimulate hair growth but do not prevent hair loss and probably do not influence the course of the disease [6, 7]. Improved future treatments may be immunosuppressive or immunomodulatory targeting of the autoimmune pathogenesis of AA, or they may otherwise protect hair follicles from the injurious effects of inflammation (4). Any treatment has to be suitable for long-term therapy, because AA is a disease that can persist for many years or even for life. The choice of therapy depends primarily on the patient’s age and the extent of the hair loss [5, 8].

Corticosteroid Therapy

Corticosteroids are probably most popular form of treatment for patchy AA [4, 6]. The mechanism of steroid effect in AA is speculated to be immunomodulatory. Corticosteroids decrease production and/or secretion of interleukin 1, interleukin 2 and monocyte chemotactic factor [6]. Topical steroids decrease Langerhans cell members as well as Langerhans cell-dependent T-lymphocyte activation [7]. Which of these or perhaps other steroid effects are relevant to hair regrowth in AA is unknown at this time. Corticosteroids can be administered in four different ways: topically as a cream, foam or lotion, intralesionally as local injection into the bald patches, and systemically either as injections into a muscle or taken orally. These different methods of application vary in their potency.
Topical Corticosteroids

Topical corticosteroids are widely used to treat all types of AA and they are the mildest form of steroid treatment. Response to topical steroid in therapeutic trials has been mixed. Reports of nearly 100% response for prepubertal children have been reported alongside a response rate of just 33% in adults [6, 7]. The failure of topical corticosteroids is most likely due to the insufficient penetration of topically applied drugs forms ointments, creams or lotions into the hair bulb [4]. In order to increase the effect of topical corticosteroids, an occlusive dressing technique can be applied in the treatment. Side effects of topical steroids include local folliculitis, acne outbreaks, local atrophy and very occasionally hypertrichosis. If doses of topical steroids are too high there is a small risk of systemic absorption and the potential associated effects [7]. Topical corticosteroids are the treatment of choice in children.

Intralesional Corticosteroids

Intrallesional corticosteroids were first described in 1958 with the use of hydrocortisone [9]. This method is very popular compromise between topical application and systemic use. It involves the injection of a steroid solution (usually triamcinolone acetonide) intradermally every four to six weeks. The intention is to get as much of the steroid directly to the root of the affected hair follicles where the associated inflammatory infiltrate is present. Corticosteroids suppress the T-cell mediated immune attack on the hair follicle. The recommended dose per treatment is up to 3 mL of a 5 mg/mL solution injected into the mid-dermis in multiple sites 1 cm apart. The amount injected into each site is 0.1 mL. For the eyebrows and face, 2.5 mg/mL can be used. After each injection, a gentle massage of the treated area is recommended to help prevent treatment-induced atrophy. Initial regrowth is often seen in four weeks although it can take up to two months before noticeable hair growth develops [7]. Several studies reported hair regrowth at the site of injection in the majority of cases [3, 4, 6]. Other dermatologist report less successful response rates [4, 6, 7]. Injections in frontoparietal areas are not recommended because of the potential risk of thrombosis in the central retinal artery due to the formation of crystalline deposits. Ferrando and Moreno propose the use of mesotherapy multi-injectors with 5 or 7 needles, an approach which has the advantage of optimizing the process while economizing on product use and ensuring homogeneity, with a shorter application time and a decrease in painful injections [10]. Side effects can include pain from the injections and atrophy of the skin around the injection site. However, a topical anesthetic
cream such as lidocain—prilocaine can be applied 30 to 60 minutes before treatment to reduce discomfort. This is particularly useful when treating the pediatric population. The risk of atrophy can be minimized by injecting into the mid-dermis rather than into the epidermis or the subdermal fat [11]. Use of steroid injections is a popular form of treatment for eyebrow hair loss [8]. This treatment is not appropriate in rapidly progressing or very extensive forms. Children under ten years of age not usually treated with intralesional steroids.

**Systemic Corticosteroids**

Dillaha and Rothman introduced into the treatment of alopecia areata systemic corticosteroids since 1952 [12]. Systemic application (oral, intravenous, intramuscular) is the most powerful form of corticosteroid treatment. They are frequently effective, but their use is limited because of the high relapse rate after reduction of the dose [8]. In addition, the presence of side effects with long-term systemic steroid therapy may suggest a dose reduction or even discontinuation of the treatment. To avoid these complications, pulse-therapy had been introduced. Several modalities for use of high doses in the form of pulses in different oral and intravenous regimens have been reported.

**Photochemotherapy (PUVA)**

Photochemotherapy (PUVA) is term for a combination of using UV-A light with a photosensitizing drug psoralen (P). The mechanism of action of PUVA on AA is believed to be a photoimmunologic action. It may affected T-cell function and antigen presentation and possibly inhibits local immunologic attack against the hair follicle by depleting Langerhans cells [6].

Psoralen inhibits mitosis by binding covalently to pyrimidine bases in DNA when photoactivated by UV-A [13]. This drug has been administrated topically (1% 8-MOP ointment or 0.1% solution) or orally (0.6 mg/kg 8-MOP) and followed in 1 or 2 hours, respectively, by UV-A radiation. Treatments are given two to three times weekly with a gradual increase in UV-A dosage and clinical responsiveness is usually seen within 20 to 40 treatments. Success rates with PUVA treatment have varied from 20% to 50%, although the relapse rate is high [7, 8].

Side effects include nausea with orally administered drug and burning erythema [7]. The possibility of skin cancer formation with prolonged treatment should also be considered. PUVA-turban is a method of admini-
strating a dilute psoralen solution (8-MOP 0.0001%) selectively to the scalp for 20 minutes using a cotton towel as a turban. The patient's scalp is then exposed to UV-A radiation [14].

It is a well tolerated therapy with minimal local phototoxic side effects and without the systemic side effects of PUVA. Technical improvements, such as a comb emitting UV-A light have been tried, but so far no results have been reported. PUVA is generally limited to patients over age 12.

Topical Sensitizers

Topical immunotherapy (contact sensitization) is one of the more effective treatments for patients with chronic AA affecting more then 50% of the scalp [7]. The patients are sensitized by application to the scalp of a potent contact allergen, and allergic contact dermatitis is subsequently elicited by weekly applications of the same agent [15]. Initial hair regrowth is usually visible after 8-12 weeks [4].

Response rates of treatment with contact sensitizers vary from 29% to 78% [5, 15, 16]. The differences may be explained in part by the different extent and duration of AA prior to treatment for the patients in each study, and in part by differences in methods of treatment [4]. In 1978, Daman et al. first reported the use of dinitrochlorobenzene (DNCB) to induce hair growth in two patients with AA [17].

This chemical was first found to be a potent contact allergen in 1912. Today, diphenylcyclopropenone (DPCP) or squaric acid dibutylester (SADBE) are widely used. The mechanism by which contact sensitization suppresses AA is uncertain but may involve the generation of nonspecific suppressor T-cells or the inhibition of proinflammatory cytokines [15, 16]. Happle proposed the concept of "antigenic competition" where an allergic reaction generates suppressor T cells that non-specifically inhibit the autoimmune reaction against a hair follicle constituent [18]. Contact allergens also tend to attract a new population of T cells in to the treated areas of the scalp, and thus enhancing a clearance of putative follicular antigen [19].

The other events noted are a decrease in the raised interferon γ levels, increase in mRNA expression of interleukins 2, 8, 10, and tumor necrosis factor α in the lesional skin [20]. Recent studies demonstrated that treatment with a contact sensitizer induces apoptosis in perifollicular T cells [21]. The adverse effects of topical immunotherapy include itching, vesicular or bullous
reaction, urticaria, facial and scalp edema, pigmented disturbances and cervical lymphadenopathy, which are invariably present [7, 16].

**Anthralin**

Anthralin is the only irritant substance generally agreed to induce hair regrowth in AA [22]. The mechanism of anthralin effect in AA can only be speculated on. Anthralin induces inflammation in a possibly unique manner, primarily by generation of free radicals [23]. Reactive oxidants are potent antiproliferative and immunosuppressive agents that inhibit chemotaxis, IL-2 production, cytotoxic activity of natural killer cells, and mitogen induced transformation of B and T lymphocytes [6, 23, 24]. Anthralin has been shown to be toxic to Langerhans cells. Concentrations of between 0.25 and 1% applied overnight can be used. Alternatively, so called "short-contact therapy" may be used, which involves applications of 30 minutes with progressive increases until reaching an exposure of 1 hour. When therapy is effective, new hair growth is usually seen within 2 to 3 months after the start of treatment, and about 25% of patients may have cosmetically acceptable growth in about six months [6, 15]. It takes 24 or more weeks for a cosmetically acceptable response [7]. Application of topical anthralin may cause pruritus, erythema, scaling, folliculitis and regional lymphadenopathy [25]. Anthralin is a good choice for children or for those individuals with extensive AA.

**Minoxidil**

Minoxidil is a piperidinopyrimidine derivate that acts as a smooth muscle vasodilator in the treatment of hypertension. Although minoxidil has been used as a hair regrowing treatment for more than 20 years, its mechanism of action of on hair growth promotion is still unclear. It does not have any hormonal effects or immunosuppressant effects; rather, it has direct effects on the proliferation and differentiation of follicular keratinocytes in *vitro*, and regulates hair physiology independently of blood flow influences [7]. Both topical and oral minoxidil therapy have been tried in AA [26]. Topically, concentrations ranging from 1 to 5% twice daily have been used. The results reported in the literature have been highly variable, ranging from little benefit to response rates of over 50% [7, 8].

The average time to response with topical minoxidil is 2 to 3 months [6]. The time to maximum response is generally about 1 year, although it can be longer [15]. This drug may be useful in treatment of patchy AA but not
alopecia totalis or universalis. It is generally used at a concentration of 5% in combination with a topical corticosteroid or anthralin, which enhance its action by increasing absorption. Topical minoxidil has also been used in combination with systemic corticosteroids because this seems to limit hair loss after suspending corticosteroid therapy [27].

Side effects are limited to mild local irritation and, less frequently allergic contact dermatitis, and localized facial hypertrichosis. Oral minoxidil (a dose of 10 mg/d) may result in more extensive and more rapid hair growth. Adverse effects, including fluid retention, head-ache, depression, palpitations and tachycardia, may make oral minoxidil an unacceptable mode of therapy for AA [7, 27].

New Immunomodulatory Therapies

Remarkable progress during the last two decades has brought much progress in the understanding of the immunopathogenesis of alopecia areata, leading to the development of more targeted therapies. These therapies have a common therapeutic goal: to reduce or eliminate the pathogenic effects of T cells in alopecia areata.

Topical immunomodulators are a relatively new class of agent that acts locally on T cells by suppressing cytokine transcription [28]. They are now emerging as the therapy of choice for several immune-mediated dermatoses, because of their comparable efficacy, ease of application and greater safety than their systemic counterparts [29]. The two most studied topical immunomodulators are tacrolimus and pimecrolimus. A third new member of this group is topical cyclosporine A (CsA). All three drugs inhibit calcineurin, thereby inhibiting interleukin-2 production and limits CD4 lymphocyte cell activity [30].

Topical Tacrolimus (Protopic)

Tacrolimus is macrolide lactone, produced by Streptomyces tsukabaensis, a fungus found in the soil of Mount Tsukuba, the science city of Japan, where initial isolation and characterization of this drug was performed in the year 1987. The name of the drug is neologism, composed of tsukuba, macrolide and immunosuppression,
Tacrolimus is an immunosuppressive agent that can be applied topically to the skin. It acts directly on T-cells to inhibit IL-2 transcription, which results in decreased growth and proliferation of T lymphocytes in response to foreign antigens [31]. It also inhibits other cytokines, including TNF-α and IFN-γ, both important in T-cell activation. Moreover, topical application of tacrolimus also has a hair growth stimulatory effect, independent of its T-cell suppressive effect [32]. Tacrolimus ointment does not cause skin atrophy, pigment changes, or teleangiectasia. Therefore, tacrolimus is promising candidate for the treatment of AA [33].

**Topical Pimecrolimus (Elidel)**

Pimecrolimus is a semi-synthetic product of ascomycin, which is fermentation product of *Streptomyces hygroscopicus* var. *ascomycetes*. Similar to tacrolimus, it is a cell-selective cytokine inhibitor developed for the treatment of inflammatory skin diseases [34]. It binds to macrophilin-12, inhibits calcineurin, inhibits synthesis of inflammatory cytokines, such as IL-2 and IFN-γ, and inhibits T-lymphocytes and mast cell activation. Pimecrolimus has high skin-specific anti-inflammatory activity with low potential for affecting the systemic immune response [30]. The cream 1% formulation is safe and effective and does not cause skin atrophy or teleangiectasia.

Unfortunately, the cream is not expected to be effective for hair regrowth because it permeates no lower than the superficial dermis, which is an insufficient depth for targeting T-cells involved in AA [30].

**Topical Cyclosporine A (Psorban)**

Cyclosporine A (CsA), isolated from the fungus *Tolypocladium gamu*, is a lipophilic cyclic polypeptide and calcineurin inhibitor. CsA is a potent immunomodulatory agent whose mechanism involves inhibition of T-4 lymphocyte activation [35]. Cyclosporine therapy reduces the number of T cells infiltrating the hair follicle and the perifollicular area, and CsA is a potent inhibitor of interleukin 2, a cytokine that stimulates the proliferation of T lymphocytes [36].

It is known that cyclosporine stimulates T cells and the pilosebaceous unit, thereby inducing hypertrichosis and sebaceous hyperplasia. Although systemic CsA appears to be effective in AA, the adverse effect profile, recurrence rate
after treatment discontinuation and inability to produce long-term remissions make CsA unattractive for the treatment of AA. In the past topical formulations of CsA were ineffective because of poor skin penetration. To surmount this problem, a heptamer of arginine was conjugated to CsA thought a pH-sensitive linker designed to release CsA at psysiologic pH within the skin [37].

The oligoarginine transporters enable full-skin-thickness penetration of CsA into cells throughout the epidermis and dermis of human skin, with functional inhibition of cutaneous inflammation [38]. A recent publication reports the use of mixture of ethanol and phospholipids in the formulation of new topical cyclosporine preparations in order to increase penetration [39].

New Biologic Therapies

Biologics are pharmacologically active proteins extracted from animal tissue or synthesized through recombinant DNA techniques. They are designed to mimic the action of normal human proteins or to interact with circulating proteins or cellular receptors. There are three distinct classes of biologic agents: monoclonal antibodies, fusion proteins and recombinant cytokines or growth factors [40].

They include Etanercept, Infliximab, Efalizumab and Alefacept. Biologic therapies target cell surface receptors, and their theoretical advantage is that their greater specificity will provide better safety profiles [30]. The advent of the new biologic medications raised hopes for successful control of many immune-mediated diseases, including AA. Based on current hypothesis regarding AA immunopathogenesis, two main therapeutics approaches have emerged: modulating either T cells activation or cytokines.

Owing to the suspected involvement of tumor necrosis factor α in the pathogenesis of alopecia areata, one might expect that biologic therapies with anti TNF-α agens might be beneficial [41]. On the other hand, there is evidence suggesting that other biologic therapies that target T cells may represent an effective treatment modality for AA. Some clinical trials are ongoing to evaluate the efficacy of the newer biologic therapies in the treatment of AA.
Liposomes

Another novel approach in treating AA is to create a vehicle that allows penetration to the subcutaneous fat where the bulbs of anagen hair follicles are located and where the pathomechanism takes place [4]. Liposomal drug delivery may increase penetration of skin and allow slow release of active compound locally with diminished toxicity.

At present, liposomes seem to be the best candidate as a vehicle topical treatment. Topically applied liposomes have been shown to deliver melanin, proteins, genes and various small molecules selectively to hair follicles and hair shafts of mice in vivo [42].

Liposome-targeting of molecules to human hair follicles has been demonstrated in human scalp in histoculture [43]. However, future experiments have to show whether liposomes are able to deliver molecules to the hair bulb in human scalp in vivo.

Miscellaneous Agents

Sulfasalazine

Sulfasalazin is an anti-inflammatory agent composed of a sulfonamide and salicylate. It was developed in 1938 for the treatment of rheumatoid arthritis [44]. Sulfasalazine has both immunomodulatory and immunosuppressive actions that include suppression of T cell proliferation and reducing the synthesis of cytokines, including interleukin 1, 2, 6, and 12, tumor necrosis factor α [45].

It also inhibits the release of prostaglandin E2 and antibody production. Several reports showed good hair regrowth with sulfasalazine in the treatment of AA. Sulfasalazine was started at 500 mg twice daily for one month, 1 g twice daily for one month, and then 1 g three times daily [46]. Treatment with sulfasalazine is generally well tolerated and characterized by a lower incidence of serious side effects in comparison with other systemic therapies like corticosteroids and methotrexate. Side effects include gastrointestinal distress, fever, dizziness and headache. Sulfasalazine could be considered as a therapeutic alternative in the treatment of AA, because of its safety profile, cosmetically acceptable efficacy, and good tolerability.
Inhibition of the Fas-Fasl System

Induction of hair follicle apoptosis by the Fas-FasL system seems to be involved in the pathogenesis of AA [47]. Therefore, inhibition of the Fas-FasL system might protect hair follicles from injury caused by the inflammatory infiltrate. However, such treatment could only be applied topically and specifically limited to hair follicles, because systemic inhibition would disturb essential control mechanisms of lymphocyte homeostasis [4].

Imiquimod

Imiquimod is the first member of a new class of immune response modifier; it was first improved 1997 for the topical treatment of genital warts. It is a synthetic molecule, which enhances both innate and acquired immune response, in particular, cell mediated pathways, by stimulating monocytes and macrophages via binding to cell surface receptors to produce several specific cytokines including IFN-α, IL-1, 6, 8, 10, 12 and tumor necrosis factor [48], resulting in local immunoregulatory activity. Imiquimod also stimulates natural killer and B cells and enhances migration of Langerhans cells. The clinical outcomes obtained with imiquimod have been inconsistent, some authors have reported regrowth whereas others have found no response [49, 50]. In the future, imiquimod and newer generation of imidazoquinolines (resiquimod) require further investigation for potential clinical utility in treating AA.

Bexarotene

Bexarotene is a member of a subclass of retinoids that selectively activate retinoid X receptor. It was noted that topical bexarotene yielded significant hair regrowth when used to treat patients with follicular mucinosis or folliculotropic mycosis fungoides, and thus it was theorized that topical bexarotene may also induce hair regrowth in AA [51]. Although the mechanism for its action in AA is not completely understood, bexarotene induced T-cell apoptosis. Topical bexarotene 1% gel application is well tolerated and possibly effective [52]. Mild irritation is a common side effect. A randomized placebo-controlled trial should be conducted.

Nonpharmacologic Methods

Laser Therapy

The 308-nm excimer laser is a system that offers high doses of long-wave monochromatic UVB radiation. Gundogan et al. are the first to discuss
successful treatment of two patients with AA with the 308-nm xenon chloride eximer laser [53]. The laser induces T-cell apoptosis in vitro, which is analogous to topical treatment of AA. In another study, the authors observed hair regrowth in all patients with patchy AA, whereas no hair regrowth was observed in patients with either AA totalis or universalis [54]. Each lesion was treated twice a week for a maximum of 24 sessions. The untreated areas did not show any regrowth, suggesting that the regrowth observed was most probably not a spontaneous phenomenon. The only side effects described were erythema and mild hyperpigmentation. Treatment was well tolerated and so the authors suggested that this type of laser could be a good therapeutic option. Also, the use of excimer laser in children with AA has been reported to have a good success rate [55]. However, further studies are needed to confirm these findings.

**Cosmetic Treatments**

Cosmetic treatments for patients with AA include dermatography and hairpieces transplants. Dermatography has been used to camouflage the eyebrows of patients with AA. The procedure is relatively easy, provides permanent camouflage, and is generally devoid of any significant adverse effects [56]. Hairpieces and transplants may be the only options available for persons with severe disease that remains unresponsive to available medical treatments [57]. Patients with extensive disease may wear wigs, or other scalp coverings.

**Conclusion**

Alopecia areata is a non scarring inflammatory hair disease, frequently recurrent. Because of their psychological stigmatization, the medical attendance and therapy of patients who suffer from distinct form of AA is difficult to challenge. Although spontaneous remission is possible, it occurs rarely. The success of treatment depends on the age of onset of the disease and the extent of hair loss. The most important prognostic factors are the extent and pattern of disease. Alopecia totalis, alopecia universalis, and ophiasis have the worst outcomes, with lower rates of spontaneous remission and poorer responses to therapy than other presentations. Onset before puberty, long disease duration, co-existing atopy, nail dystrophy, associated autoimmune diseases, and positive family history are risk factors for more severe disease.
At present, corticosteroids are the most popular form of treatment and can be given topically, intralesionally, or, in rare case systemically. Minoxidil has had limited success in stimulating hair regrowth without altering the course of AA. Topical immunotherapy with diphenylcicpropenone or PUVA therapy may be effective in long-standing and wide-speared disease. Unfortunately, none of these agents is curative or preventive. These treatments stimulate hair growth but do not prevent hair loss and probably do not influence the course of the disease. The treatment of patchy AA is usually successful. However, the therapy for extensive AA may be prolonged and difficult. In selected cases observation and supportive therapy may be indicated. An individualized treatment approach is recommended for each patient.

As long as no causal treatment is available, future approaches should focus on a more specific targeting of the underlying pathomechanism with a topical action around the hair bulbs and without serious side-effects. New immunomodulators and biologic therapies target specific immunologic responses and offer new strategies for treating pathogenic T cells and the cytokines they produce. Future success in treating of AA will require continued research on the regulation of the hair-growth cycle and basic hair biology, the development of new therapeutic approaches, and the judicious use of existing drugs.

References


