# Management of alopecia areata: an update

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#### Abstract

Alopecia areata is a common, non-scarring, autoimmune disorder affecting any hair-bearing area. It is often psychologically devastating. This disorder occurs in both the sexes, in all age groups, and is characterized by the sudden appearance of circumscribed areas of hair loss on the scalp or other parts of the body. Various therapeutic approaches are presently available for managing alopecia areata including corticosteroids, contact sensitizers and immunosuppressants, but none have been shown to alter the course of the disease on a consistent basis. Keywords

Alopecia areata, treatment, autoimmune, corticosteroids, recent advances, contact sensitizers

#### Introduction

Alopecia areata is a non-scarring autoimmune, inflammatory hair loss affecting the scalp and/or body. Although the etiopathogenesis of alopecia areata is still unknown, the most widely accepted hypothesis is that it is a T-cell mediated autoimmune condition that occurs in genetically predisposed individuals. The term 'alopecia areata' was first used for this disorder by Savages<sup>1</sup>. Alopecia areata has a reported incidence of 0.1-0.2%, with a life-time risk of 1.7%<sup>2-4</sup>. The disease can begin at any age, but the peak incidence is between 20 and 50 years of age5. Both the sexes are equally affected and there is no racial variation reportedClinically, alopecia areata may present as a single well demarcated patch of hair loss, multiple patches, or extensive hair loss in the form of total loss of scalp hair (alopecia totalis) or loss of entire scalp and body hair (alopecia universalis). Histopathologically, alopecia areata is characterized by an increase in the number of catagen and telogen follicles and the presence of perifollicular lymphocytic infiltrate around the anagen phase hair follicles. The condition is thought to be self-limited in majority of cases, but in some the disease has a progressive course and needs active treatment in the form of oral or topical therapeutic options. Progressive alopecia areata is associated with severe social and emotional impact.

### **Clinical features**

Alopecia areata mostly presents as a sudden loss of hair in well demarcated localized areas. The lesion is usually a round or oval flat patch of alopecia with normal skin colour and texture involving the scalp or any other region of the body. The patch of alopecia may be isolated or there may be numerous patches. It usually has a distinctive border where normal hair demarcates the periphery of the lesion. In acute phases, the lesions can be slightly erythematous and oedematous. The patches of alopecia areata are usually asymptomatic, although several patients may sometimes complain of local paraesthesia, pruritus or pain. The affected hairs undergo an abrupt conversion from anagen to telogen, clinically seen as localized shedding. Characteristic hairs, known as 'exclamation point hairs' may be seen within or around the areas of alopecia. The hairs are tapered towards the scalp end with thickening at the distal end. These hairs may also demonstrate deposition of melanin pigment in the distal extremity, also known as Wildy's sign. Although not absolutely pathognomonic, it strongly suggests the diagnosis of alopecia areata. Hair pull test conducted at the periphery of the lesion may be positively correlated (six or more) with disease activity. In the chronic phases, the test is negative, since the hair is not plucked as easily as in the acute phases.

Another important clinical sign that can aid in the diagnosis is the presence of 'cadaverous hair'. These are the hairs in which there occurs a fracture of the shaft inside the hair follicle, producing blackened points inside the follicular ostia resembling comedones. In alopecia areata, the hair loss progresses in a circumferential pattern. Often, distinct patches merge to form large patches. Upon regrowth, hairs will often initially lack pigment resulting in blonde or white hairs<sup>7</sup>.

#### Extrafollicular involvement in alopecia areata:

a) Nail changes: Nail changes are more frequent in children (12%) than in adults (3.3%)<sup>8</sup>. The prevalence of nail changes is greater in the more severe forms of alopecia areata such as alopecia universalis and alopecia totalisFinger nails are more commonly involved than the toe nails. Pitting is the most common finding. Other nail changes include koilonychias, onycholysis, onychomadesis, punctuate leukonychia, trachyonychia, Beau's lines and red lunulae<sup>8-11</sup>.

b) Ocular changes: Various ocular changes have been reported to occur in alopecia areata. These include focal hypopigmentation of the retina<sup>12</sup>, lens opacities, posterior subcapsular cataracts<sup>13</sup> decrease in visual acuity, Horner's syndrome, heterochromia of the iris<sup>14</sup>, miosis and palpebral ptosis.

### Treatment of alopecia areata

Treatment of alopecia areata is not mandatory in every affected patient because the condition is benign in majority and spontaneous remission is common. Treatment is mainly directed towards halting the disease activity as there is no evidence that the treatment modalities influence the ultimate natural course of the disease. Treatment modalities are usually tailored as per the extent of hair loss and the patient's age. Addressing the impressive inflammatory process occurring in alopecia areata, corticosteroids have by far been the most commonly used treatment modality<sup>-16</sup>Few treatments have been subjected to randomized control trials and except for contact immunotherapy, there is a paucity of published data on their long term outcomes. Currently, new treatments targeting the immune system are being explored for the use in alopecia areata.

Topical treatments
Topical steroids
Intralesional steroid injections
Topical contact sensitizers
Anthralin
Minoxidil
Topical retinoids
Tacrolimus
Systemic treatments
Systemic corticosteroids
Sulfasalazine
Azathioprine
Methotrexate
Oral zinc sulphate
Photo-and photochemotherapy
PUVA
NBUVB
Excimer laser
Miscellaneous and Non-pharmacological treatment
Dermatography, wigs
Hypnotherapy etc

#### Topical treatment options

#### Topical corticosteroids:

Several topical corticosteroids with varying levels of efficacy have been used to treat alopecia areata. These include fluocinolone acetonide cream<sup>17</sup>, fluocinolone scalp gel, betamethasone valerate lotion<sup>18</sup>, clobetasol propionate ointment<sup>19</sup>, dexamethasone in a penetration-enhancing vehicle and halcinonide cream<sup>20</sup>. They are a good option in children because of their painless application and wide safety margin<sup>21</sup>.

Topical corticosteroids are ineffective in alopecia totalis/universalisFolliculitis is a common side effect of corticosteroid treatment, appearing after a few weeks of treatment. Telangiectasia and local atrophy have also been reported. Treatment must be continued for a minimum of 3 months before regrowth can be expected and maintenance therapy often is sometimes necessary.

### Intralesional corticosteroids:

Intralesional corticosteroids are widely used in the treatment of alopecia areata. In fact, they are the first-line treatment in localized conditions involving <50% of the scalp<sup>22</sup>. Hydrocortisone acetate (25mg/ml) and Triamcinolone acetonide (5-10mg/ml) are commonly used. Triamcinolone acetonide is administered usually in the concentration of 5mg/ml using a 0.5 inch long 30-gauge needle in multiple 0.1 ml injections approximately 1 cm apart<sup>22-23</sup>. The solution is injected in or just beneath the dermis and a maximum of 3 ml on the scalp in one visit is recommended23. Lower concentrations of 2.5mg/ml are used for eyebrows and face. Regrowth usually is seen within 4-6 weeks in responsive patients. Treatments are repeated every 3-6 weeks. Skin atrophy at the sites of injection is a common side effect, particularly if triamcinolone is used, but this usually resolves after a few months. Repeated injections at the same site or the use of higher concentrations of triamcinolone should be avoided as this may lead to prolonged skin atrophyPain limits the practicality of this treatment method in children who are less than 10 years of age. Severe cases of alopecia areata, alopecia totalis, alopecia universalis as well as rapidly progressive alopecia areata respond poorly to this form of treatment<sup>25</sup>.

# Anthralin:

Dithranol (anthralin) or other irritants have been used in the treatment of alopecia areata. The exact mechanism of action is unknown, but is believed to be through immunosuppressant and anti-inflammatory properties with the generation of free radicals. 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<sup>26-27</sup>. In an open study, 25% patients with severe alopecia areata were shown to respond positively to local applications of 0.5-1% anthralinMore placebo control studies are needed to justify the use of anthralin in alopecia areata.

#### <u>Minoxidil:</u>

Minoxidil appears to be effective in the treatment of alopecia areata. It's mechanism of action has yet to be determined, but it is known to stimulate DNA synthesis in hair follicles and has a direct action on the proliferation and differentiation of the keratinocytes<sup>28</sup>. In one clinical study, hair growth was demonstrated in 38% and 81% of patients treated with 1% and 5% minoxidil respectively. Thus 5% minoxidil solution is usually recommended as a treatment option in alopecia areata. No more than 25 drops are applied twice per day regardless of the extent of the affected area. Initial regrowth can be seen within 3 months, but continued application is needed to achieve cosmetically acceptable regrowth. Minoxidil has also been studied in combination with anthralin<sup>29</sup>, topical betamethasone propionate<sup>30</sup> and prednisolone<sup>31</sup>. Minoxidil is of little benefit to patients of severe alopecia areata, alopecia totalis or alopecia universalisThe possible side effects from minoxidil are allergic and irritant contact dermatitis and hypertrichosis which is usually reversible with the interruption of the treatment.

# Topical immunotherapy:

Topical immunotherapy is the best documented treatment so far for severe and refractory cases of alopecia areata. Topical immunotherapy is defined as the induction and periodic elicitation of allergic contact dermatitis by applying a potent contact allergen<sup>33</sup>. In 1965, the alkylating agent triethyleneimino benzoquinone was the first topical sensitizer used to treat cutaneous disease, but it was abandoned on account of its mutagenic potential. Later nitrogen mustard, poison ivy, nickel, formalin, and primin were tried, mainly as topical immunotherapy, for alopecia areata and warts. Contact immunotherapy was introduced in 1976, by Rosenberge and Drake. potent Later, contact allergens namely dinitrochlorobenzene (DNCB) and diphenylcyclopropenone (DPCP) replaced the allergens that were used earlier<sup>33</sup>. DNCB is mutagenic against Salmonella tymphimurium in the Ames test and is no longer usedNeither SADBE, nor DPCP are mutagenic. DPCP is more stable in solution and is usually the agent of choice.

Mechanism of action: Topical immunotherapy acts by varied mechanisms of action. The most important mechanism is a decrease in CD4 to CD8 lymphocyte ratio which changes from 4:1 to 1:1 after contact immunotherapy. A decrease in the intrabulbar CD6 lymphocytes and Langerhan cells is also noted. Happle et al, 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. Expression of class I and III MHC molecules, which are normally increased in areas affected by alopecia areata disappear after topical immunotherapy treatment<sup>34</sup>.A 'cytokine inhibitor' theory has also been postulated<sup>34</sup>.

Method of sensitization: The protocol for contact immunotherapy was first described by Happle et al in 1983 The scalp is the usual sensitization site. For the initial sensitization a cotton-tipped applicator saturated with 2% DPCP in acetone is applied to a small area. Patients are advised to avoid washing the area and protect it from sunlight for 48 hours. After 2 weeks 0.001% solution of DPCP is applied on the scalp and then the application of contact allergen is repeated weekly with increasing concentrations. The usual concentration of DPCP that ultimately causes mild contact eczema is 0.01-0.1% and this is repeated weekly till a response is seen. An eczematous response indicates that sensitization has taken place. Only 1-2% of the patients fail to sensitize. It is important to remember that DPCP is degraded by light and should thus be stored in the dark and the patient should also wear a wig or hat during the day after application of DPCP. DPCP immunotherapy has even been combined with oral fexofenadine treatment with good effect<sup>36</sup>.

Evaluation of efficacy: The clinical response after six months of treatment is rated as per the grading system proposed by Mcdonald Hull and Norris<sup>37:</sup>

Grade 1- Regrowth of vellus hair.

Grade 2- Regrowth of sparse pigmented terminal hair. Grade 3- Regrowth of terminal hair with patches of alopecia. Grade 4- Regrowth of terminal hair on scalp.

If no regrowth is observed within six months of treatment, the patient is considered to be a non-responder. Evaluation of plucked hair is done using light microscopy, for evaluation of anagen/telogen ratio.

A review of most of the published studies of contact immunotherapy concluded that 50-60% of patients achieve a worthwhile response but the range of response rates was very wide (9-87%)Patients with extensive hair loss are less likely to respond. Other reported poor prognostic factors include the presence of nail changes, early onset disease and a positive family history<sup>39</sup>.

Topical immunotherapy can lead to certain side effects such as persistent dermatitis, painfull cervical lymphadenopathy, generalized eczema, blistering, contact leukoderma, and urticarial reaction. Systemic manifestations such as fever, arthralgia and yellowish discoloration of hair are noted more often with DNCB.

In poor responders to DPCP, squaric acid dibutylester (SADBE) can be tried as a contact sensitizer. The method of application is the same as with DPCP but the applications are done once or twice weekly<sup>40</sup>.

Good care should be taken to avoid contact with the allergen by handlers, including pharmacy and nursing staff. Those applying the antigen should wear gloves and aprons. There is no available data on the safety of contact immunotherapy during pregnancy and it should not be used in pregnant women or in women intending to become pregnant.

# Tacrolimus:

Tacrolimus is a topical calcineurin inhibitor that inhibits transcription following T-cell activation of several cytokines including IL-2, IFN-gamma and TNF- $\alpha$ . Yamamoto et al reported in their findings that tacrolimus stimulated hair growth in mice<sup>41</sup>, although subsequent studies have shown conflicting resultsRecently, Price et al reported an 11-patient study in which none of the patients had terminal hair growth in response to tacrolimus ointment 0.1 % applied twice daily for 24 weeks<sup>43</sup>.

# Topical garlic

Garlic is a very commonly used home remedy in the treatment of alopecia areata in India and even in the rest of the world. One study analyzed the effect of a combination of topical garlic gel and betamethasone valerate ointment in alopecia areata in a double-blind study. The study found the combination useful in majority of the patients with a statistically significant difference between the treatment and control groups<sup>44</sup>.

#### **Topical** retinoids:

Among topical retinoids, tretinoin and bexarotene have been tried in alopecia areata with mixed results<sup>-46</sup>Irritation of the skin is a very common side effect and the efficacy is doubtful in the absence of double-blind randomized trials.

# Prostaglandin analogs:

The propensity of certain prostaglandin analogues used as antiglaucoma eye drops to cause hypertrichosis has been employed in the treatment of alopecia areata. These prostaglandin analogues include Latanoprost and Bimatoprost and they are used in the treatment of alopecia areata involving the eyelashes<sup>48</sup> However, the results obtained with these drugs have not been really encouraging<sup>49</sup>.

#### Systemic treatments

Systemic treatments, as a rule, are used only in progressive forms of alopecia areata and going by the immune nature of the disease, majority of these treatment options are immunosuppressants or immunomodulators in nature.

#### Systemic corticosteroids:

The use of systemic corticosteroids for the treatment of alopecia areata is under much debate. Some authors support a beneficial role of systemic steroids on halting the progression of alopecia areata, but many others have had poor results with this form of therapy. The suggested dosages are 0.5-1mg/kg/day for adults and 0.1-1 mg/kg/day for children<sup>50</sup>. Treatment course ranges from 1-6 months, but prolonged courses should be avoided to prevent the side effects of corticosteroids. Side effects profile of corticosteroids in conjunction with the long-term treatment requirements and high relapse rates make systemic

corticosteroids a more limited option. In addition to the daily oral administration of corticosteroids, there are several reports of high-dose pulsed corticosteroid treatments employing different oral and intravenous regimens<sup>51-53</sup>. Many of these regimens have been tried in alopecia areata with encouraging results but the majority of these studies have been non-blind open studies. One such pulsed administration employs a high dose oral corticosteroid on two consecutive days every week with a gap of 5 days between the two pulses. This modality of treatment is known as oral minipulse therapy (OMP) and it has been tried in many skin diseases in addition to alopecia areata like vitligo<sup>54-55</sup> and lichen planusSome open label studies on corticosteroid OMP therapy have reported encouraging results in alopecia areata<sup>53</sup>.

# Sulfasalazine:

Because of its immunomodulatory and immunosuppressive actions, sulfasalazine has shown good hair regrowth in the treatment of alopecia areata. The drug is administered orally usually as enteric coated tablets to minimize the gastrointestinal side effects. The treatment is started at a lower dose, usually in the range of 500 mg twice daily and then the dose is gradually increased to 1 g three times a dayAdverse effects include gastrointestinal distress, liver toxicity and haemotological side effects. Sulfasalazine helps in alopecia areata because it causes inhibition of T cell proliferation, and natural killer cell activity and also inhibits antibody production. It also inhibits the secretion of interleukin (IL)-2, IL-1, TNF- and IFN-gamma and even IL-6<sup>67</sup>.

A number of clinical studies have documented a positive effect of sulfasalazine in alopecia areata. In one clinical study, 23% patients showed a really good response with satisfactory hair growth after sulfasalazine therapyOther studies have also shown a beneficial effect of this treatment option in resistant cases of alopecia areata<sup>66,69</sup>.

# Azathioprine:

Azathioprine, being an immunosuppressive agent has also been tried in alopecia areata. The drug is used in many cutaneous disorders owing to its effect on circulating lymphocytes as well as Langerhan cells. In a limited study on 20 patients hair regrowth was demonstrated in about half of the patients with a dosage regimen of 2g/day<sup>70</sup>.

# Cyclosporine:

This drug has proven effective in the treatment of alopecia areata because of its immunosuppressive and hypertrichotic properties. The side effect profile and high rate of recurrence render the drug a poor choice for the use in alopecia areata. So the drug is to be attempted only in severe forms of alopecia areata not responding to treatment<sup>71</sup>.

# Methotrexate:

Methotrexate either alone or in combination with prednisolone has been used in the treatment of alopecia areata in various studies with variable success rates<sup>72</sup>.

# Oral zinc sulphate

Serum zinc levels have been found to be lower in patients with alopecia areata than in control populationIn a study on 15 patients, hair regrowth was observed in 9 patients (67%) after oral zinc gluconate administration<sup>74</sup>.

# **Biological agents:**

Tumour necrosis factor inhibitors such as Adalimumab, Infliximab and Etanercept have been tried in alopecia areata, but the results have not been encouraging<sup>-76</sup>Clinical trials conducted till now have failed to demonstrate the efficacy of any biological agent in alopecia areata.

#### Photo-and photochemotherapy

### Photochemotherapy:

Several uncontrolled studies regarding PUVA therapy for the treatment of alopecia areata exist. All types of PUVA (oral PUVA, topical PUVA, local or whole body UVA irradiation) have been used with success rates of up to 60-65%<sup>57-59</sup>. The mechanism of action is considered to be the interference in the presentation of follicular antigens to T-lymphocytes by depletion of the Langerhan cells. The relapse rate following treatment is high, sometimes demanding repeated treatments for a prolonged period with implications for carcinogenic risks<sup>60</sup>. To mitigate the side effects of systemic psoralens, PUVA-turban therapy is used for alopecia areata involving the scalp. In this form of photochemotherapy, very dilute solutions of 8-methoxy psoralen are applied on the scalp by utilizing a cotton towel as a turban. The patient's scalp is exposed to UVA after keeping the 'turban' in contact with the scalp for about 20 minutesThe efficacy of this form of PUVA therapy has been seen to be about 70%<sup>61</sup>.

### Phototherapy

Although narrowband UVB is among the most effective treatment options in a number of immune mediated skin diseases, the same efficacy has not been found in alopecia areata. Properly designed randomized trials are needed to elucidate whether NBUVB has any role in the management of alopecia areata<sup>62-63</sup>.

### Excimer laser and excimer light

Excimer laser and excimer light are two more recent additions to the phototherapeutic armamentarium for many skin and hair disorders. While the main use of these phototherapeutic modalities remains to be psoriasis and vitiligo, their immunomodulatory effect can be made use of in many other skin disorders. Some clinical studies have documented the efficacy of excimer laser and excimer light in alopecia areata<sup>64-65</sup>. In one such study, 41.5% patches were shown to respond to excimer laser therapy administered over 12 weeks<sup>64</sup>. Another study on childhood alopecia areata found regrowth in 60% lesions after a treatment period of 12 weeksThe treatment is well tolerated with erythema of the skin as the only adverse effect reported.

### Miscellaneous therapies

Various non-conventional therapeutic agents have been used in alopecia areata with some degrees of success. These include fractional Er-Glass laser<sup>77</sup>, topical azelaic acid<sup>78</sup>, topical onion juice<sup>79</sup>, topical 5-fluorouracil ointment<sup>80</sup> and photodynamic therapyThe efficacy and safety of these therapeutic agents need to be confirmed in large-scale, double-blind, placebo-controlled trials before they can be recommended for treatment of alopecia areata.

### Non-pharmacological methods

Cosmetic treatments for patients with alopecia areata include the following:

a) Dermatography: It has been used to camouflage eyebrows of patients with alopecia areata. In this treatment tiny pigment dots of pigment are used on the skin on the region of the eyebrows to mask the underlying alopecia<sup>81</sup>.

b) Wigs or Hair pieces: These are useful for patients with extensive disease and allow them to carry on their usual social life.

#### Conclusion:

Alopecia areata is now regarded as an autoimmune disease involving the cellular immunity through the CD8 lymphocytes that act on follicular antigens. The pathogenesis of alopecia areata is being unravelled with various animal and human studies.

The localized forms often heal spontaneously or respond to simple treatments such as topical or intralesional corticosteroids. The severe forms have a reserved prognosis and are difficult to treat. In these cases the best results are achieved by topical immunotherapy technique.

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**Competing Interests** 

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