



## RESENT TREATMENT OF ALOPECIA AREATA

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### ABSTRACT

Alopecia areata (AA) is a non-scarring and autoimmune hair disease which affects hair on the scalp and/or other parts of the body. The AA occurs in people of all ages and affects 1–2% of humans. Etiology and pathogenesis are still unknown. The purpose of this paper is to present the recent knowledge on the treatment of AA. Treatment depends on the type of hair loss, extent of changes, general health status, the patient's age, and his/her motivation. Treatment methods should be chosen individually for each patient.

**Keywords:** alopecia areata, topical steroid, minoxidil, stem cell therapy, prostaglandin, biologic agents.

## INTRODUCTION

Alopecia areata (AA) is a disease involving non-scarring hair loss determined by autoimmune disorders and inflammation. Different types of AA include[1, 2]:1. alopecia areata focalis – hair loss occurs in patches on the scalp or on other parts of the body (e.g. face, abdomen, extremities), 2. alopecia areata totalis – the loss of all hair on the scalp (including eyebrows and eyelashes),3. alopecia areata universalis – the loss of all or almost all body hair,4. alopecia maligna – is a generalized long-term loss of hair, resistant to treatment, 5.ophiasis or alopecia areata marginata – snake-shaped hair loss around the circumference of the head in the temporal, occipital and frontal areas, 6.ophiasis inversus – the inverse pattern of hair loss, which expands from the central to the marginal area of the head,7. alopecia areata reticularis – diffuse or reticular hair loss where no separate bald patches can be distinguished. Histopathology is characterized by an increased number of telogen follicles and presence of inflammatory lymphocytic infiltrate in the peribulbar region. Nails are affected in about 7–60% of patients[3]. Poor prognostic factors include bald patches persisting for more than 1 year, aggravation or onset of hair loss before puberty, positive family history of AA, ophiasis pattern of involvement, associated nail changes, atopy, and Down syndrome [1].

### Diagnosis:

Alopecia areata is diagnosed based on trichoscopy, the hair pull test and trichogram. Histopathological examination can be carried out if diagnosis is uncertain. Trichoscopy is a modern method and is very useful in the monitoring of treatment for AA and the evaluation of its efficacy. This is a non-invasive, easy to use and painless test, which enables the objective assessment of disease activity. Trichoscopy analyzes[4] the structure and size of growing hair shafts, providing diagnostic clues for inherited and acquired causes of hair loss. Types of hair shaft abnormalities observed include exclamation mark hairs (alopecia areata, trichotillomania, chemotherapy-induced alopecia), Pohl-Pinkus constrictions (alopecia areata, chemotherapy-induced alopecia, blood loss, malnutrition), comma hairs (tinea capitis), corkscrew hairs (tinea capitis), coiled hairs (trichotillomania), flame hairs (trichotillomania), and tulip hairs (in trichotillomania, alopecia areata). Patients need no hair shaving or dying, images can be recorded, and the only requirement is the considerable experience of the operator.

### Treatment:

Because the etiology of AA remains unknown, the treatment is symptomatic and does not prevent disease relapse. The efficacy of many treatment methods has been questioned by many scientific authorities' due to the lack of reliable clinical studies. Treatment methods should be chosen individually for each patient. Selection of a therapy for a patient with alopecia areata (AA) is frequently based on the age of the patient, disease extent, perhaps disease duration, patient expectations, cost of therapy in terms of time commitment, and financial resources, as well as the results of screening laboratory studies that rule out the presence of

other co-morbidities such as anemia, low iron stores, thyroid abnormalities, low vitamin D, or other autoimmune diseases. Although there is currently no cure for AA and no universally proven therapy that induces and sustains remission, many therapies are available which can be of benefit to both affected children and adults as describe in table 1.

Table 1. Treatments for alopecia areata [5, 6]

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**1.Corticosteroids**

Topical

Intralesional

Pulsed methylprednisolone

Oral

**2.Topical minoxidil**

**3.Topical immunotherapy**

DPCP (Diphencyprone)

SADBE (Squaric Acid Dibutylester)

**4.Anthralin**

**5.Phototherapy**

Psoralen plus UVA light

Narrow-band UVB light

Laser therapy—excimer laser/fractional photothermolysis laser

Photodynamic therapy

**6. Immunosuppressive agents**

Methotrexate

Cyclosporine

**7. Prostaglandin analogues**

**8. Biologics**

**9. JAK inhibitors**

### **Corticosteroid:**

Corticosteroid therapies can include intralesional injections or topical application.

### **Intralesional steroids:**

They are used widely in the treatment of alopecia areata. Intralesional steroids are the first-line treatment in localized conditions and are usually superior to topical corticosteroids[7]. In a study including 85 patients[8], regrowth on treated areas was present in 92% of patients with patchy alopecia areata and 61% of patients with alopecia totalis. Regrowth persisted 3 months after treatment in 71% and 28% of patients respectively. Regrowth usually is seen within 4-6 weeks in responsive patients. Patients with rapidly progressive, extensive, or long-standing alopecia areata tend to respond poorly. Hair growth may persist for 6-9 months after a single injection. Injections are administered intradermal using a 3-mL syringe and a 30-gauge needle[8]. Triamcinolone acetonide is commonly used drug; concentrations vary from 2.5-10 mg/ml[9]. The lowest concentration is used on the face. A 2015 study showed no difference in regrowth when using 2.5 mg/mL, 5 mg/mL, or 10 mg/mL and all were superior to placebo. The lowest concentration should always be used on the face to avoid skin atrophy. Caution should be used in patients with glaucoma when treating the eyebrows. Adverse effects mostly include pain during injection and minimal transient atrophy (10%). Although intralesional injections of triamcinolone acetonide are usually recommended for alopecia areata with less than 50% involvement, a report showed that 6 of 10 patients had regrowth[10]. Although injections may work in extensive alopecia areata, results are unlikely if no response is observed at 6 months.

### **Topical steroids:**

They are useful, especially in children [11] who cannot tolerate injections. Such as Fluocinonide acetonide cream 0.2% twice per day induced a satisfactory-to-excellent response in patients.

Betamethasone dipropionate cream 0.05% (Diprosone) showed similar efficacy[12]. A 2005 study by Tosti et al in patients with alopecia totalis or alopecia universalis showed that the use of 2.5 g of clobetasol

propionate under occlusion with a plastic film 6 d/week for 6 months induced regrowth in 8 (28.5%) of 28 patients. Regrowth was seen 6-14 weeks after the onset of therapy. Regrowth was maintained for at least 6 months after cessation of therapy in 5 (62.5%) of 8 patients. Even though only 17.8% of patients showed long-term benefits from that treatment, it should be kept in mind that the study was performed in a subgroup of patients that is usually refractory to treatment. Treatment must be continued for a minimum of 3 months before regrowth can be expected, and maintenance therapy often is necessary. The most common adverse effect is local folliculitis, telangiectasia and local atrophy[9].

### **Immunotherapy:**

It is defined as the induction and periodic elicitation of an allergic contact dermatitis by topical application of potent contact allergens[13]. The mechanism of action of topical immunotherapy is unknown. Antigenic competition has been hypothesized. That is, the introduction of a second antigen can initiate a new infiltrate containing T-suppressor cells and suppressor macrophages that may modify the preexisting infiltrate and allow regrowth. Commonly used agents for immunotherapy include squaric acid dibutylester (SADBE) and diphencyprone (DPCP)[14]. These are compounded investigational agents not approved by the US Food and Drug Administration for use in alopecia[15]. The most common side effect, which is desired, is a mild contact dermatitis (redness, scaling, itching). Adverse effects include cervical lymphadenopathy and pigment changes[16].

### **Anthralin:**

Anthralin is a synthetic tarlike compound that has been used in the treatment of AA for many years. The mechanism of action of anthralin is unknown. Most likely, it creates inflammation by generating free radicals, which have antiproliferative and immunosuppressive actions. Anthralin concentrations varied from 0.2-1%. The treatment can be used in both adults and children[11]. While evidence is limited, small studies demonstrate adequate results in 25% to 75% of patients depending on the severity of involvement[17]. When prescribing anthralin, we begin with daily administration of a topical formulation of 1% or 2% anthralin, applied for 10 to 15 minutes before being washed off with shampoo. Patients increase the total application time weekly until a constant low-grade irritation is produced. Some individuals might need to increase their treatment time such that they apply the anthralin before going to bed and then wash it off upon waking in the morning. It is important to warn patients that the purple color of anthralin might cause discoloration and staining of bed sheets, towels, and the bathtub. Adverse effects include pruritus, erythema, scaling folliculitis, local pyoderma, and regional lymphadenopathy[18].

### **Minoxidil:**

Minoxidil appears to be effective in the treatment of alopecia areata in patients with extensive disease (50-99% hair loss). Response rates in that group vary from 8-45%. Minoxidil was of little benefit in patients with alopecia totalis or alopecia universalis[19]. The 5% solution are applied twice per day in the

affected area appears to be more effective. Initial regrowth can be seen within 12 weeks, but continued application is needed to achieve cosmetically acceptable regrowth. Minoxidil usually is well tolerated. Adverse effects include distant hypertrichosis (5%) and irritation (7%)[3].

### **Prostaglandin Analogs:**

Retrospective studies using either latanoprost or bimatoprost showed some regrowth of the eyelids while using intralesional triamcinolone concomitantly on the scalp and eyebrows[20], but all prospective studies using either drugs did not show statistically significant changes when used to treat either the eyelids or eyebrows[21].

### **Systemic Treatments:**

#### **Psoralen Plus Uv-A:**

Many studies have been performed regarding the efficacy of psoralen plus UV-A (PUVA) in the treatment of alopecia areata, and the initial response rate varies from 20-73%[22]. The relapse rate, unfortunately, is high (50-88%). Most patients relapse within a few months (mean 4-8 months) after treatment is stopped. Both systemic and topical PUVA therapies have been used. A younger age at onset, a longer duration of disease, and the presence of alopecia totalis or alopecia universalis appear to indicate a poorer outcome. In one of the study 9 patients[23] were treated with severe, rapidly progressing, treatment-resistant alopecia areata with PUVA-turban treatment as a modification of bath-PUVA therapy. At each treatment session, a cotton towel was soaked with a 0.0001% 8-MOP solution (1 mg/L) at 37 degrees C, wrung gently to remove excess water, and wrapped around the patient's head in a turban fashion for 20 minutes. This was directly followed by UVA radiation. Treatment sessions were initially performed 3 to 4 times per week upto 24 weeks. After up to 10 weeks of treatment, hair regrowth could be noticed in 6 of 9 patients. Two patients did not respond to the treatment, and one patient showed only vellus hair regrowth. PUVA-turban therapy can be considered a useful method of administering a dilute psoralen solution selectively to the scalp of patients. It has been shown to be a well-tolerated and, in some patients, efficient therapeutic alternative in the treatment of alopecia areata.

#### **Prednisolone:**

The use of systemic steroids for the treatment of alopecia areata is sometimes justifiable, but hair loss frequently follows discontinuation of the medication and benefits must be carefully weighed against long-term risks. Some authors support a beneficial role of systemic steroids in halting the progression of alopecia areata[24], but many others have had poor results with this form of therapy.

The rate of regrowth varies greatly (27-89%), and many dose regimens have been used in these studies. Although the initial regrowth appears promising, the prednisone dose necessary to maintain cosmetic growth usually must be high enough that adverse effects are inevitable, and most patients relapse

after therapy is discontinued. Adverse effects from systemic therapy were common in these reports and included diabetes, weight gain, hypertension, psychological changes, osteoporosis, suppression of the adrenocorticotrophic axes, striae, acne, hypertrichosis, and purpura[25]. Systemic steroids most likely are effective via their immunosuppressive effects. Systemic prednisone is not an agent of choice for alopecia areata because of the adverse effects associated with both short- and long-term treatment. Methylprednisolone[6] administered at a dose of 500 mg/day for 3 days or 5 mg/kg twice a day over 3 days has been used in patients with widespread disease causing severe emotional distress. Risks and benefits of systemic steroid therapy must be weighed carefully. Predictors of response include disease duration of 6 months or less, age younger than 10 years at disease onset, and multifocal disease.

### **Cyclosporine:**

Cyclosporine has been used both topically and systemically in the treatment of alopecia areata[26]. The mechanism of action of cyclosporine remains unclear. It may act through its immunosuppressive effect, because, in patients who regrew hair, clearance of immune cells from the hair follicles and alteration in the balance of regulatory lymphocytes occurred (ie, decrease of the CD4/CD8 ratio). Cyclosporine causes hypertrichosis in patients treated for conditions unrelated to hair loss. In conclusion, topical cyclosporine has shown limited efficacy.

### **Methotrexate:**

Methotrexate is an immunosuppressant used in various dermatoses and recently introduced as a therapeutic option for alopecia areata[27]. In a retrospective[28], non-controlled study, 31 patients with alopecia areata were treated with methotrexate to assess the therapeutic response according to sex, age, pattern of alopecia areata, disease duration, cumulative dose of methotrexate, use of systemic corticosteroids or other treatments, and drug safety. Regrowth greater than 50% was observed in 67.7% of patients, with the best responses observed in those with <5 years of disease progression (79%), age over 40 years (73.3%), male patients (72.8%), cumulative dose of methotrexate 1000-1500 mg, and multifocal alopecia areata (93%). Among patients receiving systemic corticosteroids in combination with methotrexate, 77.3% had greater than 50% regrowth, compared with 44.4% in those who used methotrexate alone. The therapeutic dose ranged from 10-25 mg/week. No patient had serious adverse effects. Relapse was observed in 33.3% of patients with more than 50% regrowth. Methotrexate appears to be a promising and safe medication for the treatment of severe alopecia areata when used alone or in combination with corticosteroids.

### **Biological Agents:**

In the last few years, several biologic agents acting on tumor necrosis factor (TNF)  $\alpha$  and intercellular adhesion molecule [29] have been considered as possible treatments for alopecia areata (AA), despite clinical

trials of some biologic agents such as etanercept, efalizumab, infliximab and alefacept showing no significant hair regrowth in AA. However, new agents inhibiting interleukin-6, interferon gamma, and several co-stimulatory pathways are entering clinical phase I and II trials and may also be available in a few years. New biologic drugs[30] under development include Abatacept, Anakinra, Rituximab, Humeira, and Fontolizumab among others. Animal model research suggests that of biologics under development, CTLA4Ig (Abatacept) and perhaps anti-IFN $\gamma$  (fontolizumab) may have the most potential as an effective treatment for alopecia areata.

### **Jak Inhibitors:**

Have a significant body of data supporting their efficacy. Janus kinase-signal transducer and activator of transcription (JAK-STAT) [31] is an intracellular signaling pathway upon which many different proinflammatory signaling pathways converge. Numerous inflammatory dermatoses are driven by soluble inflammatory mediators, which rely on JAK-STAT signaling, and inhibition of this pathway using JAK inhibitors might be a useful therapeutic strategy for alopecia areata. Growing evidence suggests that JAK inhibitors are efficacious in atopic dermatitis, alopecia areata, psoriasis, and vitiligo. Additional evidence suggests that JAK inhibition might be broadly useful in dermatology, with early reports of efficacy in several other conditions. JAK inhibitors can be administered orally or used topically and represent a promising new class of medications. Oral alitretinoin shows some promise[32].

### **Stem Cell Therapy:**

Mesoderm-derived stem cells are promising as a potential treatment option. Clinical data[33] demonstrated that patients with severe AA achieved improved hair regrowth and quality of life after receiving Stem Cell Educator therapy. Flow cytometry revealed the up-regulation of Th2 cytokines and restoration of balancing Th1/Th2/Th3 cytokine production in the peripheral blood of AA subjects. Immunohistochemistry indicated the formation of a "ring of transforming growth factor beta 1 (TGF- $\beta$ 1)" around the hair follicles, leading to the restoration of immune privilege of hair follicles and the protection of newly generated hair follicles against autoimmune destruction[34]. Mechanistic studies revealed that co-culture with CB-SC may up-regulate the expression of coinhibitory molecules B and T lymphocyte attenuator (BTLA) and programmed death-1 receptor (PD-1) on CD8 $\beta$  (+) ,natural killer group {2D NKG2D (+)} effector T cells and suppress their proliferation via herpesvirus entry mediator (HVEM) ligands and programmed death-1 ligand (PD-L1) on CB-SCs.

### **Zinc:**

One study showed a correlation between low serum zinc levels and disease severity, as well as duration and resistance to therapies[35] and a few reports show some benefit to using zinc gluconate (30-50



mg/day) in the treatment of alopecia areata[36].However, another study did not find a statistically significant difference in zinc concentration in serum and hair between alopecia areata patients and controls[1].

## CONCLUSION

Numerous treatments are available for Alopecia areata as discussed above. Future treatment approaches for alopecia areata include use of drugs that: (i) block the natural killer group D (NKGD-activating ligand) and NKG2D receptor interaction, (ii) halt activated T cells, or (iii) modification of the inflammatory cytokine network. The new clinical and translational research observations and clinical trials with the Jak inhibitors and IL- 2 have excited the clinical and Alopecia areata patient communities and all look forward to moving from the trials and off-label use to focused use of these medications either orally, systemically, or topically in a coordinated, cost effective, safe manner in both children and adults. Many drugs currently being used or being evaluated for other autoimmune diseases that work through these mechanisms might prove to be very effective in alopecia areata.

### Conflict of Interest:

There are no conflicts of interest.

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