

# **General Overview of Management of Alopecia Areata**

**MansorEmhammed Ahmed Algowil , Abdalla Hasan Kandel , Khaled Mohamed Gharib**

Dermatology, Venereology and Andrology Department, Faculty of Medicine, Zagazig University, Egypt

**Corresponding Author:** MansorEmhammed Ahmed Algowil

**Email:** Mans7madrid@gmail.com

## **Abstract**

Although the exact etiology of alopecia areata is unknown, it is accepted that it is an organ-specific autoimmune disease in a genetically predisposed individuals, which is triggered by different environmental factors like emotional stress, anemia, parasitic infestations, and thyroid disorders. Alopecia areata (AA), an autoimmune condition, characterized by a chronic remitting-relapsing course of patchy hair loss, affects approximately 2.1% of the population. It typically presents with sharply demarcated round patches of hair loss and may present at any age, AA is the second-most frequent non-scarring alopecia, after male and female pattern alopecia

**Keywords:** Alopecia Areata

## **Introduction**

Historically, numerous hypotheses on the causes of AA have been proposed, such as infection, a trophoneurotic hypothesis (based on the association between the time of onset of AA and emotional or physical stress and/or trauma), thallium acetate poisoning (owing to a similar clinical presentation), thyroid disease and hormonal fluctuations (for example, in pregnancy or menopause) (1).

Inflammation of the hair follicles in AA mediated by leukocytes was described over a century ago; yet the involvement of the immune system in the pathogenesis of AA has only been recognized as the primary underlying cause since the late 1950s, when several immune-related and several key pathogenetic effector cells were identified (2).

The formation of the National Alopecia Areata Registry in the United States in 2000 provided access to data and clinical samples from >10,000 patients (3). The registry enabled the application of genome-wide association studies (GWAS) that have identified candidate genes associated with susceptibility to AA (4), as well as an evaluation of important epidemiological and socio-medical issues, such as quality of life (QOL) (5).

## **EPIDEMIOLOGY**

AA is an autoimmune condition that attacks the hair follicles, causing non-scarring hair loss. Population studies from the Rochester Epidemiology Project estimate a lifetime incidence of AA of 2.1%, in a population, with no difference in incidence between genders (6).

### ***Incidence and prevalence***

AA affects approximately 2% of the general population at some point during their lifetime, as documented by several large epidemiological studies from Europe, North America and Asia. The prevalence of AA in the early 1970s was reported to be between 0.1% and 0.2%, with a lifetime incidence of 1.7% (1).

## **ETIOLOGY AND RISK FACTORS**

A high degree of phenotypic and genotypic variability is observed in AA, which is a complex genetic disease determined by genetic and environmental factors. The reported prevalence, age of onset, history and concurrent diseases vary widely (1).

### **Genetic factors**

Several lines of evidence support the notion that AA has a genetic basis. In general, the prevalence of adult patients with a family history is estimated to be between 0% and 8.6% (7), whereas, in children, the data have been reported between 10% and 51.6% (8). One study found that men were more likely to have a positive family history and is diagnosed at an earlier age than women (9).

### **Concurrent diseases**

AA is associated with several concurrent diseases (comorbidities) including depression, anxiety and several autoimmune diseases, such as thyroid disease (hyperthyroidism, hypothyroidism, goitre and thyroiditis), lupus erythematosus, vitiligo, psoriasis, rheumatoid arthritis and inflammatory bowel disease (10; 11).

## **MECHANISMS/PATHOPHYSIOLOGY**

### **Genetics**

Studies aimed at elucidating the complex genetics of AA have been undertaken by several groups using techniques ranging from candidate gene association studies to transcriptional profiling of affected skin to large GWAS.

The initial genetic studies concentrated on single genes that were known to be involved in related autoimmune diseases. Interestingly, many of these genes did in fact have a role in AA, in addition to inflammatory bowel disease, multiple sclerosis, psoriasis and type 1 diabetes mellitus (4).

Owing to the focus on an autoimmune etiology, the HLA region, which encodes MHC molecules in humans, was initially identified as a major contributor to the AA phenotype (12).

### **DIAGNOSIS**

The diagnosis is typically clinical and may be aided by findings such as a positive hair pull test or trichoscopy. On trichoscopy, active disease is characterized by yellow dots, black dots, “exclamation mark” or tapering hairs, and broken hairs. Vellus hair in lesions is another marker of AA and may indicate late or inactive disease (13). Biopsy may be taken in uncertain cases (14).

### **Clinical Features**

AA typically presents as smooth, sharply demarcated, round patches of hair loss without atrophy with “exclamation point hairs” observed on the periphery of the patches (15).

Special designations of the disease include alopecia universalis (AU) (total body hair loss), alopecia totalis (AT) (total scalp hair loss), or alopecia in an ophiasis pattern (band-like hair loss on the temporal and occipital scalp) (15).

### **PROGNOSIS**

The prognosis of the disease is unpredictable. Current data suggest 34%–50% of patients recover within 1 year, while 14%–25% of patients will progress to AT or AU, at which point patients rarely fully recover (16).

In a retrospective chart review in patients with AU/AT for 10 years, it was found that 12 out of 70 patients with AT/AU (17.1%) had complete hair regrowth. Seventeen out of 70 patients with AT/AU (24.2%) reported hair regrowth  $\geq 90\%$ . Thirty patients with AU (65.2%) had no improvement, and five patients with AT (20.8%) showed no hair regrowth (17).

### **TREATMENT**

#### **Low-level light therapy**

Low-level light therapy (LLLT) has primarily been used for androgenic alopecia, but there are some studies examining its use for AA. The HairmaxLasercomb<sup>®</sup> (Boca Raton, Florida, USA) was used to treat heat-induced AA in C3H/HeJ mice. At the end of the trial, the laser-treated mice had increased hair regrowth and increased hair follicles in the anagen phase on histology in comparison to the sham control (18).

However, in a similar study done by King et al. (19) with spontaneous or graft-induced AA in C3H/HeJ mice, there was no increase in hair regrowth. They postulate this may be due to a difference between heat-induced AA and spontaneous AA.

In a solitary trial with a pulsed infrared diode 904 nm laser, 32 of 34 treated patches demonstrated hair regrowth without any adverse events (20). However, this pulsed laser treatment may affect the body differently than the more constant light of traditional LLLT devices such as the HairmaxLasercomb<sup>®</sup>.

#### **Abatacept**

Sundberg et al. (21) suggested CTLA-4 is a receptor present in the surface of immune cells that through its signaling pathways is believed to be a critical regulator of AA onset and maintenance. Sundberg et al. (21) performed a comparative human gene array to identify dysregulated genes in AA.

One of the genes studied was CTLA-4, a co-stimulatory T-cell ligand that binds B7.1 (CD80) and B7.2 (CD86) on antigen-presenting cells (21).

Abatacept, a monoclonal antibody directed against this receptor, effectively prevented the onset of AA in a mouse model (22; 23). However, John et al. (24) defined CTLA-4 as a major candidate gene for AA susceptibility in humans.

Abatacept as an immunosuppressive drug is used to treat many rheumatologic treatments and acts on the CTLA-4 pathway (25). Due to many adverse effects, it should be used cautiously.

#### **JAK inhibitors**

JAK inhibitors have been approved to treat diseases such as rheumatoid arthritis and myelofibrosis. Oral and topical JAK inhibitor treatments have both prevented and reversed AA in mouse models. It is thought that JAK inhibitors act by preventing the upregulation of IFN- $\gamma$  that is necessary for the immune response of AA (2).

No randomized controlled studies have been completed yet, but there have been several case series and reports demonstrating hair regrowth in patients with AA and AU (26). Many clinical trials are ongoing involving JAK inhibitors such as ruxolitinib, tofacitinib, and baricitinib.

#### **Platelet-rich plasma**

Platelet-rich plasma (PRP) is thought to initiate wound healing through secretion of various growth factors and cytokines. It has recently been used to treat AA. In mice, PRP has been shown to prolong the anagen phase through increases in B-catenin and fibroblast growth factor-7 and also has an antiapoptotic effect on dermal papilla cells (27).

In randomized studies, PRP demonstrated significantly improved hair regrowth compared to placebo and triamcinolone scalp injections without any noted adverse events (28). However, in another trial in chronic severe AA, there was a variable effect with PRP treatment (29). A recent trial comparing PRP, topical minoxidil, and placebo showed both significantly increased hair regrowth with PRP compared to placebo and significantly earlier response than topical minoxidil (30). More randomized studies will be necessary to determine the comparable efficacy of this treatment to standard therapy.

#### **Statins**

Statins have anti-inflammatory and immunomodulatory effects that may improve hair regrowth (31). Statins are theorized to affect hair regrowth by inhibiting STAT phosphorylation that activates several important inflammatory cytokines and also by altering the balance of Th1/Th2, suppressing IL-17, decreasing mast cell degranulation, and inhibiting lymphocyte migration (32).

#### **Vitamin A**

Immune cells are highly responsive to oxidative damage (33). Provitamin A and  $\beta$ -carotene have well-known antioxidant properties, and vitamin A itself has physiologic roles in immune modulation (34).

#### **Valproic acid**

Valproic acid (VPA) is a mood stabilizer. VPA affects signaling pathways including protein kinase C, extracellular signal-regulated kinase, and Wnt/ $\beta$ -catenin pathways (35).

Lee et al. (36) performed topical application of VPA to male C3H mice and found that it stimulated hair regrowth and induced terminally differentiated epidermal markers such as filaggrin and loricrin, and the dermal papilla marker alkaline phosphatase. More research has to be done to prove its effectiveness in humans.

#### **Microneedling**

Microneedling is a new procedure performed by superficial puncturing of the skin by rolling with miniature needles. Traditionally, it has been used as a collagen induction therapy for scars and skin rejuvenation; and as a transdermal delivery system for therapeutic drugs and vaccines (37) and previously in androgenic alopecia (38).

#### **Electroacupuncture**

Electroacupuncture (EA) involves insertion of needles into the skin and underlying tissues at acupuncture points with pulsating electrical current. Evidence has indicated that EA stimulation may enhance immune function in several animal models of inflammatory diseases (39).

#### **References.**

1. Pratt CH, King LE, Messenger AG, et al. (2017). Alopecia areata. *Nature Reviews Disease Primers*.3: 17011.
2. Xing L, Dai Z, Jabbari A, Cerise JE, Higgins CA, Gong W, et al. (2014). Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. *Nat Med*. 20:1043–1049.
3. Duvic M, Christiano AM, Hordinsky MK, et al. (2013). The National Alopecia Areata Registry — update. *J. Investig. Dermatol. Symp. Proc*. 16: S53.
4. PetukhovaL, Duvic M, Hordinsky M, et al. (2010). Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature*. 466: 113–117.
5. Shi Q, Duvic M, Osei JS, et al. (2013). Health-related quality of life (HRQoL) in alopecia areata patients — a secondary analysis of the National Alopecia Areata Registry data. *J. Investig. Dermatol. Symp. Proc*. 16: S49–S50.

6. **Mirzoyev SA, Schrum AG, Davis MD, et al. (2014).** Lifetime incidence risk of alopecia areata estimated at 2.1% by Rochester Epidemiology Project, 1990–2009. *J. Invest. Dermatol.* 134: 1141–1142.
7. **Guzmán-Sánchez DA, Villanueva-Quintero GD, Alfaro N, et al. (2007).** A clinical study of alopecia areata in Mexico. *Int. J. Dermatol.* 46: 1308–1310.
8. **Rocha J, Ventura F, Vieira AP, et al. (2011).** Alopecia areata: a retrospective study of the paediatric dermatology department (2000–2008). *Acta Med. Port.* 24: 207–214.
9. **Lundin M, Chawa S, Sachdev A, et al. (2014).** Gender differences in alopecia areata. *J Drugs Dermatol.* 13:409–13.
10. **Chu SY, Chen YJ, Tseng WC, et al. (2011).** Comorbidity profiles among patients with alopecia areata: the importance of onset age, a nationwide population-based study. *J. Am. Acad. Dermatol.* 65: 949–956.
11. **Fricke ACV, and Miteva M. (2015).** Epidemiology and burden of alopecia areata: a systematic review. *Clin. Cosmet. Investig. Dermatol.* 8: 397–403.
12. **Hordinsky MK. (2013).** Overview of alopecia areata. *J Investig Dermatol Symp Proc.* 16:13–15.
13. **Mubki T, Rudnicka L, Olszewska M, et al. (2014).** Evaluation and diagnosis of the hair loss patient: Part II. Trichoscopic and laboratory evaluations. *J Am Acad Dermatol.* 71:431.e1–431.e11.
14. **Darwin E, Hirt PA, Fertig R, et al. (2018).** Alopecia Areata: Review of Epidemiology, Clinical Features, Pathogenesis, and New Treatment Options. *Int J Trichology.* 10(2): 51–60.
15. **Alkhalifah A. (2013).** Alopecia areata update. *Dermatol Clin.* 31:93–108.
16. **Tosti A, Bellavista S, and Iorizzo M. (2006).** Alopecia areata: a long-term follow-up study of 191 patients. *J. Am. Acad. Dermatol.* 55: 438–441.
17. **Jang YH, Hong NS, Moon SY, et al. (2017).** Long-term prognosis of alopecia totalis and alopecia universalis: A Longitudinal study with more than 10 years of follow-up: Better than reported. *Dermatology.* 233:250–6.
18. **Wikramanayake TC, Rodriguez R, Choudhary S, Mauro LM, Nouri K, Schachner LA, et al. (2012a).** Effects of the lexingtonLaserComb on hair regrowth in the C3H/HeJ mouse model of alopecia areata. *Lasers Med Sci.* 27:431–436.
19. **King LE, Jr, Silva KA, Kennedy VE, Sundberg JP. (2014).** Lack of response to laser comb in spontaneous and graft-induced alopecia areata in C3H/HeJ mice. *J Invest Dermatol.* 134:264–6.
20. **Waiz M, Saleh AZ, Hayani R, Jubory SO (2006).** Use of the pulsed infrared diode laser (904 nm) in the treatment of alopecia areata. *J Cosmet Laser Ther.* 8: 27-30.
21. **Sundberg JP, McElwee KJ, Carroll JM, King LE. (2011).** Hypothesis testing: CTLA4 co-stimulatory pathways critical in the pathogenesis of human and mouse alopecia areata. *J Invest Dermatol.* 131:2323–2324.
22. **Carroll JM, McElwee KJ, King LE, Byrne MC, Sundberg JP. (2002).** Gene array profiling and immunomodulation studies define a cell-mediated immune response underlying the pathogenesis of alopecia areata in a mouse model and humans. *J Invest Dermatol.* 119:392–402.

23. Sun J, Silva KA, McElwee KJ, King LE, Jr, Sundberg JP. (2008). The C3H/HeJ mouse and DEBR rat models for alopecia areata: Review of preclinical drug screening approaches and results. *Exp Dermatol.* 17:793–805.
24. John KK, Brockschmidt FF, Redler S, Herold C, Hanneken S, Eigelshoven S, et al. (2011). Genetic variants in CTLA4 are strongly associated with alopecia areata. *J Invest Dermatol.* 131:1169–72.
25. Keating GM. (2013). Abatacept: A review of its use in the management of rheumatoid arthritis. *Drugs.* 73:1095–119.
26. Anzengruber F, Maul JT, Kamarachev J, Trüeb RM, French LE, Navarini AA, et al. (2016). Transient efficacy of tofacitinib in alopecia areata universalis. *Case Rep Dermatol.* 8:102–6
27. Li ZJ, Choi HI, Choi DK, Sohn KC, Im M, Seo YJ, et al. (2012). Autologous platelet-rich plasma: A potential therapeutic tool for promoting hair growth. *Dermatol Surg.* 38:1040–6.
28. Trink A, Sorbellini E, Bezzola P, Rodella L, Rezzani R, Ramot Y, et al. (2013). A randomized, double-blind, placebo- and active-controlled, half-head study to evaluate the effects of platelet-rich plasma on alopecia areata. *Br J Dermatol.* 169:690–694.
29. d'Ovidio R, and Roberto M. (2014). Limited effectiveness of platelet-rich-plasma treatment on chronic severe alopecia areata. *Hair Ther Transplant.* 2014:4.
30. El Taieb MA, Ibrahim H, Nada EA, Seif Al-Din M. (2017). Platelets rich plasma versus minoxidil 5% in treatment of alopecia areata: A trichoscopic evaluation. *Dermatologic therapy.* 30:1.
31. Lattouf C, Jimenez JJ, Tosti A, Miteva M, Wikramanayake TC, Kittles C, et al. (2015). Treatment of alopecia areata with simvastatin/ezetimibe. *J Am Acad Dermatol.* 72:359–61.
32. Egesi A, Sun G, Khachemoune A, Rashid RM. (2010). Statins in skin: Research and rediscovery, from psoriasis to sclerosis. *J Drugs Dermatol.* 9:921–7.
33. Thompson JM, Mirza MA, Park MK, Qureshi AA, Cho E. (2017). The role of micronutrients in alopecia areata: A review. *Am J Clin Dermatol.* 18:663–679.
34. Holler PD, and Cotsarelis G. (2013). Retinoids putting the “a” in alopecia. *J Invest Dermatol.* 133:285–6.
35. Gould TD, Chen G, and Manji HK. (2004). *In vivo* evidence in the brain for lithium inhibition of glycogen synthase kinase 3. *Neuropsychopharmacology.* 29 :32–8.
36. Lee WR, Shen SC, Aljuffali IA, Li YC, Fang JY. (2014). Erbium-yttrium-aluminum-garnet laser irradiation ameliorates skin permeation and follicular delivery of antialopecia drugs. *J Pharm Sci.* 103: 3542-52.
37. Singh A, and Yadav S. (2016). Microneedling: Advances and widening horizons. *Indian Dermatol Online J.* 7:244–54.
38. Dhurat R, Sukesh M, Avhad G, Dandale A, Pal A, Pund P, et al. (2013). A randomized evaluator blinded study of effect of microneedling in androgenetic alopecia: A pilot study. *Int J Trichology.* 5:6–11.
39. Maeda T, Taniguchi M, Matsuzaki S, Shingaki K, Kanazawa S, Miyata S, et al. (2013). Anti-inflammatory effect of electroacupuncture in the C3H/HeJ mouse model of alopecia areata. *Acupunct Med.* 2013; 31:117–9.