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Alopecia Areata: Review of Epidemiology, Clinical Features, Pathogenesis, and New Treatment Options

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Abstract

Alopecia areata (AA) is a complex autoimmune condition that causes nonscarring hair loss. It typically presents with sharply demarcated round patches of hair loss and may present at any age. In this article, we review the epidemiology, clinical features, pathogenesis, and new treatment options of AA, with a focus on the immunologic mechanism underlying the treatment. While traditional treatment options such as corticosteroids are moderately effective, a better understanding of the disease pathogenesis may lead to the development of new treatments that are more directed and effective against AA. Sources were gathered from PubMed, Embase, and the Cochrane database using the keywords: alopecia, alopecia areata, hair loss, trichoscopy, treatments, pathogenesis, and epidemiology.

Key words: Alopecia, alopecia areata, alopecia totalis, alopecia universalis, hair loss

METHODS

Articles were gathered from PubMed, Cochrane Reviews, and Embase using the following keywords: Alopecia, alopecia areata, hair loss, trichoscopy, treatments, epidemiology, and pathogenesis. Articles were selected for their relevance and innovative perspective related to the epidemiology, clinical features, pathogenesis, and treatment of alopecia areata (AA).

EPIDEMIOLOGY

AA is an autoimmune condition that attacks the hair follicles, causing nonscarring hair loss. Population studies from the Rochester Epidemiology Project estimate a lifetime incidence of AA of 2.1%, in a population in Olmsted County, Minnesota, with no difference in incidence between genders.[1] A systemic review of the epidemiology of AA indicated a similar worldwide lifetime incidence of around 2%.[2] Some smaller studies indicate a slight female-to-male gender bias, but this may be due to higher female concern regarding hair loss and subsequent treatment.[3] The disorder can occur at any age and the lifetime incidence appears to increase at an almost linear rate.[1] The median age at diagnosis is 33.[1] Male patients may be more likely to be diagnosed in childhood, while females are more likely to present in adolescence and have greater concomitant nail involvement or concomitant autoimmune diseases.[3]

CLINICAL FEATURES

AA typically presents as smooth, sharply demarcated, round patches of hair loss without atrophy [Figure 1] with "exclamation point hairs" [Figure 2] observed on the periphery of the patches.[4] Special designations of the disease include alopecia universalis (AU) (total body hair loss), alopecia totalis (AT) (total scalp hair loss) [Figure 3], or alopecia in an ophiasis pattern (band-like hair loss on the temporal and occipital scalp) [Figure 4].[4] Less common variants include the diffuse variant with widespread thinning of hair across the scalp or the reticular pattern with recurrent hair loss in one area and spontaneous hair regrowth in another.[4] Ophiasis inversus causes band-like hair loss in the frontoparietotemporal area.[4]

Nail abnormalities are associated with the disease with an incidence estimated between 7% and 66%.[5] Most frequently, nail pitting is observed, although AA is also associated with trachyonychia, Beau's lines, onychorrhexis, nail thinning or thickening, onychomadesis, punctate or transverse leukonychia, red spot lunulae, and koilonychias.[4] Other commonly associated conditions are thyroid disease (8%–28%),[6] vitiligo (1.8–16%),[6,7] and atopy (1%–52%).[6]

Other skin conditions that may be confused with AA include traction alopecia, temporal triangular alopecia, androgenic alopecia, trichotillomania, tinea capitis, secondary syphilis, pressure-related alopecia, aplasia cutis, chemotherapy-induced alopecia, telogen effluvium, and the many forms of cicatricial alopecia.[8,9]

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.[10,11] In a retrospective chart review in patients with AU/AT during 10 years, it was found that 12 out of 70 patients with AT/AU (17.1%) had complete hair regrowth.[12] Seventeen out of 70 patients with AT/AU (24.2%) reported hair regrowth ≥90%.[12] Thirty patients with AU (65.2%) had no improvement, and five patients with AT (20.8%) showed no hair regrowth.[12] Patients may have several incidents of hair loss and subsequent regrowth throughout their lives. Family history of AA, young age at onset, nail dystrophy, extensive hair loss, ophiasis, a history of atopy, or the presence of other autoimmune diseases are associated with a poor prognosis.[13]

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.[9,14] Biopsy may be taken in uncertain cases.

HISTOPATHOLOGY

The histopathology of the disease will vary per the disease stage. In the acute and subacute stages, there is a peribulbar lymphocytic infiltrate in a “swarm of bees” pattern composed of CD4+ and CD8+ T-cells around anagen follicles [Figure 5].[15,16] In addition, there is a shift from the catagen hair growth stage to the telogen phase (resting phase), with follicle miniaturization.[15] Edema, microvesiculation, apoptosis, macrophages, and foreign body giant cells may be seen around the hair follicles. In the chronic stage, the inflammation may or may not resolve, but the number of catagen or telogen hairs increases, and there is pigmentary incontinence.[15] In the recovery stage, there is minimal inflammation and anagen hair (actively growing hair) count increases.[16]

PATHOPHYSIOLOGY

The exact pathophysiology of the disease is currently unknown. However, evidence suggests that AA is caused by an autoimmune reaction to the hair follicles due to both genetic and environmental factors.[16] Animal models used for treatment and pathophysiologic mechanisms are summarized in Table 1.

Genetic factors

Observational studies show a high correlation (10%–42%) between AA and family history.[26,27] Genome-wide association studies have identified numerous single-nucleotide polymorphisms (SNPs) associated with AA. In a recent meta-analysis, human leukocyte antigen-DR (HLA-DR) on chromosome 6 appears to be the largest risk factor for AA.[28] These HLA class II genes are highly linked to CD4+ and CD8+ T-cells, which are important effector cells in AA.[28] In addition, this study implicated BCL2-like protein 11, also known as BIM, which helps to regulate autophagy in the disease pathogenesis.[28] Genes encoding for natural killer cell receptor D ligands and downstream effectors of the JAK pathway also influence AA susceptibility.[29,30] Other implicated pathways include T-regulatory cells (Tregs), autophagy, and apoptosis, although more information is needed to determine the exact mechanisms.[28]

Environmental factors

Environmental factors likely exacerbate or induce AA. Stress is an often-cited cause of AA, but the literature from human studies is inconclusive.[31,32,33] However, in a mouse model, the activity of the central and peripheral hypothalamus pituitary adrenal axis was higher compared to normal mice. The elevated adrenocorticotropic hormone, corticosterone, and estradiol correlated to elevated pro-inflammatory cytokine levels in the skin, suggesting a potential role of psychological and physiological stressors to cause AA.[34] Other potential environmental stressors that may be implicated in AA include infections,[35] vaccinations, hormone fluctuations, and diet, although their exact impact is unknown.[16,36] In the mouse model, soy products have been associated with AA, and there are new studies emphasizing a correlation between AA and Vitamins A and D levels.[16,37] It is likely that multiple environmental factors impact the disease course.

Immune privilege zone

In the normal hair follicle, there is a zone of immune privilege due to downregulation of MHC I and β2 macroglobulin molecules, production of immunosuppressant molecules such as α-melanocyte-stimulating hormone and transforming growth factor-β (TNF-β) and decreased antigen-presenting cell activity.[38,39] However, it is hypothesized that there is a collapse of this immune privilege zone in AA from an unknown autoantigen.[38] Interferon-γ (IFN-γ) and interleukin (IL)-2 can then induce infiltration of CD8+, CD4+, and other inflammatory cells into the immune privilege zone.[36] All of these alterations are translated in inflammation of the hair follicle and may result in hair loss.[40]

CURRENT TREATMENTS

Few high-quality randomized controlled trials have been completed for the management of AA, although this has begun to change with the addition of the Severity of Alopecia Tool which provides guidelines for clinical research in AA.[41] Hair loss may spontaneously remit, although the timeframe for regrowth may be months to years.[42] Traditional medical therapies include corticosteroids, immunotherapy, and light therapy.[42,43]

Topical corticosteroids

The underlying mechanism of topical corticosteroid use is containment of inflammation and hastening of the recovery of damaged hair follicles.[42,44] Results vary, but approximately 57% of patients demonstrate complete regrowth of hair during the course of treatment.[44] Intralesional corticosteroids show slightly better results, with 63% demonstrating complete hair regrowth within 4 months in one study.[45] The main side effect is increased risk of cutaneous atrophy at the site of treatment.[42] Systemic corticosteroids are used in refractory cases, with one study demonstrating that 62% of patients had full hair regrowth.[46] However, the therapy may be associated with adverse events.[46,47] Relapse rates in AA are high regardless of therapy, and with corticosteroids vary between 33% and 75%.[48]

Immunotherapy

Squaric acid dibutylester and diphencyclopropenone are immunotherapeutic agents used as the second-line treatments for AA. The postulated mechanism is induction of antigenic competition which distracts CD4+ T-cells from attacking hair follicles.[49] Urticaria, dermatitis, blistering, and depigmentation are common side effects.[42] Response rates vary from 9% to 87%, but one study showed that 20%–30% of patients get a response sufficient to avoid the need for a hair piece.[42]

Other less commonly used treatments include topical minoxidil,[50] plus ultraviolet A radiation or excimer laser,[43,51] and systemic immunomodulators.[43]

INVESTIGATIONAL TREATMENTS AND FUTURE DIRECTIONS

Interleukin-2

Tregs are impaired in autoimmune diseases such as AA.[52,53] Low dose IL-2 is known to induce Treg proliferation, which might reduce the immune response against hair follicles.[53,54] A pilot study of IL-2 for 6 months of treatment indicated that low-dose treatment can improve AU with minimal adverse events.[52] Biopsy of lesions demonstrated a decrease in CD8+ T-cells and an increase in Tregs.[52]

However, IL-2 may also have a paradoxical effect, increasing NK cell proliferation, and potentially exacerbating AA.[53]

Interleukin 17

IL-17 SNPs are associated with AA, and TH17 cells are increased around hair cells in AA.[55,56] IL-17 activation can increase inflammatory cytokines such as TNF-β, IL-6, and IFN-γ.[56,57] It is postulated that therapy to limit TH17 cells would inhibit IL-17, and therefore help to treat AA.[56] However, there have been no clinical trials to date.

Phenol

Many contact allergens have been studied for the treatment of AA.[58] Phenol (carbolic acid) is a contact irritant, which acts as an immunomodulative drug and through "antigenic competition" decreases the immune response against the hair follicle.[58] Savant and Shenoy documented a response to 88% phenol in 69 patches of AA but did not reported specific changes regarding pigmentation, density, and texture of hair regrowth.[59] Chikhalkar *et al*. in 2011 performed a prospective study using 88% phenol topically on AA patches and found a 78% improvement regarding texture and pigmentation of hair.[58]

Quercetin

Quercetin is an anti-inflammatory bioflavonoid that has been tested in mice to treat AA.[60] Previous studies have shown that it can inhibit Heat Shock Protein 70 and nuclear factor-kappa B transcription factors that activate inflammatory cytokines such as TNF-β, IL-1, IL-2, and IL-6.[60] In Wikramanayake *et al*., all mice treated with quercetin demonstrated hair regrowth, whereas none of the sham-treated mice showed any hair regrowth.[60] In addition, 24% of the heat-treated mice (a method to induce AA) with sham-injections developed AA, while none of the mice receiving quercetin developed the disease.[60]

Antidepressants

Tianeptine is an antidepressant sold outside the US that acts as an opioid agonist and serotonin reuptake enhancer. In one animal study, tianeptine was given to mice with ultrasonic wave stress-induced AA-like lesions.[61] At the end of the study, treated mice demonstrated reduced hair loss, regrowth, improved hair thickness, and increased hair-cycle recovery.[61] There was also decreased mast cell degranulation surrounding hair follicles and increased synthesis of collagen and elastic fibers.[61] Small clinical trials have demonstrated some hair regrowth with imipramine[62] and paroxetine,[63] although no trial has demonstrated complete regrowth.

Parathyroid hormone

Parathyroid hormone (PTH) is thought to be a hair cycle stimulator.[64] It has been tested on the C3H/HEJ mouse model of AA with promising results.[64] Forty mice were treated with either PTH bound to a bacterial collagen binding domain (PTH-CBD) or a control.[64] Eight weeks after treatment, 13/21 mice (62%) treated with PTH-CBD showed reduced hair loss, while only 3/10 (30%) in the control group demonstrated retained hair.[64] There was no change in immune response on immunohistochemistry, but increased anagen hair follicles and increased beta-catenin (anagen hair growth initiator) were noted.[64]

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 Hairmax Lasercomb® (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.[65] However, in a similar study with spontaneous or graft-induced AA in C3H/HeJ mice, there was no increase in hair regrowth.[66] The authors postulate this may be due to a difference between heat-induced AA and spontaneous AA.[66] In a solitary trial with a pulsed infrared diode 904 nm laser, 32 of 34 treated patches demonstrated hair regrowth without any adverse events.[67] However, this pulsed laser treatment may affect the body differently than the more constant light of traditional LLLT devices such as the Hairmax Lasercomb®.

Abatacept

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.[68] Sundberg *et al*. in 1994 performed a comparative human gene array to identify dysregulated genes in AA.[69] 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.[68] Abatacept, a monoclonal antibody directed against this receptor, effectively prevented the onset of AA in a mouse model.[17,20] Recently, John *et al*. defined CTLA-4 as a major candidate gene for AA susceptibility in humans.[70] Abatacept as an immunosuppressive drug is used to treat many rheumatologic treatments and acts on the CTLA-4 pathway.[71] 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-γ that is necessary for the immune response of AA.[72] 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.[73,74,75] Many clinical trials are ongoing involving JAK inhibitors such as ruxolitinib, tofacitinib, and baricitinib [Table 2].

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.[76] In randomized studies, PRP demonstrated significantly improved hair regrowth compared to placebo and triamcinolone scalp injections without any noted adverse events.[77] However, in another trial in chronic severe AA, there was a variable effect with PRP treatment.[78] 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.[50] 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.[79]

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.[80,81] The clinical trial data are conflicting. In one trial, 19 patients with 40–70% hair loss completed the treatment, and 14 patients were considered responders to treatment.[79] However, in another study in patients with 70% or greater hair loss or AU/AT treated with simvastatin, there was no demonstrated hair regrowth.[82] It is unclear if the lack of response in this later trial was due to the increased severity of the disease or if the therapy was ineffective. Larger randomized controlled clinical trials should be conducted for further evaluation.

Vitamin A

Immune cells are highly responsive to oxidative damage.[83] Provitamin A and β-carotene have well-known antioxidant properties, and vitamin A itself has physiologic roles in immune modulation.[84] Deficiency or excess in vitamin A can result in AA. Duncan *et al*. documented an upregulation of genes that play a role in retinoid metabolism in AA patch biopsies from humans and mouse model C3H/HeJ.[85] Mice fed with high levels of vitamin A presented earlier with the disease.[85] Suo *et al*. confirmed a role for vitamin A in the initiation of the anagen hair cycle in C3H/HeJ mice, which likely increases follicle susceptibility to autoimmune destruction and it was dose-dependent.[86]

Valproic acid

Valproic acid (VPA) is a mood stabilizer. VPA affects signaling pathways including protein kinase C, extracellular signal-regulated kinase, and Wnt/β-catenin pathways.[87,88] Lee *et al*. in 2012 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.[89] 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[90] and recently in androgenic alopecia.[91] Microneedling has also been combined with topical triamcinolone acetonide application in AA.[92] Ito *et al*. in 2017 used a three microneedle device for intralesional corticosteroid administration in patients with AA with beneficial results.[93] Deepak *et al*. in 2014 also reported positive results in three cases of resistant AA treated with scalp roller therapy.[94]

Electroacupuncture

Electroacupuncture (EA) involves insertion of needles into the skin and underlying tissues at acupuncture points with pulsating electrical current.[18] Evidence has indicated that EA stimulation may enhance immune function in several animal models of inflammatory diseases.[18] Maeda *et al*., applied EA stimulation at the ST36 point in C3H/HeJ mice with AA, and found a significant reduction of mast cell degranulation around hair follicles, improving AA.[18]

CONCLUSION

AA is a complicated multifactorial disease with a variable prognosis. While many patients will heal

spontaneously, other patients may have chronic disease. There are no FDA approved treatments, although corticosteroids are considered first line. Potential new avenues of therapy have been explored here and will require more extensive review before their use can be recommended [Tables 2 and 3]. Further research into the mechanism of the disease may also elucidate further treatment options.

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Conflicts of interest

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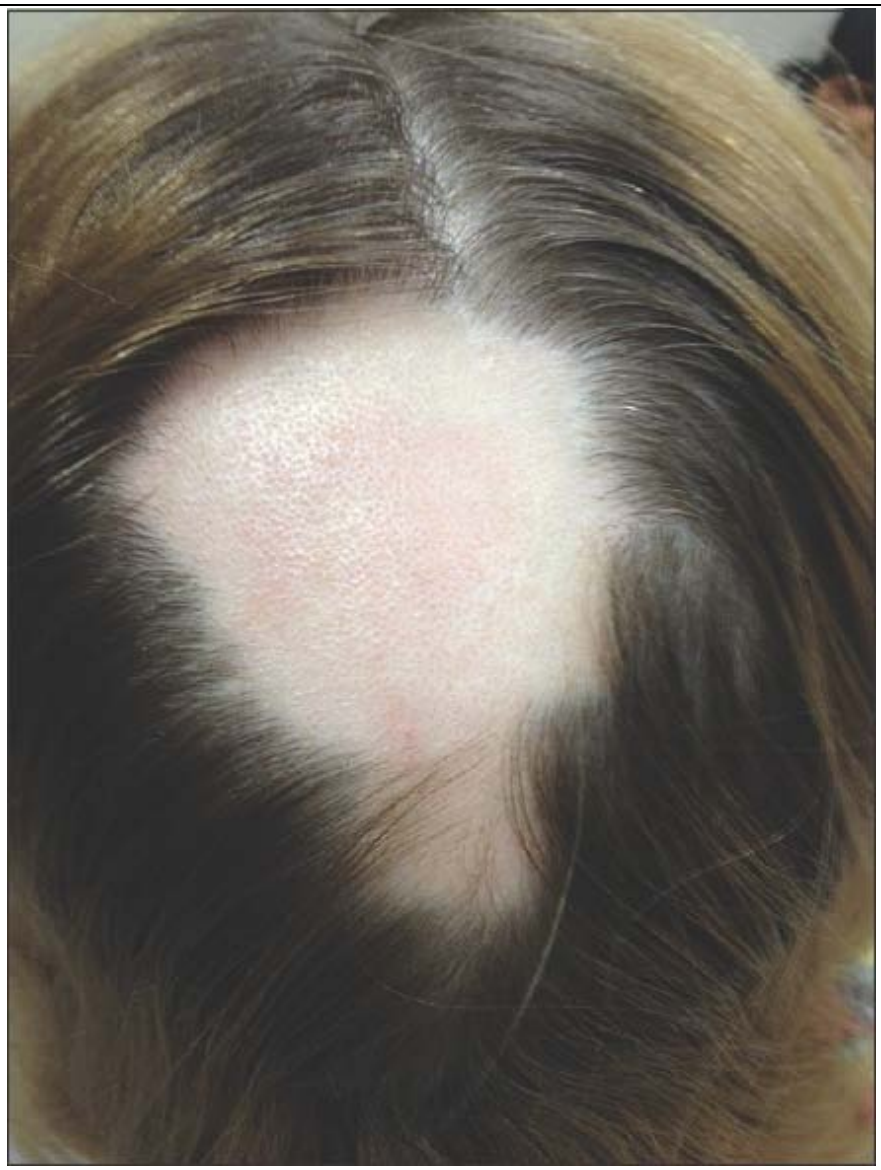
Figures and Tables

Figure 1

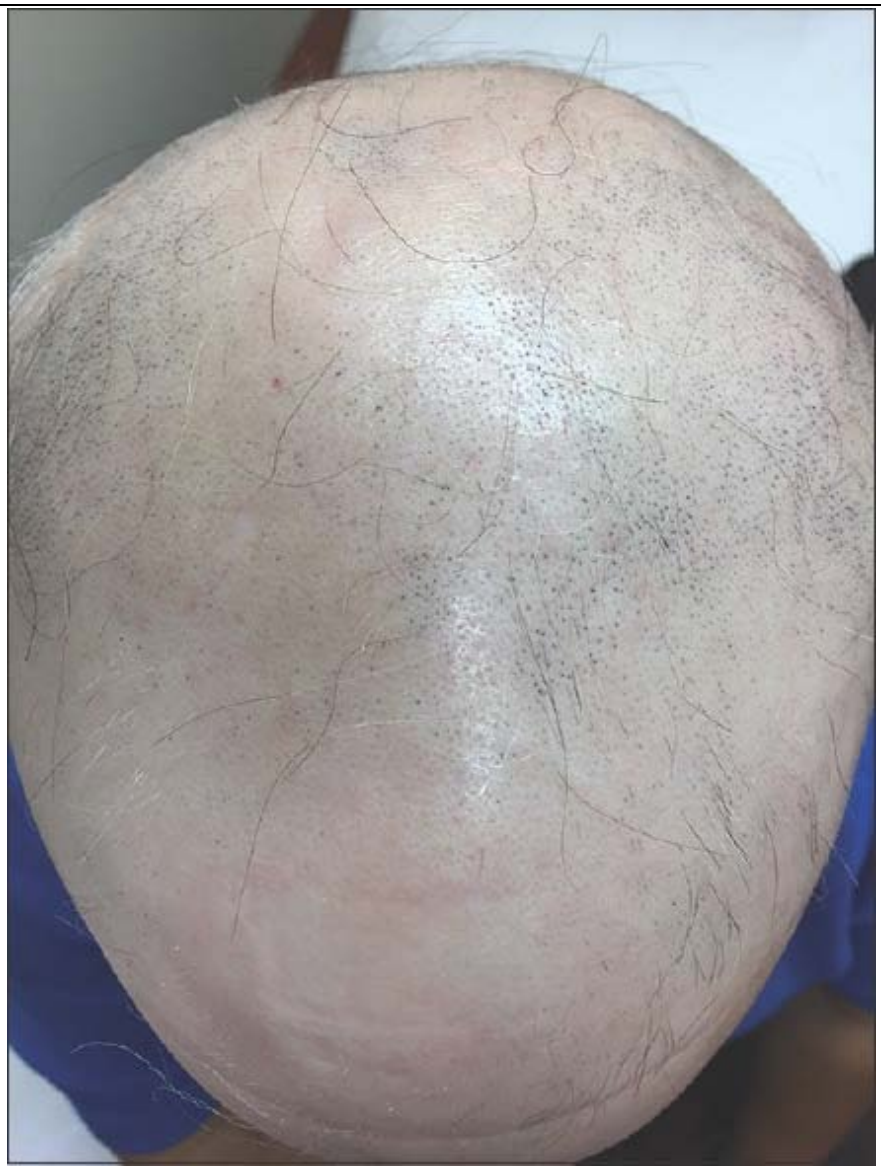


Patchy alopecia areata

Figure 2

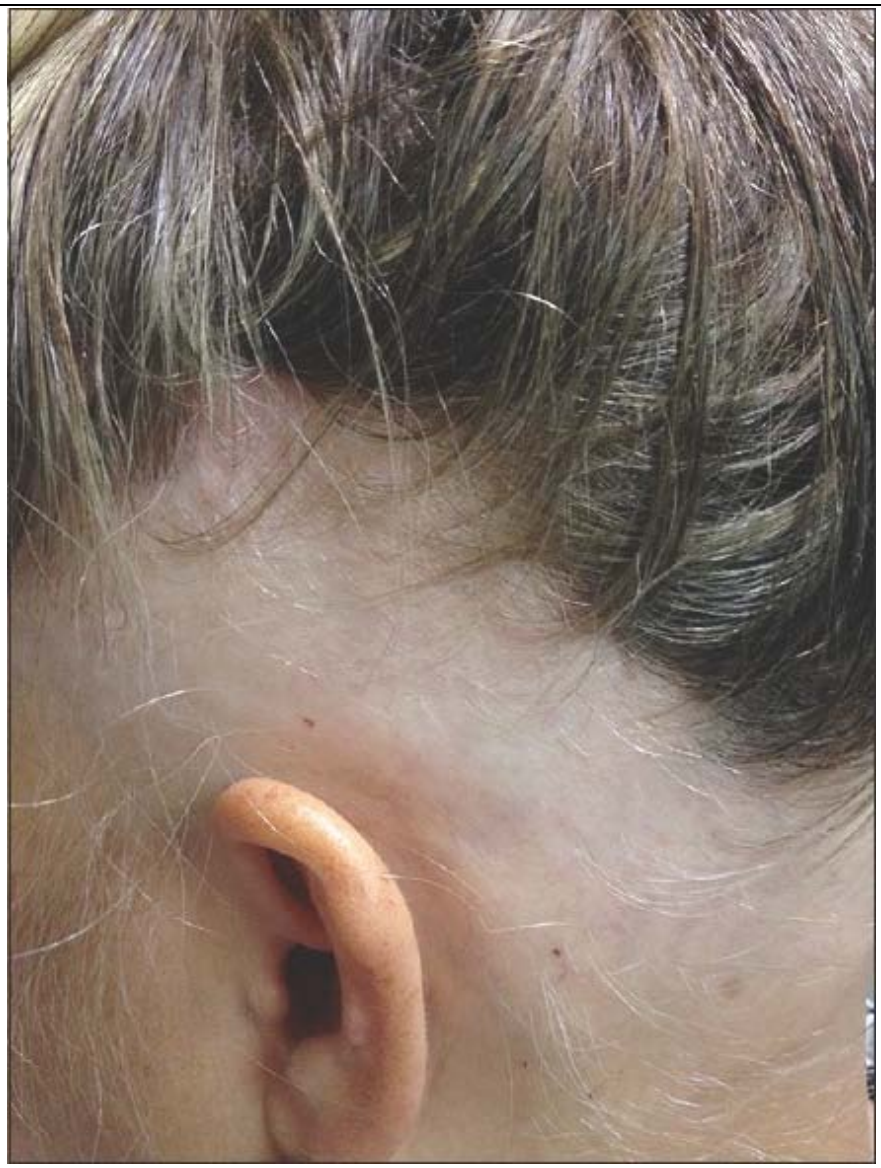
Exclamation point hairs are thicker at the apex of the hair shaft and progressively thin toward the base of the hair shaft

Figure 3



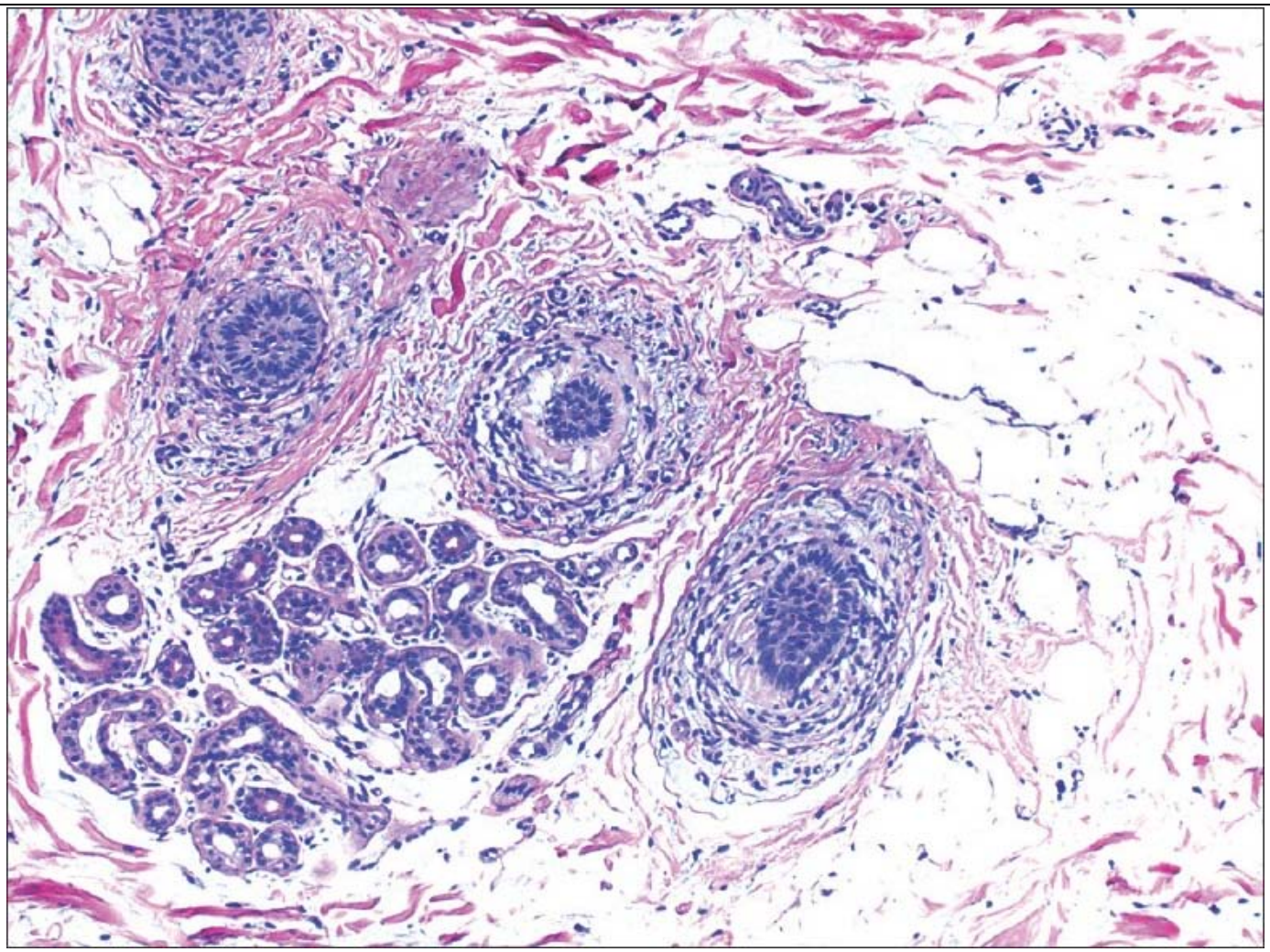
Alopecia totalis

Figure 4



Alopecia in an ophiasis pattern

Figure 5



"Swarm of bees" pattern of lymphocytes surrounding the hair follicle

Table 1

Current murine models used in alopecia areata

Model name	Description	References
C3H/HeJ	Most commonly used model in AA Near 20% develop AA spontaneously by 18 months[17] AA can be induced in younger mice by either (1) localized heat shock[18] or (2) transferring full-thickness skin grafts from older, affected mice[19]	[19-21]
1MOG244.1	Retroviral, transgenic mice on a $Rag1^{-/-}$ background, where T-cells express only C57BL/6J (B6)-derived CD8+ T-lymphocytes which specifically target the hair follicle On average, develop AA at 6-7 weeks	[22]
B6-KM.AA	Most AA lesions develop at 4 weeks Follicles are reduced in quantity but are normal overall	[23]
C3H/HeN A/J MRL/MpJ SJL/J SWR/J	These mouse strains were subjected to proteomic analysis which revealed unique qualities in the hair shafts of C3H/HeJ mice that predispose them to AA later in life	[24]
SCID	Healthy human scalp skin is transplanted on SCID mice, whereby peripheral blood mononuclear cells, cultured with IL-2, are injected into the graft High concentrations of IL-2 induce a NK phenotype	[25]

AA – Alopecia areata; SCID – Severe combined immunodeficiency; NK – Natural killer; IL-2 – Interleukin-2; $^{-/-}$Rag1 knockout mice

Table 2

Ongoing interventional clinical trials related to alopecia areata[a]

Intervention	Trial number	Phase	Description
Tofacitinib	NCT02299297	2	Will assess efficacy of tofacitinib taken for 6 months in AA patients followed by incidence of AA recurrence after 6 months off-drug period
	NCT02812342	2	A small open-label trial exploring efficacy of a tofacitinib gel in AA patients for a maximum of 6 months
Apremilast	NCT02684123	Pilot study	Will assess the safety and efficacy of apremilast in patients with moderate-to-severe AA
Ruxolitinib analog (CTP-543)	NCT03137381	2	Double-blind, randomized, placebo-controlled, multicenter study of the efficacy and safety of CTP-543 in AA participants. Experimental group will follow ascending dose order
Abatacept	NCT02018042	2	Will explore improvements in AA severity during a 6 months on-drug phase and 6 months off-drug phase
Tralokinumab	NCT02684097	2	Will assess the safety and efficacy of tralokinumab in patients with moderate-to-severe AA
Intralesional triamcinolone	NCT01898806	4	Will investigate outcomes of dose response to intralesional steroid injections in patients with patch-type AA
Novel JAK inhibitors (PF-06651600 and PF-06700841)	NCT02974868	2	Will explore the safety profile and efficacy of two investigational JAK inhibitors in patients with AA
Histone deacetylase inhibitor (SHAPE gel)	NCT02636244	2	Multicenter, open-label study to assess safety/efficacy outcomes of SHAPE gel in AA patients
IL-2	NCT02557074	3	Will compare the long-term efficacy of low doses of IL-2 versus placebo in patients with AA
MTX	NCT02037191	3	Will investigate MTX efficacy in severe AA Experimental group will receive MTX alone or in combination with prednisone for 6 months
Biocellular regenerative therapy	NCT03078686		Will investigate the safety/efficacy profile of a biocellular mixture of emulsified AD-tSVF and HD-PRP in AA
Hair loss prevention lotion (MEXIS, M.P.A.F., M6S PATENT)	NCT02604888		Will assess the efficacy of a novel therapeutic lotion in the treatment of AA
Garlic concentrate	NCT02684123	3	Will measure therapeutic effectiveness of topical garlic concentrate in children with AA
Phosphate cream	NCT02553330	2	Will assess the potential beneficial effects and safety of topical phosphate cream in participants with AA

[a]Ongoing trials were gathered from clinicaltrials.gov. MTXL – Methotrexate; AA – Alopecia areata; AD-tSVF – Adipose-derived tissue stromal vascular fraction; HD-PRP – High-density platelet-rich plasma concentrate; IL-2 – Interleukin-2

Table 3

Investigational treatment options for alopecia areata

Treatment	Mechanism of action	Administration	Side effects	Study model	References
Antidepressants (tianeptine, imipramine, paroxetine)	Stress reduction	Systemic	Not reported in trials	Murine, Human prospective	[61-63]
Electroacupuncture	Reduced mast cell degranulation	Regional	None reported	Murine	[18]
JAK inhibitors	Downregulation of inflammatory cytokines	Systemic	Increased risk of infection	Murine, Human prospective	[72-75]
IL-2	Promotes Treg proliferation; lowers lesional CD8+count	Systemic	Fatigue, arthralgia, urticaria, local reaction at injection site	Human prospective	[52]
LLLT	Hair cycle stimulator	Regional	None reported	Murine, Human prospective	[65-67]
Microneedling	Recruits blood supply and growth factors	Regional	None reported	Human prospective	[92-94]
Phenol	Antigenic competition	Topical	Hyper/hypopigmentation, erythema	Human prospective	[58,59]
PRP	Prolongs anagen phase; reduces apoptosis of dermal papilla cells	Intralesional	None reported	Murine, Human prospective	[50, 76-78]
PTH-CBD	Hair cycle stimulator	Systemic (subcutaneous injection)	Not reported in trials	Murine	[64]
Quercetin	Reduction in inflammatory cytokines	Systemic	None reported	Murine	[60]
Statins	Repress inflammatory cytokines; inhibit lymphocyte function	Systemic	Myopathy, headache	Murine, Human prospective	[79,82]
VPA	Enhances growth signaling pathways	Topical	Hair loss (only oral intake)	Murine	[89]

LLLT – Low-level light therapy; PRP – Platelet-rich plasma; PTH-CBD – Parathyroid hormone-collagen binding domain; VPA – Valproic acid; IL-2 – Interleukin-2