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ALOPECIA: AN AUTOIMMUNE DISEASE

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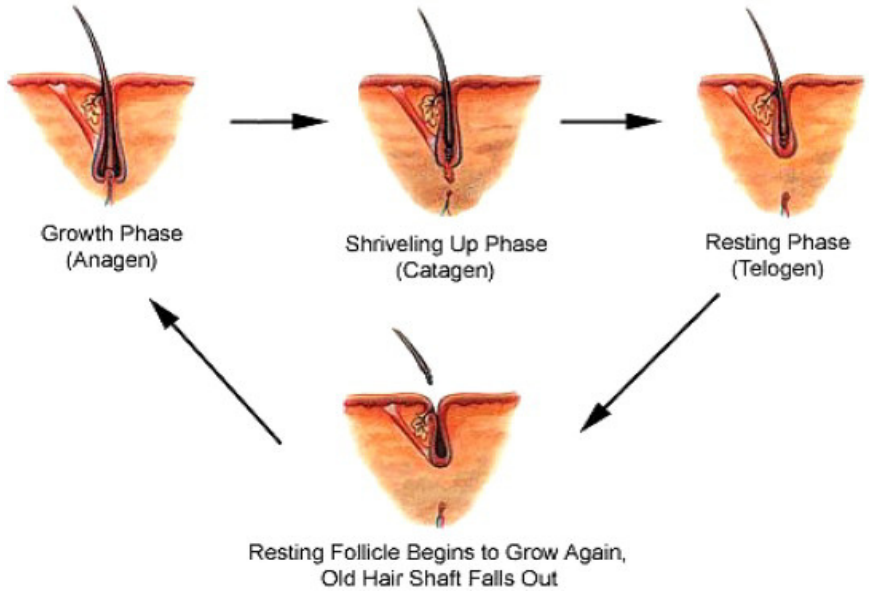
Abstract

Alopecia areata (AA) is a nonscarring, autoimmune hair loss on the scalp, and/or body. Etiology and pathogenesis are still unknown. The most common site affected is the scalp in the form of solitary or multiple patches of alopecia. Histopathology is characterized by an increased number of telogen follicles and presence of inflammatory lymphocytic infiltrate in the peribulbar region. Corticosteroids are the most popular drugs for the treatment of this disease. This review precisely outlines the etiologic and pathogenic mechanisms, clinical features, diagnosis and management of alopecia areata.

Introduction

Alopecia areata (AA) is a common cause of non-scarring alopecia that occurs in a patchy, confluent or diffuse pattern. It may involve loss of hair from some or all areas of the body, usually from the scalp (Odom, 2006). In 1–2% of cases, the condition can spread to the entire scalp (Alopecia totalis) or to the entire epidermis (Alopecia universalis). AA has a reported incidence of 0.1–0.2% with a lifetime risk of 1.7% with men and women being affected equally (Safavi et al., 1995). Sharma et al. in their decade long prospective study observed an incidence of 0.7% among new dermatology outpatients (Sharma et al., 1996). The etiology of AA has eluded investigators for years and therefore a multitude of associations have been proposed by researchers in the field of trichology. One of the strongest associations is with autoimmunity (McDonagh and Tazi-Ahnini, 2002, Hordinsky and Ericson, 2004). This view has been supported by the occurrence of AA in association with other autoimmune disorders like vitiligo, lichen planus, morphea, atopic dermatitis, Hashimoto's thyroiditis, pernicious anemia and diabetes mellitus (Brenner, 1979). More recently, it has been reported that there is a high prevalence of mood, adjustment, depressive and anxiety disorders in patients with AA (Ruiz-Doblado et al., 2003). This element of psychiatric morbidity has widely been purported to be both, a cause and effect of AA. A multipronged approach is therefore warranted in the management of such patients. Though corticosteroids have been the mainstay in therapy, a wide array of evidence-based therapies have come into force for management of AA. The present study attempts to systematically review the various aspects in the natural history of alopecia areata and the pros and cons in the different treatment modalities.

Dynamics of hair loss Hair follicle growth occurs in cycles (Fig. 1). Each cycle consists of a long growing phase (anagen), a short transitional phase (catagen) and a short resting phase (telogen). At the end of the resting phase, the hair falls out (exogen) and a new hair starts growing in the follicle beginning the cycle again. There are considerable variations in the length of the three phases, with the duration of the anagen determining the type of hair produced, particularly its length. Normally about 100 strands of hair reach the end of their resting phase each day and fallout (Trueb, 2010). Hair loss in non-scarring alopecias, including alopecia areata essentially represents a disorder of hair follicle cycling (Paus, 1996). It is believed that in AA, an as yet unidentified trigger stimulates an autoimmune lymphocytic attack on the hair bulb. This inflammation is specific for anagen hairs and causes anagen arrest. A disruption of the growing phase, that is anagen arrest, causes abnormal loss of anagen hairs (anagen. conversion from anagen to telogen (anagen release), clinically seen as localized shedding of hair in the telogen and morphologically identified as hair with a depigmented bulb (Wasserman et al., 2007).



Etiopathogenesis

The etiology of AA has experienced considerable drift over the years and different schools of thought have assigned varied etiologies to the condition (Fig. 2). A viral etiology was proposed in the late 1970s but subsequent articles have demonstrated no connection (Tosti et al., 1996). A genetic study by Yang et al. found that 8.4% of the patients had a positive family history of AA, suggesting a polygenic additive mode of inheritance (Yang et al., 2004). It has now been widely postulated that AA is an organ-specific autoimmune disease with genetic predisposition and an environmental trigger (McMichael, 1997, McDonagh and Tazi-Ahnini, 2002). An association between AA and human leukocyte antigen (HLA) has been demonstrated. Kavak et al. reported patients with AA had HLA-A1, HLA-B62, HLA-DQ1, and HLADQ3 (Ay Se et al., 2000). Recently, in the United States, Barahmani et al. demonstrated that a non-HLA molecule including the major histocompatibility complex class I chain-related gene A (MICA) is associated with AA. It could be a potential candidate gene and part of an extended HLA haplotype that may contribute to susceptibility and severity of this entity (Barahmani et al., 2006). HLA class I molecules are expressed on virtually all nucleated cells and platelets and present antigens to CD8+ T cells. HLA class II molecules have three main subclasses (DR, DQ, and DP); they are found on specific immune cells, including B cells, activated T cells, macrophages, keratinocytes, and dendritic cell and present peptides to CD4+ T cells. Because class II molecules are associated with antigen presentation, many studies have focused on this area of the HLA molecule (Mari, 2004).These associations with HLA-DR and HLA-DQ suggest a role for T cells in this disease as well as autoimmunity. Patients with AA have an increased frequency of autoantibodies to follicular structures; however, there is little consistency in which follicular structures are labeled by the antibodies (Gilhar and Kalish, 2006). Other diseases that

are reported to be associated with AA are at higher rate than the normal population. They are atopic dermatitis, vitiligo, thyroid disease, and Down's syndrome (Tan et al., 2002). Most of the research in the field of AA thus demonstrates a strong case for the implication of autoimmunity in the etiopathogenesis. Other potential offenders proposed in the causation of AA are psychologic stress, anemia, parasitic infestations, hypothyroidism, hyperthyroidism and diabetes

Animal models in the understanding of pathogens

Animal models have also suggested a role of vitamin A in the regulation of both the hair cycle and immune response to alter the progression of AA. Gene array in graft-induced C3H/HeJ mice revealed that genes involved in retinoic acid (RA) synthesis were increased, whereas RA degradation genes were decreased in AA compared with sham controls. RA levels were also increased in C3H/HeJ mice with AA. C3H/HeJ mice were fed a purified diet containing one of the four levels of dietary vitamin A or an unpurified diet 2 weeks before grafting and disease progression followed. High vitamin A accelerated AA, whereas mice that were not fed vitamin A had more severe disease by the end of the study. More

hair follicles were in anagen in mice fed with high vitamin A. Both the number and localization of granzyme B-positive cells were altered by vitamin A. IFNγ was the lowest and IL13 highest in mice fed with high vitamin A. Other cytokines were reduced and chemokines increased as the disease progressed (Duncan et al., 2013).

Psychological factors

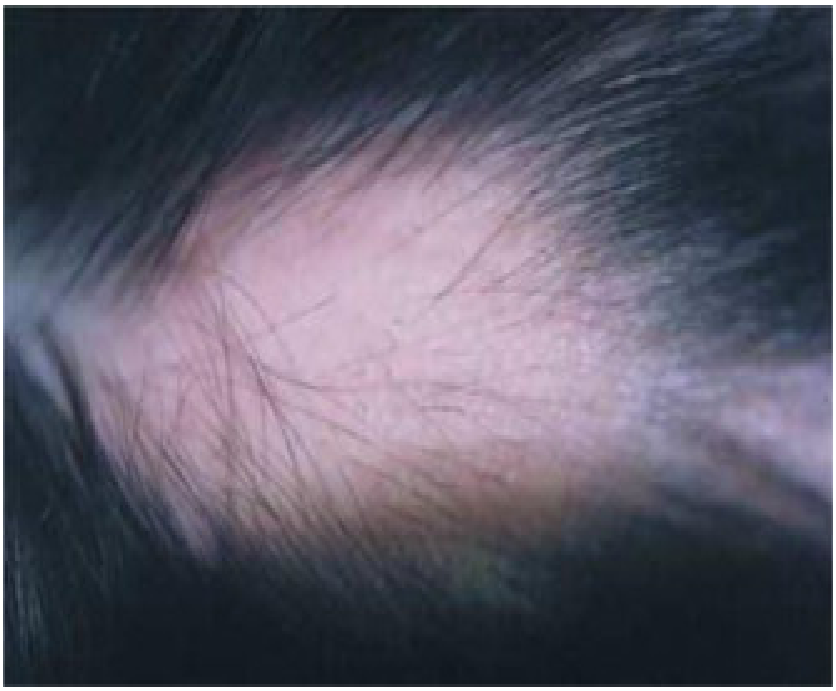
Some studies have suggested that emotional stress contributes to the appearance of alopecia areata, given the observation that emotional trauma precedes the process (Baker, 1987) together with the high prevalence of psychological disorders occurring in these patients (Colon et al., 1991). While, on the contrary, other studies have demonstrated that there is no participation of emotional phenomena in the development of alopecia areata (van der Steen et al., 1992).

A possible explanation of the pathogenic mechanisms provoked by emotional conditions lies in the production of neuromodulators capable of interfering in the immunity. Some studies have revealed a decrease in the expression of calcitonin gene related peptide (CGRP) and substance P in the scalp of alopecia areata patients (Hordinsky et al., 1995a, Hordinsky et al., 1995b). CGRP has an anti-inflammatory action, (Raud et al., 1991) and its decrease in alopecia areata could favor the characteristic follicular inflammatory phenomena. Substance P is capable of inducing hair growth in mice (Paus et al., 1994) and its decrease in alopecia areata could be a contributing factor to the reduced proliferation of pilar follicles.

Clinical features

The diagnosis of AA is essentially made on clinical grounds. Age at onset, duration and progression of disease, personal and family history of atopy, family history of similar disease with special reference to autoimmune disease and other systemic complaints are noted in detail. Routine investigations like complete hemogram, anemia panel, erythrocyte sedimentation rate, thyroid function tests, serum calcium, serum proteins, etc. should be carried out to arrive at a specific diagnosis. Skin biopsy and autoimmune panel may be performed in selected cases. Alopecia areata most commonly manifests as a sudden loss of hair in localized areas. The lesion is usually a round or oval patch of alopecia and may besolitary (Alopecia Areata monolocularis) or numerous (Alopecia Areata multilocular is). The patch of alopecia usually has a distinct border where normal hair demarcates the periphery of the lesion (Fig. 3). The scalp is the most common site affected by AA (90%) Tan et al., 2002, Camacho, 1997. Scalp and body hair such as eyebrows, eyelashes, beard, underarm hair, and pubic hair may be affected (Alopecia Totalis), as well as the entire body (Alopecia Universalis). The ophiasis pattern refers to a severe form of AA extending along the posterior occipital and temporal scalp margins. The affected skin appears normal with no grossly evident epidermal alterations such as scaling or follicular abnormalities (Diana Draelos, 2007). In all forms “exclamation point hairs” are found, that become narrower along the length of the strand closer to the base may be seen within or around the areas of alopecia (Cline, 1988). Upon

regrowth, hair often initially lack pigment resulting in blonde or white hair (Finner, 2011). Nail changes can be seen in a portion of patients (10–66%) of AA. Small shallow pits (30%) up to trachyonychia (sandpaper nails; 10%) are typical, rarely other changes can also be seen. A red-spotted lunula and periungual erythema have been postulated as a sign of acute nail involvement (Olsen, 2003).



Quantitating hair loss

Hair pull tests conducted at the periphery of the lesion may be correlated with disease activity and also assist in determining the etiology of alopecia. A few clinical tests are presented below:

The pull test: this test helps to evaluate diffuse scalp hair loss. Gentle traction is exerted on a group of hair (about 40–60) on three different areas of the scalp. The number of extracted hairs is counted and examined under a microscope. Normally, <3 hairs per area should come out with each pull. If >10 hairs are obtained, the pull test is considered positive.

The pluck test: In this test, the individual pulls hair out “by the roots.” The root of the plucked hair is examined under a microscope to determine the phase of growth and used to diagnose a defect of telogen, anagen, or systemic disease. Telogen hairs are hairs that have tiny bulbs without sheaths at their roots. Telogen effluvium shows an increased percentage of hairs upon examination. Anagen hairs are hairs that have sheaths attached to their roots. Anagen effluvium shows a decrease in telogen-phase hairs and an increased number of broken hairs.

Scalp biopsy: This test is done when alopecia is present, but the diagnosis is unsure. The biopsy allows for differing between scarring and nonscarring forms in case there is clinical distinction is difficult. Hair samples are taken from areas of inflammation, usually around the border of the bald patch.

Daily hair counts: This is normally done when the pull test is negative. It is done by counting the number of hairs lost. The hair that should be counted are the hairs from the first morning combing or during washing. The hair is collected in a clear plastic bag for 14 days. The strands are recorded. If the hair count is >100/day, it is considered abnormal except after shampooing, where hair counts will be up 250 and be normal.

Tracheoscopy: Tracheoscopy is a non-invasive method of hair and scalp evaluation. The test may be performed with the use of a had held dermo scope or a videodermoscope. In alopecia areata trichoscopy shows regularly distributed "yellow dots" (hyperkeratotic plugs), micro-eclamation mark hairs, and "black dots" (destroyed hairs in the hair follicle opening.

Nails as described earlier, show changes in the form of pitting or trachyonychia (Olsen et al., 2004). Stigmata of organ specific autoimmunity may be present on systemic examination.

Gauging severity of disease

Researchers have devised a clinical scale in order to assess the severity of AA (Ay Se et al., 2000), presented as follows:

1 Mild: Three or less patches of alopecia with a widest diameter of <3 cm or disease limited to eyelashes and eyebrows.

2 Moderate: Existence of more than three patches of alopecia or a patch greater than 3 cm at the widest diameter without alopecia totalis or universalis.

3 Severe: Alopecia totalis or alopecia universalis.

4 Ophiasis: Severe form in which loss of hair occurs in the shape of a wave at the circumference of the head (described above-mentioned

The National Alopecia Areata Foundation working committee has devised "Severity of Alopecia Tool score" (SALT score) Price and Gummer, 1989. Scalp is divided into four areas namely, Vertex – 40% (0.4) of scalp surface area; right profile of scalp – 18% (0.18) of scalp surface area; left profile of scalp – 18% (0.18) of scalp surface area; Posterior aspect of scalp – 24% (0.24) of scalp surface area. Percentage

of hair loss in any of these areas is percentage of hair loss multiplied by percent surface area of the scalp in that area. SALT score is the sum of percentage of hair loss in all above-mentioned areas.

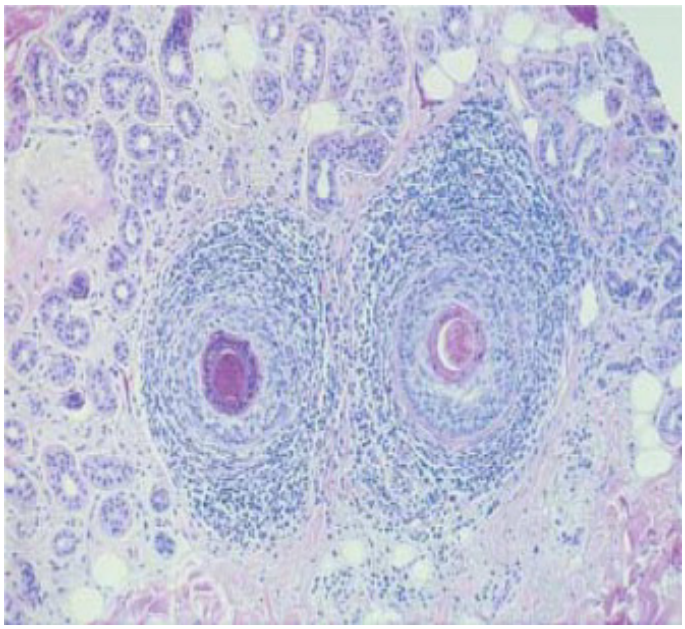
Differential diagnosis

Though alopecia areata is a form of non-scarring alopecia, it is sometimes confused with different varieties of scarring alopecia as well. This is also because many alopecia types are biphasic in their natural history. The first step, therefore is to distinguish between scarring and non scarring alopecias. Scarring alopecias have loss of follicular ostia, or atrophy. Clinical inflammation is frequently, but not always, present. Histologic inflammation may be present. Ultimately, histologic confirmation is the best method to confirm the presence of a fibrosing/scarring process with loss of hair follicles. A few entities in scarring alopecias are Lichen planopilaris, Central centrifugal cicatricial alopecia, Pseudopelade, Discoid lupus and Traction alopecia. The main confounders in diagnosis are the other varieties of non-scarring alopecias. They are:

- Trichotillomania: this condition probably causes most confusion and it is possible that it coexists with alopecia areata in some cases. The incomplete nature of the hair loss in trichotillomania and the fact that the broken hairs are firmly anchored in the scalp (i.e. they remain in the growing phase, anagen, unlike exclamation mark hairs) are distinguishing features.
- Tinea capitis: the scalp is inflamed in tinea capitis and there is often scaling but the signs may be subtle.
- Early scarring alopecia.
- Telogen effluvium.
- Anagen effluvium (drug-induced) may mimic diffuse alopecia areata.
- Systemic lupus erythematosus.
- Secondary syphilis.
- Loose anagen hair syndrome: This is a disorder of abnormal anagen hair anchorage. It is commonly found in children and has an autosomal dominant inheritance (Lew, 2009).
- ADTA: Acute diffuse and total alopecia (ADTA) is a new subtype of alopecia areata with favorable prognosis. ADTA has been reported to have a short clinical course ranging from acute hair loss to total baldness, followed by rapid recovery, sometimes even without treatment (Garcia-Hernandez, 2000).
- SISAPHO: This is an unusual form of Alopecia, in which a band-like pattern is found on the frontal hairline. This can be clinically confused with frontal fibrosing alopecia. The opposite of

ophiasis type, where hairs are lost centrally and spared at the margins of the scalp, is called sousaphone. It may mimic androgenetic alopecia (Ragunatha et al., 2008).

Ragunathan et al. in their case report have demonstrated infantile scurvy also, as a cause of diffuse non



scarring alopecia of the scalp (Whiting, 2003

Histopathology

The histopathologic features of alopecia areata depend on the stage of the current episode and do not vary with the age, sex or race of the patient (Igarashi et al., 1981). In the acute stage, terminal hairs are surrounded by bulbar lymphocytes (‘swarm of bees’) (Fig. 4). In the subacute stage, decreased anagen and increased catagen and telogen hairs are characteristically found. In the chronic stage, decreased terminal and increased miniaturized hairs are found, with variable inflammation. Immunofluorescence studies have shown deposits of C3, IgG, and IgM along the basement membrane of the inferior part of the hair follicle (Shimmer and Parker, 2001). During recovery, increasing numbers of terminal anagen hairs from regrowth of miniaturized hairs and a lack of inflammation are noted. Alopecia areata should histologically be suspected when high percentages of telogen hair or miniaturized hair are present, even in the absence of a peribulbar lymphocytic infiltrate. The histopathology of the lesion in ADTA reveals infiltration of mononuclear cells around the hair follicles and prominent pigment incontinence (Garcia-Hernandez, 2000).

Swarm of bees' appearance of the inflammatory infiltrate around terminal hair follicles in alopecia areata. (H&E stain).

Management

Management of patients with alopecia areata is a challenging task as a number of risk factors have been implicated in its etiology. No definitive cure has been established, and treatment has focused mainly on containing disease activity.

Glucocorticoids

Topical and intralesional steroids have been the mainstay of therapy, and have been used as first line agents for the management of the same. Glucocorticoids have been harnessed for their overarching anti-inflammatory effects for AA (Ross and Shapiro, 2005).

Intralesional corticosteroids

For circumscribed AA involving less than 50% of the scalp, intralesional corticosteroids are the first-line approach (Madani and Shapiro, 2000). Triamcinolone acetonide in a concentration of 10 mg/ml is administered using a 0.5-inch long 30-gauge needle in multiple 0.1 mL injections approximately 1 cm apart (Pascher et al., 1970). Initial results of intralesional treatment are often seen in 1–2 months. Additional treatments are repeated every 4–6 weeks.

Topical corticosteroids

Several forms of topical corticosteroids have been reported to exhibit varying levels of efficacy in AA. Some of the topical therapies have included fluocinolone acetonide cream, fluocinolone scalp gel, betamethasone valerate lotion and clobetasol propionate ointment (Tosti et al., 2003, Camacho, 1997). They remain a very good option in children because of their painless application and wide safety margin.

Systemic corticosteroids

Systemic corticosteroids do not constitute the first line treatment for alopecia areata because of their extensive side effect profile. The dosages necessary to maintain hair regrowth in AA are between 30 and 150 mg daily (Burton and Shuster, 1975). Treatment course can range from 1 to 6 months, but prolonged courses should be avoided secondary to the numerous side effects of these drugs especially when children are treated. Systemic steroids are thus not preferred in the treatment of alopecia areata except for some

cases as a short course only. Its side effect profile in conjunction with the long-term treatment requirements and high relapse rates make systemic corticosteroids a more limited option. Friedli et al. (1998) have also reported successful therapy with pulsed methylprednisolone (250 mg IV twice daily for three consecutive days) in patchy AA. Contraindications and side effects should however be discussed at length with patients considered for this therapy.

Oral mini pulse steroids

To avoid the side effects of daily steroids, pulse therapy was conceived.In a study conducted by Pasricha et al., betamethasone oral mini-pulse therapy is a convenient and fairly effective treatment modality for extensive alopecia areata (Pasricha and Kumrah, 1996). However, it is proposed that randomized controlled trials with standard therapies on a larger number of patients are required to give more insight into the efficacy and safety of oral mini-pulse therapy for extensive alopecia areata. Oral mini-pulse therapy (OMP) with corticosteroids has been successfully used for the treatment of alopecia areata with minimal side effects. Persistent hiccups is a rare complication of oral and intravenous corticosteroid therapy (Dickerman and Jaikumar, 2001).

Minoxidil

- First introduced as an antihypertensive agent, its side effect of hypertrichosis led to its use as treatment for various forms of alopecia. Minoxidil directly affects follicles by stimulating proliferation at the base of the bulb and differentiation above the dermal papilla, independent of its vascular influences (Fiedler et al., 1990). Minoxidil has shown considerable results in the management of AA and it is believed that patients resistant to minoxidil treatment often suffer from severe AA, AT or AU (Buhl, 1991, Frans way and Muller, 1988). Combination therapy of minoxidil 5% lotion and anthralin have been documented to show better results by few authors (Price, 1987).

Anthralin

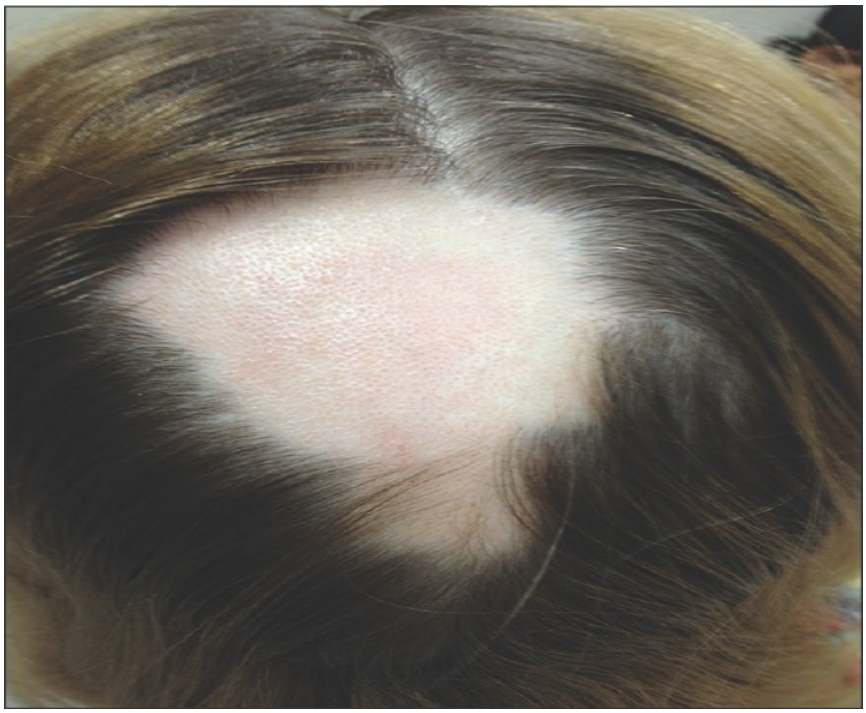
Anthralin exerts its effect through its irritant contact properties. It also acts through its immunosuppressive and anti-inflammatory properties via the generation of free radicals (Madani and Shapiro, 2000). Patients are instructed to apply 0.5–1% anthralin cream to bare areas for 20–30 min daily over 2 weeks, gradually increasing daily exposure until low-grade erythema and pruritus develops, which when once achieved is continued for 3–6 months (Ross and Shapiro, 2005). It is believed to be a suitable agent for children under 10 years of age (Thapa and Vijayakumar, 2001). Adverse effects include scaling, staining of treated skin and fabrics, folliculitis, and regional lym

.**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).

CLINICAL FEATURES

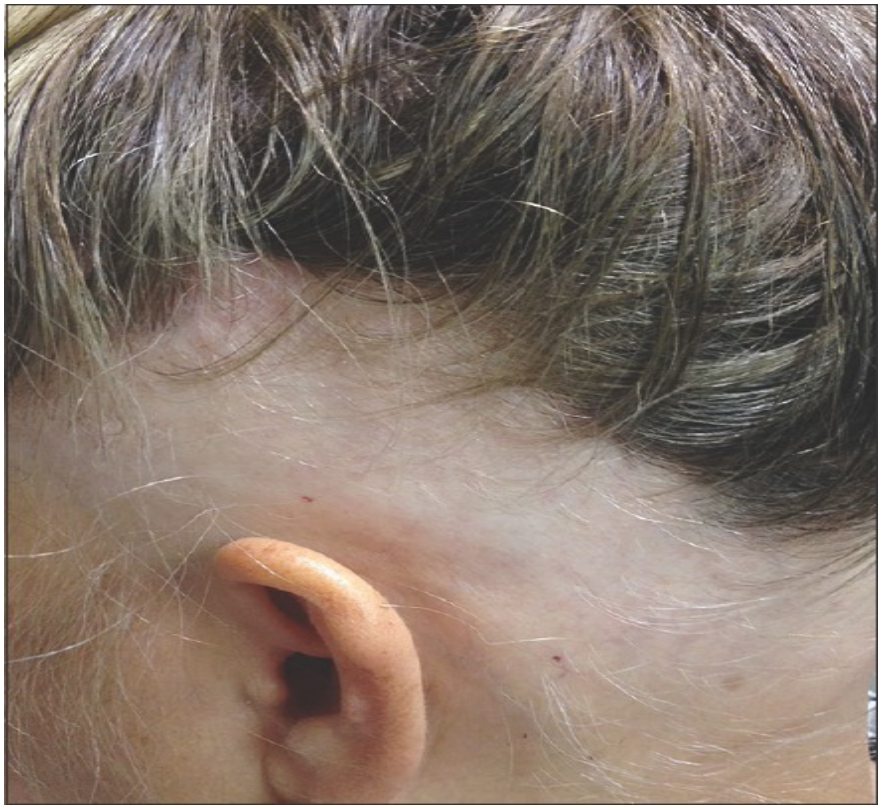
AA typically presents as smooth, sharply demarcated, round patches of hair loss without atrophy [Figure 1] with "exclamation point hairs" [Figure 2] observed on the peripheryof thepatches.[4] Special



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 fronto parieto temporal area.

PROGNOSIS

The prognosis of the disease is unpredictable. Current data suggest 34%–50% of patientsrecover 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]

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.

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

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 DipHE cyclopropenone 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 immunomodulate 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 Wickramanayake 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 Laser comb® (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 has 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].

Intervention	Trial number	Phase	Description
Tofacitinib	NCT02969616	3	Will assess efficacy of tofacitinib taken for 6 months in AA patients followed by incidence of AA recurrence after 6 months off-drug period
	NCT03334435	3	A small open-label trial exploring efficacy of a tofacitinib gel in AA patients for a maximum of 6 months
Abatacept	NCT03688555	Pilot study	Will assess the safety and efficacy of abatacept in patients with moderate-to-severe AA
Ruxolitinib analog (CTP-543)	NCT03732638	3	Double-blind, randomized, placebo-controlled, multicenter study of the efficacy and safety of CTP-543 in AA participants. Experimental group will follow escalating dose study
Apatacept	NCT03570463	3	Will explore improvements in AA severity during a 6 month on-drug phase and 6 months off-drug phase
Tofacitinib	NCT03899597	3	Will assess the safety and efficacy of tofacitinib in patients with moderate-to-severe AA
Intralesional triamcinolone	NCT03898908	4	Will investigate outcomes of dose response to intralesional steroid injections in patients with batch-type AA
Novel JAK inhibitors (PF-06651600 and PF-06700841)	NCT03715868	3	Will explore the safety profile and efficacy of two investigational JAK inhibitors in patients with AA
Histone deacetylase inhibitor (SHAPE del)	NCT03763344	3	Multicenter, open-label study to assess safety/efficacy outcomes of SHAPE del in AA patients
IL-3	NCT03572074	3	Will compare the long-term efficacy of low doses of IL-3 versus placebo in patients with AA
MTX	NCT03731481	3	Will investigate MTX efficacy in severe AA Experimental group will receive MTX alone or in combination with prednisone for 6 months
Glucocellular regenerative therapy	NCT03738888		Will investigate the safety/efficacy profile of a glucocellular mixture of amplified AD-SVF and HD-PRP in AA
Hair loss prevention lotion (MEXIS, M.D.A.E. MS2 PATENT)	NCT03804888		Will assess the efficacy of a novel therapeutic lotion in the treatment of AA
Garlic concentrate	NCT03888533	3	Will measure therapeutic effectiveness of topical garlic concentrate in children with AA
Phosphate cream	NCT03333330	3	Will assess the potential beneficial effects and safety of topical phosphate cream in baricitinib naive AA

Ongoing trials were retrieved from clinicaltrials.gov. MTX – Methotrexate; AA – Alopecia areata; AD-SVF – Adipose-derived stromal vascular fraction; HD-PRP – High-density platelet-rich plasma concentrate; IL-3 – Interleukin-3

Platelet-rich plasma

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

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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

Prove 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.

Micro needling

Micro needling 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] Micro needling 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 [Tables22 and and3].3]. Further research into the mechanism of the disease may also elucidate further treatment options.

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

Table 3

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