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Review Article

## Alopecia Areata: Pathophysiology, Diagnosis, and Treatment

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### Abstract

Alopecia areata is a type of non-scarring hair loss resulting from an autoimmune response towards the hair follicle, with genetic and environmental factors playing significant roles. It has a chronic, relapsing course and is a frequent complaint encountered in the dermatologic practice. However, the treatment options currently available have variable efficacy, and none are curative. In order to provide better treatment options, extensive research on the disease pathophysiology is being performed. In this comprehensive review article, we discuss the disease clinical presentation, pathophysiology, relevant animal models and current and potential treatment options for further investigation.

**Keywords:** Abatacept; Alopecia Areata; Jak Inhibitors; Methotrexate; Phenol; Platelet Rich Plasma; Quercetin, Stat; Statins

### Abbreviations:

| | |
|---|---|
| AA | : Alopecia Areata; |
| FDA | : Food and Drug Administration; |
| IL | : Interlekin; |
| JAK | : Janus Kinase; |
| MHC I | : Major Histocompatibility Complex Class I; |
| PRP | : Platelet Rich Plasma; |
| PTH | : Parathyroid Hormone; |
| PUVA | : Psoralen Ultraviolet A; |
| TNF | : Tumor Necrosis Factor |

## Introduction

Alopecia areata (AA) is a non-cicatricial alopecia resulting from autoimmune attack of the hair follicle. Both genetic and environmental factors contribute to the disease etiology and severity. Disease prevalence ranges from 0.1-0.2% in the United States, with the ratio of male to female susceptibility ranging from 2.6:1 to 1:1.9 according to different reports [1-3]. It is common for the disease to present between the second and fourth decades [2]. However, males typically have a childhood disease onset, while females more frequently have an adolescent disease onset [3].

## Clinical features

The typical presentation of AA is round, smooth patches of hair loss, with "exclamation point" hairs frequently observed in the periphery of the patches. AA can present as alopecia totalis (loss of all scalp hair), alopecia universalis (loss of all hair), or alopecia in an ophiasis pattern (hair loss in a band-like pattern in the temporal and occipital scalp). Uncommon variants of AA include the reticular variant, which is characterized by recurrent patchy disease with hair loss in one area and spontaneous hair growth in another, and the diffuse variant, in which there is extensive thinning or thinning only affecting the top of the head [1]. Premature hair whitening is rare and may be associated with AA as well as somatic or psychological factors [4]. A recently described variant is acute diffuse and total alopecia (ADTA), which has rapid disease progression but carries a favorable prognosis [2].

Disease prognosis depends on several factors, including the subtype of AA, disease involvement, family history, and age of onset. Greater disease extent, long duration of disease, positive family history, and young age of onset can be associated with poorer prognosis [5]. Initial hair regrowth is hypopigmented, with normal hair color returning with time [2]. The nails can be involved in up to 66% of AA patients, presenting as nail pitting, trachyonychia, onycholysis, brittle nails, koilonychia, and onychomadesis [1,6]. Commonly associated diseases include thyroid disorders, vitiligo, and atopy [7,8].

## Differential diagnosis

The differential diagnosis for AA includes tinea capitis, trichotillomania, temporal triangular alopecia, traction alopecia, secondary syphilis, loose anagen syndrome, pressure related alopecia, aplasia cutis, and "burnt-out" cicatricial alopecia [1,9,10]. A greater degree of inflammation and scale is usually observed in tinea capitis. Trichotillomania may present as irregular or oddly shaped patches of hair loss, with broken hairs of different lengths.

## Diagnosis

A clinical diagnosis is usually sufficient. The use of trichoscopy (dermoscopy and videotrichograma) may aid in making a diagnosis [9,11]. Exclamation hairs are a classic feature of AA [2,9]. The presence of yellow dots may be a useful indicator, but these can also be seen in androgenetic alopecia [2]. A scalp biopsy should be performed to confirm doubtful presentations.

## Pathology

Histopathologic examination will vary according to disease stage [2]. The presence of an increased amount of eosinophils in lesional skin at any stage is debatable [2,12]. In acute stages, there is a peribulbar lymphocytic infiltrate – likened to a "swarm of bees"—around anagen follicles [12]. This infiltrate is composed mainly of CD4+ and CD8+ cells, with the CD4/CD8 ratio being higher in active disease [2]. Affected hair follicles will have surrounding edema, microvesiculation, apoptosis, macrophages and foreign body giant cells. Lymphocytes may also infiltrate the hair matrix and root sheaths. Pigment incontinence, vacuolar damage, and keratinocyte necrosis might be observed. An uncommon but characteristic finding of is the presence of focal matrix cell vacuolization [13]. In the catagen phase, the hair shaft is weakened, causing breakage at the level of the skin surface [2]. When such hair goes into the telogen phase, the frayed thicker hair tip protrudes, resulting in what is observed as an "exclamation mark" hair. Hair shaft narrowing or pencil point hair is a sign of active disease. Residual inflammation surrounding hair follicles might be observed.

In chronic AA, anagen follicles are miniaturized and are at a deeper location than vellus follicles [2]. An intermediate stage between terminal and vellus hairs is characteristic of this phase. An inflammatory infiltrate around hair follicles and papillary dermis might be observed as well as fibrous tracts along the site of previous terminal follicles extending to the subcutis. In the recovery stage, the terminal/vellus ratio is normal, anagen hairs increase, and there is minimal to no inflammation [2] .When compared to a healthy scalp, the number of follicles may be decreased [13].

## Pathophysiology

Disease etiology remains unknown, and different theories are debated [14]. However, current evidence suggests AA is an autoimmune reaction towards the hair follicle in which both genetic and environmental factors play an important role in disease development and prognosis.

### Genetic factors

There is a strong genetic component in AA development [15]. This is supported by the observation that many patients with AA have a family history of AA [7,8]. Furthermore, both patients and their family members may also have other, associated autoimmune diseases [7,8]. The presence of family history is associated with a poor prognosis, rapid progression of disease, and a more chronic course. A case-control genome wide association study (GWAS) identified numerous single nucleotide polymorphisms (SNP) associated with the disease, implicating genes of both innate and adaptive im-

munity [16]. Specifically, the genes involved include those which control proliferation and activation of T regulatory (Treg) cells and HLA regions. Association was also found for regions of certain genes expressed in the hair follicle, the products of which may serve as autoantigens.

**Environmental factors**

Stress has also been implicated in the development of AA [17]. A case control study evaluated the effect of several psychological factors in AA as well as its effect on the quality of life of patients [18]. From this, it was concluded that major life events, anxiety, and depression disorders are implicated in disease manifestation. Patients with AA reported a greater number of stressful life events than control patients. Furthermore, in a model of C3H/HeJ mice with induced AA, an altered stress response was observed in the central hypothalamic-pituitary-adrenal (HPA) axis of affected mice and linked to cytokine levels in the skin [19]. However, from this study alone, the role of stress in the onset of AA could not be determined. Viral agents, such as Epstein-Barr virus, have also been implicated in disease development [20].

**Immune privilege zone**

The inflammation observed in AA and other non-cicatricial alopecias does not permanently affect the bulge area of hair follicles [21,22]. It is hypothesized that this area (i.e., the central and proximal hair follicle) is a zone of immune privilege maintained by down-regulation of MHC I and β2-microglobulin molecules, the presence of immunosuppressant molecules such as TGFβ and α-MSH, and diminished antigen-presenting cell activity [23,24]. In AA, however, as-of-yet unidentified autoantigens drive the collapse of this zone by augmenting MHC I expression. IFN-γ, substance P, and IL-2 drive infiltration of auto-reactive CD8+ cells, NK-G2D+ cells and other inflammatory cells and cytokines into this zone. Interaction between mast cells and CD8+ cells also seems to be increased and abnormal in AA [17,25].This results in significant inflammation towards the hair follicle, affecting the stem cells and the hair cycle.

An altered Th1/Th2 balance has been observed in AA, with an up-regulated Th1 response (IL-2, IL-12, and IFN-γ)[26]. IL-17A has also been demonstrated to be significantly increased in AA [27]. Uncontrolled proliferation of these cells and therefore continuous expression of inflammatory cytokines can lead to autoimmune disorders and chronic inflammation.

**Treatment**

Spontaneous resolution of AA within one year has been observed in up to 50% of patients [2]. Current treatments aim to control the disease, as there is no cure at present. Their efficacy is mostly based on experience rather than on randomized, sham- controlled trials [28,29]. The treatment of choice depends on disease extent and severity [29]. Individual drug treatments can be used alone or in combination to achieve maximal efficacy. Corticosteroids can be used in topical, intralesional, or systemic forms [1,30-33]. Minoxidil can be used as adjunctive therapy. Patients with extensive disease can be treated with systemic steroids, but relapses are common upon cessation of therapy [32]. Topical immunomodulators are an alternative for patients with generalized disease [29,33,34]. The 308nm excimer laser has been reported to be an efficient treatment for limited patchy AA, and clinical trials are ongoing [35,36]. Other, less efficient methods with serious adverse effects include psoralen with UVA light (PUVA) and systemic immunomodulators [1]. Therefore, their use is only recommended with unresponsive or extensive disease. Antidepressant treatments have been described to show some improvement but not total regrowth of hair [29].

Numerous clinical trials are being performed to test available treatment options for AA, such as the Excimer laser and PUVA. Other trials are testing drugs with AA as a new potential indication, such as abatacept and ruxolitinib, which seem to work by more specifically modulating the immune response towards the hair follicle. Table 1 summarizes some of the ongoing clinical trials for AA.

**Investigational treatments**

A significant amount of research has been done to better understand the pathophysiology behind AA. Cellular interactions, variation in cellular markers, and the effects of pro-inflammatory products on the hair follicle are being studied in detail. Various animal models have been established to investigate pathobiology, providing useful tools for drug development and testing. The most commonly used model to study AA is the C3H/HeJ mouse strain, which spontaneously develops the disease. Animal models for AA have been described and are summarized in Table 2 [37-43]. Overall, these models have been useful to investigate and better understand the complex mechanisms involved in this predominantly CD8+ T cell dependent disease, to identify the immune privilege zone of the hair follicle and its collapse in AA, and to assess *in vivo* responses to different therapies.

**Interleukin-2**

Treg cells are impaired in AA and other autoimmune diseases [44,45]. Low doses of IL-2 can induce their proliferation, diminishing the immune response towards the hair follicle [46]. A pilot study demonstrated that low dose IL-2 improved AA universalis after 6 months of treatment with minimal adverse effects [44]. Lesional biopsies demonstrated an increase in Treg cells and a decrease in the CD8+ infiltrate. Alternatively, the use of topical diphenycyclopropene can also increase the levels of IL-2 and should be further studied [45]. However, caution is advised as high doses of IL-2 may induce T cell proliferation and NK cell activity precipitating or exacerbating AA [45].

**Interleukin 17**

Th17 cells, activated by IL-17, have been implicated in AA pathogenesis [47,48]. Additionally, a case-control

**Table 1:** Ongoing clinical trials related to alopecia areata

| Drug | Trial number | Phase | Description |
|---|---|---|---|
| *Interleukin-2* (aldesleukin, Proleukin ®) | NCT01840046 | 1/2 | • Will evaluate the efficacy and tolerability of recombinant IL-2 in severe or resistant AA. |
| *Abatacept* | NCT02018042 | 2 | • Will measure the proportion of subjects obtaining at least a 50% hair re-growth from baseline using SALT score after 24 weeks of therapy. |
| *Ruxolitinib* | NCT01950780 | 2 | • Will evaluate the safety and efficacy of ruxolitinib for 3 months. |
| *Stem cell educator* | NCT01673789 | 1/2 | • Will explore the therapeutic effectiveness of a stem cell educator, following patients for 54 weeks. |
| *Methotrexate (MTX)* | NCT02037191 | 3 | • Will evaluate MTX efficacy in severe AA.<br>• Experimental group will receive MTX alone or in combination with prednisone for 6 months. |
| *PUVA* | NCT01559584 | | • Will evaluate the efficacy of phototoxic PUVA in AA<br>• Control group was treated with monthly injections of potent corticosteroids. |
| *Excimer laser* | NCT01802177 | | • Split lesion, single blinded randomized trial to evaluate the safety and efficacy of Excimer laser. |
| | NCT01736007 | | • Will assess the safety and response of Excimer laser in patchy AA in children. |

**Table 2:** Research models used in alopecia areata

| Mouse model | Description | Reference |
|---|---|---|
| **C3H/HeJ** | • Most commonly used animal model of AA<br>• Up to 20% spontaneously develop AA by 18 months of age [37].<br>• AA can be induced in younger mice (and to a greater extent) by transferring full thickness skin grafts from affected, older mice [38].<br>• AA can be induced by localized heat shock in younger mice [39]. | 37<br>38<br>39 |
| **1MOG244.1** | • Retroviral transgenic mice on a *Rag1*$^{-/-}$ background, where T cells solely express C57BL/6J (B6)-derived CD8$^{+}$ T lymphocytes specifically targeting the hair follicle.<br>• These develop AA at 6-7 weeks on average [40]. | 40 |
| **B6.KM-AA** | • AA skin lesions develop at 4 weeks of age [41].<br>• Hair follicles are normal but reduced in number. | 41 |
| **C3H/HeN**<br>**A/J**<br>**MRL/MpJ**<br>**SJL/J**<br>**SWR/J** | • Proteomic studies of hair shafts of these mouse strains showed that C3H/HeJ mice may have abnormalities in their hair shaft that predispose them to developing AA later in life [42]. | 42 |
| **SCID** | • Healthy human scalp skin is transplanted onto SCID mice and peripheral blood mononuclear cells previously cultured with IL-2 are injected into the graft [43].<br>• Exposure to high doses of IL-2 induces lymphocytes to express NK phenotype. | 43 |
| **DEBR rats** | • No longer used.<br>• Up to 70% spontaneously developed AA [37]. | 37 |

association study found that IL17R SNPs were associated with either AA development or AA onset [49]. Activation of the IL-17R, which is expressed by all immune cells, leads to the expression of inflammatory cytokines including IL-β, TNF and IL-6 [49]. Therefore, by diminishing the Th17 cell population or inhibiting the effects of IL-17, AA outcome may be improved. This notion was supported by the observation that ADTA, which responds better to treatment and has a better prognosis, showed lower concentration of IL-17 cells [48].

**Abatacept**

Defects in T cell activation resulting from dysregulation of the *CTL4* gene have been implicated in the development of AA [50,51].This gene codes for a co-stimulatory ligand expressed on activated T cells that binds CD80 and CD86 on antigen presenting cells and is required for T cell activation. The immunosuppressive drug abatacept can block this activation signal by selectively binding to CD80 and CD86 on antigen-presenting cells.[52] Therefore, abatacept also decreases the production of inflammatory cytokines. However, because of its immunosuppressive effects, this drug has been associated with an increased risk of infections [50].

**JAK inhibitors**

It has been demonstrated that IL-15 levels are increased in AA and that blocking its signaling through the JAK/STAT pathway can reduce the inflammation observed in AA. Il-15 promotes the survival of CD8+ T lymphocytes, including self-reactive memory cells, facilitates production of certain immunoglobulins and contributes to NK cell survival [53]. The main signaling pathway of IL-15 and IL-2 involves JAK1/3 and STAT3/5, whereas IFNγ signaling activates JAK1/2 and, consequently, STAT1[53-54]. By blocking the pathways induced by these cytokines, the subsequent inflammatory effects can be reduced, [53] as direct blockage of IL-15R alone could prevent but not reverse AA in mice [54].

Tofacitinib is an FDA-approved JAK3 inhibitor for the treatment of rheumatoid arthritis. It has been observed to inhibit damage to dermal sheath cells induced by IL-15 [54]. In fact, a patient with AA universalis was reported to have complete hair growth after 8 months of treatment with tofacitinib [55].

Ruxolitinib is an FDA-approved JAK 1/2 inhibitor for the treatment of myelofibrosis. This drug was able to inhibit the effects of IFN-γ-induced IL-15 expression and STAT1 activation in dermal sheath cells [54]. Systemic administration of either JAK inhibitor in mice was able to prevent and reverse AA. Topical application also served to reverse AA [54]. Furthermore, near complete hair growth was observed in patients with moderate to severe AA treated for 3-5 months [54].

Despite the encouraging results obtained with JAK inhibitors, these drugs should be used with caution until further research is conducted, given their potential adverse effects and unknown effects on other systems [56]. For example, recent long-term studies with tofacitinib indicated a reversible, dose-dependent increase in serum creatinine [57]. This increase seems to be directly induced by tofacitinib, though the underlying mechanism remains unknown.

**Platelet rich plasma (PRP)**

PRP consists of a concentrate of growth factors and other bioactive compounds obtained from platelets that may have anti-inflammatory effects in AA. However, treating AA with PRP has shown inconsistent results. In one study, significant hair growth was observed in mice after PRP injections [58]. The authors demonstrated that PRP administration resulted in an increase of β-catenin (inducing anagen), FGF-7 (prolonging the anagen phase), and Bcl-2 (having an anti-apoptotic effect) in treated dermal papilla cells [58]. In another study, the authors demonstrated formation of new hair follicles and accelerated hair formation in grafts performed in nude mice treated with PRP [59] In a randomized trial, PRP significantly increased hair growth in patients with chronic AA compared to triamcinolone [60]. However, another study performed in patients with severe, chronic AA showed a variable response to PRP, and it failed to prevent disease involvement of new affected sites [61]. The authors hypothesized that a positive response might be mediated by TGF-β immunosuppressive actions [61]. Further studies are needed to investigate the efficacy of PRP for treating AA.

**Statins**

Statins have been found to have immunosuppressive properties, making them potentially useful in the treatment of AA [62]. They are able to alter the Th1/Th2 balance, interfere with the antigen presentation process, suppress IL-17 effects, inhibit mast cell degranulation, and inhibit lymphocyte migration [62]. Statins can inhibit STAT phosphorylation, which normally activates the transcription of several inflammatory cytokines [63-66]. Atorvastatin, for example, can also decrease the expression of MHC II. This leads to a reduction in antigen presentation and therefore reduced T cell activation and disruption of the immune privilege zone [62,67-69].

A case of AA universalis was reported to have hair regrowth 2 months after treatment with simvastatin and ezetimibe [70]. The authors hypothesized that statins shifted the Th1/Th2 balance in favor of Th2, limiting the production of IFN-γ. However, casualty could not be proven. Later, another two cases of AA totalis reported improvement after receiving the same treatment [71]. It is known that the combination of simvastatin and ezetimibe significantly decreases CRP levels [72]. We have observed prevention of HSP-induced AA development by simvastatin in mice (unpublished data). The untreated group had overall increased numbers of T cells, with CD4+ and CD8+ cells significantly increased.

**Phenol**

Contact irritants have been successfully used to "deviate" the immune attack typically directed against hair follicles in AA—specifically, phenol has been shown to have some efficacy as a contact irritant in AA [73]. A prospective study was performed using 88% phenol topically on AA patches [74]. After 9 weeks of treatment, the texture and pigmentation of hair significantly improved with 78% of patients showing a good to excellent response. Temporary hypopigmentation was noted in 10% of patients.

**Quercetin**

Quercetin is a bioflavonoid with anti-inflammatory properties that may be helpful in preventing and treating AA. Quercetin inhibits HSP70 and nuclear factor kappa B (NF-kB) [75].When extracellular, HSP70 can induce the production of inflammatory cytokines by means of NF-kB. Mice with AA showed hair regrowth after 8 days of subcutaneous quercetin treatment [75].It was also demonstrated that quercetin was able to prevent AA onset in heat-induced AA. Systemic administration of quercetin prevented and reduced AA onset in treated mice [75].

**Valproic acid**

It has been observed that valproic acid promotes hair growth in mice through increasing expression of β-catenin [76]. Activation of the Wnt/β-catenin pathway induces the hair follicles to enter anagen. The authors further described the effects of valproic acid on human hair follicles *in vitro* [77]. To date, its effectiveness has only been tested in androgenetic alopecia [78].

**Tianeptine**

Tianeptine is an anxiolytic and antidepressant (not available in the United States) that was proven to be effective in treating mice with AA-like lesions induced by ultrasonic wave stress [79]. Following treatment, increases in vitamin D receptor expression, hair cycle recovery, and synthesis of collagen and elastic fibers were observed along with mast cell degranulation and apoptosis around the hair follicle. However, tianeptine treatment was not more efficient than already-approved medications for the treatment of hair loss.

**Parathyroid hormone (PTH)**

The effects of PTH on the hair cycle have been studied with variable results [80]. PTH activates the Wnt signaling pathway in keratinocytes, increasing nuclear β-catenin, which in turn promotes the hair follicles to enter anagen [81]. A group of authors observed hair growth after the first day of treatment with PTH that lasted for 1-2 weeks [81]. Histological examination showed an increase in anagen follicles despite ongoing inflammatory response.

**Vitamin D**

Vitamin D deficiency has been implicated in autoimmune disorders because of its effects on lymphocytes [82]. It was demonstrated that AA correlated with vitamin D deficiency [82,83]. and its levels negatively correlated with disease severity [83]. Seasonal variations in AA have also been observed; those with chronic or frequently relapsing AA had reduced vitamin D levels, although these reductions were not statistically significant [84].

It was demonstrated that an adequate hair cycle generation required functional vitamin D receptors in keratinocytes, regardless of vitamin D levels [85]. A different study observed that a decreased expression of vitamin D receptors was associated with suppression of the wnt/β-catenin pathway and consequently suppression of proliferation and differentiation of hair follicles [86]. Overall, these data showed that correcting vitamin D levels in patients with AA might result in a positive outcome.

**Vitamin A**

Deficiency or excess of vitamin A can result in alopecia by different mechanisms. Vitamin A can promote strong immune responses and therefore affect AA [87-89]. Duncan *et al.* demonstrated an increased expression of genes involved in the metabolism of retinoids in AA [88]. Therefore, modulation of retinoid metabolism and its role in AA should be further studied.

**Microneedling**

The use of microneedling has been applied to improve acne scars, facial rejuvenation, and hair growth [90]. It has been hypothesized that this technique stimulates hair growth by stimulating the dermal papillae and stem cells, improving blood flow to hair follicles, and recruiting growth factors induced by the microinjury [91]. In a study of two patients with refractory AA, the combination of microneedling and triamcinolone acetonide led to excellent results with no recurrence at 3 months and no adverse effects, in both patients [91]. In another study, refractory AA was treated with a scalp roller and application of a mixture of triamcinolone acetonide, minoxidil, and a solution rich in growth factors and amino acids [92]. All showed notable improvement, with patchy AA showing the most improvement, followed by AA universalis and AA in ophiasis pattern.

**Low-level Laser Therapy (LLLT)**

The use of low-level laser therapy in hair loss has been studied mostly in androgenetic alopecia with positive results [93-95]. The LaserComb® device, for example, is cleared by the FDA for the treatment of androgenetic alopecia in men and women. When the LaserComb was used to treat heat-induced AA in C3H/HeJ mice, hair regrowth and an increased number of hair follicles in anagen phase on histology were observed in comparison to controls [96]. However, these results were not reproduced in mice with spontaneous or graft-induced AA [97]. This could be due to the differences of the animal models used (the later has persistent, extensive AA) or the locations of treatment (dorsal versus ventral) [97].

**Electroacupuncture**

It has been reported that acupuncture can improve hair loss and decrease the medication dose used in AA patients [98]. Electroacupuncture to the ST36 *Zusanli* point has been demonstrated to significantly reduce mast cell degranulation around the hair follicle in mice with AA, improving hair loss [99]. The mechanism of action remains unknown.

## Conclusion

AA is a common disease entity with multifactorial and complex etiology that can be very frustrating for patients and their physicians. Here we have summarized recent literature in an attempt to better elucidate the pathophysiology of the disease. Additionally, we discussed current treatment options under investigation that could more specifically target AA, including those undergoing clinical trials. However, many of these drugs are systemic and have potential adverse effects. Therefore, further research is needed to improve local targeting of the disease and develop drug delivery systems in order to treat patients more effectively.

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