



Review

The autoimmune basis of alopecia areata: A comprehensive review

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ABSTRACT

Alopecia areata (AA) is a common, non-scarring dermatologic condition regularly distinguished by patches of hair loss on the scalp also manifesting in other, severe forms, including *alopecia totalis* (total loss of hair on the scalp) and *alopecia universalis* (complete loss of hair on the scalp and body). AA is a clinically heterogeneous disease with greatly varying yet typical symptoms, but the etiology for AA remains an enigma. However, clinical and experimental studies have pointed to autoimmune involvement, specifically regarding immune privilege sites of the hair follicles and the infiltration of CD4+ and CD8+ T cells and a predominant Th1 cytokine profile. Environmental insults, such as viral infections, trauma and genetic predisposition are also believed to contribute to the disease process. Multiple treatment options including the use of broad acting corticosteroids appear to be relatively effective in mild cases, however the clinical management of more severe forms of AA is much more difficult. Recent studies suggest that intervention of the JAK pathway may have a potential therapeutic efficacy for AA.

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1. Introduction

Autoimmunity can be the underlying cause of a broad spectrum of human disorders. As such, autoimmune diseases are difficult to diagnose and are often based on a multitude of clinical/laboratory markers [1,2]. For example, patients with autoimmune diseases often have a positive family history for the same disease, or for other diseases known to have an autoimmune etiology. Immunologically, there are prominent mononuclear cell infiltrations in the affected organ or tissue, high titer of serum autoantibodies and the presence of preferential usage of certain HLA haplotypes. The deposition of antigen–antibody complexes in the affected organ or tissue which is evident often leads to pathological damage; clinical symptoms are often improved with

Abbreviations: AA, alopecia areata; BECs, biliary epithelial cells; CMV, cytomegalovirus; CRH, corticotropin-releasing hormone; DNCB, dinitrochlorobenzene; DPCP, dephnylcyclopropenone; HF, hair follicle; HLA, human leukocyte antigen; GWAS, genome wide association studies; SNP, single nucleotide polymorphism; HPA, hypothalamic–pituitary–adrenal; NK, natural killer, ORS, outer root sheath; PBC, primary biliary cirrhosis; SADBE, squaric acid dibutyl ester.

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the use of immunosuppressive agents [3,4]. Autoimmune diseases are conventionally treated by immunologists according to the type of organ involvement, and are classified as organ specific or systemic autoimmune diseases. Autoimmune diseases are common, affecting 8% of the American population [5]. Some autoimmune diseases are rare while others are highly common. Although autoimmune diseases are more common in females, some autoimmune disorders such as alopecia areata are more prevalent in males. In this article, we will discuss the natural history, epidemiology, etiology, contribution of the autoimmune responses and the clinical treatment of one of the most common autoimmune disorders, alopecia areata (AA).

2. Natural history/clinical features of AA

AA is extremely unpredictable and varies greatly from person to person, causing the disease to have a wide spectrum of features (Table 1). This extensive range of symptoms makes AA difficult to diagnose, and no regulated consistencies of disease analysis have been agreed upon. The most common clinical presentation of AA is a circumscribed area of bald skin on the scalp, which is usually isolated from other patches, as seen in 90% of clinical diagnoses (Fig. 1). There is typically no scarring or inflammation on the scalp itself. Remaining hairs take on an 'exclamation point' resemblance, consisting of short, thin hairs tapering to the end. These hair-loss characteristics, however, may also be found in other patterns, such as reticular thinning or diffusion. Such extensive patterns may include the distribution-ophiasis form usually with a band of hair loss around the scalp, or its complete opposite—a scalpsisapho pattern that includes hair loss on the central part of the scalp [6]. Since AA is so dynamic, patches may be seen in other areas of the body such as elbow, arms and thigh (Fig. 2). In addition, the disease may involve facial hair, including eyelashes, eyebrows, and the beard area. As previously mentioned, alopecia totalis includes total hair loss on the scalp, and alopecia universalis is diagnosed with 100% loss of both scalp and body hair. Pitting of the nails is also common in AA patients, seen in anywhere between 10% and 66% of cases [7]. AA is a systemic disease because, in addition to the hair follicles, it can also affect the nails and the eyes.

AA may also be responsible for the unfortunate sensation known as 'overnight graying', as it usually only causes darker hairs to fall out. Because alopecia is a non-scarring disease, hair regrowth is possible at diseased hair follicles. Non-pigmented hairs are usually spared by disease spreading, and grow back prior to normal pigmented hairs [8]. Less serious forms of AA can almost guarantee remission over a patient-dependent period of time, but even extreme cases such as alopecia universalis may be overcome at some point. Remission is fundamentally dependent on the prognostic factors presented by the individual. Poor prognosis that may foreshadow the prolonging of AA include early age of disease onset, a positive family history and atopy.

[9]. Otherwise, spontaneous regrowth of hair in the isolated bald patches can be expected.

Immunohistologically, AA is characterized by the presence of lymphocytic infiltration, comprised of T-cells, adjoining the HF site [10, 11]. CD4+ T-cells constitute the majority of lymphocytes in the HF area, whereas CD8+ T-cells are commonly seen in the follicular epithelium. These immunological findings reflect the potential contribution of autoimmune responses to AA, as opposed to other dermatological conditions on the scalp [12]. Apart from AA, multiple other dermatological conditions with similar symptoms exist, often making it difficult to distinguish one disease from another [13,14] (Table 1).

3. Epidemiology

AA is a relatively frequent disease with a prevalence of 0.1%–0.2% worldwide [15,16]. Among different races and ethnic groups, the prevalence can range, from 0.9% to 6.9% [17]. Notably, individuals with Down's syndrome seem to have a slightly higher incidence [12]. In the United States, one study reported that about 14.5 million patients suffer from AA, constituting about 2% of the national population [17], while another study suggested that only about 5.3 million in the U.S. are clinically affected [18]. Overall, AA seems to account for about 0.7%–3% of all patients in the United States [19], and about 2% in the United Kingdom [12] (Table 2).

The likelihood of diagnosis of AA during one's lifetime is thought to be around 1.7%, regardless of demographical location, affecting both genders and all age groups [13,15,20,21]. Although both men and women are affected, men seem to be more frequently associated with the more severe cases of alopecia than women [17]. The onset of AA is more likely early in life. For example, various studies have reported that the peak incidence of AA occurs prior to 20 years of age, with about 60% of cases experiencing their first manifestation of hair loss during their late childhood/early adulthood [12,17,22]. Other studies report that only 44% of patients manifest disease onset before their 20s, but still agree that less than half of AA patients are diagnosed after age 40 [15]. In fact, a study of a cohort of Asian AA patients reported that 85.5% of the AA patients had their first episode of AA before the age of 40 years [19,23]. Of note, diagnoses of AA in prepubescent individuals seem to indicate poor prognosis [12,22].

The epidemiology of AA also reflects the contribution of heredity factors. Of the 0.1% of the human population that developed AA, 10% to 42% reported a positive family history of AA, usually involving at least one first-degree relative [13,17,24]. The age of onset of AA also reflects familial history, with nearly 40% of cases having a positive familial history if diagnosed before age 30, but only about 7% if onset occurred later on in life [24]. Twin studies tend to show a concordance rate of about 55% [24], implicating the contribution of heredity factors in AA (Table 2).

Table 1
Clinical features of AA and related dermatological disorders.

Disease	Clinical features	Classification	Affected populations
Alopecia areata (AA)	-One or more circular bald patches around the scalp -Presentation of 'exclamation point' hairs -Loss of pigmented hairs, white hairs remaining on scalp -Ophiasis or sisipho patterns display AA variations	-Inflammatory -Non-scarring	-1.7% prevalence -No male/female discrimination
Alopecia totalis (AT)	-Complete loss of hair on the scalp -Most extreme form of AA		
Alopecia universalis (AU)	-Complete loss of scalp, facial, and body hair		
Androgenetic alopecia (AGA)	-Miniatrization, not complete loss, of hairs -Bitemporal/vertex pattern of balding	-Non-inflammatory -Non-scarring	-Predominant in Caucasian men -50% prevalence by age 50
Female pattern hair loss (FPHL)	-Miniatrization similar to AGA -Widespread thinning in the central area of the scalp	-Non-inflammatory -Non-scarring	-Predominant in women -20%–30% prevalence by age 50
Telogen effluvium (TE)	-Uniform hair loss across the scalp, not just the crown/discrete patches -Generalized hair shedding, club hairs from hair-pull test -Rapid disease onset following distinct trigger	-Non-inflammatory -Non-scarring	-More prevalent in women -Triggers include physical/emotional stress, childbirth

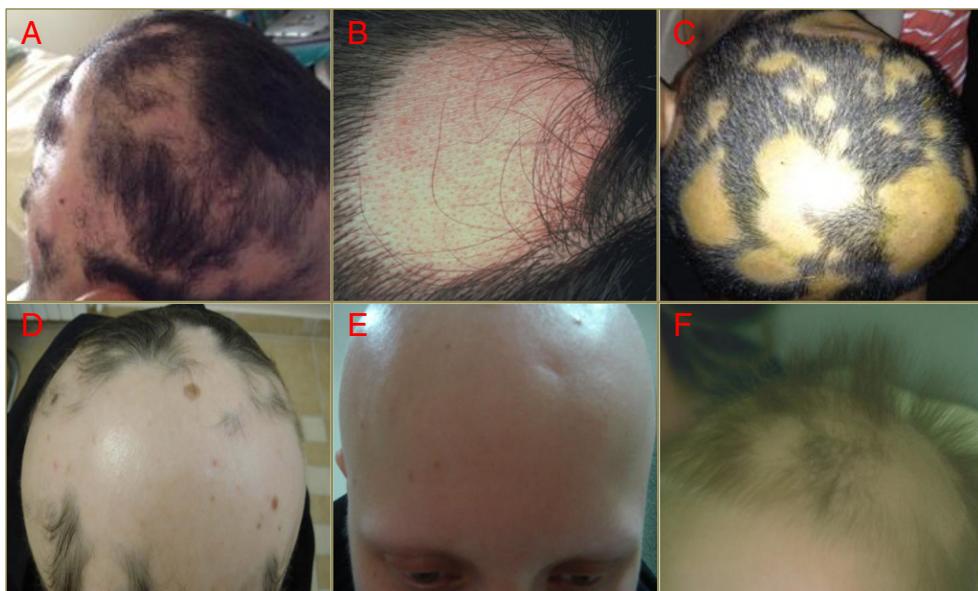


Fig. 1. Clinical manifestation of alopecia in the scalp. Alopecia can presented in a wide spectrum characterized by focal patches of hair loss on the scalp to extensive involvement of the scalp (A, B, C, D) and total loss of hair over the entire scalp and involving the eyebrows (E). Alopecia is also seen in infant. In this age group, it is more common to see patchy alopecia resulting from tinea capitus (F).

4. Etiology

The etiology of AA is still unclear. Herein, we will examine the current literature with respect to genetic susceptibility, environmental factors, and the contribution of autoimmune responses within the hair follicle autoimmune privilege site in AA.

4.1. Genetic susceptibility

The genetic basis of AA is strongly supported by its observed heritability in first degree relatives, twin studies and genetic linkage analysis of AA families. In AA patients, first-degree relatives are associated with the disease in about 10% to 42% of cases. Among them, 7% of patients have at least one parent with AA, 3% have at least one sibling with the disease, and a minority of 2% have a child who also suffers from AA. In addition, there is a very high concordance in monozygotic twins [25]. A genome wide search for linkage of 20 families with AA consisting of 102 affected and 118 unaffected individuals demonstrated the association of HLA with AA [26]. Of the HLA class II genes that are known to have associations with AA, the DQ3, DQ7, DR4, DR5, and DPW4 alleles are particularly involved. In addition to class II alleles, AA also includes the involvement of particular class I HLA alleles as well, albeit less frequently. For example, A1, B13, B18, B52-Cw*0704, B27, B40, B44, B62 are involved. Along with these HLA alleles that potentially

contribute to the diagnosis of AA, certain regions of the human genome are associated with the more severe disease. DQ3, DR11, and DQ7 are suggested to predispose to alopecia totalis and alopecia universalis. Another notable genetic association is DRB1*04 in patients that suffer from AA, and a reduction in DRB1*03 alleles. These alleles are more or less specific to various ethnic identities, and therefore genetic associations depend on the patient's particular geographical location and ethnic background [17,20,27,28] (Table 3).

In a GWAS study of 1054 AA cases and 3278 controls, Petukhova et al. [18] reported that eight genomic regions, including loci encoding genes in both innate and adaptive immunity are associated with AA. These include loci on chromosome 2q33.2 containing the CTLA4 gene, chromosome 4q27 containing IL-2/IL-21 genes, chromosome 6p21.32 containing the HLA segment, chromosome 6q25.1 containing the ULBP genes, chromosome 10p15.1 containing IL-2RA (CD25), chromosome 12q13 containing Eos (IKZF4) and ERBB3 genes, chromosome 9q31.1 containing the syntaxin 17 gene and chromosome 11q13, upstream from peroxiredoxin 5 (PRDX5). A follow up study of this GWAS on five of these loci including IL-2/IL-21, ULBP, IKZF4/ERBB3, syntaxin 17, PRDX5 confirmed their validity, in addition IL-13 and KIAA0350 were also identified as susceptibility loci in AA [29]. Using a genome wide pooling approach, a SNP corresponding to an intronic region of the SPATA5 (spermatogenesis-associated protein 5) gene on chromosome 4 was identified as a potential susceptibility locus for AA [30]. More recently, additional loci within the IL-4 intron 3, promoter regions



Fig. 2. Clinical manifestation of alopecia in other parts such as in elbow (A), arms (B), beard area (C) and thigh (D).

Table 2
Epidemiology of alopecia areata.

Disease prevalence	Disease incidence	Age	Family history	Miscellaneous	References
Higher prevalence with Down's syndrome 0.1%–0.2% worldwide	1.7% worldwide	60% before age 20	20% of patients	More prevalent with Down's syndrome	[104,105]
0.1%–0.2% worldwide	1.7% worldwide	60% before age 20; Peak: 30–59 years	8.7%–20% of patients	Dermatology clinics: 2%–3% (US/UK); 3.8% (China); 0.7% (India)	[23,106–111]
0.1%–0.2% worldwide	–	44% before age 20; 30% after age 40	–	0.7%–3.8% of dermatology clinics	[108,112,113]
0.1% worldwide; 2% of US; 8.8% with Down's syndrome 1%–2% worldwide	1.7% worldwide	60% before age 20; 70% between ages 10 and 25	10%–42% of patients	3%–42% heritability of disease; Severity distribution 63% men, 36% women	[7,108,114–118]
–	–	–	55% twin concordance; 5%–6% recurrence in children of patients	–	[108,119,120]
5.3 million in US 1%–2% worldwide	1.7% worldwide	–	–	–	[108,121]
0%–1% worldwide	–	–	–	–	[108]
1%–2% worldwide	1.7% worldwide	30%–48% before age 20 60% before age 20	20%–40% of patients 10%–42% of patients	4.5%–30% are more severe cases 20%–30% of patients have other autoimmune diseases	[48,108,122,123]
–	1.7% worldwide	85.5% before age 40 in Asian population	–	0.7%–3.7% of dermatology clinics	[23,106,107]

of Foxp3 and ICSOLG genes have been found to be associated with AA [31,32].

4.2. Environmental factors

Clinical and experimental studies showed that environmental insults such as emotional/physical stressors, hormones and infections contribute to autoimmunity [33–36]. Stress hormones, in their efforts to maintain dermatological homeostasis in reaction to their environment, are known to affect AA [19]. These particular stressors in relation to diagnosed hair loss include exposure to ultraviolet light, natural and chemical bodily offenses, physical injury, and emotional distress. The human hair follicle (HF) appears to parallel the basic functionality of the hypothalamic–pituitary–adrenal (HPA) axis in the skin, incorporating the specific stress hormones that are accepted as prospective origins of alopecia [37]. Corticotropin-releasing hormone (CRH) is widely known to be a significant stress-induced component of the larger HPA axis [37]. Studies have shown that CRH and its receptors, CRH-R1, are expressed within the outer root sheath (ORS) of the HF, and the gene transcriptions of both hormone and receptor take place at the HF site [38]. Clinical observations document that in the affected dermatological lesions of AA patients, there appeared a distinct association with

CRH-2B (a subset of the CRH). This is in contrast to the much weaker signals of CRH-2B in both healthy subjects and the unaffected skin in AA [39]. The diseased areas, especially the epidermis and sebaceous glands of the HF, also have an increased expression of CRH, adrenocorticotropic hormone, and α -melanocyte-stimulating hormone when compared to healthy individuals [39–41].

The association of cytomegalovirus (CMV) was initially proposed by Skinner based upon the presence of CMV DNA sequences in skin biopsies of patients with AA [42]. However, this has been refuted [43]. Other viruses, including hepatitis B, hepatitis C, Epstein–Barr, and swine flu have also been suggested to trigger AA [44–48]. Theories have also been put forward regarding seasonal associations, with evidence of increased disease relapses between the months of February and March. This may also be a result of the high multitudes of viruses in early spring, supporting the hypothesis that AA may be an effect of certain viral infections.

4.3. Contribution of autoimmune responses in AA

Autoimmunity generally arises from defects in immune tolerance, which results in the generation and proliferation of autoreactive T cells and autoantibodies [49–51]. We discuss primary biliary cirrhosis

Table 3
HLA gene associations with alopecia by nationality.

Geographic location	HLA class	Genetic alleles	Associated disease
America [17]	HLA class I	B40	Alopecia areata
China [128]	HLA class I	B52-Cw*0704	Alopecia areata
Denmark [17,129]	HLA class II	DQ7 (DQB1*0301)	Alopecia areata
Denmark [17,129]	HLA class II	DR4	Alopecia areata
Denmark [17,129]	HLA class II	DPW4	Alopecia areata
Finland [130]	HLA class I	B44 (B12)	Alopecia Areata
Israel [131]	HLA class I	B18	Alopecia areata
Italy [17]	HLA class II	DR4	Alopecia areata
Russia [132]	HLA class I	B13	Alopecia areata
Russia [133]	HLA class I	B27	Alopecia areata
Turkey [17,133]	HLA class I	A1	Alopecia areata
Turkey [17,133]	HLA class I	B62, CW3	Alopecia areata
United Kingdom [17]	HLA class II	DR4	Alopecia areata
United States [17,134]	HLA class II	DQ3 (DQB1*03)	Alopecia areata
United States [17,134]	HLA class II	DQ3 (DQB1*03)	Alopecia totalis/universalis
United States [17]	HLA class II	DQ7 (DQR1*0301)	Alopecia totalis/universalis
United States [17]	HLA class II	DR4	Alopecia areata
United States [17]	HLA class II	DR5 (DR11)	Alopecia areata
United States [17]	HLA class II	DR11 (DRB1*1104)	Alopecia totalis/universalis

(PBC) because it is also an organ specific disease and has many analogies to the specificity of AA [52–60]. PBC is a chronic cholestatic liver disease histologically characterized by the immune mediated destruction of biliary epithelial cells (BECs) and small bile ducts with portal inflammatory cell infiltration. Damaged BECs lead to the development of fibrosis, cirrhosis and liver failure. Serologically, over 95% of patients with PBC also have high titers of antimitochondrial antibodies [52,56,61]. Extensive efforts in defining the target mitochondrial autoantigens, T and B cell epitopes, the innate and adaptive immune responses, the immunobiology of the biliary epithelium, and the pathology of biliary cell destruction have greatly advanced the knowledge of the molecular mechanisms in the pathogenesis of PBC [54,59,61–68]. These have led to therapeutic designs in mouse models and clinical trials in patients with PBC [69–72].

Autoimmunity in AA is strongly supported by clinical observations that patients with AA are often diagnosed with one or more other autoimmune disorders, including vitiligo, lupus erythematosus, myasthenia gravis, scleroderma, ulcerative colitis, Type I diabetes, thyroiditis, celiac disease, and rheumatoid arthritis [48,73]. In addition, the effectiveness and efficacy of various immunosuppressive agents including cyclosporine and systemic corticosteroids; immunotherapy drugs, particularly contact sensitizers, such as dinitrochlorobenzene (DNCB), squaric acid dibutyl ester (SADBE), and diphnylcyclopropenone (DPCP) [74] also suggest an autoimmune mechanism. Further, the human leukocyte antigens (HLA) has been reported to play a major role in the etiology of autoimmunity [75,76]. A confirmation of this specific hypothesis in AA lies in the increased expression of specific HLAs in AA patients such as HLA-DR, HLA-A, HLA-B, and HLA-C, which are rarely seen in healthy individuals [11,77] as well as the identification of a number of genetic risk factors within various innate and adaptive immunity gene loci [18].

The most widely accepted hypothesis for the effector mechanism of AA is the destruction of the HF, an immune privilege site. Within the HF itself, individuals without AA maintain immune privilege in multiple ways, such as omitting MHC class 1 in the proximal outer root sheath (ORS). Conversely, patients identified with AA have a strong association with those same MHC class 1 alleles. Autoreactive cytotoxic T cells

target specific autoantigens, especially melanogenesis-associated peptides expressed by anagen HFs that produce the melanin pigment [78, 79]. This is consistent with sparing of unpigmented hairs, and regrowth of initially white or gray hairs following onset of AA [80]. Additionally, it has been proposed that follicular melanocytes are also affected. The general exposure of these autoantigens in the follicles of diseased individuals then attracts a multitude of lymphocytes in the hair bulb area [21]. The repertoire of cells at the HF is comprised of natural killer (NK) cells, 20%–40% CD8+ T-cells, and 60%–80% CD4+ T-cells [81, 82]. Another associated cytokine, IFN- γ , has been observed to potentially upregulate MHC class 1 alleles, increasing the possibility of the destruction of the HF immune privilege [83]. Chemokines are involved with the development of autoimmune interactions [84–87], involving Th1 chemokines (specifically CXCL9/MIG and CXCL10/IP-10) that are more prominent in AA patients than healthy individuals [88]. Other cytokines that may potentially be associated are IL-1, IL-2, IL-4, and IL-10, along with macrophage migration inhibitory factor and tumor necrosis factor (TNF, including the B-cell activating factor subset) [16]. Apart from research of AA-involved cytokines and chemokines, studies in the chemotaxis of lymphocyte accumulations demonstrated distinct activity of CXCL10 in regard to histological outcomes of acute AA [89,90].

With the growing interest of the NK cells in autoimmunity [91–93], its role in the pathogenesis of AA has also been investigated. NKG2D is expressed in these NK cells, although they also are components of various T-cells. These cells attack by recognizing certain glycoproteins and CMV UL16 proteins, and MHC class I related proteins MICA/MICB [94]. In AA patients, the outer root sheath presents MICA proteins, leading NKG2D+ NK cells to target the HF [82]. The HF immune privilege of AA is maintained by being MHC class I negative, MICA negative with a low expression of NKG2D NK cells. The breaking of tolerance in HF and subsequent change in cytokine/chemokine profiles leads to infiltration of lymphocytes [18,19] (Fig. 3).

The C3H/HeJ mouse is a spontaneous mouse model of AA, which manifests the clinical pathological features of human AA including infiltration of CD8+ NKG2D+ T cells around the epithelial layers of HFs [95, 96]. Interestingly, the adoptive transfer of CD8+ NKG2D+ cells from

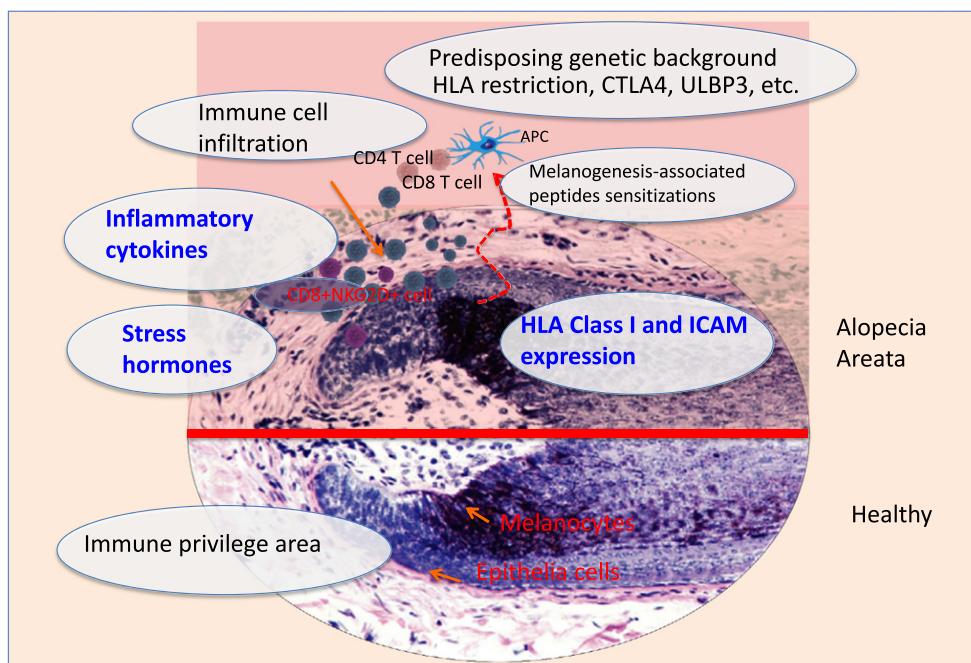


Fig. 3. Immunological cascade in the hair follicle in patients with alopecia areata. External stressors and inflammatory cytokines/chemokines lead to strong association of MHC class I, infiltration of autoreactive CD8+ and CD4+ T cells targeting the melanogenesis associated peptides on HFs and CD8+NKG2D+ cells within the immune privilege area of the hair follicle leads to immune mediated destruction of the hair bulb area and pathological development of AA.

alopecia C3H/HeJ mice induces AA in healthy recipient mice whereas the transfer of lymph node cells lacking NKG2D+ had no effect. C3H/HeJ mice also develop characteristics of AA when injected with IFN- γ , prompting MHC class I and II manifestations at HF. Global transcriptional profiling analyses of alopecia skin tissues from both human and C3H/HeJ mice identified three gene expression signatures including IFN response genes, cytotoxic T cell specific transcripts, and γ_c cytokines. Administration of blocking antibodies to either IL-2 or IL-15R β inhibit accumulation of CD8+ NKG2D+ cells in T skin, abrogate MHC regulation and prevent AA in a skin graft model of AA. Interestingly, systemic administration of Janus kinase (JAK) inhibitors including ruxolitinib and tofacitinib were able to inhibit the downstream effects of type 1 cytokines and eliminated the IFN γ signature and prevented the development of AA in the C3H/HeJ mice model of AA. Furthermore, topical administration of ruxolitinib and tofacitinib markedly reduced CD8+ NKG2D+ cells in treated skin. More importantly, the clinical response of a small number of AA patients receiving 20 mg ruxolitinib twice a day orally had near complete hair regrowth within three to five months of treatment [96].

5. Clinical treatments

The onset of hair loss, especially in women and children, may cause psychological distress [22,97]. Treatment options are limited and still being developed [12]. AA patients with only mild forms of the disease are normally advised to avoid unnecessary medication, as spontaneous regrowth is probable [22]. Broad-acting intralesional corticosteroids are relatively effective (Table 4). However, the severe forms of alopecia are much harder to treat, and the only potential medications known to have efficacy with handling these diseases are allergic contact sensitizers

through immunotherapy. This method of management works by inducing mild dermatitis on the affected skin, therefore averting the diseased HFlymphocytes from the scalp to the newly irritated area on the epidermis [98]. Unfortunately, the efficacy of this treatment has not always been recapitulated. Other treatments have also been suggested, including various formulations of corticosteroids, minoxidil, anthralin, topical immunotherapy, and sulfasalazine [74]. Biologics are actively sought as possible therapeutics in autoimmune diseases as in the case of primary biliary cirrhosis [69–71,99]. Medications for AA are still being developed and researched, and hopefully will provide a suitable treatment for alopecia in the future.

6. Future directions

AA is a relatively common dermatological and autoimmune disorder. Although AA is not life threatening, it can cause severe emotional and psychological distress. Data from epidemiological studies, clinical observations, immunological and pathological studies together with familial and molecular genetic studies indicate that autoimmune disorders are cumulative results of immunological, environmental, and genetic factors [57,100–103]. Continuous advances in dissecting underlying mechanisms will likely make inroads towards better treatments. At present, a multitude of questions remains to be answered in AA: how do genetic factors, such as HLA associations and MHC allele expressions, affect disease vulnerability or prognosis? What are the factors that regulate the HF immune privilege and the AA process? How do we apply understanding of the biology of HF to the pathogenesis of AA? How do AA autoantigens play a role in the pathogenesis of the disease? In order to answer these impending inquiries, new research strategies to further understand the etiology and pathogenesis of AA must be developed.

Table 4
Treatments for alopecia areata.

Name of treatment	Dosage recommendations	Efficacy	Other information
Topical corticosteroids	<ul style="list-style-type: none"> -Fluocinolone acetonide 0.2% cream; betamethasone deprolon dipropionate 0.05% lotion; betamethasone valerate 0.1% foam; clobetasol 0.05% foam; OR 0.1% halcinonide -Apply on affected area and 1 cm beyond circumference of bald patch 	<ul style="list-style-type: none"> -28.5%–61% achievement of regrowth -37.5% of patients did suffer relapses 	<ul style="list-style-type: none"> -Usually primary stage of treatment due to convenient application -Recommended for children diagnosed with AA -Potential side effects include atrophy, folliculitis, or telangiectasia
Intralesional corticosteroids	<ul style="list-style-type: none"> -Triamcinolone acetonide is best option -Inject with 30-gauge needle 5 in. long -Repeat at different sites, 1 cm apart -10 mg/ml for scalp, 2.5 mg/ml for face -Max. 20 mg/ml per injection (every 4–6 weeks) 	<ul style="list-style-type: none"> -Success rates 60%–75% -Disease remission should be seen in 4 weeks 	<ul style="list-style-type: none"> -Potential side effects include skin atrophy, hypopigmentation, telangiectasia, heightened cataract/intra-ocular pressure, or anaphylaxis (rarely)
Systemic corticosteroids	<ul style="list-style-type: none"> -0.5 mg/kg/day of oral dexamethasone -40 mg/month intramuscular triamcinolone acetonide -Prednisolone 200 mg/week for 3 months -5 mg betamethasone twice a week/6 months 	<ul style="list-style-type: none"> -26.6%–36.6% success for dexamethasone -60% success prednisolone -75% success betamethasone 	<ul style="list-style-type: none"> -Extended periods of use should be avoided -Effective for AA patches, but not as beneficial for more extensive forms of the disease (AU, etc.) -Potential side effects include dermatitis or pruritus -Studies show that 3% female consumers grew undesired facial hair
Minoxidil	<ul style="list-style-type: none"> -Applied twice a day -2% or 5% solution (2% less effective) -Combination with corticosteroids promotes efficacy -Foam form less likely to stimulate side effects 	<ul style="list-style-type: none"> -Effective in extensive AA (but not AT or AU) 	<ul style="list-style-type: none"> -Studies show that 3% female consumers grew undesired facial hair -May be good choice for children with AA -Potential side effects include folliculitis, regional lymphadenopathy, or irritation -Physical contact with allergen should be avoided by using gloves and aprons -No data on safety during pregnancy -Allergic reactions may occur, due to the mechanisms of the contact sensitizers
Anthralin	<ul style="list-style-type: none"> -Short-contact cream, 0.5%–1% -Applied for 20–30 min. daily, 2–3 weeks 	<ul style="list-style-type: none"> -Efficacy not well established 	
Topical immunotherapy/contact sensitizers	<ul style="list-style-type: none"> -Dinitrochlorobenzene (DNCB), diphenyl-cyclo-propenone (DPCP) OR squaric acid dibutyl ester (SADBE) -2% solution is advised -Apply onto 4 cm \times 2 of affected scalp, left on for 1–2 days 	<ul style="list-style-type: none"> -36% acceptable regrowth with DNCB -50%–60% success with DPCP/SADBE 	
Sulfasalazine	-0.5 g twice daily/month, then 1 g twice daily/month, then 1.5 g twice daily/3 months	-Moderate disease remission in 23%–25.6% of cases	<ul style="list-style-type: none"> -Potential side effects may include gastrointestinal distress, fever, rash, hepatotoxicity, headache, or hematological abnormalities

Take-home messages

- Alopecia areata is a non-scarring hair loss disorder that has a relatively high prevalence with no discrimination as to age, gender, or ethnicity.
- Etiology for this disease may be attributed to genetic predispositions, environmental factors, or autoimmune conditions specific to the patient.
- The destruction of the hair follicle immune privilege site may contribute to the pathogenesis of the disease, resulting in a predominantly CD8+ T-cell infiltrate at location of the follicle.
- No current treatments have been widely accepted to have complete and satisfactory efficacy. Current clinical management of AA are primarily directed towards the symptoms and psychological distress.

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Neutrophil-mediated IFN activation in the bone marrow alters B cell development in human and murine systemic lupus erythematosus.

In appropriate activation of type I IFN plays a key role in the pathogenesis of autoimmune disease, including systemic lupus erythematosus (SLE). In this study, **Palanichamy A. et al (J Immunol. 2014; 192(3): 906-18)** report on the presence of IFN activation in SLE bone marrow (BM), as measured by an IFN gene signature, increased IFN regulated chemokines, and direct production of IFN by BM-resident cells, associated with profound changes in B cell development. The majority of SLE patients had an IFN signature in the BM that was more pronounced than the paired peripheral blood and correlated with both higher autoantibodies and disease activity. Pronounced alterations in B cell development were noted in SLE in the presence of an IFN signature with a reduction in the fraction of pro/pre-B cells, suggesting an inhibition in early B cell development and an expansion of B cells at the transitional stage. These B cell changes strongly correlated with an increase in BAFF and APRIL expression in the IFN-high BM. Furthermore, they found that BM neutrophils in SLE were prime producers of IFN- α and B cell factors. In NZM lupus-prone mice, similar changes in B cell development were observed and mediated by IFN, given abrogation in NZM mice lacking type-I IFNR. BM neutrophils were abundant, responsive to, and producers of IFN, in close proximity to B cells. These results indicate that the BM is an important but previously unrecognized target organ in SLE with neutrophil-mediated IFN activation and alterations in B cell ontogeny and selection.