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## **Alopecia Areata: A multifactorial autoimmune condition**

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### **Highlights**

- Alopecia areata is a polygenic and multifactorial autoimmune disease characterised by non-scarring hair loss.
- Autoreactive CD8<sup>+</sup>, CD4<sup>+</sup>, natural killer cells and plasmacytoid dendritic cells infiltrate around the hair follicles during the growth (anagen) phase.
- Increased cytokine activity, particularly IFN- $\gamma$ , results in disruption of the hair follicle immune privilege and premature termination of the anagen phase, followed by hair follicle atrophy and dystrophy in persistent disease.

### **Abstract**

Alopecia areata is an autoimmune disease that results in non-scarring hair loss, and it is clinically characterised by small patches of baldness on the scalp and/or around the body. It can later progress to total loss of scalp hair (Alopecia totalis) and/or total loss of all body hair (Alopecia universalis). The rapid rate of hair loss and disfiguration caused by the condition causes anxiety on patients and increases the risks of developing psychological and psychiatric complications. Hair loss in alopecia areata is caused by lymphocytic infiltrations around the hair follicles and IFN- $\gamma$ . IgG antibodies against the hair follicle cells are also found in alopecia areata sufferers. In addition, the disease coexists with other autoimmune disorders and can come secondary to infections or inflammation. However, despite the growing knowledge about alopecia areata, the aetiology and pathophysiology of disease are not well defined. In this review we discuss various genetic and environmental factors that cause autoimmunity and describe the immune mechanisms that lead to hair loss in alopecia areata patients.

### **Keywords**

Alopecia areata; polygenic autoimmune disease; autoreactive lymphocytes; oxidative stress; infection; JAK inhibitors

**Abbreviations:**

AIRE: Autoimmune regulator gene

CNS: Central nervous system

CXCL: Chemokine ligand

CXCR: Chemokine receptor

DC: Dendritic cell

DNCB: Dinitrochlorobenzene

DPCP: Diphenylcyclopropenone

GZMB: Granzyme B

HLA: Human leukocyte antigen

ICI: Immune checkpoint inhibitors

IFN- $\gamma$ : Interferon gamma

IgG: Immunoglobulin G

JAK: Janus kinase

MHC: Major histocompatibility complex

MIF: Migration inhibitory factor

NK: Natural killer cell

NKG2D: Natural killer cell receptor D

NKG2DL: Natural killer cell receptor D ligand

PDC: Plasmacytoid dendritic cell

ROS: Reactive oxygen species

SNP: Single nucleotide polymorphism

SOD: Superoxide dismutase

STAT: Signal transducer and activator of transcription

TCR: T cell receptor

TGF- $\beta$ : Transforming growth factor beta

Th1/17: T-helper cell

TNF- $\alpha$ : Tumour necrosis factor alpha

Tregs: Regulatory T cells

## 1. Introduction

Alopecia areata is an autoimmune disease characterised by hair loss due to inflammatory responses that target the hair follicles. Incidence of disease in the USA and UK is about 2%, but the data varies for different populations and in different studies, with global incidence ranging from 0.57% to 3.8% [1–4]. In addition, some paediatric studies report a higher prevalence in children ranging from 10-50%, especially for those with a family history of alopecia areata, indicating a genetic basis for disease development [5–8].

The onset and progression of alopecia areata are unpredictable. Spontaneous hair re-growth is estimated to occur in 80% of patients within a year after the first incidence of alopecia, and relapse or progression to alopecia totalis and universalis can occur at any stage [1,2,4,9]. Due to the high percentage of patients that experience recovery, alopecia areata has been described as a short-term transient condition, although, based on genetic studies of sufferers and from mouse models the disease can also have a chronic phase which is more likely to progress to more advanced stages characterised by widespread hair loss [10–12].

Although the exact cause of alopecia areata is poorly understood, genetics and immunity are confirmed as the most important contributors to disease. Infiltrates of T helper (Th) cells, cytolytic T cells, natural killer cells and plasmacytoid dendritic cells surround the lower part of the hair bulb during the anagen, the growth phase, where their autoimmune activities cause the collapse of the hair follicle immune privilege and alopecia (Figure 1) [10–18]. CD8<sup>+</sup> cells recruit early in disease and are thought to be the main cell type that initiates alopecia areata [12,15,16]. Autoreactive Th1, Th17, NK and CD8<sup>+</sup> cells produce IFN- $\gamma$  which disturbs hair follicle functioning and causes disruption of the hair growth cycle, premature hair loss and inhibition of hair growth [11,12,14,15,19]. Type 1 interferons, chemokines (e.g. CXCL10) and cytokines (e.g. IL-12/23, TNF- $\alpha$ ), have also been implicated in the maintenance of immune infiltrates and

disease manifestation [13,17,20]. Despite the autoimmune perturbations, the hair follicle is not destroyed, so the outcome is hair fall without scarring or permanent loss of tissue [11,12,14].

There are no therapeutics available for the prevention or cure alopecia areata. Various treatment options that target immune cells exist for the disease (Table 1), however the effectiveness varies between individuals and is dependent on the duration and stage of disease at commencement of treatment [21–23]. In addition, most treatments have a high relapse rate after the termination and are followed by negative side effects [21,23–25]. Sudden hair loss and disfiguration puts a psychological and economic burden on alopecia areata sufferers, and increases the risk of poor psychological health, low self-esteem and psychiatric morbidities [4].

Therein, we discuss the link between genetics, the immune response and other external factors which when combined result in alopecia areata pathophysiology. Understanding the cellular and molecular mechanisms underpinning this disease is crucial to the informed development of effective therapeutics for the treatment and cure of alopecia areata.

## **2. Inheritance of susceptibility for developing alopecia areata**

Alopecia areata is more likely to occur in patients with a family history of disease. Prevalence of disease in adult patients with a family history is estimated to range from 0% to 8.6% [1,2,4], and in children between 10% and 51.6% [5–8]. In addition, the occurrence of the disease in identical twins [26–28], siblings [29] and several generations of the same family [30,31], provides further evidence to support a genetic link. However, due to the frequency of the condition and variability in prevalence amongst individuals with a family history, the onset of alopecia areata is difficult to be predicted and does not follow any pattern. This suggests susceptibility to developing the alopecia areata is heritable, but that disease onset is likely to be environmental.

## **3. Alopecia areata is a polygenic autoimmune disease**

Genetic studies in both mouse models and in the human population have shown that alopecia areata is a complex, polygenic condition [10–12,32]. Many of the genes which are strongly associated with alopecia areata are also involved in a variety of other autoimmune diseases such as type 1 diabetes mellitus, multiple sclerosis, psoriasis, and inflammatory bowel disease (Table 2) [11,33,34]. Hundreds of single nucleotide polymorphisms (SNPs) have been identified in alopecia areata patients, many of which are found in genomic regions that control immune cell phenotypes, such as the activation and proliferation of regulatory T cells ( $T_{reg}$  cells), cytotoxic T lymphocytes, interleukin expression and antigen presentation (Table 2) [11,13,35]. The human leukocyte antigen (HLA) region that encodes important key regulators in humans and the major histocompatibility complexes (MHC), has been identified as a major genetic contributor to the phenotype of disease [33,36–39]. Another locus on chromosome 6 which contains the genes encoding the natural killer (NK) cell receptor D (NKG2D; *KLRK1*) and its ligands NKG2DL3 (*ULBP3*) and retinoic acid early transcript 1L protein (*RAET1L*; also known as *ULBP6*), has been found to be implicated only in alopecia areata and not in other autoimmune diseases, suggesting a crucial role in this disease (Table 2) [11,12,34].

These observations are further supported by findings in the C3H/HeJ mouse model, which is genetically susceptible to alopecia areata. The mouse equivalent of human leukocyte antigen (HLA) locus is the mouse histocompatibility locus H2, located on chromosome 17, which also contains several other orthologous genes which may be associated with human autoimmune alopecia [40]. C3H.SW-H2b/SnJ mice, that are C3H/HeJ congenic mice in which the H2k susceptibility locus is replaced with the H2b resistance locus, do not develop alopecia areata, further supporting the importance of HLA polymorphisms in disease [40]. Additionally, mouse models have identified another minor locus on chromosome 9 as being linked to alopecia phenotype, although underlying mechanisms have yet to be elucidated [40]. Similar to what is observed in humans, microarray studies on mouse models have identified around 42 genes which relate to inflammatory responses, expressed in early disease. An alteration in expression of 114 genes occurs in chronic stages of disease, with many of them regulating immunoglobulin responses [10]. Overall, similar to what is observed in humans, studies in C3H/HeJ mice have also shown the polygenic nature of the condition [10,32].

Another gene associated with alopecia areata is the autoimmune regulator (*AIRE*) on chromosome 21, mutations of which result in polyendocrinopathy candidiasis ectodermal dysplasia syndrome (APECED), which is associated with multiple autoimmune disorders (Table 2) [41–44]. Different polymorphisms of *AIRE* gene have also been associated with alopecia areata and universalis [41–43]. Patients with APECED have a 30% risk for developing severe and early-onset alopecia areata [41]. In addition, SNPs of *AIRE* have also been identified in people with alopecia areata without APECED, showing that they can be a major component of the genetic risk for developing the disease [43]. This gene encodes a protein which plays an important role in immunity by regulating the expression of autoantigens and negative selection of autoreactive T-cells in the thymus (NCBI, Gene ID: 326). The involvement of this gene in alopecia areata is supportive of the strong autoimmune nature of this disease [41,44].

#### **4. Immune responses and cells involved in Alopecia areata.**

Alopecia areata onset and progression is strongly influenced by the immune system. Skin biopsies of affected patients show lymphocytic infiltrates in and around the lower part of the hair follicle in the anagen (hair growth) phase [12,14]. The autoimmune activity at the site of the hair follicle has been linked to the disruption of the hair cycle and hair loss [4,11,12,45] In many cases alopecia areata coexists with other autoimmune diseases, such as thyroid disease, celiac disease, rheumatoid arthritis, and lupus erythematosus, with which can share the pathways that initiate autoimmunity [4,12,46].

Based on the genes identified as being dysregulated in alopecia areata, it is suggested that both the innate and the adaptive immunity contribute to the disease phenotype [10–12]. Upregulation of genes that control antigen presentation and co-stimulation suggests a role for dendritic cells and T cells in the development of antigen-specific immune mediated pathology. Many other genes such as NKG2D implicate cytolytic T cells and natural killer cells (NK), whereas the upregulation of immunoglobulin genes in late disease as seen in mouse models

implicates B cells and antibody production [10,11]. Predictions based on gene analysis can be confirmed in patients and mouse models. CD4<sup>+</sup> T cells are located alongside CD8<sup>+</sup> T cells in the hair follicle during the anagen phase in alopecia affected skin of human and mice [14]. Monoclonal antibody depletion of CD4<sup>+</sup> and CD8<sup>+</sup> cells in a murine model of chronic alopecia areata has been shown to improve hair regrowth [10]. In addition, anti-hair-follicle IgG antibodies are present in patients with alopecia areata, and reducing them by means of topical immunotherapy causes hair regrowth [47].

#### **4.1. CD8<sup>+</sup> lymphocytes as the main contributors in disease**

CD8<sup>+</sup>NKG2D<sup>+</sup>T cells (cytotoxic T cells) have been identified as major contributors of hair loss in alopecia areata and the first to infiltrate around the hair follicles (Figure 1) [12,15,16,48]. These cells are necessary and sufficient for the induction of the disease in mouse models [12,15]. The gene encoding NKG2D is upregulated in alopecia areata patients, and associated ligands NKD2DL3 and RAET1L are found overexpressed in the hair follicle cells of alopecia patients but not in unaffected individuals or those affected by any other inflammatory scalp disease [11]. In addition, *Cd8a* transcripts, the alpha component of the CD8 costimulatory molecule on CD8<sup>+</sup> T cells, increase early after engraftment of alopecia areata skin on mice, suggesting CD8<sup>+</sup> T cells recruit early in disease [14]. Similarly, transcriptional profiling of mouse and human affected skin has revealed gene expression signatures indicative of cytotoxic T cell infiltration, such as increased production of interferon- $\gamma$  (IFN- $\gamma$ ) and  $\gamma$ -chain ( $\gamma_c$ ) cytokines and receptors which are known to promote the activation and survival of IFN $\gamma$ -producing CD8<sup>+</sup>NKG2D<sup>+</sup> effector T cells (Figure 1) [15]. When IFN- $\gamma$ , interleukin-2 (IL-2) or interleukin-15 receptor beta (IL-15R $\beta$ ) are inhibited, the disease development is prevented by reducing the accumulation of CD8<sup>+</sup>NKG2D<sup>+</sup> T cells and the dermal interferon response on the skin of mouse models [15].

There is evidence that the CD8<sup>+</sup> T cells attack the hair follicle using Granzyme B (GZMB), a cytotoxic molecule produced by effector CD8<sup>+</sup> T cells (Figure 1). In hair follicles of humans affected by alopecia areata, Granzyme B (GZMB) and cytotoxic granule associated RNA binding protein I (TIA1) are both elevated [13]. In alopecia affected C3H/HeJ mice however, only *Gzmb* transcripts are increased, with no *Tia1* expression, suggesting that GZMB secretion may be more important for CD8<sup>+</sup> T cell driven pathology [14].

#### **4.2. Role of the Th17 and Treg cells in alopecia areata**

CD4<sup>+</sup> subtypes Th17 (CD4<sup>+</sup>IL-17A<sup>+</sup>) and Treg cells are found to contribute to autoimmunity in alopecia areata [19,49]. In alopecia areata patients, Th17 cells are infiltrated in dermis and around the hair follicles, and can be involved in cell-mediated autoimmunity [19]. These cells are also implicated in psoriasis and vitiligo, two autoimmune diseases reported as comorbidities of alopecia areata [4,12,19]. In addition, alopecia areata sufferers have an imbalance between Th17 and Treg cells, with Th17 levels in blood exceeding the Treg levels during active stages of disease [49]. For more severe alopecia areata however, Treg cells exceed the Th17 [49]. Such imbalance between Th17 and Treg cells in alopecia areata can result in inflammation and

autoimmunity through similar pro-inflammatory mechanisms reported in other autoimmune diseases [50].

#### **4.3. Plasmacytoid dendritic cells: a link between the innate and adaptive responses?**

Plasmacytoid dendritic cells (PDC) have been identified in infiltrates around the hair follicles of alopecia areata patients [17]. These are specialized dendritic cell populations with plasma cell morphology, express CD4, CD123, HLA-DR, blood-derived dendritic cell antigen-2 (BDCA-2) and Toll-like receptor (TLR)7 and TLR9 within endosomal compartments [17,51]. The PDCs are a link between the innate and adaptive immunity by controlling the function of myeloid DCs, T, B and NK cells [17,51]. They are absent from normal skin but can infiltrate upon injury or pathology, and are linked to inflammation towards infections, as well as autoimmunity in diseases such as lupus and psoriasis [17,51], two comorbidities of alopecia areata [46]. Upon activation they produce large quantities of type I interferons (IFN- $\alpha/\beta$ ) [51], which have been implicated in alopecia areata for inducing CD4<sup>+</sup>, CD8<sup>+</sup> and NK responses towards the hair follicles (Figure 2) [13]. How they recruit at the hair follicles is still undetermined, but it has been suggested that they could be the link between the innate and adaptive immune responses that eventually leads to hair loss in alopecia areata [17].

#### **4.4. Cytokine activity in alopecia areata**

Interferon gamma (IFN- $\gamma$ ) has been implicated in the pathogenesis of alopecia areata by interfering with the maintenance of the immune privilege of the hair follicle (Figure 1). The immune privilege of the hair follicle is usually maintained at the anagen phase by downregulation of expression of MHC class I molecules [16,52,53] and expression of NK and CD8<sup>+</sup> cell inhibitors such as macrophage migration inhibitory factor (MIF) and transforming growth factors (TGF)  $\beta$ 1 and  $\beta$ 2 [12,16,53,54]. IFN- $\gamma$  causes collapse of the hair follicle immune privilege by inducing ectopic expression of MHC molecules and ligands that stimulate NK-cell receptors (NKG2D) in the anagen hair bulb (Figure 1) [11,12,16,55,56]. Upregulation of these molecules on the hair follicle cells is responsible for the autoreactivity seen in alopecia areata (Figure 1) [12,16,53]. Furthermore, alopecia areata susceptible C3H/HeJ mice are protected from disease following deletion of the IFN- $\gamma$  gene, providing evidence of the important role of this cytokine in disease development [57].

In addition, IFN- $\gamma$  induced JAK/STAT signalling can interfere with the hair growth cycle. JAK/STAT signalling is suppressed in hair follicles during the anagen [58,59], as such signalling can inhibit proliferation and activation of hair stem cells [58], and result in reduction of angiogenesis [60]. Therefore, IFN- $\gamma$  induced JAK/STAT signalling could be the reason of the premature termination of the anagen phase in alopecia areata [16,53]. Inhibition of JAK/STAT signalling has shown to reverse alopecia symptoms and induce hair growth [59].

Tumour necrosis factor-alpha (TNF- $\alpha$ ) has been found to be increased in the serum of patients with alopecia areata and the extensive forms totalis and universalis compared to healthy control groups [61,62]. TNF- $\alpha$  is a proinflammatory cytokine involved in infections and



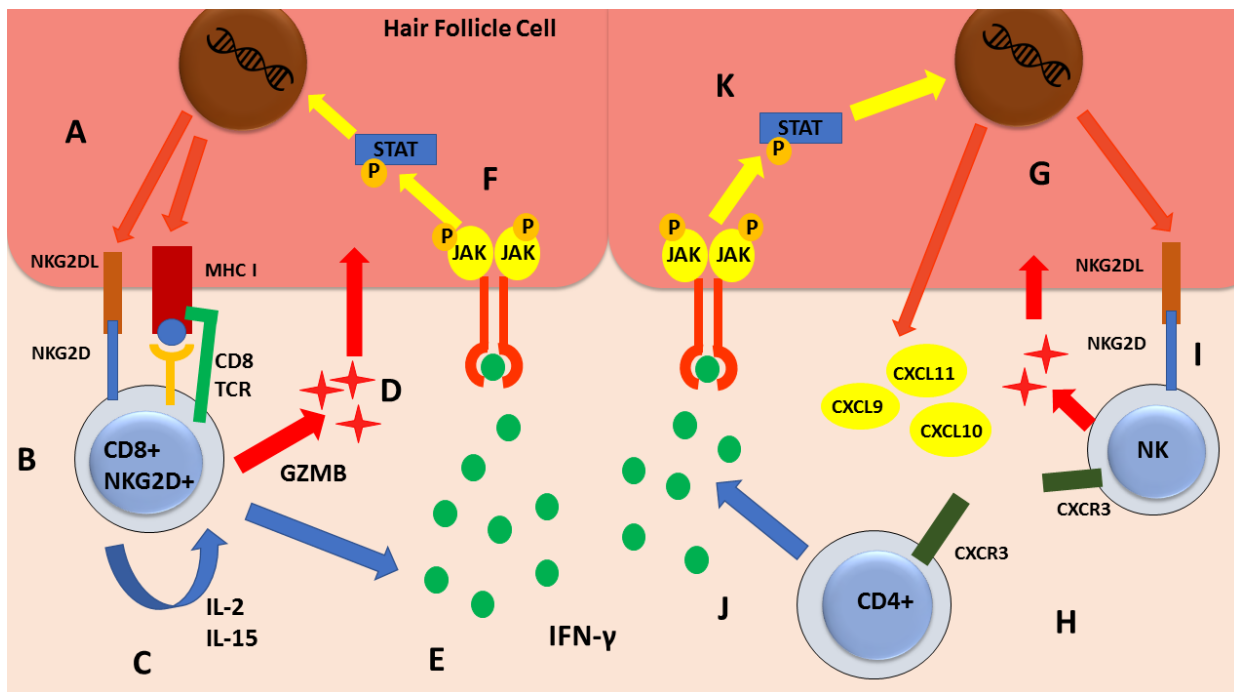
inflammatory disorders, and it is also a signalling molecule involved in differentiation and proliferation of cells [63]. This cytokine has shown to have both damaging and protective effect in a variety of autoimmune disorders such as rheumatoid arthritis, multiple sclerosis and systemic lupus [64], and certain polymorphisms of *TNFA* have also been implicated in alopecia areata [65] ( Table 2).

In alopecia areata skin TNF- $\alpha$  originates from T cell infiltrates [18]. The cytokine has shown to have anti-proliferation effect on epithelial cells and keratinocytes [18,61], and in *ex vivo* hair follicles the cytokine has disturbed the hair cycle and induced catagen morphology [20]. This means that the increased TNF- $\alpha$  in alopecia areata patients could be responsible in addition to other cytokines like IFN- $\gamma$  for the manifestation of disease. However, blocking TNF- $\alpha$  has not only been ineffective to treat alopecia areata, but such process has also induced the disease [66–68]. Interestingly, some studies have reported that TNF- $\alpha$  can inhibit MHC class I upregulation caused by IFN- $\gamma$  in hair follicle cells [69,70]. In addition, TNF- $\alpha$  is known to suppress the development of PDCs that produce high IFN- $\alpha$  levels which are responsible for the coordination of CD4<sup>+</sup>, CD8<sup>+</sup> and NK cell responses [17,71]. It has been suggested that the antagonism of TNF- $\alpha$  leads to alopecia areata by allowing uncontrolled IFN- $\alpha$  production from PDCs [17], as well as by interfering with the protection the cytokine could provide against IFN- $\gamma$  upregulation of MHC class I [69,70]. It can therefore suggested that TNF- $\alpha$  could be elevated in alopecia areata patients to provide some protection from IFN- $\alpha$  and IFN- $\gamma$  responses [17,69,70], but that nevertheless interferes with the keratinocyte differentiation and causes hair cycle disturbance (Figure 2) [20].

In addition, mouse models have shown an upregulation of CXCR3 and CXCR3 ligands, CXCL9 and CXCL10, around the hair follicle during early development of alopecia areata, resulting in the recruitment of lymphocytes and initiation of autoimmunity at the site (Figure 1) [14]. Mx2, the mouse homolog of human myxovirus protein A (MxA), an IFN $\gamma$ -related protein, has also shown to be upregulated. These observations are consistent with results from human studies where CXCR3 and MxA are found increased around the hair follicles of alopecia areata sufferers [13].

CXCR3 and ligands CXCL9, CXCL10, and CXCL11, all of which are strongly induced by IFN- $\gamma$ , are associated with many other autoimmune diseases including, rheumatoid arthritis, type I diabetes, psoriasis and systemic lupus erythematosus (Table1) [14,72]. CXCR3 is expressed primarily on Th1 CD4<sup>+</sup> T cells, CD8<sup>+</sup> T cells, NK and NKT cells, while CXCR3 ligands are secreted by many tissue resident cells including dendritic cells. Secretion of these chemokines results in recruitment of lymphocytes and enhanced Th1-mediated and natural killer cell (NK) mediated immune responses, with a positive feedback loop driven by further IFN- $\gamma$  produced by the Th1 and NK effector cells [72,73]. The recruitment of lymphocytes at the hair follicle can result in the onset of alopecia areata, whereas the positive IFN- $\gamma$  feedback loop can explain the duration and progression of disease by maintaining the lymphocytic infiltrates and enhancing Th1 activities.

Interestingly, the proinflammatory environment does not destroy the hair follicle tissue so the possibility remains for rescue of physiological function and hair growth [4,11,12,45]. The autoimmune responses disrupt the hair growth cycle by prematurely terminating the anagen phase forcing the hair follicle into the catagen phase that is followed by hair loss [12,16,53]. The hair follicle experiences dystrophy, but not complete destruction [16,53]. In addition, involvement of *STX17*, a gene involved in premature hair greying, and *ACOXL/BCL2L11* that control apoptotic and autophagy pathways, may indicate intrinsic issues related with the hair follicle cells that can result in loss of function independent of immune cell involvement [11,34]. This is indicative that the mechanisms by which the hair follicles are impaired in alopecia areata are not fully understood and more research is needed to elucidate the cellular and molecular events within the hair follicle before and during disease onset.



**Figure 1: Immune responses in the hair follicle during development of alopecia areata.** The hair follicle cells upregulate expression of MHC molecules, NKG2D (A) and chemoattractants (G). CD8<sup>+</sup> T cells expressing NKG2D become effector cells upon binding MHC class I-antigen complex and NKG2D ligand on hair follicle cells (B). Effector CD8<sup>+</sup> cells are maintained by the production of IL-2 and IL-15 (C), and produce Granzyme B (D) and IFN-γ (E). Granzyme B may promote cell lysis (D), but evidence suggests that the hair tissue is not fully destroyed in alopecia areata. IFN-γ which accumulates at the site of inflammation, signals through the JAK-STAT pathway and can induce further abnormal expression on hair follicle cells and impair the hair growth cycle (F). CD4<sup>+</sup> and NK cells are recruited to the hair follicle (H), as a result of chemokine expression by the hair follicle cells (G). NK cells also express the NKG2D and may attack the hair follicle cells upon binding the NKG2D ligand in similar manner as the CD8<sup>+</sup> cells (I). Effector CD4<sup>+</sup> and NK cells both produce IFN-γ (J), which then further induces the production of chemokines and other inflammatory molecules in a positive feedback loop (K, F).

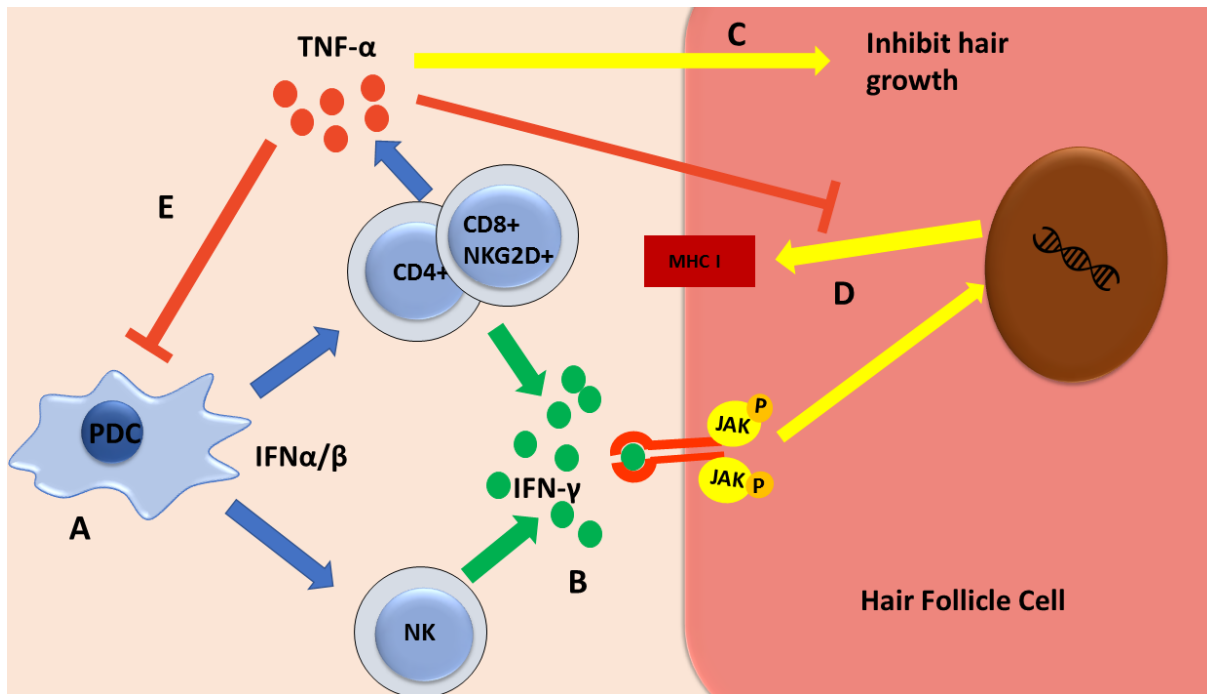


Figure 2: Plasmacytoid dendritic cells (PDC) are a source of type 1 IFNs in alopecia areata (A). They enhance CD8<sup>+</sup>, CD4<sup>+</sup> and NK cell activities and IFN-γ production (B). Lymphocytic infiltrates also produce TNF-α, a cytokine upregulated in alopecia areata patients. TNF-α can disrupt the development of keratinocytes and epithelial cells and thus affect the hair growth (C). However, it can also have protective effects as it has shown to inhibit IFN-γ induced MHC class I upregulation in hair follicle cells (D), as well as regulating IFN-α production by inhibiting PDC activity.

## 5. Other factors involved in initiation and progression of autoimmune Alopecia areata

In addition to the genetic predisposition for developing alopecia areata, there are different environmental factors that could initiate autoimmunity and disease. Different studies discussed further in this review indicate that alopecia areata is a multifactorial autoimmune disease with genetic and environmental aetiology (Figure 3).

### 5.1. Oxidative stress may damage hair follicles and initiate disease.

Alopecia areata and other skin diseases have shown to be affected by oxidative stress [74,75]. In alopecia areata patients, single nucleotide polymorphisms of antioxidant-encoding genes *PRDX5* and *ALDH2* have been identified to be associated with the disease phenotype, both hypothesised to interfere with the growth cycle of hair [11,34]. Furthermore, alopecia areata sufferers have higher levels of circulating malondialdehyde, a product of lipid peroxidation, and increased antioxidant activity of superoxide dismutase (SOD), when compared to healthy individuals [76]. In one study, 32% of patients suffering from alopecia areata were sero positive

for reactive oxygen species (ROS)-damaged SOD antibodies [75]. This study suggests that oxidative stress and SOD damage may be involved in compromised hair follicle function and disease progression. However, the oxidative processes in hair follicle cells are not well identified, and contradicting results can be found. To explain the accumulation of ROS, one particular regional study investigated polymorphisms of *SOD2* (MnSOD Ala-9Val), linked to increased H<sub>2</sub>O<sub>2</sub> accumulation and increased ROS production [77], and *GPX1* (GPx1 Pro 198 Leu), which impacts the optimal antioxidant response of GPx1, but found no association with alopecia areata [78]. This however, does not completely rule out that impairment of antioxidant function is responsible for increased oxidative damage, and expanding the range of antioxidants and participant populations is required to further elucidate.

In addition, ROS can be produced in response to different factors such as cigarette smoking, consumption of alcohol, prescription of nonsteroidal anti-inflammatory drugs, chronic infections, and inflammatory disorders [79]. Therefore, the presence of ROS in patients with alopecia areata can also be a result of treatment, infections, and/or chronic inflammation caused by the immune responses and other comorbidities.

## **5.2. Psychological stress as trigger of Alopecia areata?**

The relationship between psychological stress and the development of alopecia areata is controversial. Different studies have shown no influence of such stress in the onset of the disease [80,81]. Other studies however have shown that psychological stress can be a precipitating or aggravating factor for the onset of alopecia areata, as many patients have reported pre-onset stressful events compared to healthy control groups [82,83]. Some of these events go back years and as far as childhood, giving the disease a psychosomatic nature [83,84]. However, the psychosomatic aspects are also controversial as other studies have failed to record stress episodes from alopecia areata patients not late from the onset [85,86]. Since most studies have gathered data on patients with more than six months [83] to years [84] from the onset, the reliability is low as distant psychological events could have been linked with alopecia areata after the hair loss, in addition to the inability to recall events correctly after months of stressful living with the disease [86].

From a biological point of view, there is certain evidence to suggest role of the central nervous system (CNS) and acute stress in alopecia areata pathology [87,88]. Both corticotropin releasing hormone receptors (CRHRs) and adrenocorticotrophic hormone (ACTH) are upregulated in the skin of alopecia areata patients in response to acute emotional stress [87,89,90]. Immune cells, such as T and B cells, DC and macrophages can interact with the nervous system, particularly with the cholinergic system, as they express components such as muscarinic and nicotinic acetylcholine (ACh) receptors (mAChRs and nAChRs, respectively), choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) [91,92]. In acute stress the upregulation of hormones such as acetylcholine (ACh) can lead to modulation of immune cells functioning as well as upregulation of TNF- $\alpha$ , IFN- $\gamma$  and IL-6 secretion [91,92], and it can be speculated that in alopecia areata predisposed patients that could result in inflammation and onset of disease.

More evidence on the interaction of the CNS with the hair follicles is observed in anatomical abnormalities of the nerve supply of alopecia areata affected hair follicles [87,93]. In addition, the substance P (SP), a neuropeptide, in *ex vivo* hair follicles induces upregulation of nerve growth factor (NGF) and its apoptosis- and catagen-promoting receptor (p75NTR), as well as MHC class I and beta2-microglobulin [94]. Such upregulation results in disruption of the hair cycle by inducing premature catagen development, as well as collapse of the hair follicle immune privilege [94], two of the characteristic features of alopecia areata [44,53]. Therefore, although controversial, the influence of the psychological stress in the onset of alopecia areata is possible.

### **5.3. Infectious agents are linked to onset and progression of alopecia areata.**

A link exists between *Helicobacter pylori* infection and alopecia areata [95,96]. The coexistence of *H. pylori* infection in different autoimmune conditions, many of which affect skin, has suggested that the bacterium may impact upon pathology [97]. The association of *H. pylori* and alopecia areata is controversial. One study found higher prevalence of *H. pylori* infection in patients with alopecia areata [95], while other studies have failed to identify such association [98,99]. In one case however, a single adult patient that had been diagnosed with both alopecia areata and *helicobacter pylori*, was cured of both diseases after treating the infection with antibiotics [96]. *Helicobacter pylori* infection may cause alopecia areata by inducing Th1 and Th17 cell responses, which result in inflammation characterised by IFN- $\gamma$  secretion [100]. In addition, the bacterium has shown to induce Treg expansion at the site of infection [100,101], and this may cause the disruption in Th17/Treg balance seen in alopecia areata sufferers [49], although the exact mechanisms are yet to be elucidated.

Viral agents have also been associated with the disease. Alopecia areata incidence was increased in patients who were infected by the swine flu virus during the outbreak of 2009-2010 [102]. Upon Influenza infection, overproduction of IFN- $\gamma$  with high fever can result in induction of Th1 immune responses [102,103], collapse of hair follicle immune privilege and alopecia areata. Cytomegalovirus (CMV) has been reported to trigger alopecia areata [104], although the causative link is controversial and not all studies have agreed on such association [105,106]. The disease has also been reported to be triggered in patients with infectious mononucleosis caused by Epstein–Barr virus [107].

Low incidence of alopecia areata has also been observed shortly after vaccinations against a variety of human pathogens including, hepatitis B virus [108], *Clostridium tetani* [109], herpes zoster virus [110], Japanese encephalitis [111] and human papillomavirus [112]. The disease in these cases may be a result of a hypersensitive reaction to vaccines in patients that are genetically predisposed. This response can induce the activation of IFN $\gamma$ -producing cells, including the autoimmune cells, during antigen presentation in the secondary lymphoid tissues of alopecia areata predisposed patients.

### **5.4. Immune checkpoint inhibitors used in cancer treatments**

Immune checkpoint inhibitors (ICI), such as anti-programmed cell death-1 (PD-1) and anti-programmed cell death ligand-1 (PD-L1), have shown exceptional activity in many cancers [113,114]. Many cancer cells evade the immune system by overexpression of PD-L1, which binds to PD-1 on T cells and suppresses their activity [113,115]. Therefore, by inhibiting such interaction the anti-tumour immune responses are enhanced [113,115]. Nivolumab and pembrolizumab are IgG antagonist antibodies against PD-1, while avelumab, atezolizumab and durvalumab are IgG antibodies against PD-L1 [113]. There is a wide range of adverse cutaneous morphologies seen with PD-1/PD-L1 inhibitors such as generalized pruritus, vitiligo, maculopapular lesions, lichenoid skin eruptions and non-scarring alopecia areata [113].

Recently, it has been shown that alopecia areata is a common side effect of such immunotherapies, particularly nivolumab [116]. In addition, this antibody has been reported to cause a strange case of persistent curly hair in an individual that never had such feature [117].

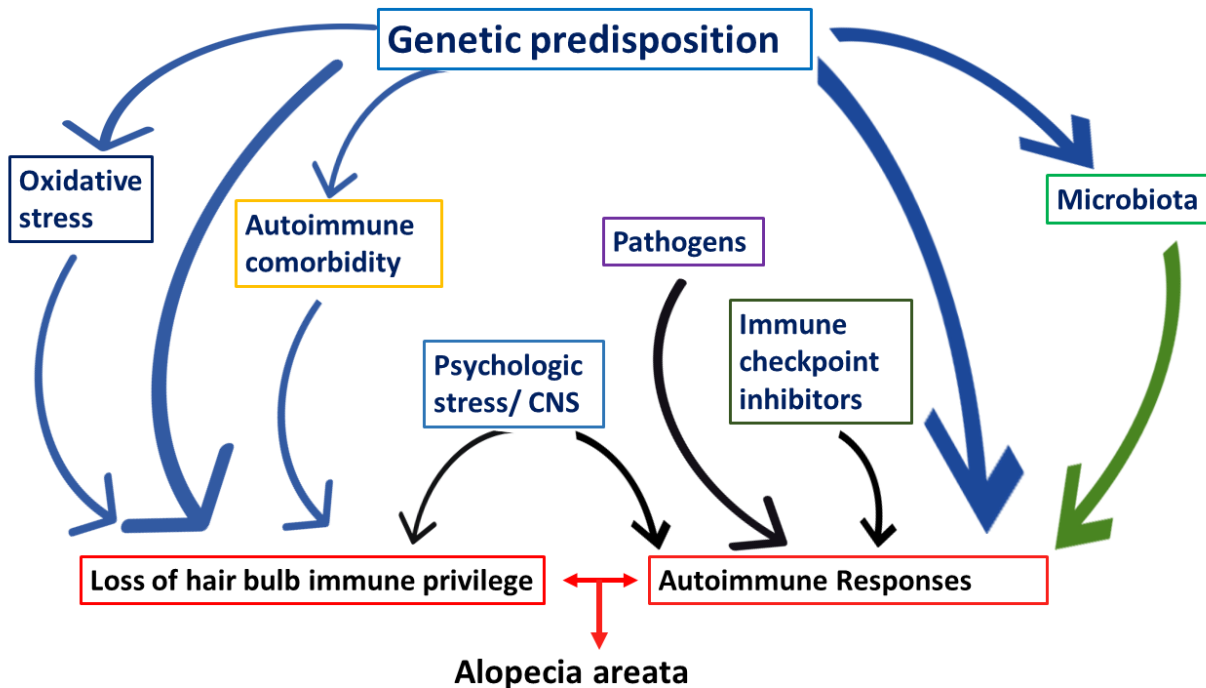
Although the mechanism of action that leads to alopecia areata in ICI treatments is yet to be elucidated, it has been suggested that the re-activated T cells might cause inflammation and cross-react with dermal antigens [113,118]. Another suggestion is that since PD-1 pathways are involved in tolerance to self-antigens and autoimmunity [119], then ICI treatment may allow development of autoimmunity by “unmasking” pre-existing autoreactive cells and/or amplify their response [118]. The observation that such treatments cause alopecia areata is another example of the strong immunological roots for the disease.

### **5.5. Microbiota and diet.**

The influence of the human microbiota in health and disease is an exciting and rapidly developing field of biological research. There is a potential link between microbiota and alopecia areata. C3H/HeJ alopecia areata mouse models are also by inheritance susceptible to developing colitis [120]. As a matter of fact, ulcerative colitis has been reported as a comorbidity of those suffering from alopecia areata [121]. The host-microbe relationship is important for overall health and well-being, and disruption thereof has been linked with several inflammatory diseases [122]. Evidence suggests that genotype determines the early microbial colonizers of the infant gut, and that there is a strong link between genetic profile and the microbiota [123,124]. This can suggest that genes that are related to alopecia may also affect the gut colonization with certain microbes that can be more immunogenic and induce chronic inflammation. For example, in celiac disease, the genes allow colonization of the gut with microbes that induce a Th1 response followed by IFN- $\gamma$  production [124]. Since alopecia areata patients are sensitive to IFN- $\gamma$  responses (Figure 1), then exposure to Th1-like inflammation for prolonged periods of time, could lead to initiation of autoimmunity.

In addition, epidemiological studies suggest a geographical influence on the life-time risk for developing alopecia areata, associated with diet [125]. For example, in the US where the majority of people follow a western diet, the lifetime risk for alopecia areata is estimated around 1.7% [4,126], whereas in Japan where people follow soya-based eastern diets, the life

time risk is no more than 1 % [125]. However, Japanese people living in the US have a similar lifetime risk as the rest of American population [127]. These geographical differences have been linked to differences in diet, and hypotheses have been raised that a soy-rich diet characteristic of eastern Asia can delay the onset of alopecia areata or reduce susceptibility [125]. Apart from these observations in humans, soy-rich diet has been reported to interfere with development of alopecia areata in mouse models [125,128]. Even though the benefits of such diets are thought to be related to compounds found in soya [125], since there is a strong link between dietary nutrients and microbiota [129], the gut bacteria may also have a role in modifying the onset of alopecia areata.



**Figure 3: Different factors are involved in the initiation of autoimmune alopecia. Alopecia areata results when the immune privilege of the hair bulb during the anagen is lost and autoreactive infiltrates target the hair follicle cells. These events can be strongly influenced by the genetics. However, different environmental factor can initiate disease in genetically predisposed patients by inducing Th1-like inflammatory responses, interfering with hair follicle cells and disrupting the hair growth cycle. Oxidative stress and inflammation triggered in the vicinity of the hair follicles in comorbidities or infections could result in impairment of the immune privilege and initiation of autoimmunity. Other factors like pathogens, microbiota and immune checkpoint inhibitors could enhance autoreactive cell activity and decrease their selection during maturation. However, the mechanisms at which these factors lead to autoimmunity are poorly understood at the present. Better understanding of how they influence disease could help prevent and treat alopecia areata.**

**6. Treatments for alopecia areata are focused at targeting the autoimmunity**

Genetic and immunological observations suggest a strong cell-mediated response for the onset and progression of disease, therefore representing an attractive target for therapeutics. In fact, some of the most successful therapies that exist for alopecia areata target the immune cells and their activity (Table 1). The mechanism of action for many of these drugs involves inhibition of cytokine signalling (e.g. JAK inhibitors), altering the Th1-type immune responses (e.g. contact sensitizers) and suppression of immune cell activity (e.g. corticosteroids) [15,21,130–132].

### **6.1. Inhibitors of IFN- $\gamma$ induced signalling**

Janus kinase (JAK) inhibitors are considered a potential therapeutic approach for alopecia areata, and many trials have shown positive effects of their administration in autoimmune alopecia patients [12,15,59,131,132]. JAK family protein tyrosine kinases (Figure 1) are downstream effectors of the IFN- $\gamma$  and  $\gamma_c$  cytokine receptors that are expressed in the immune cells and hair follicle cells [12,15,23]. Inhibition of JAK/STAT signalling can help in alopecia areata by reducing the negative effects of IFN- $\gamma$  on hair follicle cells, as well as by interfering with the maintenance of lymphocytic infiltrates during the anagen [59]. In addition, studies have shown that JAK/STAT signalling is involved in the hair cycle, and it is upregulated in the catagen and telogen phases, but suppressed in the anagen [58,59]. Inhibition of the JAK/STAT signalling has shown to promote hair growth by stimulating the activation and/or proliferation of hair follicle stem cells [58] and inducing angiogenesis [60], characteristic processes occurring during the anagen phase when the hair is growing [59,60].

Ruxolitinib is a selective inhibitor of JAK1 and JAK2 [59]. In addition, ruxolitinib has been shown to have anti-inflammatory effects, which are thought to be due to interruption of the IL-17 signalling axis [133]. Decreased levels of circulating inflammatory cytokines such as TNF- $\alpha$  and IL-6 have been observed in mice treated with ruxolitinib [134]. Different studies have shown varying results of effectiveness of ruxolitinib in alopecia areata patients, and further investigation is needed for optimisation of treatments involving this drug [59].

Tofacitinib is a JAK1 and JAK3 inhibitor approved for the treatment of rheumatoid arthritis, and it has recently shown to be successful for treating alopecia areata [135–137]. Tofacitinib treatment has resulted in hair growth and its mechanisms have shown to involve decreasing clonally expanded CD8<sup>+</sup> T cell populations in alopecia areata scalp [48], reducing chemokine CXCL10 levels [136], and promoting angiogenesis by upregulation of vascular endothelial growth factor (VEGF) [60]. However, the drug has failed to completely remove CD8<sup>+</sup> cells from affected skin or blood, which could explain the relapse after the treatment stops [48]. Topical tofacitinib and ruxolitinib have also shown to be effective and cause hair growth in alopecia areata patients [137]. Despite the effectiveness of tofacitinib, more investigation is needed as results have shown to vary based on disease severity and treatment progression [24].

### **6.2. Contact sensitizers**



Topical immunotherapy is another method of treatment which utilises an allergen known as Diphenylcyclopropenone or diphencyprone (DPCP) to induce hair growth in both adults [25,130] and children suffering from alopecia areata [138]. The response rate to DPCP varies from 17% in patients with alopecia totalis or universalis, to 60% to 100% in patients with early patchy alopecia areata, making it a very successful treatment when applied early in disease [130]. The mechanisms of action of DPCP are not fully understood, but it is speculated that the drug can redirect the cellular responses in autoimmunity through antigen competition and reduction of anti-hair-follicle antibodies [23,47,139].

Another contact sensitizer used as topical immunotherapy is dinitrochlorobenzene (DNCB) [140]. In a recent report, 50.98% of patients responded to DNCB, compared to 34.43% who responded to DPCP [140]. In the past DNCB has also shown positive results when tested for alopecia areata, totalis and universalis, and for different disease duration periods (Table 1) [22]. The negative aspect of DNCB that makes it less favourable than the DPCP is that it has shown to be strongly mutagenic by increasing in the exchange of chromosomal material between the sister chromatids in human skin fibroblasts [141]. The mechanisms of action by which DNCB reverses alopecia areata are unknown, but similar to DPCP, it may involve antigen competition.

### **6.3. Regulation of cytokine activity**

Another treatment option, regulating the cytokine activity in alopecia areata, has proven to be complex and controversial regarding effectiveness. Attempts to treat alopecia areata with biological, immunosuppressive, and anti-psoriasis drugs which target specific molecules such as TNF- $\alpha$  (adalimumab, etanercept, infliximab), CD2 (alefacept) or CD11a (efalizumab), have been unsuccessful [142].

Ustekinumab is an IgG antibody against the p40 subunit of IL-12 and IL-23 which inhibits their activity and subsequent induction of IFN- $\gamma$ , IL-17A, TNF- $\alpha$ , IL-2, and IL-10 secretion from the immune cells [143–145]. The IL-12 and IL-23 cytokines are characteristic of Th1 and Th17 responses which are linked to alopecia areata and other autoimmune skin conditions such as psoriasis and vitiligo, so inhibiting them can be therapeutic in autoimmunity [144–147]. However, despite the theory, inhibition of these cytokines has shown controversial results. One study observed that alopecia areata coexisting with psoriasis, was improved after ustekinumab treatment [147]. Other studies however, have shown that while such treatment is effective for psoriasis, it has a negative effect for inducing alopecia areata even in patients without family history of disease [144,145]. The authors of these studies have hypothesised that the hair loss observed during ustekinumab and anti-psoriasis treatment could be because the immune system during severe psoriasis inhibits development of alopecia areata, in patients who would otherwise have the disease [144,145]. Successful therapy of psoriasis may act as an immune switch which induces the development of alopecia areata in these patients [144].

## **7. Conclusion**

Alopecia areata is an autoimmune disease with genetic and environmental aetiology. The disease manifests when the immune privilege of the hair follicles is impaired and immune cells infiltrate around the hair bulb during the anagen phase. The autoreactive immune responses lead to the disruption of the hair cycle by prematurely terminating the anagen followed by hair follicle atrophy and dystrophy in persistent disease. However, the hair follicle tissues are not destroyed, so reversing alopecia areata remains as a possibility. Treatment of alopecia areata is focused at inhibition of autoimmunity, by targeting cytokine signalling and the immune cell infiltrates, which are the major contributors to disease.

The prevention of autoimmune alopecia is challenging because of the multifactorial aetiology which may require difficult genetic testing and strict avoidance of environmental factors, the effect of which is yet not fully understood. Better diagnosis of comorbidities and identification of initiating factors can lead to patient-specific therapies that can be more effective than the current ones. In addition, alopecia areata patients may also need treatments for the psychological aspects that are associated with the disease, such as clinical depression. This will reduce the burden from patients and improve their overall well-being. Ongoing research will provide deeper understanding of the underlying mechanisms that lead to development of alopecia areata, so that they can be manipulated in order to prevent or cure the disease.

**Table 1: Current treatments for alopecia areata\***

<b>Therapy</b>	<b>Administration</b>	<b>Effectiveness</b>	<b>Side effects</b>
Topical corticosteroids (e.g. Clobetasol propionate)	Topical foam or cream	Inconclusive. It is reported that >25% of patients experience more than 50% hair growth, but conflicting data exist[21] Relapse rate: 37- 63%	Folliculitis, Skin atrophy, Telangiectasia.
Intralesional corticosteroids (e.g. triamcinolone acetonide)	Topical. Injected in the skin	Inconclusive. More effective in adult patients. Treatment must stop if no improvement observed in 6 months.	Skin atrophy, Telangiectasia,
Minoxidil	Topical foam or cream	Response rate: 38% for 1% Minoxidil 81% for 5% Minoxidil	Contact dermatitis, Hypertrichosis,
Anthralin	Topical cream	Response rate 75% in patchy AA 25% in alopecia totalis Cosmetic response:25%	Severe irritation, Folliculitis, Regional lymphadenopathy,

			Staining of skin
Diphenylcyclopropenone (DPCP)	Topical cream	Cosmetic regrowth in: 17.4% of patients with alopecia totalis/universalis, 60.3% with 75–99% AA, 88.1% with 50–74% AA, 100% with 25–49% AA.	Severe irritation, Lymphadenopathy Facial and scalp oedema, Contact urticaria, Flu-like symptoms, Erythema multiforme-like reactions, Pigmentary disturbances, Vitiligo
Dinitrochlorobenzene (DNCB)	Topical solution	Hair growth (%) [22]: 10–90% hair loss of <5 years duration: 90% 10–90% hair loss of >5 years duration: 60% Alopecia totalis of <5 years duration: 70% Alopecia totalis of >5 years duration: 40% Alopecia universalis of <5 years duration: 50% Alopecia universalis of >5 years duration: 25%	Mutagen, Potential skin carcinogen, Erythema, Pruritus
Psoralen plus ultraviolet A (PUVA)	Phototherapy	Inconclusive. Hair regrowth is reported in 41.5% of treated alopecia areata patches	Insufficient studies, Cutaneous malignancies,
Janus kinase (JAK) inhibitor (Ruxolitinib)	Oral intake	Response rate: 75% Regrowth in >50% of patients Relapse: 3 weeks after treatment stops	Upper tract respiratory infections, Urinary infections, Gastrointestinal complaints
Janus kinase (JAK) inhibitor (Tofacitinib)	Oral Intake	Regrowth in >50% of patients Relapse: expected after 3-6 months after treatment stops	Oedema, Different infections, Gastrointestinal complaints
Janus kinase (JAK) inhibitor (Ruxolitinib, Tofacitinib)	Topical Solution	Growth in >50% of patients Less effective compared to oral intake.	Leukopenia
Systemic Corticosteroids (e.g. prednisolone)	Oral intake	Response rate: 82% Relapse rate: 4-100%	Hyperglycaemia, Osteoporosis, Cataracts,

			Immunosuppression, Mood changes, Obesity, Dysmenorrhea, Acne, Cushing syndrome
Cyclosporine	Oral intake	Response rate 25 to 76.7%	Nephrotoxicity, Severe immune suppression, Hypertension
Methotrexate	Oral intake alone or in conjunction with prednisone	Response rate: Adults 64% Children 38%.	Liver toxicity, Nausea, Lymphocytopenia.

**N.B.\*: Treatments that are usually applied in patients suffering from alopecia areata [21–23,59,132,135–137].**

**Table 2: Genes with strong association with alopecia areata\***

Location	Genes associated with Alopecia areata	Immunity-related function	Involved in other autoimmune diseases
HLA Region (Chromosome 6)	<i>NOTCH4</i>	Haematopoiesis, T cell differentiation	T1D, RA, MS
	<i>C6orf10</i>	Unknown function <i>in vivo</i>	T1D, RA, PS, GV
	<i>BTNL2</i>	Co-stimulation	T1D, RA, UC, CD, SLE, MS
	<i>HLA-DRA</i>	Antigen presentation (MHC II)	T1D, RA, CeD, MS, GV
	<i>HLA-DQA1</i>	Antigen presentation (MHC II)	T1D, RA, UC, CD, SLE, MS, CeD, GD
	<i>HLA-DQA2</i>	Antigen presentation (MHC II)	T1D, RA
	<i>HLA-DQB2</i>	Antigen presentation (MHC II)	RA
	<i>HLA-DOB</i>	Antigen presentation (MHC II)	SLE
	<i>HLA-A</i>	Antigen presentation (MHC I)	T1D, MS, PS, GD
Chromosome 6	<i>KLRK1</i>	NK and T cell activation (NKG2D)	T1D, RA, MS, CD, CeD, SLE
	<i>MICA</i>	NKG2D Activating Ligand	T1D, RA, UC, CeD, PS, SLE
	<i>ULBP6</i>	NKG2D Activating Ligand	None
	<i>ULBP3</i>	NKG2D Activating Ligand	None
	<i>TNFA</i>	Proinflammatory cytokine	RA, MS, IBD, SLE
Chromosome 12	<i>Eos (IKZF4)</i>	Transcription factor in Treg cells	T1D, SLE
	<i>ERBB3</i>	Proliferation and differentiation	T1D, SLE
	<i>SH2B3</i>	Negative regulator of cytokine signalling via receptor tyrosine kinases and JAK signalling	Allergies
	<i>ALDH2</i>	Antioxidant	RA
Chromosome 21	<i>AIRE</i>	Autoimmune regulator, selection of auto-reactive cells	APECED, T1D, GV, HT
Chromosome 2	<i>CTLA4</i>	Co-stimulation	T1D, RA, CeD, MS, SLE,

			GD
	<i>ICOS</i>	Co-stimulation	T1D, MS
Chromosome 4	<i>IL-21</i>	Th17 and NK cell proliferation	T1D, RA, CeD, PS
	<i>IL-2</i>	T and B cell proliferation	T1D, RA, CeD, PS
Chromosome 10	<i>IL-2RA</i>	T-cell proliferation	T1D, MS, GD, GV
Chromosome 5	<i>IL-13/IL-4</i>	Th2 differentiation	Not defined
Chromosome 7	<i>IL-6</i>	Inflammatory cytokine	T1D, RA, CeD
Chromosome 12	<i>IL-26</i>	T cell differentiation	MS
	<i>IFNG</i>	Regulation of immune responses	SLE
Chromosome 16	<i>SOCS1</i>	STAT inhibitor, regulator of IFN- $\gamma$ response	T1D, CeD
Chromosome 18	<i>PTPN2</i>	Phosphatase involved in cell signalling	T1D, CeD
Chromosome 11	<i>PRDX5</i>	Antioxidant enzyme with roles in inflammation	MS
	<i>IL-18</i>	Proinflammatory cytokine that augments natural killer cell activity and stimulates IFN $\gamma$ production in T-helper type I cells	RA, SLE
Chromosome 9	<i>STX17</i>	No known inflammatory role. It is involved in premature hair greying	None
Chromosome X	<i>Cxcr3</i>	Chemokine receptor	RA, T1D, PS, SLE
Chromosome 4	<i>Cxcl9</i>	Chemoattractant for lymphocytes	RA, T1D, PS, SLE
	<i>Cxcl10</i>	Chemokine: Monocyte, NK and T cell stimulation	RA, T1D, PS, SLE
	<i>Cxcl11</i>	Chemokine: Chemotaxis of activated T cells	RA, T1D, PS, SLE
Chromosome 2	<i>ACOXL/BCL2L11</i>	Apoptosis, Autophagy regulation	T1D, IgA Nephropathy, primary sclerosing cholangitis
Chromosome 11	<i>GARP (LRRC32)</i>	Treg differentiation and activity	IBD, Allergies

**N.B.\*: Inheritance of these genes means inheritance of susceptibility for developing the disease. The majority of these genes are also involved in a variety of other autoimmune and inflammatory diseases, such as Type 1 Diabetes (T1D), Rheumatoid arthritis (RA), Systemic Lupus Erythematosus (SLE), Psoriasis (PS), Multiple Sclerosis (MS), Crohn's disease (CD), Celiac Disease (CeD), Inflammatory Bowel Disease (IBD), Ulcerative Colitis (UC), Generalized Vitiligo (GV), Graves' Disease (GD), Hashimoto thyroiditis (HT) and allergies. Two genes encoding for NKG2D activating ligands, *ULBP6* and *ULBP3*, have been associated only with alopecia areata phenotype. *STX17*, a gene involved in premature hair greying, is not linked to autoimmune responses, and instead may indicate intrinsic problems that can disrupt the hair cycle, with or without the involvement of the immunity. Table constructed with information from [11,12,72,148–153,14,34,35,41–43,64,65].**

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