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Alopecia Areata: Complex Roots and Potential Cures

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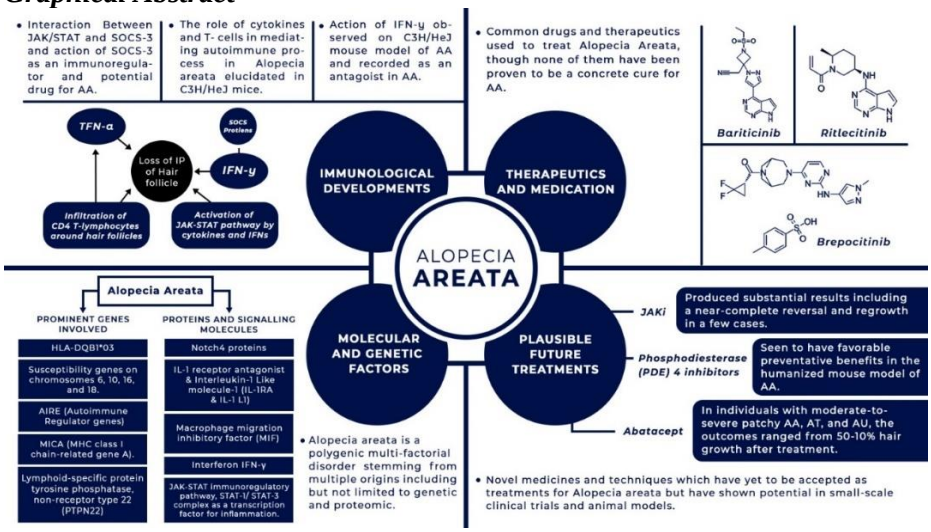
Abstract

Autoimmunity is when the healthy organs of an individual's body are attacked by its own immune system, leading to illness or functional abnormalities. The hair follicles (HFs) are wrongly destroyed by the immune system in a condition known as Alopecia Areata and results in chronic non-cicatricial hair loss discernible by spherical patches. It's a severely worsening or relapsing malady that can be permanent during severe falling out of hair. In 'Alopecia areata', the phenomenon of lymphocytic penetration is also detected during the 'anagen phase' of proliferating HFs. The 'JAK-STAT' pathway is a critical factor that carries out the coordination of the self-inflammatory system ('Immune system'), helps in polarizing 'T-helper cells', and carries out multiple functions via several transmembrane receptor families. A major participant in alopecia areata is the infiltrating interferons 'IFN-γ' and the 'TNF-α' in the HF. This compensates HF's immunity and upregulates the expression of MHC-I. Importantly, the SOCS-3 protein exercises a major part in preventing CD8+ T cell maturation and IFN-γ signaling. Immunoglobulin-G (IgG) also appears prevalent in AA victims. The objective covered in the review article is to converse about the diverse immunological, molecular, therapeutic elements in addition to the clinical assessments and their findings that result in loss of hair in AA subjects.

Graphical Abstract



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Keywords: Autoimmunity, Alopecia areata, Hair loss, JAK-STAT, SOCS-3

INTRODUCTION

Alopecia Areata (AA) is a self-inflammatory non-scarring hair loss, differentiated by circular bald spots. An immunological disorder and a diverse, frequently recessing etiology with a potential to be permanent, particularly when hair loss is severe. Approximately two percent of the common population suffers from alopecia, sometime during their lives. In AA-affected skin

biopsies, lymphocytic infiltration can be detected in and around the bulb or bottom section of HF (hair follicles) during the ‘anagen (hair growth) phase’. One of the primary causes of AA is thought to be a breakdown in the immunological benefit of HF[1].

Importance of 'hair' includes UV radiation protection, heat loss prevention, and tactile perception. Vellus, intermediate, and terminal hairs make up the various hair types. The conventional definition of hair includes hair on the scalp, axillae, beard, brows, pubic region, and eyelashes. On the other hand, vellus hairs are short in length and usually unpigmented. They surround the individual. 'Intermediate hairs' display features that occur between terminal and vellus hairs [2].

Alopecia Totalis (AT) is chronic, a situation which causes hair total hair loss on scalp in a subgroup of people with AA. When this ailment is detected and treated early in its course, treatment outcomes are best. Alopecia Universalis is recognized by ‘total hair loss’ on ‘the body and scalp (AU)’. It’s a more acute form of AA [3].

Humans are born with around $5x10^6$ follicles, and it is assumed that no further follicles form after birth. Anagen, telogen, and catagen are the three stages of the HF cycle, which starts in utero. Anagen being the longest phase, lasting an average of three years but varying from one to six years depending on where it is located in the body. At any given time, around 90-95% of all HF undergoing ‘anagen phase’, making it most prevalent stage as well. Anagen is the period of growth when there is a lot of mitotic activity; hence, a longer anagen phase means longer hair. 'Androgenetic alopecia (AGA)', frequently observed patterned hair loss, is caused by dihydrotestosterone (DHT) shrinkage of HFs. The most prevalent kind of alopecia in adult male and female, acting on fifty percentage all adult male and forty percentage of women by the age of 50 [2].

'Loose anagen hair syndrome (LAS)' is a genetic condition with partial penetrance that can occur sporadically or in an autosomal dominant way. It is distinguished by non-scarring alopecia and rapid hair loss due to poorly connected anagen hairs. Hair is more prone to breaking due to keratinization that occurs too soon beneath the 'inner root sheath’, which often involves poor attachment to the hair shaft cuticle. Hair length is reduced as a result of a shortened anagen phase [4].

MOLECULAR AND GENETIC UNDERPINNINGS OF ALOPECIA AREATA

Several investigations have revealed that AA has a substantial genetic foundation. AA is a complicated gene-influenced illness in nature, according to family linkage studies and genome-wide association studies [5]. Alopecia is classified as a polygenic illness since it is caused by a combination of multiple alleles with distinct loci on chromosomes, i.e., as shown in (Table 1). AA has a non-mendelian polygenic etiology that makes it difficult to forecast and trace its inheritance across families during genetic and epidemiological investigations.

AA in itself primarily happens as a direct outcome of disabling immunological exemption of HFs, i.e., infiltration and damage caused by one’s immune cells, in this case, CD8+ T-cells [6]. This loss of immunological privilege can be attributed to a variety of circumstances, such as stress, dietary inadequacy, hereditary abnormalities, hormonal stress, local skin problems, and so on [6].

HLA-DR and DQ are cell surface receptor protein genes found on chromosome 6 that are expressed in antigen-exhibiting cells possessing 'Major Histocompatibility Complex (MHC) class-II'. Autoimmune disorders can be caused by undesirable alleles of these rapidly developing genes. Human leukocyte antigen (HLA) alleles were the first to be linked to AA in recent research on genetics, and both case-control and family-based studies have revealed that particular DQB and DR alleles or mutations provide a considerable risk for disease, as also depicted in Figure 1. ‘Interleukin (IL)-1 cluster genes,’ notably the ‘IL-1 receptor antagonist’ (which regulates cell-to-cell contact in immune cells), show a strong correlation with the progression of AA and a spectrum of auto-immune and inflammatory illnesses [7].

Table 1. Summary of prominent genes and proteins involved in AA whose polymorphisms and presence influence the severity and occurrence of AA.

S. N.	Genes/Proteins	General function	Involvement with alopecia areata	References
1.	*HLA-DQB1*03*	The HLA-DQB1-type genes are part of a broader family commonly known as 'the human leukocyte antigen complex (HLA).' The leukocyte-antigen complex aids our defense system in distinguishing between proteins created by the body and proteins made by outside invaders such as viruses and bacteria.	Considered a general susceptibility gene in AA patients. Around 80% of patients diagnosed with AA reported its presence.	[11, 12]
2.	*MICA (MHC class I chain-related gene A)*	MICA and MICB stray from typical HLA molecular behavior by not participating in antigen presentation.	MICA (*)6 was shown to be significantly related to all AA phenotypes. MICA (*)5.1 was shown to have a strong correlation with patchy alopecia.	[13]
3.	AIRE (Autoimmune Regulator genes)	The AIRE gene in humans encodes a protein known as the autoimmune regulator. It is a 545-amino acid, 13-kb gene on chromosome 21q22.3.	The occurrence of AA is known to increase by 30% in individuals afflicted by auto-immunological, poly-endocrinopathy candidiasis ectodermal dysplasia syndrome (APECED), which is a genetic disease manifesting due to an AIRE gene mutation.	[14]
4.	'Lymphoid specific protein tyrosine phosphatase, non-receptor type-22' (PTPN22)	PTPN22 sequence stores a 'lymphoid-specific tyrosine phosphatase' (Lyp) which contributes to autoimmunity by inhibiting unsolicited T-cell initiation along with the inactivation of T-cell receptor- associated kinases (and ligands).	The alleles of PTPN22 are known to influence the severity of AA in patients carrying them.	[15]
5.	'IL-1 Receptor Antagonist' and 'Interleukin-1 Like molecule-1' (IL-1RA and IL-1 L1)	The IL-1 family is a set of 11 cytokines that regulate immunological responses.	IL-1RN/ IL-1L1 polymorphisms or linkage disequilibrium in IL-1RN and IL-1L1 genes contribute to more adverse manifestations of AA, according to research.	[16]
6.	'Macrophage migration inhibitory factor' (MIF)	The pleiotropic protein, MIF, participates in immunological responses. MIF was first deduced to be a lymphokine implicated in delayed hypersensitivity and a variety of macrophage activities, including phagocytosis, dissemination, and tumoricidal activity.	The study found that polymorphisms in the 'MIF-173*C' allele increases vulnerability to various types of AA, particularly with early illness onset. MIF is thus thought to be involved in the pathophysiology of more severe AA.	[17]
7.	Notch4	Notch protein family members regulate cell fate decisions in a range of developmental events. The Notch signaling system is an intercellular signaling route that has evolved to govern interactions between physically nearby cells.	The preliminary data analysis found a significant relationship between AA and the Notch4 (T+1297C) polymorphism. Homozygous individuals were more susceptible to AA than heterozygotes. These findings back up earlier findings that distinct HLA alleles are linked to moderate and severe levels of AA.	[18]
8.	Genes on chromosomes 6, 10, 16, and 18	_	Multiple sequences on chromosomes 6, 10, 16, and 18 were located during the GWAS linkage analysis of about 118 healthy and 102 afflicted individuals from the United States and Israel.	[19]

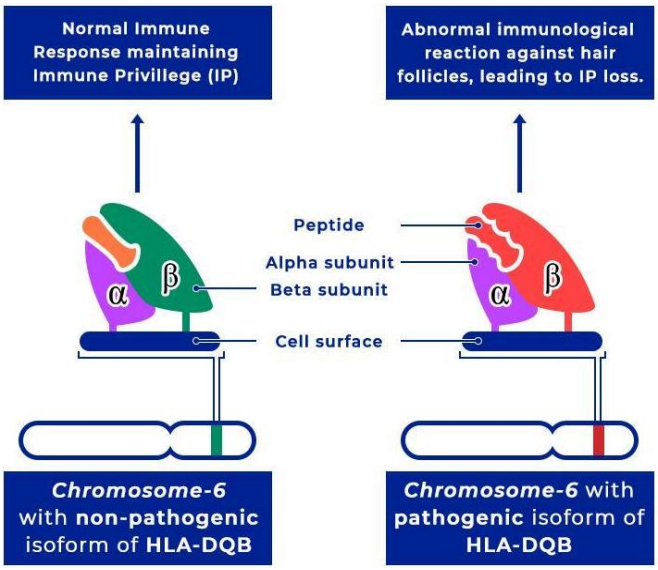


Figure 1. HLA-DQ cell surface receptor protein is composed of two subunits, of which particular isoforms of the Beta subunit formed as a result of 'single nucleotide polymorphisms (SNPs)' in its coding locus have been identified to have a pathogenic impact in the case of AA [11] [12].

The cytokine Interferon-*γ* (gamma) is involved in innate as well as adaptive immune responses against microbial infections. Interferon-*γ* serves as a significant stimulator in macrophage cells and promotes the production of MHC class II molecules. Atypical IFN-*γ* production has been linked to numerous auto-inflammatory/ immune disorders, including AA. IFN-*γ* is quite significant for the immune system due to its immuno-stimulatory and regulatory properties. IFN-*γ* is majorly synthesized as part belonging to the 'innate immune response system' by 'natural killer (NK) and natural killer-T-cells (NKT),' along with 'CD8 cytotoxic T lymphocyte (CTL) effector T-cells and CD4 Th1', during the development of immunity specific towards antigens [8].

IL-1 might operate a crucial part in (HF) genesis as well as development; as observed in in-vitro HF tissue cultures, IL-1 suppresses hair strand maturation and generates morphological alterations similar to those found in AA [9]. A direct correlation has been observed in studies on the etiopathology of autoimmune diseases, linking elevated concentrations of IFN-*γ*, and interleukins like 'IL-6' in individuals diagnosed with AA [10].

IMMUNOLOGICAL OUTLOOK ON AA

The immunological component of AA disorder is significantly influenced by the 'Janus Kinase - Signal Transducers and Activators of Transcription' (JAK-STAT) pathway and the protein signaling of the inhibitor of cytokine signaling (SOCS). Every mature mammalian species participates in the 'JAK-STAT' pathway, making it a crucial cycle. The JAK/STAT mechanism also regulates stem cell maintenance, hematopoiesis along with inflammatory responses, and embryonic development. (Figure 2). G-CSF (granulocyte colony-stimulating factor) and erythropoietin (which is a glycoprotein hormone) are primary members which make up the Type-I receptor group. Type-IIa receptors are 'GM-CSF (granulocyte-macrophage colony-stimulating factor receptors)', while type IIb receptors are IL-6 and leukemia-inhibiting factor receptors. Janus kinases, also known as dormant kinases (JAKs), and their receptors' intracellular tails are intimately intertwined.

When a ligand binds to the receptor, it alters the orientation of the JAKs connected to that receptor by undergoing some conformational changes. This phosphorylation turns inactive JAKs into catalytically active tyrosine kinases [20].

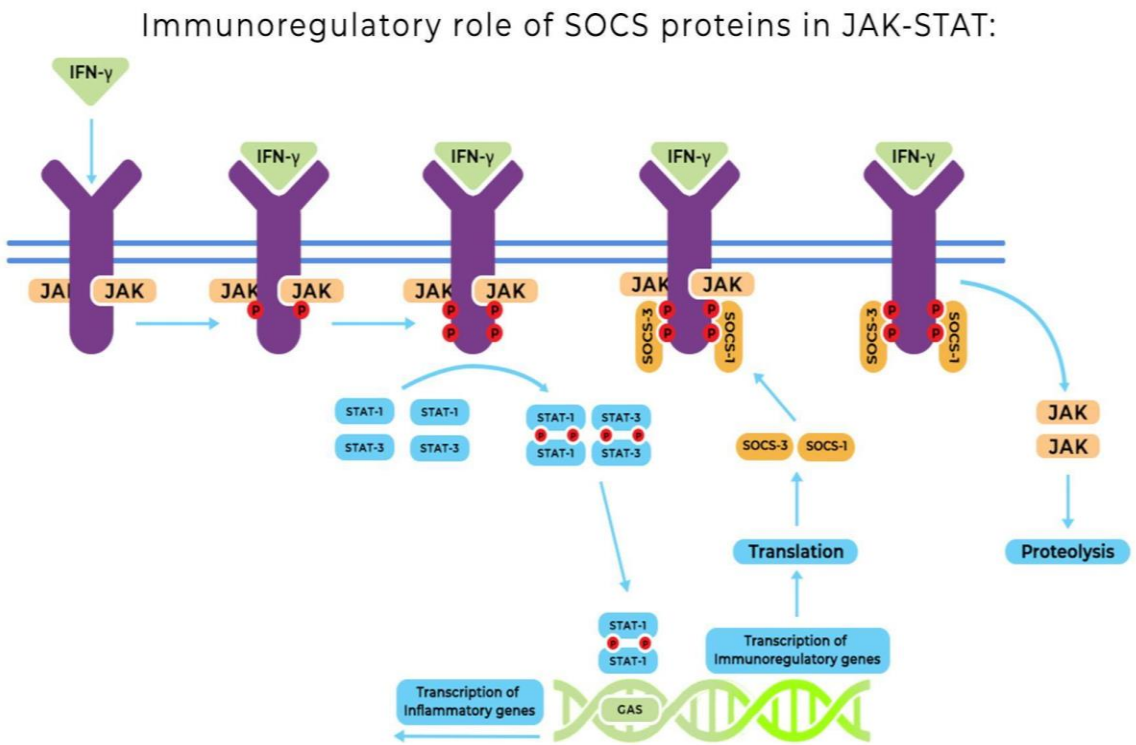


Figure 2. Molecular representation of the immunoregulatory effect of SOCS-3 protein through JAK-STAT signaling.

Despite the fact that AA is a common disorder, it is difficult to carry out in-depth research to comprehend pathophysiology and develop novel therapeutic approaches in humans. Therefore, it is advantageous to develop suitable animal models. It is possible to study the genetics, pathophysiology, and treatment of AA using the well-known AA models, the 'C3H/HeJ mouse model' and the 'Dundee experimental bald rat model (DEBR)'. By transferring tissue from the epidermis of an afflicted mouse to a positively histocompatible recipient, it is possible to experimentally produce AA within the C3H/HeJ mouse model, providing the opportunity to investigate the effects of various variables on the course of illness.

One of the immune exempted organs in our body is the anagen HF [21, 22]. The loss of HF's immunological exemption has been assumed to be the chief of pathological symptoms. IFN-γ, increased in AA lesions and promoting MHC-I expression in HF, is deemed to be a major culprit in development of AA and also advances the loss of HF immunological exemption by promoting MHC-I expression. In the humanized mouse model of AA [23], IFN-γ therapy enhances expression of MHC-I follicles, leading to the collapse of HF immunological privilege and hair loss (Figure 3). Furthermore, IFN-mediated activation of 'CXCL9/10/11' and its receptor, 'CXCR3', results in 'NKG2D+ CD8+ T cell' accumulation and AA. Blocking IFN-γ dramatically reduces the progression of AA in 'C3H/HeJ mice'. (Figure 3) [24, 25].

Fas-mediated programmed cell death is ordinary when a spectrum of auto-immune diseases are onset [26]. Fas L-neutralizing antibodies, in particular, reduce HF response and hair loss. SOCS proteins mediate the cytokine signals that influence CD4+ T-cell differentiation and the transition of; CD8+ T-cells' from naïve to effector memory. Furthermore, SOCS proteins have a crucial part in the therapy of autoimmune disorders [27]. SOCS-3 overexpression has been shown to protect pancreatic cells against autoimmune damage resulting from CD8+ T lymphocytes. As a result, we propose that SOCS proteins may be a viable method to make HF resistant to various cytokines.

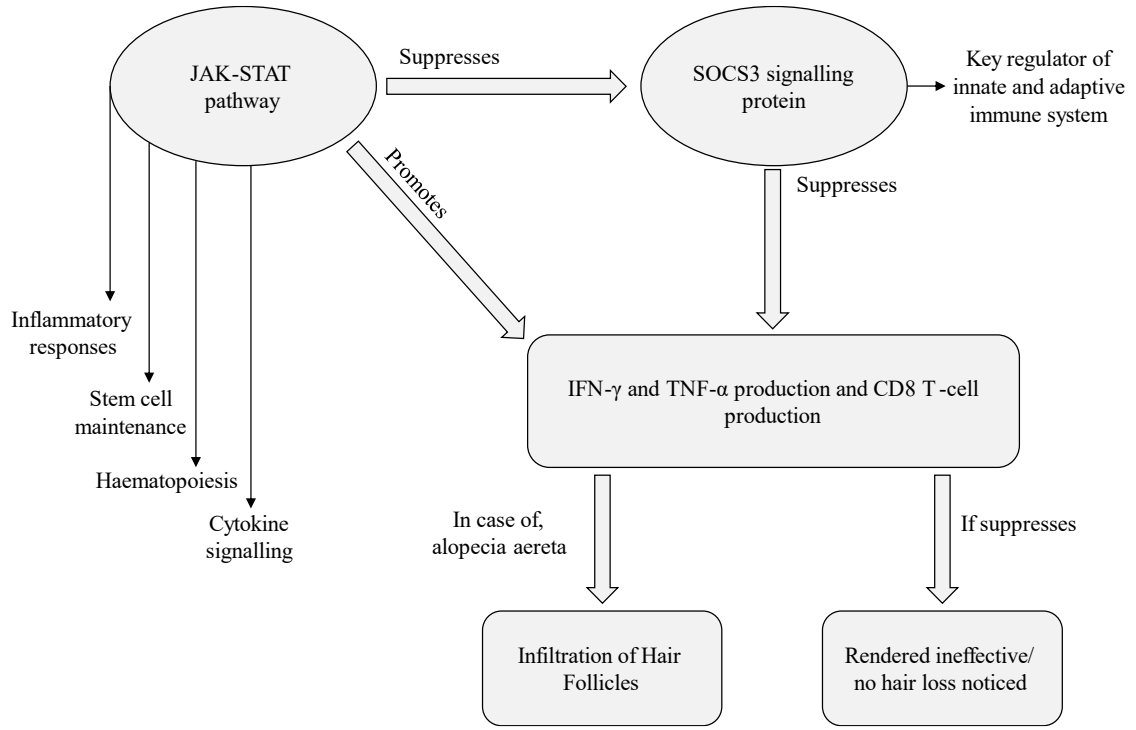


Figure 3. Descriptive representation of the role played by JAK-STAT pathway, SOCS-3 protein, and interferons in hair loss.

Treatment with SOCS-3 to Ameliorate the Advances on Alopecia Areata

It was found that treatment with SOCS-3 is unable to stop CD4+ and CD8+ T-Cell movement to inflammatory areas [28]. The failure of SOCS-3 treatment to control T-cell growth in skin cell and T-cell co-cultures was further demonstrated. These findings indicate that, whereas SOCS-3 reduces AA formation, T-Cell movement and infiltration remain unchanged. SOCS-3 therapy reduces 'CD44 high' 'CD62L low effector memory CD8+ T-cells', leading to lower 'IFN-γ' production. Within C3H/HeJ AA mice, '15.8%' of 'CD8+ T-cells' in SDLNs are 'CD44 high' and 'CD62 low', whereas SOCS-3 therapy significantly reduces both these populations and 'effector memory CD8+ T-cells'. SOCS-3 reduces the development of 'IFN-γ-producing CD8+ T-cells' in transplant patients' skin. SOCS-3-treated skin cells stimulate T-cells, leading to reduced interferon levels.

MHC-I expression in HFs is upregulated by the courtesy of IFN-γ, which guides to the deprivation of immune benefit. Beneath C3H/HeJ multiple mouse specimens, IFN-γ therapy induces follicular expression of MHC-I, leading to downregulation of HF self-inflammatory benefit and auto-immune HF loss. MHC-I expression is greater in 'C3H/HeJ AA' animals than in 'C3H/HeJ mice', although SOCS-3 treatment greatly decreases it. As a result, we emphasize that little is known about the mechanism behind the SOCS-3-induced drop in MHC-I expression. SOCS-3's potential to impede cytokine-mediated 'MHC-I expression' in skin cells has been demonstrated in lab study. TNF-α and IFN-γ increase MHC-I expression on skin cells, while SOCS-3 therapy dramatically reduces this effect. In vitro tests validated SOCS-3's capacity to impede Cytokine-mediated FAS expression in epidermis cells. Cytokine-induced Fas expression in skin cells. SOCS-3 therapy effectively reduces 'TNF-α/IFN-γ-induced Fas expression' while increasing Fas expression on skin cells. These results essentially show that SOCS-3 reduces the formation of AA by reducing the IFN-induced activation of Fas and MHC-I [29].

Subcutaneous SOCS-3 injection was found to significantly reduce the occurrence of AA 14 weeks after the transfer, while '71% of recipients have patchy, non-scarring hair loss'. 'CD8+ T-cells in epidermis belonging to the receivers produced lower pooling of IFN-Y when subjected to the SOCS-3 course. It was also observed that nearly 14.1% of 'CD8+ T-cells' from the IgG-treated group were found

to be CD44 high and CD62L low in recipients after the transfer, whereas SOCS-3 treatment decreased the frequency of CD44 high and CD62L low cells, suggesting that SOCS-3 suppresses CD8+ T-Cell maturation' (Figure 3). The SOCS-3-treated set has a reduced potential to produce IFN-Y than the 'control group.' The downregulation of 'Fas and MHC-I' inside the epidermis of the receiver when treated with SOCS-3. Similarly, Q-PCR as well as immunofluorescence data reveals that FAS is sharply upregulated in major alopecic skin tissues in comparison to controls. 'Thirty-one human alopecic skin tissues, SOCS-3, and Fas levels were found to be negatively correlated.' MHC-I expression was shown to be greater in the majority of human alopecic skin tissues when compared to healthy controls, and SOCS-3 and 'MHC-I' levels were revealed to be adversely related in 30 different human alopecic skin tissues. As a result, we propose that SOCS-3 may be a unique, underutilized target for reducing AA, an illness for which no viable therapies are currently available [30].

The Interplay of Cytokines and T-cells in Modulating the Self-inflammatory Phenomena in Alopecia Areata, as Observed in C3H/HeJ Mice

According to research using the 'C3H/HeJ mouse and the DEBR,' several levels and elements of the pathophysiology of this T-cell-regulated self-inflammatory illness. This insight might lead to the development of novel therapy options, such as monoclonal antibodies that block co-stimulation or an anti-CD44v10 antibody that inhibits lymphocyte homing. Human treatment may be futile until a new vehicle that allows tacrolimus to penetrate all the way to the hair bulb is identified, according to therapeutic tests on the previously mentioned mouse model.

Current mouse research is being undertaken to explain how touch sensitizers work in the treatment of AA, with the goal of designing more tailored therapies based on the therapeutic influence of contact sensitizers [31].

'The T-cell helper-to-suppressor cell ratio' in the peripheral blood is not believed to be a useful predictor of disease activity. T-cell-mediated trauma may occur primarily in the 'peribulbar regions of the HFs' in the progressive disease areas (region of exclamation-mark hairs) based on the 'intrabulbar and peribulbar distribution of Langerhans cells, T-cells, and HLA-DR expression in and around anagen HFs.' This statement supports the idea that the 'dermal papilla' (capillary network) is the main source inducing immunological damage during the early stages of AA and hence a good target for testing novel therapies [32].

With just a few cells expressing the CCR4 receptor, the bulk of invading CD4 T-lymphocytes around HFs in AA patients are CCR5-positive, stipulating that Th1 cells predominate in the lesion. Baldness in the humanized mouse model was successfully treated with local IL-4 injections and nullifying anti-IFN-γ antibodies. In the afflicted alopecic skin, intralesional injection of interleukin-4 inhibited elevated interferon-gamma mRNA expression and decreased CD8 T-Cell infiltration around HFs, according to semi-quantitative RT-PCR data. Additionally, by lengthening hair shafts in C3H/HeJ mice with alopecia, cationized gelatin-conjugated short interfering RNAs targeting the Th1 transcription factor T-box21 reduce alopecia. Collectively, it is an advanced, progressive, and safe strategy to exercise gelatin-small interfering RNA conjugates as a replacement for gene remedies [33].

To produce the AA phenotype artificially, the Th1 cytokine IFN-gamma gene was selectively removed from mice, resulting in homozygous negative (-/-) and double positive (+/+) mice for wild-type (WT) mice. Ninety percent of WT mice with AA lost hair, whereas the homozygous negative (-/-) individuals did not. Immunohistochemistry analysis of skin samples revealed that homozygous negative (-/-) mice lacked 'skin-invading CD8 (+) T-cells' and had significantly fewer 'CD4 (+) cells', whereas controls showed abundant 'peri- and intra-follicular infiltration' of 'CD4 (+) and CD8 (+) T-cells'. Irregular expression of MHC class I and II in normal immune individuals. AA-resistant homozygous-negative (-/-) mice exhibited weaker infra-infundibulum HFs than control mice. Flow cytometry data shed light on the fact that homozygous negative (-/-) individuals contained leukocytes,

which exhibited no reaction towards the grafted AA-affected tissue. AA-resistant homozygous negative (-/-) mice showed no increase in T-cell mobilization factors or Th1 cytokines in draining lymph node cells or skin-invading leukocytes, unlike the homozygous positive (+/+) mice. Homozygous negative (-/-) individuals also do not exhibit an increase in regulatory T-cells or a change to a Th2 cytokine profile. The homozygous negative (-/-) mice's failure to instigate Th1 cells as a reaction to transplanted autoantigens suggests that 'IFN-γ-mediated Th1 activation' is essential for the development of AA [34].

In the following paragraph, a hypothesis by Paus et al. has been summarized, wherein and they stated that the intense cytotoxic T-Cell response observed in AA afflicted individuals is primarily initiated due to the sequentially generated self-antigens which otherwise go undetected due to the lack of 'MHC class-I expression'. In the 'proximal anagen hair bulb', proinflammatory cytokines produce a local degradation of MHC-I negation mechanisms as a response to micro level trauma, neuronally induced inflammation, or extra-microbial factors. The injection of self-antigens extracted from 'melanogenesis-related proteins (MRP-DP)', only formed while undergoing the 'anagen phase', results in dual rounds of self-immunogenic reactions. When the cytotoxic T-lymphocytes detect MRP-DP produced incorrectly by antigen presenting molecules on HF matrix melanocytes/keratinocytes, they initiate AA. Then, the 'CD4+' T-cells and antigen presentation cells start a new onslaught on additional autoantigens presented by MHC class II and visible on injured melanocytes and keratinocytes. The latter is principally responsible for extrafollicular disease and follicular damage, and it is heavily impacted by the patients' immunogenetic background. This complete explanation, which takes into account clinical variability and other significant aspects of the disorder, claims that AA can only be caused by the unique confluence of numerous predisposing events [31].

CLINICAL FINDINGS AND THERAPEUTIC TARGETING OF ALOPECIA AREATA

The cure for AA is limited at the moment, and the cure is limited to a handful of drugs at the most. Because of the scarcity of therapeutics, alopecia treatment trials are becoming more important.

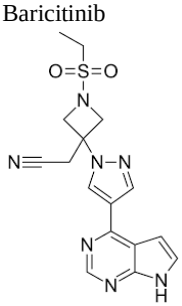
There are a variety of methods for determining the severity of AA disease. Below is an overview of two assessment tools. 'Severity of Alopecia Tool (SALT)' is widely used during the treatment rounds to assess scalp hair loss.

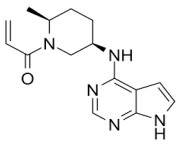
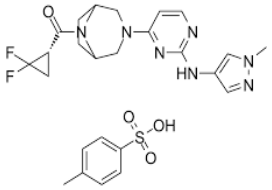
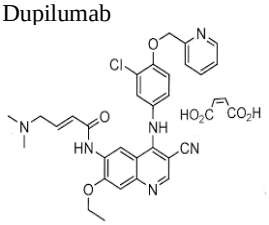
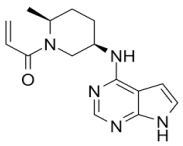
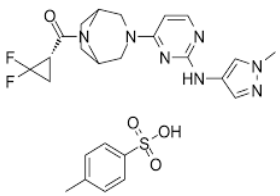
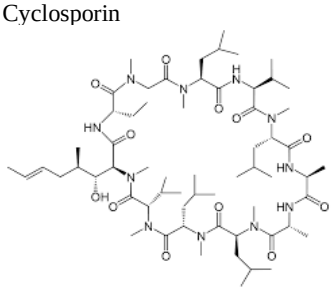
SALT scores are calculated as follows:

1. Firstly, 'the surface area of each quadrant' is multiplied with the 'percentage of hair loss' present within every single division out of the four quadrants.
2. Adding the four values together to achieve a total score

Common therapeutics (Table 2) under study for the treatment of AA include baricitinib, ritlecitinib, dupilumab, cyclosporin, diphencyprone, anthralin, and simvastatin/ezetimibe.

Table 2. Studies testing pharmaceutical products, preferably involving randomized, placebo-controlled trials, were selected for comparison purposes.

S. N.	Drug	Description	Results	Ref. no.
1.	Baricitinib 	Randomized and placebo-controlled research was conducted on people with acute AA (BRAVE-AA1 and AA2). In a 3:2:2 ratio, individuals randomly received either a placebo, or baricitinib (4 mg dose), or baricitinib (2 mg dose).	At week 36, SALT scores were '38.8%' for BRAVE-AA1 on 4-mg baricitinib, '22.8%' on 2-mg baricitinib, and '6.2%' on placebo; for 'BRAVE-AA2' phenotype, they were '35.9%', '19.4%', and '3.3%'. Other side effects including acne, fluctuating cholesterol levels and spike in creatine kinase levels were observed in baricitinib consuming patients.	[39]

2.	Ritlecitinib  and Brepocitinib 	Patients received either ritlecitinib, brepocitinib, or a placebo arbitrarily every day. The SALT score change during a 24-week period indicated the efficacy of this drug. The major secondary efficacy aim (SALT30) was to determine whether a percentage of patients saw a 30% increase in their SALT score. There were '48' ritlecitinib, '47' brepocitinib, and '47' placebo patients involved in the study.	At week 24, the LS mean difference between ritlecitinib and brepocitinib for the shift in SALT score from baseline was observed to be 31.1 (P=.0001 for both comparisons with placebo). '50%' of affected individuals on ritlecitinib, '64%' on brepocitinib, and '2%' on placebo reached SALT30. Rhabdomyolysis, a serious side event, was only experienced by two individuals in the brepocitinib group.	[40]
3.	Dupilumab 	A 24-week 'open-label phase' with dupilumab was followed by an additional 24-week phase of subcutaneous dupilumab (300 mg) therapy for patients with and without 'concomitant atopic dermatitis'. The primary goal was to change the SALT score from the baseline at week 24, but secondary goals included tracking other hair regrowth measures.	As opposed to the dupilumab arm, which showed a 2.2 improvement at the 24th week, the placebo group showed an improvement in patient condition against the disorder, with a LS mean shift in the SALT score, -6.5 (p.05). Response rates increased to 53.8%, 46.2%, and 38.5% in people with baseline IgE levels of 200 IU/mL, respectively. Results proceeding 48 weeks of dupilumab therapy displayed that '32.5%', '22.5%', and '15%' of patients had improved their SALT30, 50, and 75 scores, significantly.	[41]
4.	Ritlecitinib  and bepocitinib 	A biopsy sub study was conducted throughout the first 24 weeks of a 'phase 2a clinical trial' to deduce the effectivity and security of using ritlecitinib and brepocitinib. 46 individuals in total from the ritlecitinib (n = 18), brepocitinib (n = 16), and placebo (n = 12) batches took part in the exploratory aim, which assessed the alterations in signaling factors in biopsy samples from baseline to weeks 12 and 24.	By week 24, both the drugs had improved the lesional scalp transcriptome by more than 100% to a non-lesional profile. It was observed that Brepocitinib promoted more scalp tissue growth than ritlecitinib; nevertheless, by the 24th week, ritlecitinib had produced greater gains. Ritlecitinib and brepocitinib improved SALT scores in a way that was positive for TH1 marker expression and negative for hair keratin expression. Larger, more extensive clinical investigations are required.	[42]
5.	Cyclosporin 	'Assessment of Quality of Life-8D' (AQoL-8D), a generic preference-based HRQoL tool, and the AA Symptom Impact Scale (AASIS), a disease-specific HRQoL tool, were administered to participants in a placebo-controlled randomized study of cyclosporin. At each study, At the visit, HRQoL was assessed and compared to the baseline.	There were a total of 32 individuals examined. Health offered an average utility of '0.748'. In the third month, the cyclosporin batch outperformed the placebo group in terms of HRQoL improvement across six out of eight 'AQoL-8D' dimensions and five out of seven AASIS categories. Six of the eight 'AQoL-8D' criteria indicated poorer HRQoL than the Australian population average. Patients with AA reported an average health utility score of 0.748. For three months, evaluations of both disease-specific and generic HRQoL showed a trend towards improvement when cyclosporin was provided with a dosage of 4 mg/kg/d. AA individuals had, the average health utility was 0.748.	[43]

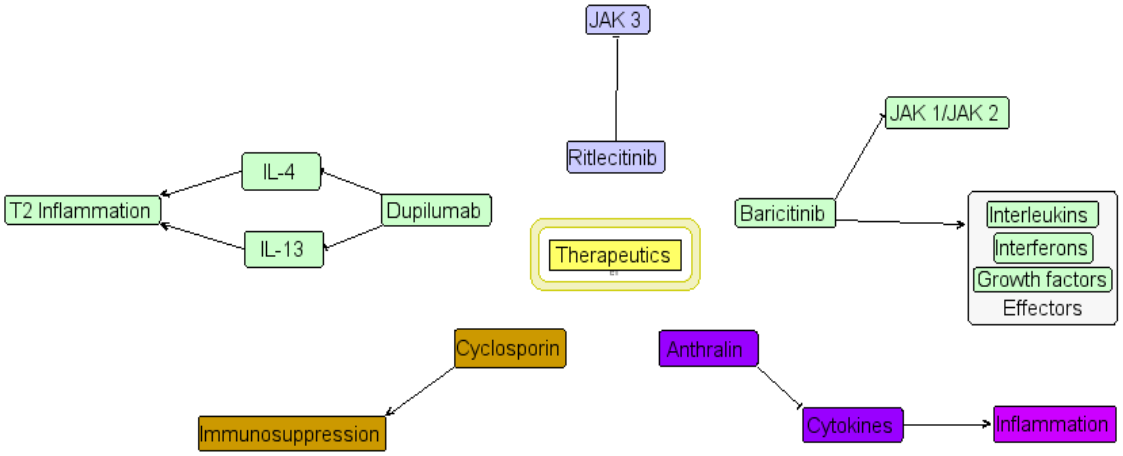


Figure 4. Rociletinib, Baricitinib, Anthralin, Cyclosporin, and Dupilumab are some of the common therapeutics applied in an attempt to alleviate AA symptoms. The mechanism through which these drugs act (JAK inhibition, immunosuppression, stopping inflammation, etc.) has been depicted above.

Baricitinib

'Baricitinib', an oral, selective, reversible Janus kinase 1 and 2 inhibitor (Figure 4), might disrupt important signaling pathways which is mainly the case in cytokine assisted signaling during the immunopathogenesis of AA. A pharmaceutical drug called baricitinib is used to treat AA and the JAK protein functioning is inhibited and there are several modifications made to diverse interleukins, interferons, and growth factors by Baricitinib. It has also been demonstrated to suppress the production of JAK1/JAK2 and to cause cell death in mutanT-cells. The absolute bioavailability of baricitinib is around 80%.

Ritlecitinib

A covalent 'kinase inhibitor' with 'high Janus kinase 3' (Figure 4) selectivity (JAK3). It is believed to function by preventing the activity of immune cells and signaling molecules, both are included in 'AA-related hair loss.' Compared to previous JAK inhibitors, ritlecitinib offers a new method of action, a quick onset, and a better safety record [35].

Dupilumab

Recent developments in studies regarding T2 inflammation indicate that it is involved in a wider spectrum of diseases. Dupilumab, a recently developed monoclonal antibody (mAb), prevents Interleukin-13 and 4 signaling. (Figure 4), Both, these cytokines are important for the T2 response. 'Prurigo nodularis, nummular eczema, allergic contact dermatitis, chronic hand eczema, spontaneous chronic urticaria, bullous pemphigoid, and AA' are among the novel possible indications being investigated [36].

Cyclosporin

Cyclosporin is an immunosuppressive medication (Figure 4) that is utilized to transplant drugs and to administer self-inflammatory illnesses. As a lipid soluble chemical, factors like food, bile, and others can impact how bioavailable it is. The liver's cytochrome P450 3A system, which differs dramatically across people, significantly metabolizes cyclosporin. In addition to physicochemical characteristics, biological transporters such as blood erythrocytes and lipoproteins also play a role in cyclosporin dispersion [37].

Anthralin

Dithranol, sometimes referred to as anthralin, is a drug that treats psoriasis and is derived from hydroxyanthrone and anthracene. It comes in creams, ointments, and pastes that have concentrations

between 0.1 and 2%. Topical anthralin is a compelling option for children with alopecia areata for scalp resurgence. With few inherent detrimental consequences, optimal effectiveness can be achieved by prolonged usage of no less than a year [38].

CONCLUSION AND FUTURE ASPECTS

AA has been a well-known T-cell-arbitrated self-inflammatory disease, and fundamental research on the disorder has defined many of its genetic, cellular, and molecular features during the course of the last decade. Early AA is distinguished by 'perifollicular' and 'intrafollicular mononuclear cell' invasion targeting anagen HFs, which are visible histologically. The macrophages, 'Langerhans cells', and activated 'CD4+' and 'CD8+' T-lymphocytes make up the majority of inflammatory infiltration, which is commonly observed in AA. TNF-alpha, interferon-gamma, and interleukin-2 are examples of type 1 cytokines that mediate the AA onset phase. HLAs specific to AA, along with those specific to other various auto-immunological disorders, determine susceptibility, severity, chronicity, and resistance.

As a direct consequence of increased data accessibility from GWAS data sets and a greater understanding of the disease progression of AA, novel therapeutic methods and techniques for its early diagnosis have been developed. They have produced substantial results, including a near-complete reversal and regrowth in a few cases where the patients were treated with a JAK1/2 inhibitor, namely ruxolitinib [44]. As of the writing of this paper, research on such medications (mentioned earlier) involving the inhibition of the JAK-STAT pathway, also known as JAKi medication, is still in its early stages and could become a vital technique in the mitigation of similar auto-immune disorders.

Molecular inhibitors, including phosphodiesterase-4 (PDE-4), which effectively control the activity of our 'innate immune system', have been seen as effective in the reduction of the immunological response by degradation of cyclic adenosine monophosphate (cAMP) [45]. The drug apremilast, for example, has been shown to have favorable preventative benefits in the refined mouse-based model of AA [46]. Numerous clinical trials on similar drugs like apremilast and crisaborole (another PDE-4 inhibitor) are presently underway [47], but they have yet to prove themselves as effective therapeutics as of the writing of this paper.

Abatacept is another immunosuppressant (it inhibits T-cell activation and proliferation) that demonstrated significant results in clinical studies on a small population of individuals. In individuals with other various isoforms of AA, the outcomes ranged from 50–10% hair growth after treatment [48].

Researchers should be aware that several of the drugs mentioned above have been documented to cause significant, unfavorable side effects when used. Before these newly developed medications can be used to control and reverse AA, much more research is required. These novel methods have made the treatment of AA a topic of intense discussion in the present day.

Author Contributions

Conceptualization of the study: Navyansh Asthana; Acquisition of data: Vidit Deshpande, Adri Raj Saha, Kedar Navsariwala and Navyansh Asthana; Writing and editing of the original draft: Atharva Shinde, Kedar Navsariwala, Vidit Deshpande; Writing and editing of the reviewed manuscript: Atharva Shinde, Kedar Navsariwala, Vidit Deshpande; Figures: Kedar Navsariwala, Vidit Deshpande; Supervision and Editorial assistance: Atharva Shinde and Kedar Navsariwala. All authors were involved in the final revisions and discussion of the manuscript.

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Disclosure Statement

The authors report no conflicts of interest.

REFERENCES

1. Pratt, C. H., King, L. E., Jr., Messenger, A. G., Christiano, A. M., & Sundberg, J. P. (2017). Alopecia areata. Nature reviews. Disease primers, 3, 17011. https://doi.org/10.1038/nrdp.2017.11
2. Qi, J., & Garza, L. A. (2014). An overview of alopecias. Cold Spring Harbor perspectives in medicine, 4(3), a013615. https://doi.org/10.1101/cshperspect.a013615
3. Buckley, J., & Rapini, R. P. (2022). Totalis Alopecia. In *StatPearls*. StatPearls Publishing.
4. Price, V. H., & Gummer, C. L. (1989). Loose anagen syndrome. Journal of the American Academy of Dermatology, 20(2 Pt 1), 249–256. https://doi.org/10.1016/s0190-9622(89)70030-x
5. Duvic, M., Christiano, A. M., Hordinsky, M. K., Norris, D. A., Price, V. H., & Amos, C. I. (2013). The national alopecia areata registry-update. *The journal of investigative dermatology. Symposium proceedings*, *16*(1), S53. https://doi.org/10.1038/jidsymp.2013.20
6. Amy J. McMichael, *The genetic epidemiology and autoimmune pathogenesis of alopecia areata, Journal of the European Academy of Dermatology and Venereology, Volume 9, Issue 1, 1997, Pages 36-43, ISSN 0926-9959, https://doi.org/10.1016/S0926-9959(97)00062-7.*
7. McDonagh, A. J., & Tazi-Ahnini, R. (2002). *Epidemiology and genetics of alopecia areata. Clinical and experimental dermatology, 27(5), 405–409. https://doi.org/10.1046/j.1365-2230.2002.01077.x*
8. Tau, G., & Rothman, P. (1999). Biologic functions of the IFN-*γ* receptors. *Allergy*, *54*(12), 1233–1251. https://doi.org/10.1034/j.1398-9995.1999.00099.x
9. Harmon, C. S., & Nevins, T. D. (1993). *IL-1 alpha inhibits human hair follicle growth and hair fiber production in whole-organ cultures. Lymphokine and cytokine research, 12(4), 197–203.*
10. Tomaszewska, K., Kozłowska, M., Kaszuba, A., Lesiak, A., Narbutt, J., & Zalewska-Janowska, A. (2020). *Increased Serum Levels of IFN-γ, IL-1β, and IL-6 in Patients with Alopecia Areata and Nonsegmental Vitiligo. Oxidative medicine and cellular longevity, 2020, 5693572. https://doi.org/10.1155/2020/5693572*
11. McDonagh, A. J., & Tazi-Ahnini, R. (2002). Epidemiology and genetics of alopecia areata. Clinical and experimental dermatology, 27(5), 405–409. https://doi.org/10.1046/j.1365-2230.2002.01077.x
12. Colombe, B. W., Lou, C. D., & Price, V. H. (1999). The genetic basis of alopecia areata: HLA associations with patchy alopecia areata versus alopecia totalis and alopecia universalis. The journal of investigative dermatology. Symposium proceedings, 4(3), 216–219. https://doi.org/10.1038/sj.jidsp.5640214
13. Barahmani, N., de Andrade, M., Slusser, J. P., Zhang, Q., & Duvic, M. (2006). Major histocompatibility complex class I chain-related gene A polymorphisms and extended haplotypes are associated with familial alopecia areata. *The Journal of investigative dermatology*, *126*(1), 74–78. https://doi.org/10.1038/sj.jid.5700009
14. Tazi-Ahnini, R., Cork, M. J., Gawkrodger, D. J., Birch, M. P., Wengraf, D., McDonagh, A. J., & Messenger, A. G. (2002). Role of the autoimmune regulator (AIRE) gene in alopecia areata: strong association of a potentially functional AIRE polymorphism with alopecia universalis. Tissue antigens, 60(6), 489–495. https://doi.org/10.1034/j.1399-0039.2002.600604.x
15. Kemp, E. H., McDonagh, A. J., Wengraf, D. A., Messenger, A. G., Gawkrodger, D. J., Cork, M. J., & Tazi-Ahnini, R. (2006). The non-synonymous C1858T substitution in the PTPN22 gene is associated with susceptibility to the severe forms of alopecia areata. Human immunology, 67(7), 535–539. https://doi.org/10.1016/j.humimm.2006.04.006
16. Tazi-Ahnini, R., Cox, A., McDonagh, A. J., Nicklin, M. J., di Giovine, F. S., Timms, J. M., Messenger, A. G., Dimitropoulou, P., Duff, G. W., & Cork, M. J. (2002). Genetic analysis of the interleukin-1 receptor antagonist and its homologue IL-1L1 in alopecia areata: strong severity association and possible gene interaction. European journal of immunogenetics : official journal of the British Society for Histocompatibility and Immunogenetics, 29(1), 25–30. https://doi.org/10.1046/j.1365-2370.2002.00271.x
17. Shimizu, T., Hizawa, N., Honda, A., Zhao, Y., Abe, R., Watanabe, H., Nishihira, J., Nishimura, M., & Shimizu, H. (2005). Promoter region polymorphism of macrophage migration inhibitory factor is strong risk factor for young onset of extensive alopecia areata. Genes and immunity, 6(4), 285–289. https://doi.org/10.1038/sj.gene.6364191

18. Tazi-Ahnini, R., Cork, M. J., Wengraf, D., Wilson, A. G., Gawkrodger, D. J., Birch, M. P., Messenger, A. G., & McDonagh, A. J. (2003). Notch4, a non-HLA gene in the MHC is strongly associated with the most severe form of alopecia areata. Human genetics, 112(4), 400–403. https://doi.org/10.1007/s00439-002-0898-9
19. Martinez-Mir, A., Zlotogorski, A., Gordon, D., Petukhova, L., Mo, J., Gilliam, T. C., Londono, D., Haynes, C., Ott, J., Hordinsky, M., Nanova, K., Norris, D., Price, V., Duvic, M., & Christiano, A. M. (2007). Genomewide scan for linkage reveals evidence of several susceptibility loci for alopecia areata. American journal of human genetics, 80(2), 316–328. https://doi.org/10.1086/511442
20. Thomas, S. J., Snowden, J. A., Zeidler, M. P., & Danson, S. J. (2015). The role of JAK/STAT signalling in the pathogenesis, prognosis and treatment of solid tumours. *British journal of cancer*, *113*(3), 365–371. *https://doi.org/10.1038/bjc.2015.233*
21. Pi, L. Q., Jin, X. H., Hwang, S. T., & Lee, W. S. (2013). Effects of calcitonin gene-related peptide on the immune privilege of human hair follicles. *Neuropeptides*, *47*(1), 51–57. https://doi.org/10.1016/j.npep.2012.07.008
22. Westgate, G. E., Craggs, R. I., & Gibson, W. T. (1991). Immune privilege in hair growth. *The Journal of investigative dermatology*, *97*(3), 417–420. https://doi.org/10.1111/1523-1747.ep12481002
23. Gilhar, A., Etzioni, A., & Paus, R. (2012). Alopecia areata. *The New England journal of medicine*, *366*(16), 1515–1525. https://doi.org/10.1056/NEJMra1103442
24. Gilhar, A., Kam, Y., Assy, B., & Kalish, R. S. (2005). Alopecia areata induced in C3H/HeJ mice by interferon-gamma: evidence for loss of immune privilege. *The Journal of investigative dermatology*, *124*(1), 288–289. https://doi.org/10.1111/j.0022-202X.2004.23580.x
25. Gilhar, A., Etzioni, A., Assy, B., & Eidelman, S. (1993). Response of grafts from patients with alopecia areata transplanted onto nude mice, to administration of interferon-gamma. *Clinical immunology and immunopathology*, *66*(2), 120–126. https://doi.org/10.1006/clin.1993.1015
26. Darwiche, R., Chong, M. M., Santamaria, P., Thomas, H. E., & Kay, T. W. (2003). Fas is detectable on beta cells in accelerated, but not spontaneous, diabetes in nonobese diabetic mice. Journal of immunology (Baltimore, Md. : 1950), 170(12), 6292–6297. https://doi.org/10.4049/jimmunol.170.12.6292
27. Freyschmidt-Paul, P., McElwee, K. J., Botchkarev, V., Kissling, S., Wenzel, E., Sundberg, J. P., Happle, R., & Hoffmann, R. (2003). Fas-deficient C3.MRL-Tnfrsf6(lpr) mice and Fas ligand-deficient C3H/HeJ-Tnfsf6(gld) mice are relatively resistant to the induction of alopecia areata by grafting of alopecia areata-affected skin from C3H/HeJ mice. *The journal of investigative dermatology. Symposium proceedings*, *8*(1), 104–108. https://doi.org/10.1046/j.1523-1747.2003.12182.x
28. Dai, Z., Xing, L., Cerise, J., Wang, E. H., Jabbari, A., de Jong, A., Petukhova, L., Christiano, A. M., & Clynes, R. (2016). CXCR3 Blockade Inhibits T Cell Migration into the Skin and Prevents Development of Alopecia Areata. *Journal of immunology (Baltimore, Md. : 1950)*, *197*(4), 1089–1099. https://doi.org/10.4049/jimmunol.1501798
29. Ito T. (2013). Recent advances in the pathogenesis of autoimmune hair loss disease alopecia areata. *Clinical & developmental immunology*, *2013*, 348546. https://doi.org/10.1155/2013/348546
30. Gao, Z., Jin, Y. Q., & Wu, W. (2017). SOCS-3 treatment prevents the development of alopecia areata by inhibiting CD8+ T cell-mediated autoimmune destruction. *Oncotarget*, *8*(20), 33432–33443. https://doi.org/10.18632/oncotarget.16504
31. Paus, R., Slominski, A., & Czarnetzki, B. M. (1993). Is alopecia areata an autoimmune-response against melanogenesis-related proteins, exposed by abnormal MHC class I expression in the anagen hair bulb?. *The Yale journal of biology and medicine*, *66*(6), 541–554.
32. Peereboom-Wynia, J. D., van Joost, T., Stolz, E., & Prins, M. E. (1986). Markers of immunologic injury in progressive alopecia areata. *Journal of cutaneous pathology*, *13*(5), 363–369. https://doi.org/10.1111/j.1600-0560.1986.tb00471.x/
33. Nakamura, M., Jo, J., Tabata, Y., & Ishikawa, O. (2008). Controlled delivery of T-box21 small interfering RNA ameliorates autoimmune alopecia (Alopecia Areata) in a C3H/HeJ mouse model. *The American journal of pathology*, *172*(3), 650–658. https://doi.org/10.2353/ajpath.2008.061249

34. Freyschmidt-Paul, P., McElwee, K. J., Hoffmann, R., Sundberg, J. P., Vitacolonna, M., Kissling, S., & Zöller, M. (2006). Interferon-gamma-deficient mice are resistant to the development of alopecia areata. *The British journal of dermatology*, *155*(3), 515–521. https://doi.org/10.1111/j.1365-2133.2006.07377.x
35. Eisman, S., & Sinclair, R. (2021). Ritlecitinib: an investigational drug for the treatment of moderate to severe alopecia areata. *Expert opinion on investigational drugs*, *30*(12), 1169–1174. https://doi.org/10.1080/13543784.2021.2012149
36. Muñoz-Bellido, F. J., Moreno, E., & Dávila, I. (2022). Dupilumab: A Review of Present Indications and Off-Label Uses. *Journal of investigational allergology & clinical immunology*, *32*(2), 97–115. https://doi.org/10.18176/jiaci.0682
37. Fahr A. (1993). Cyclosporin clinical pharmacokinetics. *Clinical pharmacokinetics*, *24*(6), 472–495. https://doi.org/10.2165/00003088-199324060-00004
38. Wu, S. Z., Wang, S., Ratnaparkhi, R., & Bergfeld, W. F. (2018). Treatment of pediatric alopecia areata with anthralin: A retrospective study of 37 patients. *Pediatric dermatology*, *35*(6), 817–820. https://doi.org/10.1111/pde.13703
39. King, B., Ohyama, M., Kwon, O., Zlotogorski, A., Ko, J., Mesinkovska, N. A., Hordinsky, M., Dutronc, Y., Wu, W. S., McCollam, J., Chiasserini, C., Yu, G., Stanley, S., Holzwarth, K., DeLozier, A. M., Sinclair, R., & BRAVE-AA Investigators (2022). Two Phase 3 Trials of Baricitinib for Alopecia Areata. *The New England journal of medicine*, *386*(18), 1687–1699. https://doi.org/10.1056/NEJMoa2110343
40. King, B., Guttman-Yassky, E., Peeva, E., Banerjee, A., Sinclair, R., Pavel, A. B., Zhu, L., Cox, L. A., Craiglow, B., Chen, L., Banfield, C., Page, K., Zhang, W., & Vincent, M. S. (2021). A phase 2a randomized, placebo-controlled study to evaluate the efficacy and safety of the oral Janus kinase inhibitors ritlecitinib and brepocitinib in alopecia areata: 24-week results. *Journal of the American Academy of Dermatology*, *85*(2), 379–387. https://doi.org/10.1016/j.jaad.2021.03.050
41. Guttman-Yassky, E., Renert-Yuval, Y., Bares, J., Chima, M., Hawkes, J. E., Gilleaudeau, P., Sullivan-Whalen, M., Singer, G. K., Garcet, S., Pavel, A. B., Lebwohl, M. G., & Krueger, J. G. (2022). Phase 2a randomized clinical trial of dupilumab (anti-IL-4Rα) for alopecia areata patients. *Allergy*, *77*(3), 897–906. https://doi.org/10.1111/all.15071
42. Guttman-Yassky, E., Pavel, A. B., Diaz, A., Zhang, N., Del Duca, E., Estrada, Y., King, B., Banerjee, A., Banfield, C., Cox, L. A., Dowty, M. E., Page, K., Vincent, M. S., Zhang, W., Zhu, L., & Peeva, E. (2022). Ritlecitinib and brepocitinib demonstrate significant improvement in scalp alopecia areata biomarkers. *The Journal of allergy and clinical immunology*, *149*(4), 1318–1328. https://doi.org/10.1016/j.jaci.2021.10.036
43. Lai, V., Chen, G., & Sinclair, R. (2021). Impact of cyclosporin treatment on health-related quality of life of patients with alopecia areata. *The Journal of dermatological treatment*, *32*(2), 250–257. https://doi.org/10.1080/09546634.2019.1654068
44. Xing, L., Dai, Z., Jabbari, A. *et al.* Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. *Nat Med* 20, 1043–1049 (2014). https://doi.org/10.1038/nm.3645
45. Poole R, Ballantyne A (2014) Apremilast: first global approval. Drugs 74(7):825–837. https://doi.org/10.1007/ s40265-014-0218-4
46. Keren A, Shemer A, Ullmann Y, Paus R, Gilhar A (2015) The PDE4 inhibitor, apremilast, suppresses experimentally induced alopecia areata in human skin in vivo. J Dermatol Sci 77(1):74–76. https://doi.org/10.1016/j.jdermsci.2014.11.009
47. NIH US (2020) National Library of Medicine. http://www.clini caltrials.gov/
48. Mackay-Wiggan J, Sallee BN, Chun Wang EH, Sansaricq F, Nguyen N, Kim C, Chen JC, Christiano AM, Clynes R (2020) An open-label study evaluating the efficacy of abatacept in alopecia areata. J Am Acad Dermatol. https://doi.org/10.1016/j.jaad.2020. 09.091

