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The molecular basis of alopecia areata and risk assessment of comorbid autoimmune diseases

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BOSTON UNIVERSITY
SCHOOL OF MEDICINE

Thesis

**THE MOLECULAR BASIS OF ALOPECIA AREATA AND RISK ASSESSMENT
OF COMORBID AUTOIMMUNE DISEASES**

by

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ALEXA MACGRANAKY-QUAYE

ABSTRACT

Alopecia areata (AA) is a non-cicatricial autoimmune condition, resulting in a patchy loss of hair from the scalp. The hair loss is not limited to the scalp and can extend to ones eyebrows and eyelashes. AA can progress into the more severe subtypes; hair loss from the entire scalp (alopecia totalis) or the entire body (alopecia universalis). AA is a multifactorial disease, citing genes and environmental factors such as stress, climate, drugs and hair styling practices as causative factors. Histologically, CD8 (+) T cells invade and attack the hair follicle, leading to disturbances in hair growth. Treatment for AA aims to reduce the amount of inflammation and re-establish the normal hair loss cycle. Treatment options fall into 3 categories: local treatments, physical treatments and systemic treatments; none are FDA approved. Some patients do not require treatment, as spontaneous remission can occur. A number of studies have examined the comorbidity of AA with other autoimmune diseases genetically and phenotypically. There is a reported increased incidence of several autoimmune diseases occurring with AA such as rheumatoid arthritis, diseases of the thyroid, psoriasis, vitiligo and even type I diabetes. This hints at a relation occurring between the molecular pathways of AA and these comorbid diseases. As AA currently has no FDA approved treatment options, molecular investigation of where these pathways coincide may yield new, long-lasting treatment alternatives for patients with AA.

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LIST OF ABBREVIATIONS

AA.....	Alopecia Areata
AASIS.....	Alopecia Areata Symptom Impact Scale
AGA	Androgenetic Alopecia
AD.....	Atopic Dermatitis
AT.....	Alopecia Totalis
AU.....	Alopecia Universalis
CCCA.....	Central Centrifugal Cicatricial Alopecia
DLE.....	Discoid Lupus Erythematosus
FFA.....	Frontal Fibrosing Alopecia
GWAS.....	Genome Wide Association Study
JAK.....	Janus Kinase
LLP.....	Lichen Planopilaris
PADI3.....	Peptidyl Arginine Deiminase Type III
RA.....	Rheumatoid Arthritis
SALT.....	Severity of Alopecia Tool
SLE.....	Systemic Lupus Erythromatosus
SNP.....	Single Nucleotide Polymorphism
SOCS3.....	Suppressor of Cytokine Signaling-3
STAT.....	Signal Transducer and Activator of Transcription
T1DB.....	Type I Diabetes
TA	Traction Alopecia

TCR.....T cell Receptor
TE.....Telogen Effluvium
TNF- α Tumor Necrosis Factor - Alpha

BACKGROUND

Alopecia areata (AA) is a non-scarring autoimmune disease of the scalp characterized by cyclical alopecia (hair loss) and scalp inflammation. Phenotypically, individuals with alopecia areata have hair loss first in small, round, uniform patches, then in a multifocal or centrifugal pattern across the scalp (Wolff et al., 2016). Morphologically, the scalp of AA patients shows black dots, broken hairs, and exclamation mark hairs, which are hairs that are thicker at the ends and taper off towards the scalp (Darkase et al., 2020). Microscopically, the hair follicle is infiltrated by lymphocytes and immune cells, which reversibly damage the follicle (Figure 1) (Stefanato, 2010; Wolff et al., 2016). In some patients, hair loss and growth cycles become cyclical with hair regrowing in the bald patches and being lost again (Alli et al., 2012). In others, spontaneous remission occurs where the hair lost regrows completely and is not lost again, while sometimes the lost hair is unable to grow back (Wolff et al., 2016).

The hair follicle is the entire unit that comprises one hair strand. The follicle starts at the epidermis, the outermost layer of the skin, and it is composed of the follicle/shaft itself, the sebaceous gland and the arrector pili muscle (Martel et al., 2021). The hair shaft is made of an inner medulla and an outer cortex (Martel et al., 2021). The sebaceous glands are holocrine glands associated with each hair follicle and produce sebum, a natural oil that works to protect the hair and scalp (Martel et al., 2021). The arrector pili muscle is responsible for the “goosebumps” phenomenon experienced when one is cold; via sympathetic stimulation, piloerection occurs and causes hair to stand erect aiding in

thermoregulation (Martel et al., 2021). The inferior segment of the hair follicle includes the bulge that contains epidermal stem cells, the hair bulb, capillaries to provide nutrients for the hair, and the follicular matrix where keratinocytes proliferate to form the hair shaft; this is how hair grows (Martel et al., 2021). Melanocytes reside among the keratinocyte matrix cells and give the hair its color (Martel et al., 2021).

The hair growth cycle proceeds in three phases: anagen, catagen and telogen. Anagen is the growth phase that can last anywhere from two to six years in an individual hair strand, where hair grows about 1 cm a month (Wolff et al., 2016). For eyelashes and eyebrows, anagen only lasts a few months (Martel et al., 2021). The next phase, catagen, is a transitional phase lasting one to two weeks in which the hair follicle regresses (Martel et al., 2021). Catagen is promptly followed by telogen the rest phase which lasts between two to four months; the hair falls out after this phase and the cycle begins again (Wolff et al., 2016). The hair follicles are not synchronized while going through the phases, so each of the 100,000 hair follicles move through the phases at various times; the follicles can become synchronized via factors like hormones, drugs, growth factors and seasons, causing an early transition from anagen to telogen, skipping catagen and causing hair loss (Wolff et al., 2016).

Worldwide, AA has a 2% prevalence rate (Gutierrez et al., 2021). Though it was assumed that AA shows no discrimination concerning gender or age group, the cohort of a recent ten year cross-sectional study conducted by Gutierrez et al. showed that AA predominantly affected females over males (65%) and typically affects younger aged

people (ages 21-40). There is no difference in prevalence among different ethnic groups (Pratt et al., 2017).

Poor prognostic factors for AA include childhood onset, a lengthy duration, familial history, concurrent atopic dermatitis, existence of other autoimmune diseases, changes to the nails most frequently nail pitting and having the ophiasis subtype of AA (Wolff et al., 2016; Darwin et al., 2018). Having a family history of AA has been found to be associated with increased symptom severity, less hair regrowth following AA relapse and a prepubescent age of AA occurrence (Wang et al., 2018). 10% to 42% of people affected by AA report having a family history of AA (Islam et al., 2015). Triggers proven to have caused relapse in patients affected by familial AA are stress, lethargy, thyroid disorder and seasonal changes (Wang et al., 2018). There is also a high concordance of AA occurrence in monozygotic (identical) twin studies (Islam et al., 2015). Prognosis is usually unpredictable, as 34%-50% of AA patients recover within one year and 14-25% of patient with AA will progress to AT or AU where recovery becomes minimal (Darwin et al., 2018).

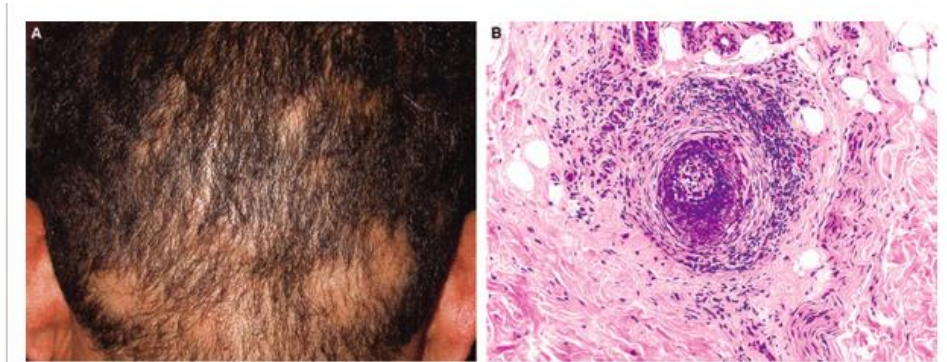


Figure 1: Alopecia Areata Phenotype and Histopathology. A. Multiple patches of hair loss. B. A hair bulb with peribulbar lymphoid cell infiltrate. Adapted from “Histopathology of Alopecia: a clinicopathological approach to diagnosis,” by C. M. Stefanato, 2010, *Histopathology*, 56(1), p.24-38. Copyright [2010] by Blackwell Publishing Ltd.

Types of alopecia

There are many classifiable forms of alopecia. One broad category for classification is cicatricial (scarring) or non-cicatricial (non-scarring) alopecias. In non-cicatricial alopecias the hair follicles are not destroyed or scarred, thus hair regrowth is possible, while in cicatricial alopecia, scarring causes permanent hair loss (Lin et al., 2018). Since humans can experience alopecia areata anywhere there is hair on the body including the beard, eyebrows, eyelashes and pubic area as seen in Figures 2 and 3, AA is best classified as a systemic disease (Kanti et al., 2018; Islam et al., 2015).



Figure 2: Alopecia of the beard and neck region. Figure shows multiple patches of alopecia. Adapted from “Beard alopecia areata: a multicentre review of 55 patients” by D. Saceda-Corralo et al., 2021, *Journal of the European Academy of Dermatology and Venereology*, 31(1), p.187-192. Copyright [2017] by John Wiley & Sons Inc.



Figure 3: Alopecia of the eyebrows. Figure shows non-scarring hair loss in the patient's eyebrows. Adapted from “Congenital symmetrical circumscribed patterned non-scarring alopecia of eyebrows: a variant of congenital triangular alopecia or an anatomical variation?” by D. Yadav et al., 2019, *British Medical Journal Case Reports* 12(5), p.435-465. Copyright [2019] by BMJ Publishing Group Limited.

Non-cicatricial alopecias

Non-cicatricial alopecias do not cause the scalp to scar and thus allow for the possibility of hair regrowth. There are several examples of non-cicatricial alopecias.

Alopecia areata, one type of non-cicatricial alopecia, features hair loss in localized patches on the scalp (Wolff et al., 2016). As the patches get larger and affect the entire scalp, AA can develop into alopecia totalis (AT) and the individual loses all hair on the scalp. If hair loss is seen on the entire body (total hair loss), it is referred to as alopecia universalis (AU) (Wolff et al., 2016). Androgenetic alopecia (AGA), which is the most common form of hair loss, is a patterned, symmetrical, and progressive form of hair loss affecting both sexes shown in Figures 4 and 5 (Chovarda et al., 2021). It is thought to occur when genetically predisposed hair follicles are exposed to androgens: testosterone and its derivative dihydrotestosterone (DHT) (Chovarda et al., 2021).



Figure 4: Male-pattern androgenetic alopecia. Figure features symmetrical patches of progressive hair loss. Adapted from “Androgenetic Alopecia” by C.H. Ho, 2021, *Journal of the German Society of Dermatology*, 16(4), p. 435-465. Copyright [2018] by Blackwell Publishing Ltd.



Figure 5: Androgenetic alopecia of the scalp. Figure shows a magnified scalp with androgenetic alopecia. Notice the variability of the hairs diameter. Adapted from “Alopecia: evaluation and treatment” by K.A. Gordon & A. Tosti, 2011, *Clinical Cosmetic Investigational Dermatology*, 11(4), p.101-106. Copyright [2011] by Gordon and Tosti.

Traction alopecia (TA) shown in Figure 6 is alopecia caused by frequent tension put on the hair, typically through tight hairstyles (Sharquie et al., 2021). Traction alopecia is common amongst African-American communities, due to tight repetitive hairstyling practices (Pratt et al., 2017; Mirmirani & Khumalo, 2014). Telogen effluvium (TE) describes the sudden hair loss experienced after a bodily insult. The hair loss is due to the excessive shedding of hairs in the telogen rest phase. The insult may be due to surgery, pregnancy and childbirth, stress, diet and disease among other things (Werner & Mulinari-Brenner, 2012). It has been suggested that the inciting event serves to trigger the hair follicles to enter into telogen early, leading to the synchronization of the hair follicles and resulting in mass shedding (Werner & Mulinari-Brenner, 2012).



Figure 6: Traction alopecia. Figure shows traction alopecia on the parietal area of the scalp. Hair density and thickness in these areas are low. Adapted from “Traction Alopecia: the root of the problem” by V. Billero & M. Miteva, 2021, *Clinical cosmetic Investigational Dermatology*, 11, p.149-159. Copyright [2018] by Billero and Miteva.

AA is not always patchy. It can result in hair loss at the scalp margin called ophiasis when affecting the posterior scalp, and sisaipho when the anterior scalp is affected. The ophiasis and sisaipho patterned subtypes are for the most part rare. The ophiasis pattern of AA, pictured in Figure 7, occurs in the nape/occipital region as a band along the back of the scalp and extending towards the temples (Gupta et al., 2014). The ophiasis subtype is associated with a worse health outcome and prognosis as it is very resistant to treatment (Gupta et al., 2014). The sisaipho subtype is the inverse of the ophiasis where hair loss occurs on the frontal part of the scalp and not extending to the parietal and occipital regions; this type mimics AGA (Gupta et al., 2014).



Figure 7: Ophiasis subtype of alopecia areata. Figure shows hair loss in the occipital and temporal regions of the scalp. Adapted from “An unusual Pattern of Alopecia Areata” by A. Gupta et al., 2014, *International Journal of Trichology*, 6(4), p.190-191. Copyright [2014] by International Journal of Trichology.

Cicatricial alopecias

Cicatricial alopecias can be classified as primary where inflammation directly damages the hair follicle, or secondary where either inflammation or physical injury to the tissue around the follicle destroys it (Kanti et al., 2018). Lichen planopilaris (LPP), a primary cicatricial alopecia, features multiple hair loss patches with hyperkeratosis and erythema pictured in Figure 8, and is thought to arise from an erroneous immune response that leads T cells to destroy follicular stem cells (Kanti et al., 2018). A variant of LLP known as frontal fibrosing alopecia (FFA), shows hairline recession mostly in the frontal, parietal and occipital regions also with hyperkeratosis and erythema, shown in Figures 9 and 10 (Kanti et al., 2018). Central centrifugal cicatricial alopecia (CCCA) is also caused by lymphocytic infiltrate and shows symmetric centrifugal progression,

hyperpigmentation, erythema, polytrichia (when multiple hairs emerge from the same follicle) and shows unaffected patches within the affected areas (Kanti et al., 2018).

Discoid lupus erythematosus (DLE) is caused by an infiltrate of both T cells and histiocytes, and shows hardened erythematous plaques with scaling and scarring, atrophy, telangiectasia, and follicular plugging (Kanti et al., 2018). Cicatricial alopecias can also be divided based on inflammatory cell type; while LLP, FFA, DLE and CCCA are mediated by a lymphocytic infiltrate, folliculitis decalvans and dissecting cellulitis are mediated by a neutrophilic infiltrate. Folliculitis decalvans commonly features pustules and papules, crusting, and tufted hairs; affected patients experience scalp pruritis, hypersensitivity and pain (Kanti et al., 2018). Dissecting cellulitis, another cicatricial alopecia mediated by neutrophils, shows perifollicular pustules and painful draining sinuses and tracts that scar and disfigure the scalp (Lee et al., 2018). Burns can be classified as causing secondary cicatricial alopecia, as deep skin burns physically injure the hair follicle so that hair is unable to regrow (Kanti et al., 2018). Initially, traction alopecia is non-cicatricial but it can become secondarily cicatricial if prolonged (Billero & Miteva, 2018).

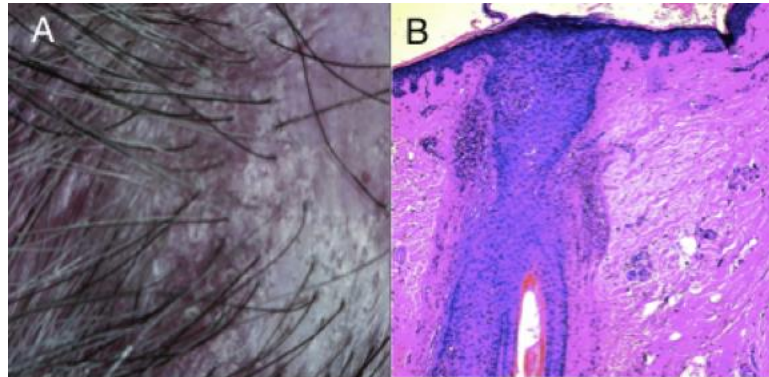


Figure 8: Lichen planopilaris phenotype and histopathology. A. An alopecic patch featuring loss of hair follicles with scarring. B. Hair follicle with immune cell infiltrate (purple cells). Adapted from “Cicatricial Alopecia” by V. Kanti et al., 2018, *Journal of the German Society of Dermatology*, 16(4), p.435-465. Copyright [2018] by John Wiley & Sons Inc.



Figure 9: Frontal fibrosing alopecia phenotype - occipital region. Figure shows hairline recession mostly in the occipital and parietal regions of the scalp. Adapted from “Cicatricial Alopecia” by V. Kanti et al., 2018, *Journal of the German Society of Dermatology*, 16(4), p.435-465. Copyright [2018] by John Wiley & Sons Inc.



Figure 10: Frontal fibrosing alopecia phenotype - frontal region. Figure shows hairline recession mostly in the frontal region of the scalp. Adapted from “Cicatricial Alopecia” by V. Kanti et al., 2018, *Journal of the German Society of Dermatology*, 16(4), p.435-465. Copyright [2018] by John Wiley & Sons Inc.

SPECIFIC AIMS

The specific aims and objectives for this literature thesis are to examine and distinguish between the different kinds of alopecia, as well as to assess the diagnostic features alopecia areata. I aim to investigate the molecular basis of alopecia areata, as well as the diseases alopecia areata may be comorbid with. This literature thesis also aims to further discuss the treatment options available for alopecia areata, not only temporarily but as an autoimmune disease, the factors surrounding the spontaneous remission of alopecia areata, and how or if molecular pathways can be targeted to treat alopecia areata and favor spontaneous long term remission of alopecia. I hope to discover molecular links between different autoimmune diseases that may help determine what may make a patient more susceptible to developing certain comorbid autoimmune diseases. Lastly, I plan to study the role of the environment in the development of alopecia and how this can also relate to comorbid diseases.

LITERATURE REVIEW

The molecular basis of alopecia areata

Alopecia areata is a complex, polygenic disease, whose mechanism has not been fully elucidated. It is presumed to proceed via an autoimmune mechanism; the immune system of patients with AA wrongly targets an unknown self-antigen in the hair follicles of the scalp and body (Coda et al., 2010). This autoimmune disease is mediated mostly by a sensitized population of CD4 and CD8 (+) T lymphocytes (Jabbari et al., 2016). Other immune cells, such as natural killer cells (NK), mast cells, eosinophils and macrophages are also thought to infiltrate the hair bulb and cause inflammation (Jabbari et al., 2016).

Normally in adaptive immunity, naïve immune cells wait quiescently until the body is infected with a pathogen. Antigen presenting cells (APCs) take pathogenic antigens to nearby lymph nodes and present these exogenous antigens to naïve B and T lymphocytes, where the antigen is correctly recognized and a mature B and/or T cell mediated response is initiated (Rossi & Young, 2005). B lymphocytes, macrophages and monocytes, dendritic cells and Langherhans cells are all APCs (Choo, 2007). Adaptive immunity is signaled to be activated via the innate immune system, our bodies first line of defense (Kabelitz & Medzhitov, 2007). APCs like dendritic cells are therefore the bridge between our innate and adaptive immune systems, taking particles of the exogenous antigen initially recognized by toll-like receptors on the innate immune system cells and initiating the presentation of them to the adaptive immune system effector cells, B and T lymphocytes (Kabelitz & Medzhitov, 2007). However in

autoimmune diseases, B and T cell populations are erroneously matured from endogenous or self-antigens. Several autoimmune diseases are associated with HLA molecules, whose role is to present peptide antigens to T lymphocytes that then use their T-cell receptor (TCR) to recognize the antigen (Kalish & Gilhar, 2003). These wrongly matured lymphocytes then cause an immune response directed towards human proteins, resulting in destruction of the autoantigen that activated the T and B lymphocytes (Thomas & Kayden, 2008).

In a blood-DNA microarray global-gene expression study, Coda et al. (2010) used skin samples to investigate patterns between 4 tested groups: patients with AA, patients with AU and healthy control groups, unaffected relatives of patients with AA and unaffected non-relatives (Coda et al., 2010). They found an ‘inheritance signature’ in that the AA, AU and unaffected relatives clustered separately from the unaffected non-relatives (Coda et al., 2010). In addition, AA and AU samples clustered separately from unaffected relative and non-relatives suggesting a ‘disease signature’(Coda et al., 2010). Then they found that AA and AU clustered separately representing a ‘severity signature’ with AU being more severe than AA (Coda et al., 2010). Finally, they found that AU clusters closer to unaffected relatives, meaning AU is more likely to have a genetic basis (Coda et al., 2010). The ‘inheritance’ gene cluster was determined to be related to pathways involving adaptive immunity: the mitogen activated protein kinase (MAPK), Hedgehog (Hh) and Wnt signaling pathways (Coda et al., 2010).

A high incidence spontaneous alopecia mouse model (the 1MOG244.1 line) was produced to show the mechanism and course of AA in a study conducted by Alli et al.

(2012). They created a CD8 (+) T lymphocyte with a TCR that had high specificity against hair follicles, and transgenic mice expressing the TCR spontaneously developed AA at a near 100% incidence (Alli et al., 2012). In mice they also showed that cyclic episodes of hair loss and growth ultimately advanced to AU (Alli et al., 2012).

After a genome-wide association study (GWAS) found that ligands for the NKG2D receptor were involved in the pathology of alopecia areata, Xing et al. (2014) sought to show that cytotoxic CD8(+), NKGD(+) T-cells cause AA in mouse models. These T lymphocytes trigger the upregulation of certain inflammatory cytokines, like IFN- γ , which when it contacts and activates the γ -c (gamma-c) receptor, the tyrosine kinase JAK/STAT pathway in AA is initiated (Xing et al., 2014). They found that when JAK inhibitors (JAKi), like ruxolitinib were used orally or topically, IFN- γ levels decreased, preventing AA progression or completely reversing the disease and prompting hair regrowth (Xing et al., 2014). They also found that both the AA mouse models and patients showed amplified levels of the phosphorylated STAT1, STAT2 and STAT3 proteins, which are affected downstream after receptor activation from IFN- γ , supporting the JAK/STAT pathway involvement in AA (Xing et al., 2014).

The JAK/STAT pathway is an intracellular signal transduction pathway that several pro-inflammatory cytokines and signals are involved in, opening up the possibility of diseases that may be ameliorated through JAK/STAT targeting (Wang et al., 2018). JAK stand for Janus kinase and STAT stands for signal transducer and activator of transcription. As previously mentioned, when the initiating cytokine binds to the JAK/STAT receptor, dimerization and autophosphorylation of the STAT proteins

occurs, initiating a signal transduction cascade, shown in Figure 11. JAK/STAT receptors can bind a number of different cytokines, implicating them in a number of different diseases, and for this reason JAKis have been used to treat several different diseases, like rheumatoid arthritis and ulcerative colitis. The JAK1 tyrosine kinase facilitates cytokine signaling for inflammatory illnesses and the JAK2 tyrosine kinase enables signaling for cytokines mostly involved in hematopoiesis; the JAK3 tyrosine kinase aids in signaling for lymphoid cells only, including B and T cells (Wang et al., 2018).

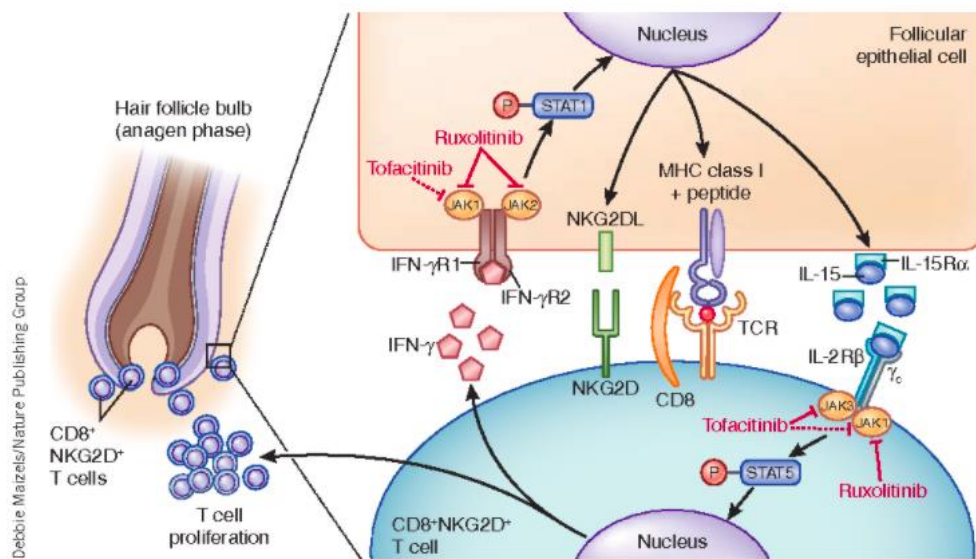


Figure 11: JAK/STAT mechanism. Figure shows that activated autoreactive CD8 (+) T lymphocytes produce the cytokine IFN- γ that contacts the IFN- γ receptor on follicular cells, and initiates the signal transduction pathway of JAK phosphorylating STAT proteins, causing the production of IL-15 which binds to the CD8 (+) T cells and recruits more autoreactive CD8 (+) T cells and IFN- γ . JAKis inhibit JAK from phosphorylating STAT proteins, breaking the positive feedback loop. Adapted from “Inhibiting Janus kinases to treat alopecia areata” by S. Divito & T. Kupper, 2014, *Nature Medicine*, 20(9), p.989-990. Copyright [2014] by Nature Publishing Group.

The commonly used C3H/HeJ mouse model has been used in alopecia research to demonstrate the pathology of spontaneously developed AA, which is comparable to that seen in humans (Petukhova et al., 2010). Another research study examined IFN- γ deficient mice aka IFN- γ (-/-) and discovered that they were resistant to developing AA (Freyschmidt-Paul et al., 2006). They grafted skin from AA infected C3H/HeJ mice onto other C3H/HeJ mice that had their IFN- γ gene deleted. For their results, they reported that 90% of the wild type C3H/HeJ mice developed AA, while none of the IFN- γ (-/-) deleted mice developed AA, which was qualified by experiencing hair loss (Freyschmidt-Paul et al., 2006).

Petukhova et al. (2010) conducted a GWAS of several loci possibly involved in alopecia areata pathogenesis. Loci were found for genes encoding for HLA molecules, ULB1, IL-2RA, and PTPN22 (Petukhova et al., 2010). HLA molecules are responsible for presenting endogenous and exogenous antigens to T and B cells, which then mount their respective humoral and cytotoxic adaptive immune responses. HLA class I molecules are located on almost all cells with nuclei and present endogenous antigens to T lymphocytes. HLA class II molecules are present only on the surfaces of B lymphocytes, T lymphocytes and APCs; they present exogenous antigens to the aforementioned APCs (Choo, 2007). A GWAS found that the HLA class II alleles DQ3, DQ7, DR4, DR5 and DPW4 are involved in the development of AA, as well as some HLA class I molecules although not as frequently (Islam et al., 2015). HLA haplotypes DQ3, DQ7 and DR11 supposedly predispose one to AT and AU (Islam et al., 2015). The ULB1 gene codes for ligands that bind the NKG2D receptor, which when activated

makes NK cells that in C3H/HeJ mice that have been shown to target and destroy hair follicles (Solimani et al., 2019). IL-2RA is the high affinity receptor for the IL-2 cytokine, and both are crucial to controlling the number of regulatory T cells (T_{reg}) available to suppress an autoimmune response (Petukhova et al., 2010). The PTPN22 gene encodes a tyrosine phosphatase enzyme of lymphoid proteins; the phosphatase removes phosphate groups, which normally helps to suppress T-cell activation (Bottini et al., 2004).

Later, Jabbari et al. (2016) discovered that single nucleotide polymorphisms (SNPs) of the ULBP3 and ULBP6 genes, specifically, give an increased susceptibility to the development of AA. As previously noted, The ULBP gene family codes for proteins that are ligands for the NKG2D receptor. When the receptor is activated, it commits immune cells to the fate of being either NK cells or cytotoxic CD8(+), NKGD(+) T-cells, which are abundant in AA skin biopsies (Petukhova et al., 2010).

In AA, the hair follicle loses its privileged immune status, which normally protects the follicle from being targeted as an antigen by autoreactive NK and T-cells (Solimani et al., 2019). The hair follicle has a downregulation of MHC I receptors making it naturally immune privileged (Darwin et al., 2018). This privileged immune status is maintained by the hair follicle through expressing several cytokines such as TGF- β 1 and TGF- β 2, α -MSH and MIF (Solimani et al., 2019). These cytokines help to thwart the degradative actions of NK and T-cells and keep the hair follicle protected from these destructive cells and out of harm's way (Solimani et al., 2019).

Alopecia areata and comorbidity

It has been shown that autoimmune diseases can develop as part of a comorbidity, meaning patients with one autoimmune disease are more susceptible to developing others. Lee et al. (2019) found that patients with AA were also at higher risk of developing other autoimmune diseases. AA has been seen to be comorbid with other inflammatory diseases like vitiligo a skin depigmentation disorder, atopic dermatitis (AD), systemic lupus erythematosus (SLE), psoriasis, and thyroid diseases (Dahir & Thomsen, 2018; Fenner & Silverberg, 2018; Lee et al., 2019).

Jabbari et al. (2016) notes that most of the implicated immune genes involved in AA have previously been associated with other autoimmune diseases like type I diabetes, celiac disease and rheumatoid arthritis, which supports a “common-cause hypothesis” of autoimmune diseases also known as the autoimmune theory. Type I diabetes mellitus (T1DB) aka insulin-dependent diabetes, results from the autoimmune antibody destruction of pancreatic β -cells (Thrasivoulos et al., 2009). Normally, β -cells secrete insulin, a protein hormone responsible for decreasing blood-sugar levels after a meal. Insulin allows cells to take in glucose, which can then be converted and used as energy to conduct cellular metabolic processes. Without insulin, acute and chronically high blood glucose levels cause clinical complications. As previously mentioned, the PTPN22 gene encodes for an intracellular tyrosine phosphate that has been associated with a handful of autoimmune diseases such as T1DB, rheumatoid arthritis, thyroid diseases, myasthenia gravis, systemic sclerosis, vitiligo, Addison’s disease and AA (Gregersen and Olsson, 2009). Bottini et al. conducted a gene association study using a T1DB sample group and

healthy sample group for comparison. Through genotyping, they discovered that the PTPN22 allele 1858T was more frequently associated with T1DB patients than healthy patients of the same ethnic background, suggesting that alleles may predispose people to developing T1DB (Bottini et al., 2004).

The autoimmune theory has also been supported through the finding of autoantibodies against melanocytes, a feature of vitiligo, and also through vitiligo's comorbidity with T1DB (Dahir and Thomsen, 2018). Melanocytes are the cells that make the skin pigment melanin via the enzyme tyrosinase converting tyrosine to DOPA, a process stimulated by UVB light (Yousef et al., 2022). They reside in the stratum basale, the deepest layer of the epidermis, where they make melanin and pass it on to keratinocytes, giving the skin its coloration (Yousef et al., 2022). In vitiligo, both autoantibodies and T-lymphocytes cause the destruction of melanocytes, leading to white skin patches from the loss of pigment. Vitiligo and AA are pathologically similar too, in that their cell infiltrates are mostly comprised of T cells and both diseases have been described as Th1 autoimmune diseases due to the involvement of CD8+ T cells (Harris, 2013). It has even been postulated that vitiligo and alopecia areata may even be preceding signs of T1DB development (Iwasaki, 2015). Iwasaki (2015) noted that among vitiligo patients, the prevalence rates for simultaneous AA and T1DB increase drastically from 5% and 1% respectively, to 10%.



Figure 12: Vitiligo presentation. Figure displays skin depigmentation on the forelimbs and hands, due to destruction of melanocytic cells that produce melanin. Adapted from “Vitiligo: A Review” by C. Bergqvist & K. Ezzedine, 2020, *Dermatology*, 236(6), p.571-592. Copyright [2020] by S. Karger AG, Basel.

Gregerssen and Olsson (2009) note that a region of chromosome 4q27 has been associated with celiac disease, a disease where the normally unproblematic antigen, gluten, irritates the intestines. There is evidence that this chromosomal region may be associated with other autoimmune diseases as well. Celiac disease results in an increased sensitivity to gluten, leading to difficulty digesting glutenous food. This seems to occur in people who express the HLA class II DQ2 or DQ8 haplotype (Guadalini and Assiri, 2014). Patients have elevated levels of autoantibodies to gluten, inflammation of the small intestine, and gastric and extraintestinal issues (Guadalini and Assiri, 2014). The inflammation leads to malabsorption of nutrients across the intestines. Based on eleven different studies and case series, Pham et al. (2020) constructed a literature review and found that of 31 patients that reportedly had concomitant celiac disease and AA, 70.9% showed improvement of AA when eating a gluten-free diet, and hair regrowth was seen

as early as 2 months in with no recurrence of AA in the following 3 years (Pham et al., 2020).

Autoimmune diseases of the thyroid, Graves' disease (hyperthyroidism) and Hashimoto's thyroiditis (hypothyroidism), were also seen to be comorbid with AA, and patients with AA have an increased likelihood of thyroid issues (Lee et al., 2019). Hyperthyroidism is the result of excessive thyroid hormone (TH) production. TH is produced by the thyroid after stimulation from the central nervous system. The hypothalamus secretes release thyroid releasing hormone (TRH) which signals the anterior pituitary to make thyroid stimulating hormone (TSH). TSH then stimulates the thyroid gland to make TH which acts as an effector hormone. TH regulates metabolic processes, and has impact on several body systems; its increase leads to symptoms such as heat intolerance, weight loss, increased sweating, tachycardia, goiters and exophthalmos. On the contrary, hypothyroidism is the result of too little TH. This results in symptoms of cold intolerance, lethargy, weight gain, bradycardia, dry skin and irritability. Frequently, abnormal levels of thyroid hormone and presence of antithyroid autoantibodies levels have been reported for AA patients (Han et al., 2018).

Atopic dermatitis (AD), also known as eczema, is a common chronic inflammatory skin disease that usually develops during childhood but can extend on into adulthood (Mohan & Silverberg, 2015). It is characterized by itchy skin and a recurring dry, scaly rash seen in Figure 13, along with fissuring and overall discomfort (Weidinger et al., 2018). Damage to the protein filaggrin, a structural protein found in the superficial epidermis, makes way for helper T-cells (TH2) to invade and cause inflammation due to

weakening of the skin barrier. A study by van den Oord and Sheikh (2009) found that defects to the filaggrin gene lead to an increased possibility of developing allergies and AD, suggesting the filaggrin gene may be used as a biomarker for allergic pathologies. Ways in which AD can develop include an allergen contacting the skin, through a disrupted skin barrier, from *Staphylococcus aureus* overgrowth in the skin microbiota, and via an IgE-mediated immune response (Weidinger et al., 2018). In a meta-analysis study conducted by Mohan & Silverberg (2015), it was found that patients with AA or vitiligo have increased rates of AD compared to patients without either of the disorders.

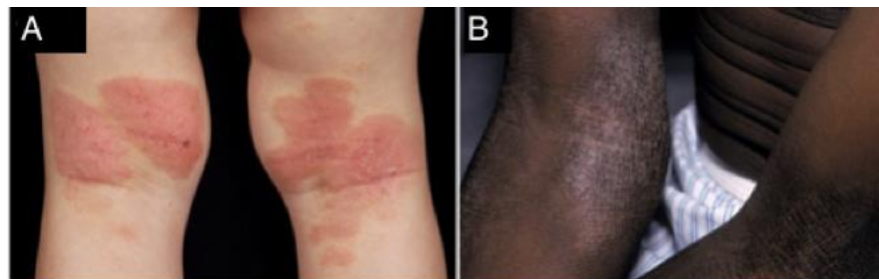


Figure 13: Atopic dermatitis presentation. Figures show the appearance of atopic dermatitis on lighter and darker skin. Note the difference in presentation based on skin tone; figure A shows an erythematous phenotype, while figure B displays a scaly, dry, non-red presentation. Adapted from “Atopic Dermatitis” by S. Weidinger et al., 2018, *Nature reviews. Disease primers*, 4(1). Copyright [2018] by Springer Nature Limited.

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease in which the immune system indiscriminately attacks the body’s tissues. SLE causes inflammation and leads to tissue and/or organ damage. Patients can present with a rash, anemia, joint pain, glomerulonephritis, photosensitivity, oral ulcers and seizures (Forouzan and Cohen, 2020). Rash is common in SLE, as more than 80% of patients experience skin

dysfunction (Justiz Vaillant et al., 2022). The classic facial rash of acute SLE is a malar rash, better known as the butterfly rash. The butterfly rash is an acute symptom of lupus, and is an erythematous rash occurring over the cheeks and nasal bridge of the afflicted shown in Figure 14 (Justiz Vaillant et al., 2022). This is a tell-tale sign and is characteristic of the disease.

Patients with AA have an approximate five-fold increased incidence of SLE, and the converse is true as well (Lee et al., 2019). Forouzan and Cohen (2020) describe a 36 year old woman diagnosed with AA on her scalp and concurrent SLE. The patient received the common AA treatment of corticosteroid injections to her scalp and experienced complete hair regrowth with no relapse after 1 year (Forouzan and Cohen, 2020). She reported having photosensitivity and joint pain in her shoulders and hand; her labs were significant for anti-nuclear antibodies (ANA), Sm/RNP antibodies and she was experiencing proteinuria (Forouzan and Cohen, 2020). The study also notes a previous study in which out of 39 patients with SLE, 10% developed alopecia areata (Forouzan and Cohen, 2020). Patients with SLE also develop short hairs on the temples, and one classification scheme revised their diagnostic criteria of SLE to include non-scarring alopecia as a symptom (Forouzan and Cohen, 2020).



Figure 14: Systemic lupus erythematosus presentation. Figure shows the characteristic facial malar rash aka the butterfly-rash; appearance of the rash is a tell-tale sign of Systemic Lupus Erythematosus, a systemic disease. Adapted from “Systemic Lupus Erythematosus” by A.A. Justiz Vaillant, A. Goyal & M. Varacallo, 2022, *StatPearls*. Copyright [2022] by StatPearls Publishing LLC.

Rheumatoid arthritis (RA) is an autoimmune disease affecting the joints which causes inflammation and joint pain (Chang et al., 2020). RA is a chronic, progressive and systemic disease, affecting the body and all joint tissues (Chang et al., 2020). Many RA patients experience inflammation in the joints of the hands resulting in hand deformities, such as the boutonnières deformity and the swan neck deformity, which cause the hand to be stiff and unable to straighten as pictured in Figure 15. AA is comorbid with RA, and may even develop before RA is identified (Chang et al., 2020). In a cohort study, Chang et al. (2020) found that the risk of developing AA was 2.64-fold higher in RA patients. They also noted that younger patients with RA (20–40 years old) had the highest risk of

developing alopecia (Chang et al., 2020). Lastly, they found that both RA and thyroid diseases occur more often concomitantly in AA patients. The association between RA and alopecia may also be caused by medications. Another case study describes the development of AU in a 56 year old RA patient being treated with the tumor necrosis factor alpha (TNF- α) inhibitor, adalimumab (Ostojic & Pavlov-Dolijanovic, 2018). Her RA went into remission while using the TNF- α inhibitor, though use was discontinued due to the complete loss of scalp and body hair, aka AU development (Ostojic & Pavlov-Dolijanovic, 2018). However, the alopecia did not resolve upon removal of the adalimumab treatment (Ostojic & Pavlov-Dolijanovic, 2018).



Figure 15: Hand deformity in rheumatoid arthritis. Figure displays characteristic hand and joint deformity that occurs due to joint inflammation in Rheumatoid Arthritis. Adapted from “Reconstruction of Digital Deformities in Rheumatoid Arthritis” by S.J. Sebastin, K. Chung, 2011, *Hand Clinics* 27(1) p. 87-104. Copyright [2011] by Elsevier Inc.

Recalling the importance of JAK/STAT pathways, Solimani et al. (2019) comments that inhibiting JAKs can block the actions of several cytokines simultaneously. Consequently, JAKis are a new drug class that are being shown to be an effective treatment for many different diseases. The oral JAKi tofacitinib was the first of three

commercially available JAKi for the treatment of rheumatoid arthritis (Solimani et al., 2019), along with baricitinib and upadacitinib (Harrington et al., 2020). Tofacitinib has also been approved to treat ulcerative colitis, a disease characterized by the inflammation of the mucosal layer of the colon (Ferrante & Sabino, 2020). While research into JAKis for AA treatment has shown promising results in its early stages, they are not FDA approved for this indication. In an experimental mouse model of C3H/HeJ mice, treatment with the same oral JAKi tofacitinib was protective against hair loss and also encouraged hair regrowth (Solimani et al., 2019). When AA patients were treated with the oral JAKi ruxolitinib, a decrease in the numbers of CD8(+) NKG2D(+) cells was noted, and there was extensive regrowth of hair resulting in improvement of their AA (Xing et al., 2014). In 2020, Abe et al. reported a 57 year old male who began experiencing hair loss due to AA by age 30. His AA was not responsive to the standard AA treatments of minoxidil, triamcinolone infiltration, and systemic corticosteroids (Abe et al., 2020). He was later diagnosed with RA that was also not responding to treatment by methotrexate, a systemic anti-inflammatory drug used as the first-line treatment. He was instead given oral tofacitinib that resulted in substantial improvement of his AA (Abe et al., 2020).

Tassone et al. (2018) via GWAS studies noted a genetic comorbid predisposition between AA and psoriasis, a chronic inflammatory skin disease. It estimated that AA patients have a 2.5-fold higher risk of developing psoriasis and the vast literature on the topic supports the claim. Psoriatic patches appear as red, scaly plaques normally on the limbs, trunk, and scalp pictured in Figure 16 (Rendon & Schäkel, 2019). These authors

also predict that AA/psoriatic patients are more likely to have one or two other autoimmune diseases in conjunction with their AA and psoriasis (Tassone et al., 2018).

TNF- α inhibitors or antagonists have been known to cause psoriasis and an associated hair loss called psoriatic alopecia. This TNF- α inhibitor induced alopecia differs from AA as the skin may also show psoriasiform plaques and a higher follicular density is seen in comparison (Craddock et al., 2017). AA is a disease mediated by mostly Th1 cells, whereas psoriasis is mediated by mostly Th17 cells. This is interesting as one active inflammatory pathway normally inhibits others; here there seems to be a switch from one pathway to another (Ovcharenko et al., 2013). This led to the discovery of the Renbok phenomenon in relation to AA and psoriasis. The Renbok phenomenon, first described in 1991, refers to the normal hair growth in sites of psoriasis in patients with AA (Criado et al., 2007). This is the opposite of the Koebner phenomenon, where an initial traumatic event causes inflammatory diseases such as psoriasis to spread; in the Renbok phenomenon psoriasis inhibits the inflammatory process. The Koebner phenomenon also contrasts with the Renbok phenomenon in that the psoriatic plaques exist and are provoked at the same sites as the alopecia (Wylie & Burden, 2011). Normally, in patients experiencing both AA and psoriasis, the psoriatic plaques surround the AA sites without invading the AA sites (Wylie & Burden, 2011). After treatment of the psoriasis, most patients with concomitant psoriasis and AA have complete regrowth of hair (Tassone et al., 2018).



Figure 16: Psoriasis presentation. Figure shows erythematous psoriatic plaques on the lower extremities. Adapted from “Psoriasis Pathogenesis and Treatment” by A. Rendon & K. Schäkel, 2019, *International Journal of Molecular Sciences*, 20(6). Copyright [2019] by A. Rendon & K. Schäkel.

DISCUSSION

Alopecia areata diagnosis

Alopecia areata is one of many autoimmune diseases, likely involving the dysregulation of multiple genes, presenting in different bodily areas, and seemingly caused by different tangible and molecular triggers. The diagnosis of alopecia areata can often be made during a clinical dermatologic examination. Patients present with small circular areas of non-scarring hair loss, sometimes with exclamation mark hairs at the periphery of the alopecic patch on close inspection (Spano & Donovan, 2015).

Sometimes the diagnosis can be complicated, especially if the patient is experiencing a comorbid autoimmune disease or if the presenting disease is a mimic of AA. In such cases, a skin biopsy and tissue culture examination can be used to confirm the diagnosis of AA and exclude other entities such as tinea capitis (a fungal infection of the scalp hair classed as ringworm), trichotillomania, which is compulsive hair pulling, telogen effluvium, or as mentioned earlier a cicatricial (scarring) alopecia (Spano & Donovan, 2015). AA histopathology often shows lymphocytes infiltrating the hair follicle's bulb (Spano & Donovan, 2015). Recall that the hair follicle is normally immunologically privileged and not subject to immune cell infiltrate.

The severity and prognosis of AA rare variable, due to age of onset, environmental factors and genetic predisposition. Young age of onset, disease severity/widespread loss, loss at the posterior scalp margin (termed ophiasis), other

simultaneous autoimmune disorders and family history of AA all contribute to a poorer prognosis (Spano & Donovan, 2015).

Diagnostic criteria have been set to help identify the severity of AA. Clinically, the Severity of Alopecia Tool (SALT) score is a clinical research tool used to assess the severity of the alopecic hair loss in patients. This is done by dividing the scalp into four different areas for scoring shown in Figure 17. The vertex or crown of the head is 40% of the scalp surface area, the left and right scalp profiles each account for 18% of the scalp surface area, and the posterior portion of the scalp is 24% of the scalps surface area (Sardesai et al., 2012). Physicians take the percentage of hair lost in each of the four areas and multiply by the percent surface area to calculate the overall percentage of hair lost in that area (Sardesai et al., 2012). The SALT score is then the total summation of the percentage of hair lost over the entire scalp. A lower SALT score is then more favorable and indicative of a less severe presentation of alopecia and vice versa. SALT scores may be used during baseline and follow-up visits following administration of an AA treatment, where they can help indicate if the treatment is working. A lower SALT score indicates regrowth, and can be used to determine efficacy of a given treatment. A study examining the effects of oral tofacitinib (5mg) used SALT scores to calculate and compare a percentage of hair regrowth before and after treatment in patients with severe AA, AT and AU (Zhou et al., 2021). They found that after 3 months of treatment 64% of patients experienced hair regrowth and 32% achieved a 50% or more improvement in their SALT score (Zhou et al., 2021). Though SALT can be used to describe the severity of a patient's AA, it is not comprehensive as it does not describe the alopecic pattern or

asses the severity of AA on other areas of the body such as the eyebrows and eyelashes (Lee et al., 2019).

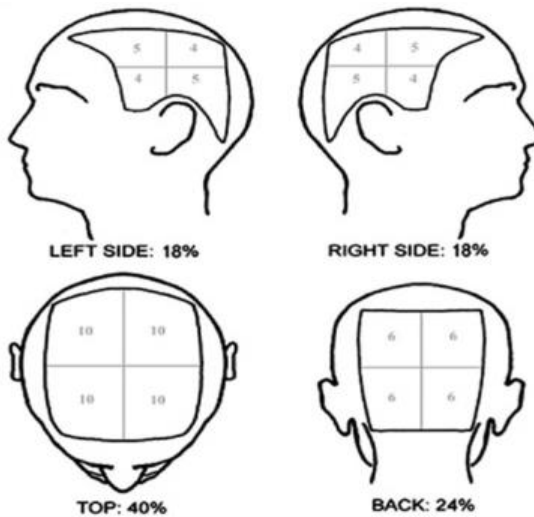


Figure 17: Clinical SALT tool. Figure visually shows the four different areas of the scalp used for SALT scoring. The left and right scalp profiles account for 18% of the surface area, the top or vertex accounts for 40%, and the back portion of the scalp is 24%. Physicians assess the scalp and estimate the percentage of hair lost from the area to calculate the SALT score. A low SALT score is favorable. Adapted from “A randomized trial of diphenylcyclopropenone (DPCP) combined with anthralin versus DPCP alone for treating moderate to severe alopecia areatas” by N. Ghandi et al., 2021, *International Immunopharmacology*, 99. Copyright [2021] by Elsevier B.V.

The Alopecia Areata Symptom Impact Scale (AASIS) is another tool used to assess AA symptoms and the impact the disease has on patients’ lives (Mendoza et al., 2018). AA can be detrimental to one’s self-confidence and expose individuals to societal judgments. AASIS is a psychometric test focusing on a patient’s mental well-being. It is a 13 question survey split into two question categories: how AA symptoms affect the individual and how AA interferes with their daily functioning. It operates on a 0-10 numeration scale where 0 indicates the issue is not present and 10 implies the issue is as

bad as can be imagined. Mendoza et al. (2018) measured the validity of AASIS in terms of how symptoms affect patient functioning and found the highest-rated symptom was the severity of hair loss from the scalp, followed by severe anxiety/worry. The highest-rated interference with daily function reported was enjoyment of life, indicating the profound effect AA has on affected patients (Mendoza et al., 2018).

Alopecia areata has a strong genetic component, which contributes to an overall worse prognosis. Familial cases of AA show a rapid progression of the disease, resistance to treatment, and frequent relapse (Biran et al., 2015). There is a noted increased risk of AA occurrence in the first-degree relatives of AA afflicted patients (Biran et al., 2015). Twin studies reveal that among identical monozygotic twins there is an approximate 42% AA concordance rate; this rate is not high enough to class AA as an autosomal dominant disease (Lortkipanidze et al., 2016). It is clear that alopecia areata etiology is multifactorial, relying on the interactions between multiple genes to produce the varied alopeic phenotype (Biran et al., 2015).

The role of the environment

While it is clear that genetic factors play a substantial role in the development of AA, there are also environmental factors that may predispose an individual to developing alopecia areata. The trigger for development of AA that has been most commonly reported is emotional or physical stress (Pratt et al., 2017). One study found that when compared to their healthy siblings, children with AA had experienced more stressful life events, and that the children with AA in the study showed higher urinary excretion of

catecholamines, epinephrine and norepinephrine (Diaz-Atienza & Gurpegui, 2011).

Catecholamines are our autonomic nervous system's way of responding to stress as they prepare the body for the "fight or flight" reaction. They, along with the stress hormone cortisol are elevated in times of stress. Through an AA mouse model, it was seen that the activity of the hypothalamic-pituitary-adrenal axis or HPA axis in affected mice was increased compared to that of an unaffected normal mouse, meaning the mice were producing more catecholamine stress hormones (Darwin et al., 2018).

Our digestive system's micronutrient environment may also have a role to play in the development of AA. Thompson et al. (2018) states that serum levels of micronutrients are altered via diet. A "threshold hypothesis" suggests that for patients with a mild risk of inheriting AA, a threshold micronutrient level may exist so that irregular levels may contribute to AA development, while for patients with high risk or no risk of developing AA, fluctuating micronutrient levels would not contribute towards AA development (Kantor et al., 2003). The research of Kantor et al. (2003) was based on the serum micronutrient ferritin in women, which reflects the body's iron store levels.

Another study suggests that AA patients may even be more sensitive to the climate environment than their unaffected counterparts, and that some climates may elicit a seasonal pattern of AA flare ups, contributing to AA pathogenesis (George et al., 2021). It had been seen previously that pediatric cases of AA flares are seen to follow a seasonal pattern, with more occurring during fall and lesser during the spring (George et al., 2021). George et al. (2021) states that atopic conditions are associated with climate and they hypothesized that UVB irradiation may contribute to the development of AA, as it

induces the skin to produce vitamin D. In colder months, when less sunlight is available and less vitamin D is being produced, they postulate that AA may develop, a notion reinforced by meta-analysis of the serum levels of vitamin D in AA patients being overall lower (George et al., 2021).

Another example of an environmental insult that may lead to the development of alopecia is hair styling practices that lead to traction alopecia. Traction alopecia is a biphasic hair loss, which begins as a reversible, non-scarring alopecia caused by repeated or prolonged tension on the hair shaft. If prolonged, it can become cicatricial as the hair follicle is secondarily destroyed. It is commonly seen at the scalp margin in black and African women. Another type of primary cicatricial alopecia seen in the same patient population is central centrifugal cicatricial alopecia (CCCA), a permanent hair loss on the central crown area of the scalp that progresses outwards (centrifugally) (Kanti et al., 2018). While it was always suspected that styling practices could contribute to CCCA, recent research has suggested genetic factors are at play as well. Through the exome sequencing research of 16 women with AA, three heterozygous missense mutations to conserved residues of the peptidyl arginine deiminase type III (PADI3) gene were found in 31% of the patients (Malki et al., 2019). The PADI3 gene encodes an enzyme that alters proteins needed for forming the hair shaft, and the mutations decrease PADI3 expression (Malki et al., 2019). Decreased expression of PADI3 was also noted in scalp biopsy samples from CCCA patients, alluding to genetic involvement (Malki et al., 2019). Individuals suffering from CCCA will not be able to regrow hair in the affected

areas, whereas persons with TA may be able to experience hair regrowth if tight styling practices are avoided (Kanti et al., 2018).

Alopecia areata treatments

Hair loss from alopecia areata is and should be reversible in principle, but in actuality AA can be difficult to treat (Wolff et al., 2016). This “reversible” damage created by cytotoxic T-cells and the cytokines they give off are what causes the hair cycle to leave anagen, causing the hair shaft to break creating “exclamation point hairs” and causing it to become stuck in an abnormal telogen cycle, perpetuating the hair loss (Wolff et al., 2016). Treatment is aimed at interrupting the accumulation of T-cells and blocking the cytokines that are made by the T-cell and hair follicle, thus allowing the follicle to re-enter anagen.

Treatment of AA varies from patient to patient and is based on a number of factors including patient age and the severity of the hair loss. There is no cure for AA although it can remit spontaneously, and there are currently no FDA approved treatments for AA. However, this does not stop clinicians from prescribing treatment that can at least manage the disease symptoms. Current treatment options available can be organized into three different categories: local treatments, physical treatments and systemic treatments.

Local treatments

Topical corticosteroids are mainly used to help reduce the inflammation caused by cell accumulation in the area, which then allows the impaired hair follicles to recover (Darwin et al., 2018). Darwin et al. (2018) postulates that approximately 57% of patients

undergoing topical corticosteroid treatment have complete hair regrowth, making it a popular treatment option. Topical steroids are better for limited use than for severe disease, and strong preparations work better than weak ones. Topical steroids can cause thinning of the skin, called atrophy, lightening of the skin (hypopigmentation), and dilated blood vessels (telangiectasia), limiting prolonged use. Injecting the steroid under the skin, or intralesional corticosteroid injection, alleviates some of these concerns. It is done most often with triamcinolone solution at various concentrations. Studies, show even better results with 63% of individuals experiencing complete hair regrowth in a four month span. Steroid injections can cause skin atrophy at the injection site, but this is typically reversible (Wolff et al., 2016; Darwin et al., 2018). Like topical steroids, intralesional injections prove most effective if the patient has few alopecic foci (Wolff et al., 2016). Systemic corticosteroids like prednisolone are often avoided due to adverse side effects, but can be used in refractory or acute AA cases. Use has resulted in 62% of patients experiencing full regrowth (Darwin et al., 2018). However, there are numerous metabolic side effects, and corticosteroid therapies exhibit high AA relapse rates (33% to 75%), limiting their use (Darwin et al., 2018).

Topical minoxidil has long been a treatment option for androgenetic alopecia but can also be used for alopecia areata. Minoxidil causes vasodilation by upregulating VEGF so more nutrients and oxygen are delivered to the hair follicle, and it activates follicular potassium channels which prolongs the anagen growth phase and reduces the telogen rest phase (Sharma et al., 2020). Topical application of minoxidil does display a dose-dependent response in hair regrowth, with a higher percentage (topical 5%

minoxidil solution) resulting in more significant hair regrowth than 2% (Sharma et al., 2020). Recently, treatment with low-dose oral minoxidil has become popular. At doses under 5mg this treatment seems to have better patient adherence than daily application and fewer side effects. In AGA, 61-100% of patients were seen to have clinical improvement after using oral minoxidil, and up to 82% of patients with AA refractory to topical minoxidil have responded well to oral minoxidil at 5mg (Sharma et al., 2020). The most commonly mentioned side effect of minoxidil use is hypertrichosis or excessive bodily hair growth, particularly on the face (Sharma et al., 2020).

Physical treatments

Physical treatments of AA include light therapy and contact sensitization therapy. One form of light therapy is through use of a 308-nm excimer laser. Excimer laser treatment has been well established as being safe and efficacious against other autoimmune skin diseases like psoriasis and vitiligo. The laser is delivered to the areas of hair loss via a hand held device in the clinician's office. Side effects are minimal, making excimer laser treatment a safe treatment option (Lee et al., 2020). Through systematic review of several databases, researchers found that cosmetically acceptable hair regrowth, denoted as being greater than or equal to 75% of the scalp surface, was observed in 50.2% of 113 AA patients treated with excimer laser (Lee et al., 2020). While the treatment's mechanism of action in AA is not clear, it can be postulated that it is a similar mechanism to that of psoriasis, where the high-energy monochromatic wavelength UV light absorbed by DNA actually complicates DNA synthesis and triggers apoptosis of the assaulting T-cells (Lee et al., 2020).

An additional phototherapeutic option for treatment of AA involves topical application of a photosensitizer, followed by ultraviolet (UV) light application. Psoralen, either taken orally or applied topically, is used to make the scalp more sensitive to light (Sterkens et al., 2021). Procedurally, psoralen can be taken or applied to the scalp and then patients are exposed to ultraviolet (UV) A radiation using a UV light box unit (El-Mofty et al., 2019). This psoralen and UVA treatment is abbreviated as PUVA. The efficacy and efficiency of PUVA has been explored, and has yielded promising results. PUVA needs to be applied slowly and cautiously as it causes a phototoxic scalp reaction, and overdose can result in painful burning, blistering and redness; after recovery treatment can be continued again (El-Mofty et al., 2019). Natural sunlight can be used a substitute for a light box if none is available. In a study in India, participants whose AA was not responsive to other forms of treatment applied a psoralen mixture under a towel wrapped around their heads in a turban-like fashion; they were then instructed to have 15 minutes maximum of sun exposure (Majumdar et al., 2018). A total of 52% of patients showed either good or moderate response to PUVA and had long term efficacy (Majumdar et al., 2018). Psoralen with UV light seems to be an effective and cheap phototherapeutic option to treat AA, although it does require frequent visits or application.

Another treatment option for AA is contact sensitization therapy (Wolff et al 2016). This is a type of immune therapy, which involves application of an allergen, typically either diphenylcyclopropenone or squaric acid dibutyl-ester. These compounds are known allergens. It is thought that they work by inducing a type IV allergy response,

competitively inhibiting the T-lymphocytes causing the AA (Wolff et al., 2016). This switches the bodies focus to controlling the allergic dermatitis reaction that is produced via the topical treatment, and gives the hair a chance to grow back. The allergen is applied once or twice weekly, and the concentration is chosen carefully so as not to not elicit a blistering eruption. It can take several months for hair to regrow, but this is an excellent option for those with severe hair loss. Another, older alternative is application of topical dithranol (anthralin). This treatment, which is best for mild, patchy AA, is useful for children and pregnant women, because it is not a steroid and has minimal side effects. These include irritation and staining of clothing and bedding (Daunton & Harries, 2018). Dithranol can be useful for patients that have not had experienced spontaneous regrowth or whose AA has not responded to other topical treatments (Daunton & Harries, 2018).

Systemic treatments

The more extensive and refractory the hair loss, the more intensive the treatment options need to be. While topical and intralesional corticosteroids can be used for mild cases of AA, oral corticosteroids, immunosuppressants and immunomodulators are used for severe cases of patchy AA, as well as AT and AU.

Oral or intramuscular treatment with methotrexate, an immunosuppressant, is used to subdue the overactive immune systems of AA patients. It has been used to treat several autoimmune diseases, like the previously described RA, SLE, psoriasis and chronic eczema (Lim et al., 2017). The drug was initially developed for chemotherapy as it is an antimetabolite that can bind and block the action of enzymes, disrupting the

normal cells metabolism and causing cell death (Lim et al., 2017). Methotrexate is also an antifolate as it blocks the actions of folic acid (Lim et al., 2017). This is favorable for cancer treatment due to cancer being a result of uncontrollable cell growth. Due to its toxicity, a low dose of methotrexate was administered to patients with refractory AA and 26 of the 29 patients showed improvement clinically; 14 of them at 100% regrowth and 12 of them between 75-90% regrowth (Lim et al., 2017). Side effects experienced by patients in the study were most commonly a transient liver dysfunction, evidenced by abnormally elevated liver enzyme levels; once treatment ceased, levels became normal and liver symptoms subsided (Lim et al., 2017).

An alternative drug to methotrexate with immunosuppressant and immunomodulatory action is sulfasalazine. Mechanistically, sulfasalazine suppresses T-lymphocyte proliferation and reduces humoral cytokine and antibody production, halting the development of AA (Alsantali, 2011). This way, excess T cells and their inflammatory modulators will not destroy the hair follicles. In an uncontrolled study on the efficacy of this medication, 25% of patients achieved greater than 60% of hair regrowth and 30% achieved a moderate response (Alsantali, 2011). It is also considered a second line therapy, similar to methotrexate, which is effective against previously untreatable AA. Sulfasalazine side effects include gastrointestinal issues and relapse rates are moderate ranging from 22 to 45% (Alsantali, 2011).

As aforementioned, the JAK/STAT pathway is implicated in AA and treatment with JAK inhibitors has been shown to reverse the AA pathology, even when severe. JAK inhibitors inhibit several types of tyrosine kinases, enzymes which add phosphate

groups from ATP to tyrosine residues of proteins, and are categorized and named by which kinases they inhibit. The first two to be approved were ruxolitinib and tofacitinib, but neither is approved for AA (Wang et al., 2018). In fact, there are currently no JAKi FDA approved for AA use, though current clinical trials aim to evaluate JAKi effectiveness in the hopes of one day establishing JAKi as a FDA approved treatment for AA.

There are currently five JAK inhibitors approved for human use, ruxolitinib, tofacitinib, baricitinib, upadacitinib and fedratinib (Nguyen & Mesinkovska, 2021). Ruxolitinib is favored for JAK1/2 inhibition and is approved for the treatment of polycythemia vera, a condition with an increased number of red blood cells (Nguyen & Mesinkovska, 2021). Tofacitinib can be used to inhibit JAK1/2, but is most commonly used for JAK3 (Wang et al., 2018). It is FDA approved to treat refractory RA, ulcerative colitis and psoriatic arthritis (Nguyen & Mesinkovska, 2021). Baricitinib is another JAK1/2 inhibitor approved for refractory RA (Nguyen & Mesinkovska, 2021). A case study of a woman with a 9 month history of AA treated with baricitinib first at 2mg daily, then at 4mg daily resulted in regrowth of 97% of her scalp hair, eyelashes and eyebrows with no adverse side effects (Olamiju et al., 2019). The second generation JAKis, upadacitinib and fedratinib inhibit JAK 1 and 2 respectively and are FDA approved to treat myelofibrosis, a precursor of bone marrow cancer (Nguyen & Mesinkovska, 2021).

One of the first uses of a JAK inhibitor for AA treatment was in a young 25 year old male patient who had AU and concomitant plaque psoriasis (Craiglow & King, 2014). Doctors recognized tofacitinib as a potentially promising treatment option that

could target both the psoriasis and the AU (Craiglow & King, 2014). After two months of tofacitinib treatment at 5mg daily, partial regrowth was observed; the dose was increased to 10mg and after 3 months he experienced complete regrowth of his scalp hair, eyelashes, eyebrows, facial and pubic hair, giving hope that JAKi may one day be a FDA approved treatment option for AA (Craiglow & King, 2014). Oral JAK inhibitors have shown to be effective in up to 75% of patients, however studies have showed numerous side effects limiting their use, making topical JAK inhibitors an option only for difficult cases of AA. A study using oral tofacitinib found that AA and its ophiasis subtype were more responsive to the JAKi treatment than the AT and AU subtypes, and 64% of the study participants responded to the treatment (Kennedy Crispin et al., 2016). Upon successful treatment and regrowth of hair, patients will likely have to continue using JAK inhibitors though the dosage may be decreased (Wang et al., 2018). More research is currently underway to study efficacy and safety of these medications in alopecia areata.

One way of avoiding systemic side effects of JAKis is to use them topically. Topical JAKis have been approved for treatment of AD, but they are not that effective in alopecia areata of the scalp due to poor penetration, though they can be used for eyebrows (Kerkemeyer et al., 2021).

The foreseeable down side of JAK inhibitors is they may possibly cause side effects systemically, like increasing the risk of cancer development due to blocking the actions of interferons and NK cells, which normally surveil for tumor development (Lee et al., 2020; Wang et al., 2018). Adverse side effects associated with oral tofacitinib and ruxolitinib are bacterial, viral and fungal infections, and bone marrow suppression (Wang

et al., 2018; Kennedy Crispin et al., 2016). All JAK inhibitors come with black box warnings for various adverse events that may occur with their use, including cardiac events, thromboembolic events such as deep venous thrombosis and pulmonary embolism, stroke, cancer, lymphoma development and death (Nguyen & Mesinkovska, 2021, Ramirez-Martin & Tosti, 2022). Fedratinib specifically has a black box warning for potentially fatal Wernicke's encephalopathy development (McLornan et al., 2021).

Spontaneous remission

Spontaneous remission often occurs with mild presentations of AA, but is much less likely to occur with severe disease. Wolff et al. (2016) reports that about one third of patchy AA patients undergo spontaneous remission of the disease within six months of the original appearance, and that of this third of patients, 50% to 80% remain without symptoms one year after remission. In general, not much is understood about the mechanisms involving spontaneous remission (Islam et al., 2015). Eight patients diagnosed with either AA or AT that experienced spontaneous regrowth of greater than 75% of hair were studied by Fernandez-Gonzalez et al. (2018). In this study they found that only one of the eight patients had developed AA during childhood, supporting the notion that younger age of onset is associated with an overall poorer prognosis and/or less chance of spontaneous remission (Fernandez-Gonzalez et al., 2018). Therefore, a factor favoring spontaneous remission of AA is adult onset of the disease. They concluded that spontaneous remission of AA can occur even in long-lasting extensive alopecia conditions, and after other treatment options fail (Fernandez-Gonzalez et al., 2018).

CONCLUSION

As alopecia areata can take on several different forms, occur in different patterns or locations, have levels of severity that drastically differ among patients ranging from a high incidence of relapse to spontaneously remitting, there are many things to factor in when considering treatment. Alopecia areata's association with a handful of autoimmune diseases, and its own classification as an autoimmune disease, suggests an interaction occurring between the comorbid diseases and their molecular pathways. This is evidenced by the fact that having one autoimmune disease gives a patient the increased risk of developing another. Research concerning alopecia areata has come a long way, making the current efforts dedicated to elucidating the full molecular pathways a hot topic in the dermatology, immunology, rheumatology and other scientific communities. While ongoing research has revealed that the Janus kinase pathway is involved in the induction of alopecia areata, more research of JAK inhibitors as an alopecia areata treatment option must be conducted. Further investigation of the molecular links between alopecia areata and other more well-known autoimmune diseases may be the key to understanding the mechanisms of spontaneous remission, establishing effective treatment options for several types of alopecia, and possibly even finding a cure.

BIBLIOGRAPHY

- Abe, D. T., Tashima, L. M., Basilio, F., & Mulinari-Brenner, F. (2020). Clinical Experience with Oral Tofacitinib in a Patient with Alopecia Areata Universalis and Rheumatoid Arthritis. *International Journal of Trichology*, 12(4), 188–190. https://doi.org/10.4103/ijt.ijt_107_20
- Alli, R., Nguyen, P., Boyd, K., Sundberg, J. P., & Geiger, T. L. (2012). A mouse model of clonal CD8+ T lymphocyte-mediated alopecia areata progressing to alopecia universalis. *Journal of Immunology*, 188(1), 477–486. <https://doi.org/10.4049/jimmunol.1100657>
- Alsantali A. (2011). Alopecia areata: a new treatment plan. *Clinical, Cosmetic and Investigational Dermatology*, 4, 107–115. <https://doi.org/10.2147/CCID.S22767>
- Billero, V., & Miteva, M. (2018). Traction alopecia: the root of the problem. *Clinical, Cosmetic and Investigational Dermatology*, 11. <http://dx.doi.org.ezproxy.bu.edu/10.2147/CCID.S137296>
- Biran, R., Zlotogorski, A., & Ramat, Y. (2015). The genetics of alopecia areata: New approaches, new findings, new treatments. *The Journal of Dermatological Science*, 78(1), 11-20. <https://doi.org/10.1016/j.jdermsci.2015.01.004>
- Bottini, N., Musumeci, L., Alonso, A., Rahmouni, S., Nika, K., Rostamkhani, M., MacMurray, J., Meloni, G. F., Lucarelli, P., Pellecchia, M., Eisenbarth, G. S., Comings, D., & Mustelin, T. (2004). A functional variant of lymphoid tyrosine phosphatase is associated with type 1 diabetes. *Nature Genetics*, 36(4), 337.
- Chang, Y. J., Lee, Y. H., Leong, P. Y., Wang, Y. H., & Wei, J. C. (2020). Impact of Rheumatoid Arthritis on Alopecia: A Nationwide Population-Based Cohort Study in Taiwan. *Frontiers in Medicine*, 7, 150. <https://doi.org/10.3389/fmed.2020.00150>
- Choo S. Y. (2007). The HLA system: genetics, immunology, clinical testing, and clinical implications. *Yonsei Medical Journal*, 48(1), 11–23. <https://doi.org/10.3349/ymj.2007.48.1.11>
- Chovarda, E., Sotiriou, E., Lazaridou, E., Vakirlis, E. & Ioannides, D. (2021). The role of prostaglandins in androgenetic alopecia. *International Journal of Dermatology*, 60(6), 730-735. <https://doi-org.ezproxy.bu.edu/10.1111/ijd.15378>
- Coda, A.B., Hysa, V.Q., Sinha, K.S., Sinha, A.A. (2010). Peripheral blood gene expression in alopecia areata reveals molecular pathways distinguishing

- heritability, disease and severity. *Genes and Immunity*, 11(7), 531.
<http://dx.doi.org.ezproxy.bu.edu/10.1038/gene.2010.32>
- Craddock, L. N., Cooley, D. M., Endo, J. O., Longley, B. J., & Caldera, F. (2017). TNF inhibitor induced alopecia: An unusual form of psoriasiform alopecia that breaks the renbök mold. *Dermatology Online Journal*, 23(3).
<https://doi.org/10.5070/d3233034290>
- Craiglow, B.G., & King, B.A. (2014). Killing Two Birds with One Stone: Oral Tofacitinib Reverses Alopecia Universalis in a Patient with Plaque Psoriasis. *Journal of Investigative Dermatology*, 134(12), 2988-2990.
<https://doi.org/10.1038/jid.2014.260>
- Criado, P. R., Valente, Y.S., Michalany, N.S., Martins, J.E.C., Romiti, R, Aoki, V, & Vasconcellos, C. (2007). An unusual association between scalp psoriasis and ophiasic alopecia areata: the Renbök phenomenon. *Clinical and Experimental Dermatology*, 32 (3), 320-321. <https://doi-org.ezproxy.bu.edu/10.1111/j.1365-2230.2006.02351.x>
- Dahir, A. M., & Thomsen, S. F. (2018). Comorbidities in vitiligo: Comprehensive review. *International Journal of Dermatology*, 57(10), 1157–1164.
<https://doi.org/10.1111/ijd.14055>
- Darwin, E., Hirt, P. A., Fertig, R., Doliner, B., Delcanto, G., & Jimenez, J. J. (2018). Alopecia Areata: Review of Epidemiology, Clinical Features, Pathogenesis, and New Treatment Options. *International Journal of Trichology*, 10(2), 51–60.
https://doi.org/10.4103/ijt.ijt_99_17
- Darkase, B. A., Chikhalkar, S. B., & Khopkar, U. S. (2020). Comparison of Dermoscopic Patterns at the Center and Periphery of Alopecia Areata Patch - A Cross-sectional Study in 100 Patients. *International Journal of Trichology*, 12(1), 24–28.
https://doi.org/10.4103/ijt.ijt_49_19
- Daunton, A., & Harries, M. (2018). Efficacy of topical dithranol (Dithrocream®) in the treatment of alopecia areata: a retrospective case series. *British Journal of Dermatology*, 180(5), 1246-1247. <https://doi-org.ezproxy.bu.edu/10.1111/bjd.17515>
- Díaz-Atienza, F., & Gurpegui, M. (2011). Environmental stress but not subjective distress in children or adolescents with alopecia areata. *Journal of Psychosomatic Research*, 71(2), 102–107. <https://doi.org/10.1016/j.jpsychores.2011.01.007>

- El-Mofty, M., Rasheed, H., El-Eishy, N., Hegazy, R. A., Hafez, V., Shaker, O., & El-Samanoudy, S. I. (2019). A clinical and immunological study of phototoxic regimen of ultraviolet A for treatment of alopecia areata: a randomized controlled clinical trial. *Journal of Dermatological Treatment*, *30*(6), 582–587. <https://doi-org.ezproxy.bu.edu/10.1080/09546634.2018.1543847>
- Fenner, J., & Silverberg, N.B. (2018). Skin diseases associated with atopic dermatitis. *Clinics in Dermatology*, *36*(5), 631–640. <https://doi.org/10.1016/j.clindermatol.2018.05.004>
- Fernandez-Gonzalez, P., Saceda-Corralo, D., Pindado-Ortega, C., Buendia-Castaño, D., Fernández-Guarino, M., & Vañó-Galván, S. (2018). Spontaneous hair regrowth in eight patients with severe alopecia areata. *Australasian Journal of Dermatology*, *59*(4). <https://doi.org/10.1111/ajd.12840>
- Ferrante, M., & Sabino, J. (2020). Efficacy of JAK inhibitors in Ulcerative Colitis. *Journal of Crohn's & Colitis*, *14*(2), S737–S745. <https://doi.org/10.1093/ecco-jcc/jjz202>
- Forouzan, P., & Cohen, P. R. (2020). Systemic Lupus Erythematosus Presenting as Alopecia Areata. *Cureus*, *12*(6), e8724. <https://doi.org/10.7759/cureus.8724>
- 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>
- George, E. A., Castelo-Soccio, L., Putterman, E., Kuhn, H., Wambier, C., Qureshi, A., & Cho, E. (2021). Influence of climate factors on pediatric alopecia areata flares in Philadelphia, Pennsylvania. *Scientific Reports*, *11*(1), 21034. <https://doi.org/10.1038/s41598-021-00433-0>
- Grant Phillips, T., Slomiany, W.P., & Allison, R. (2017). Hair Loss: Common Causes and Treatment. *American Family Physician*, *96*(6), 371-378.
- Gregersen, P. K., & Olsson, L. M. (2009). Recent advances in the genetics of autoimmune disease. *Annual Review of Immunology*, *27*(1), 363–391. <https://doi.org/10.1146/annurev.immunol.021908.132653>
- Guandalini S., & Assiri A. (2014). Celiac Disease: A Review. *JAMA Pediatrics*, *168*(3):272–278. doi:10.1001/jama\pediatrics.2013.3858

- Gupta, A., Sharma, Y. K., Dash, K., & Prakash, N. (2014). An unusual pattern of alopecia areata. *International Journal of Trichology*, 6(4), 190–191. <https://doi.org/10.4103/0974-7753.142893>
- Gutierrez, Y., Pourali, S. P, Jones, M. E, Rajkumar, J. R, Kohn, A. H, Compoginis, G. S, & Armstrong, A. W. (2021). Alopecia areata in the United States: a ten-year analysis of patient characteristics, comorbidities, and treatment patterns. *Dermatology Online Journal*, 27(10). <http://dx.doi.org/10.5070/D3271055631>
- Han, T. Y., Lee, J. H., Noh, T. K., Choi, M. W., Yun, J.-S., Lee, K. H., & Bae, J. M. (2018). Alopecia areata and overt thyroid diseases: A nationwide population-based study. *The Journal of Dermatology*, 45(12), 1411-1417. <https://doi.org/10.1111/1346-8138.14648>
- Harrington, R., Al Nokhatha, S. A., & Conway, R. (2020). JAK Inhibitors in Rheumatoid Arthritis: An Evidence-Based Review on the Emerging Clinical Data. *Journal of Inflammation Research*, 13, 519. <http://dx.doi.org.ezproxy.bu.edu/10.2147/JIR.S219586>
- Harris, J.E. (2013). Vitiligo and alopecia areata: apples and oranges? *Experimental Dermatology*, 22(12), 785-789 <https://doi-org.ezproxy.bu.edu/10.1111/exd.12264>.
- Iwasaki, H. (2015). Vitiligo and Alopecia Areata as Early Signs Preceding Type 1 Diabetes Mellitus. *General Medicine*, 16(1), 47-49.
- Islam, N., Leung, P. S.C., Huntley, A.C., Gershwin, M.E. (2015). The autoimmune basis of alopecia areata: A comprehensive review. *Autoimmunity Reviews*, 14(2), 81-89. <https://doi.org/10.1016/j.autrev.2014.10.014>
- Jabbari, A., Cerise, J. E., Chen, J. C., Mackay-Wiggan, J., Duvic, M., Price, V., Hordinsky, M., Norris, D., Clynes, R., & Christiano, A. M. (2016). Molecular signatures define alopecia areata subtypes and transcriptional biomarkers. *EBioMedicine*, 7, 240–247. <https://doi.org/10.1016/j.ebiom.2016.03.036>
- Justiz Vaillant AA, Goyal A, & Varacallo M. Systemic Lupus Erythematosus. [Updated 2022 Feb 12]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK535405/>
- Kabelitz, D., & Medzhitov, R. (2007). Innate immunity — cross-talk with adaptive immunity through pattern recognition receptors and cytokines. *Current Opinion in Immunology*, 19(1), 1-3. <https://doi.org/10.1016/j.coi.2006.11.018>

- Kalish, R.S., & Gilhar, A. (2003). Alopecia Areata: Autoimmunity—The Evidence Is Compelling. *Journal of Investigative Dermatology Symposium Proceedings*, 8(2), 164-167. <https://doi.org/10.1046/j.1087-0024.2003.00802.x>
- Kanti, V., Rowert-Huber, J., Vogt, A., & Blume-Peytavi, U. (2018) Cicatricial alopecia. *Journal of German Society of Dermatology*, 16(4), 435-461. <https://doi-org.ezproxy.bu.edu/10.1111/ddg.13498>
- Kantor, J., Kessler, L. J., Brooks, D. G., & Cotsarelis, G. (2003). Decreased serum ferritin is associated with alopecia in women. *Journal of Investigative Dermatology*, 121(5), 985–988. <https://doi.org/10.1046/j.1523-1747.2003.12540.x>
- Kennedy Crispin, M., Ko, J. M., Craiglow, B. G., Li, S., Shankar, G., Urban, J. R., Chen, J. C., Cerise, J. E., Jabbari, A., Winge, M. C. G., Marinkovich, M. P., Christiano, A. M., Oro, A. E., & King, B. A. (2016). Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. *JCI Insight*, 1(15). <https://doi.org/10.1172/jci.insight.89776>
- Kerkemeyer, K.L.S., Sinclair, R.D., Bhojrul, B. (2021). Topical tofacitinib for the treatment of alopecia areata affecting facial hair. *British Journal of Dermatology*, 185(3), 677-679. <https://doi-org.ezproxy.bu.edu/10.1111/bjd.20419>
- Lee, C. N., Chen, W. C., Hsu, C. K., Weng, T. T., Lee, J. Y. Y., Yang, C. C. (2018). Dissecting folliculitis (dissecting cellulitis) of the scalp: a 66-patient case series and proposal of classification. *Journal der Deutschen Dermatologischen Gesellschaft*, 16(10), 1219-1226. <https://doi-org.ezproxy.bu.edu/10.1111/ddg.13649>
- Lee, J. H., Eun, S. H., Kim, S. H., Ju, H. J., Kim, G. M., & Bae, J. M. (2020). Excimer laser/light treatment of ALOPECIA AREATA: A systematic review and Meta-analyses. *Photodermatology, Photoimmunology & Photomedicine*, 36(6), 460–469. <https://doi.org/10.1111/phpp.12596>
- Lee, H., Choe S. J., & Lee, W. S. (2019). Method for describing patterns and distributions of alopecia areata which may be helpful for patient characterization and predicting prognosis. *The Journal of Dermatology*, 46 (8), 739-740. <https://doi-org.ezproxy.bu.edu/10.1111/1346-8138.14989>
- Lee, S., Lee, H., Lee, C. H., & Lee, W.S. (2019). Comorbidities in alopecia areata: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology*, 80(2), 466-477.e16. <https://doi.org/10.1016/j.jaad.2018.07.013>
- Lim, S. K., Lim, C. A., Kwon, I. S., Im, M., Seo, Y. J., Kim, C. D., Lee, J. H., & Lee, Y. (2017). Low-Dose Systemic Methotrexate Therapy for Recalcitrant Alopecia

Areata. *Annals of Dermatology*, 29(3), 263–267.
<https://doi.org/10.5021/ad.2017.29.3.263>

Lin, J., Saknite, I., Valdebran, M., Balu, M., Lentsch, G., Williams, J.N., Koenig, K., Tromberg, B.J. & Atanaskova Mesinkovska, N. (2019). Feature characterization of scarring and non-scarring types of alopecia by multiphoton microscopy. *Lasers in Surgery and Medicine*, 51(1), 95-103. <https://doi-org.ezproxy.bu.edu/10.1002/lsm.23017>

Lortkipanidze, N., Zlotogorski, A., & Ramot, Y. (2016). Two Episodes of Simultaneous Identical Alopecia Areata in Identical Twins. *International Journal of Trichology*, 8(1), 47–48. <https://doi.org/10.4103/0974-7753.179398>

Majumdar, B., De, A., Ghosh, S., Sil, A., Sarda, A., Lahiri, K., Chatterjee, G., & Das, S. (2018). "Turban PUVAsol:" A Simple, Novel, Effective, and Safe Treatment Option for Advanced and Refractory Cases of Alopecia Areata. *International Journal of Trichology*, 10(3), 124–128. https://doi.org/10.4103/ijt.ijt_95_17

Malki, L., Sarig, O. Romano, M. T., Mechin, M. C., Peled, A., Pavlovsky, M., Warshauer, E., Samuelov, L., Uwakwe, L., Briskin, V., Mohamad, J., Gat, A., Isakov, O., Rabinowitz, T., Shomron, N., Adir, N., Simon, M., McMichael, A., Dlova, N.C., Betz, R. C., Sprecher, E. (2019). Variant *padi3* in central centrifugal cicatricial alopecia. *New England Journal of Medicine*, 380(9), 833-841. DOI: 10.1056/NEJMoA1816614

Martel, J.L., Miao, J.H., & Badri, T. (2021). Anatomy, Hair Follicle. In *StatPearls*. StatPearls Publishing.

McLornan, D.P., Pope, J.E., Gotlib, J., & Harrison, C.N. (2021). Current and future status of JAK inhibitors. *The Lancet*, 398(10302), 803-816.
[https://doi.org/10.1016/S0140-6736\(21\)00438-4](https://doi.org/10.1016/S0140-6736(21)00438-4)

Mendoza, T. R., Osei, J., & Duvic, M. (2018). The utility and validity of the alopecia areata symptom impact scale in measuring disease-related symptoms and their effect on functioning. *Journal of Investigative Dermatology Symposium Proceedings*, 19(1), S41-S46. <https://doi.org/10.1016/j.jisp.2017.10.009>

Mirmirani, P., & Khumalo, N.P. (2014). Traction Alopecia: How to Translate Study Data for Public Education—Closing the KAP Gap? *Dermatologic Clinics*, 32(2), 153-161. <https://doi.org/10.1016/j.det.2013.12.003>

Mohan, G.C., & Silverberg, J.I. (2015) Association of Vitiligo and Alopecia Areata With Atopic Dermatitis: A Systematic Review and Meta-analysis. *JAMA Dermatology*, 151(5), 522–528. doi:10.1001/jamadermatol.2014.3324

- Nguyen, C., & Mesinkovska, N.A. (2021). Alopecia areata—New updates with long-term use of JAK inhibitors. *Dermatological Reviews*, 2(3), 136–145. <https://doi-org.ezproxy.bu.edu/10.1002/der2.65>
- Olamiju, B., Friedmann, A., & King, B. (2019). Treatment of severe alopecia areata with baricitinib. *JAAD case reports*, 5(10), 892–894. <https://doi.org/10.1016/j.jdcr.2019.07.005>
- Ostojic, P., & Pavlov-Dolijanovic, S. (2018) Alopecia universalis in a patient with rheumatoid arthritis developed during treatment with adalimumab. *Zeitschrift für Rheumatologie* 77, 412–415. <https://doi-org.ezproxy.bu.edu/10.1007/s00393-018-0464-z>
- Ovcharenko, Y., Serbina, I., Zlotogorski, A., & Ramot, Y. (2013). Renbök phenomenon in an alopecia areata patient with psoriasis. *International Journal of Trichology*, 5(4), 194–195. <https://doi.org/10.4103/0974-7753.130397>
- Petukhova, L., Duvic, M., Hordinsky, M., Norris, D., Price, V., Shimomura, Y., Kim, H., Singh, P., Lee, A., Chen, W. V., Meyer, K. C., Paus, R., Jahoda, C. A., Amos, C. I., Gregersen, P. K., & Christiano, A. M. (2010). Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature*, 466(7302), 113–117. <https://doi.org/10.1038/nature09114>
- Pham, C. T., Romero, K., Almohanna, H. M., Griggs, J., Ahmed, A., & Tosti, A. (2020). The Role of Diet as an Adjuvant Treatment in Scarring and Nonscarring Alopecia. *Skin Appendage Disorders*, 6(2), 88–96. <https://doi.org/10.1159/000504786>
- 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>
- Ramírez-Marín, H. A., & Tosti, A. (2022). Evaluating the Therapeutic Potential of Ritlecitinib for the Treatment of Alopecia Areata. *Drug Design, Development and Therapy*, 16, 363–374. <https://doi.org/10.2147/DDDT.S334727>
- Rendon, A., & Schäkel, K. (2019). Psoriasis Pathogenesis and Treatment. *International Journal of Molecular Sciences*, 20(6), 1475. <https://doi.org/10.3390/ijms20061475>
- Rossi M., & Young J.W. (2005). Human Dendritic Cells: Potent Antigen-Presenting Cells at the Crossroads of Innate and Adaptive Immunity. *The Journal of Immunology*, 175 (3), 1373-1381. <https://doi.org/10.4049/jimmunol.175.3.1373>

- Sardesai, V. R., Prasad, S., & Agarwal, T. D. (2012). A study to evaluate the efficacy of various topical treatment modalities for alopecia areata. *International Journal of Trichology*, 4(4), 265–270. <https://doi.org/10.4103/0974-7753.111223>
- Sharma, A.N., Michelle, L., Juhasz, M., Muller Ramos, P. & Atanaskova Mesinkovska, N. (2020). Low-dose oral minoxidil as treatment for non-scarring alopecia: a systematic review. *International Journal of Dermatology*, 59(8), 1013-1019. <https://doi-org.ezproxy.bu.edu/10.1111/ijd.14933>
- Sharquie, K. E., Schwartz, R. A., Aljanabi, W. K., & Janniger, C. K. (2021). Traction Alopecia: Clinical and Cultural Patterns. *Indian Journal of Dermatology*, 66(4), 445. https://doi.org/10.4103/ijd.IJD_648_20
- Solimani F., Meier K., & Ghoreschi K. (2019). Emerging Topical and Systemic JAK Inhibitors in Dermatology. *Frontiers in Immunology*, 10, 2847. <https://doi.org/10.3389/fimmu.2019.02847>
- Spano, F., & Donovan, J. C. (2015). Alopecia areata: Part 1: pathogenesis, diagnosis, and prognosis. *Canadian Family Physician*, 61(9), 751–755.
- Stefanato, C. M. (2010). Histopathology of alopecia: A clinicopathological approach to diagnosis. *Histopathology*, 56(1), 24–38. <https://doi.org/10.1111/j.1365-2559.2009.03439.x>
- Sterkens, A., Lambert, J. & Bervoets, A. (2021). Alopecia areata: a review on diagnosis, immunological etiopathogenesis and treatment options. *Clinical and Experimental Medicine*, 21, 215–230. <https://doi-org.ezproxy.bu.edu/10.1007/s10238-020-00673-w>
- Tassone, F., Caldarola, G., De Simone, C., & Peris, K. (2018). Clinico-dermoscopic features of alopecia areata in patients with psoriasis. *JAAD Case Reports*, 4(7), 665–668. <https://doi.org/10.1016/j.jdc.2018.04.003>
- Thomas, E. A., & Kadyan, R. S. (2008). Alopecia areata and autoimmunity: A clinical study. *Indian Journal of Dermatology*, 53(2), 70. <https://doi.org/10.4103/0019-5154.41650>
- Thompson, J. M., Mirza, M. A., Park, M. K., Qureshi, A. A., & Cho, E. (2017). The Role of Micronutrients in Alopecia Areata: A Review. *American Journal of Clinical Dermatology*, 18(5), 663–679. <https://doi.org/10.1007/s40257-017-0285-x>
- Tzellos, T.G., Tahmatzidis, D.K., Lallas, A., Apostolidou, K., & Goulis, D.G. (2009). Pernicious anemia in a patient with Type 1 diabetes mellitus and alopecia areata

- universalis. *Journal of Diabetes and its Complications*, 23(6), 434-437.
<https://doi.org/10.1016/j.jdiacomp.2008.05.003>
- van den Oord, R. A. H. M., & Sheikh, A. (2009). Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. *BMJ: British Medical Journal*, 339(7712), 86–89.
<http://www.jstor.org/stable/25672060>
- Wang, E., Sallee, B. N., Tejada, C. I., & Christiano, A. M. (2018). JAK Inhibitors for Treatment of Alopecia Areata. *The Journal of Investigative Dermatology*, 138(9), 1911–1916. <https://doi.org/10.1016/j.jid.2018.05.027>
- Wang, S., Ratnaparkhi, R., Piliang, M., & Bergfeld, W. (2018). Role of family history in patchy alopecia areata. *Dermatology Online Journal*, 24(10).
<https://doi.org/10.5070/D32410041734>
- Weidinger, S., Beck, L.A., Bieber, T., Kenji, K., & Irvine, A.D. (2018). Atopic dermatitis. *Nature Reviews. Disease Primers*, 4(1). <https://doi-org.ezproxy.bu.edu/10.1038/s41572-018-0001-z>
- Werner, B., & Mulinari-Brenner, F. (2012). Clinical and histological challenge in the differential diagnosis of diffuse alopecia: female androgenetic alopecia, telogen effluvium and alopecia areata--part II. *Anais Brasileiros de Dermatologia*, 87(6), 884–890. <https://doi.org/10.1590/s0365-05962012000600010>
- Wolff, H., Fischer, T. W., & Blume-Peytavi, U. (2016). The Diagnosis and Treatment of Hair and Scalp Diseases. *Deutsches Arzteblatt International*, 113(21), 377–386.
<https://doi.org/10.3238/arztebl.2016.0377>
- Wylie, G. R., & Burden, D. (2011). Renbok phenomenon between psoriasis and alopecia areata. *Clinical and Experimental Dermatology*, 36(7), 816-817. <https://doi-org.ezproxy.bu.edu/10.1111/j.1365-2230.2011.04097.x>
- Xing, L., Dai, Z., Jabbari, A., Cerise, J.E., Higgins, C.A., Gong, W. (2014) Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by jak inhibition. *Nature Medicine*, 20(9), 1043.
- Yousef, H., Alhajj, M., & Sharma, S. (2022). Anatomy, Skin (Integument), Epidermis. In *StatPearls*. StatPearls Publishing.
- Zarbo, A., Belum, V. R., Sibaud, V., Oudard, S., Postow, M. A., Hsieh, J. J., Motzer, R. J., Busam, K. J., & Lacouture, M. E. (2017). Immune-related alopecia (areata and universalis) in cancer patients receiving immune checkpoint inhibitors. *British Journal of Dermatology*, 176(6), 1649–1652. <https://doi.org/10.1111/bjd.15237>

Zhou, C., Li, X., Wang, C., Zhang, J. (2021) Alopecia Areata: an Update on Etiopathogenesis, Diagnosis, and Management. *Clinical Reviews in Allergy & Immunology*, 61, 403–423. <https://doi-org.ezproxy.bu.edu/10.1007/s12016-021-08883-0>

CURRICULUM VITAE

