Alopecia Areata: A Complex Cytokine Driven Disease

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Alopecia areata (AA) has been recently shown to also include T-helper cell type 2/IL-23 activation, in addition to T-helper cell type 1/IFN-skewing. The success of Jak inhibition together with IL-4R antagonism and limited response to IL-17A and PDE4 (protein) inhibition in AA are increasing our understanding of the complex immune interplay in AA. Trials testing targeted therapeutics are needed to further elucidate the pathogenic contribution of various cytokines.

Deciphering the complex immune pathogenesis involved in various inflammatory skin diseases such as psoriasis or atopic dermatitis (AD) has led to rapid advances in the development of novel therapeutics. The pathogenesis of AD has evolved from being considered predominately an allergic T-helper cell type 2 (Th2)—only driven disease, with IL-4 and IL-13 inducing defects in skin barrier terminal differentiation, to also include T-helper cell type 22 (Th22) activation, with variable T-helper cell type 1 (Th1)/T-helper cell type 17 (Th17) expression, differing with disease duration and ethnicity (Sanyal et al., 2019). The current translational revolution for AD can also be extended to other inflammatory diseases such as alopecia areata (AA), a nonscarring hair loss disease with some pathogenic similarities to AD (Fuentes-Duculan et al., 2016). Having a cumulative lifetime risk of 2%, AA affects both children and adults and has a 5% risk to evolve into alopecia totalis and alopecia universalis (Suárez-Faríná et al., 2015). Comorbidities, including atopic diseases (asthma, allergic rhinitis, and eczema), autoimmune thyroid diseases, and psychiatric illnesses, are more prevalent in patients with AA (Renert-Yuval and Guttman-Yassky, 2017).

Despite the disease burden and tremendous impact on the quality of life, there are currently no curative treatments for AA. Therapeutic options for AA remain limited with unfavorable side effect profiles. Intralesional steroids are the standard of care for localized disease, with limited efficacy and painful administration that can cause atrophy and depigmentation (Strazzulla et al., 2018). Other topical immunotherapies include diphenylcycloprenone, squaric acid dibutylster, and anthralin, which are contact irritants that may lose efficacy when discontinued (Strazzulla et al., 2018). Topical calcineurin inhibitors, topical steroids, and minoxidil can be used as adjunct therapies in extensive diseases, with usage of systemic treatments such as oral corticosteroids, cyclosporine A, and methotrexate being limited due to increased adverse effects (Suárez-Faríná et al., 2015). Recent case series and uncontrolled studies have demonstrated the clinical efficacy of Jak inhibitors such as baricitinib (Jak1/Jak2), tofacitinib (Jak1/Jak3), and ruxolitinib (Jak1/Jak2) in patients with AA (Strazzulla et al., 2018). Promising novel Jak inhibitors currently investigated in placebo-controlled trials for AA include CTP-543 (Jak1/Jak2), Jak1/2, and Jak3 inhibitors that show early efficacy with significant improvements in Severity of Alopecia Tool (SALT) scores (ClinicalTrials.gov: NCT03811912, NCT02974868, and NCT03732807, respectively).

Because of their broad spectrum of inhibition and the fact that Jak inhibitors target more than one cytokine axis, such as Th1, Th2, and IL-23, these agents cannot fully elucidate the complex pathogenesis of AA (Strazzulla et al., 2018). AA is an autoimmune T-cell mediated disease and has been shown to have a predominant Th1/IFN-γ response, stimulating CD8+NKG2D+ effector T cells that infiltrate diseased scalp, leading to upregulation of major histocompatibility complexes and subsequent loss of immune privilege at the hair follicles (Xing et al., 2014). IL-15 was also found to be significantly up-regulated in AA hair follicles and to activate IFN-γ producing CD8+NKG2D+ cytotoxic T cells, working in a positive feedback loop to promote more IL-15 production, facilitating the autoimmune attack on hair follicles (Xing et al., 2014). Recently, studies have also shown a potential role for Th2 axis in AA, with significantly elevated Th2-related biomarkers found in the scalp (IL-4, IL-13, CCL18, TSLP) and serum (IL-4, IL-5, IL-6, CCL17, IgE, eosinophilia) of patients with AA (Fuentes-Duculan et al., 2016; Suárez-Faríná et al., 2015). Furthermore, GWAS of AA has identified susceptibility loci of Th2 origin (IL-4 and IL-13), with few chromosomal loci harboring dysregulated genes coinciding with those previously linked to AD susceptibility (Fuentes-Duculan et al., 2016). All AA subtypes were also associated with atopy and autoimmune diseases, with a more severe course of AA found in patients with concurrent FLG mutation, a signature barrier protein defective in AA (Renert-Yuval and Guttman-Yassky, 2017).

Our recent studies indicate that AA is a highly inflammatory disease in the scalp and the circulation, with complex etiopathogenesis involving dysregulation in several immune axes (Fuentes-Duculan et al., 2016; Song et al., 2018; Suárez-Faríná et al., 2015). We profiled 27 AA lesional and nonlesional

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patients’ scalp samples, comparing the gene expression profile with healthy controls, patients with AD, and patients with psoriasis (Suárez-Farías et al., 2015). We found upregulation of Th1 (IFNγ, CXCL10), Th2 (IL-13, CCL18, CCL26, TSLP), and IL-23 (p40 and p19 subunits), with no upregulation in Th17/Th22 axes in patients with AA (Suárez-Farías et al., 2015). Keratin gene expressions were significantly suppressed in lesional AA scalp and correlated with disease severity (Suárez-Farías et al., 2015). Several case series and reports also demonstrated preliminary success in targeting IL-12/IL-23 cytokines in refractory AA, where ustekinumab (IL-12/IL-23 inhibitor) treatment leads to significant clinical improvements in both children and adults (Aleisa et al., 2019). Ustekinumab modulated immune gene expression, where patients with higher inflammatory profile and greater suppression of hair keratins at baseline were found to achieve more normalization of Th1, Th2, IL-23, PDE, and keratin genes (Renert-Yuval and Guttman-Yassky, 2017). Similarly, mRNA expressions of IL-12/IL-23p40, IL-32, CCL18, and hair keratin (K31, K75, K86) genes were significantly modulated by corticosteroid treatment, suggesting their potential role as biomarkers in monitoring treatment response in patients with AA (Fuentes-Duculan et al., 2016).

Aside from scalp profiling studies, we also identified concurrent significant upregulation of T-cell/NK-cell/Th1 (IL-15, CXCL10)- and Th2 (IL-13, CCL17)-related markers in the serum and upregulation of both circulatory (c) Th/ε1 and Th/ε2 cells in the circulation (Song et al., 2018). Recent case reports showed dupilumab (IL-4Ra monoclonal antibody) successfully inducing hair regrowth in patients with both severe AA and AD, further supporting the potential pathogenic role of the Th2 axis in AA (Smogorzewski et al., 2019). Although targeted AA treatment presents an exciting new approach, conflicting results also exist with antagonism of the Th2 axis (dupilumab) and IL-12/IL-23 (ustekinumab) signaling, and such treatment should be reserved for refractory cases (Smogorzewski et al., 2019).

Whereas understanding the immune etiology of AA has led to the development of promising therapeutics such as Jak inhibitors, other investigated therapies targeting Th17 (IL-17A) and PDE4 (protein) have shown limited efficacy in patients with AA (Mikhaylov et al., 2019). In two pilot double-blind, randomized control trials, 11 patients with AA treated with IL-17A antagonist (secukinumab; ClinicalTrials.gov: NCT02599129), and 20 patients with AA treated with a PDE4 inhibitor (apremilast) had minimal improvements in SALT score (Mikhaylov et al., 2019). Although PDE4 gene expression was significantly elevated in AA lesions and anti-PDE4 therapy showed preliminary success in humanized AA mouse models (Suárez-Farías et al., 2015), the lack of clinical response in the pilot trial argues against a pathogenic role of PDE4 in AA. The limited response in Th17/IL-17A targeting may be explained by the lack of Th17 immune upregulation in patients with AA seen in previous profiling studies (Fuentes-Duculan et al., 2016; Suárez-Farías et al., 2015). Additional clinical trials with a larger sample size and different disease severity may be needed to adequately assess the treatment response to IL-17A and PDE4 inhibition.

AA, like many other inflammatory skin conditions, is beginning a new era of precision medicine, with rapid expansion in exploration and development of targeted and broad therapeutics aimed at pathogenic pathways. Recent success in Jak inhibitor for the treatment of AA and other inflammatory skin diseases such as AD and psoriasis initiated an exciting period of therapeutic development. Jak inhibitors were proposed to work by targeting potential pathogenic cytokines of AA, including IL-2, IL-15, and IFNγ. However, Jak inhibitors provide broader inhibition and also works for diseases with Th2 and Th17 axes activation, such as AD and psoriasis (Strazzulla et al., 2018). Thus, the efficacy of Jak inhibition in AA cannot prove the pathogenic role of Th1 axis and cannot preclude possible involvement of the Th2 axis.

Previous studies indicated that AA is a heterogeneous disease involving Th1, Th2, and IL-23 immune circuits (Fuentes-Duculan et al., 2016; Suárez-Farías et al., 2015; Xing et al., 2014). Recently, Jak inhibitors targeting Jak1/ Tyk2 and Jak3, as well as IL-4R antagonists, are promising novel therapeutics showing early efficacy in clinical trials and preliminary reports. On the contrary, targeting IL-17A and PDE4 did not show clinical benefit in patients with AA. Future clinical trials with targeted therapeutics against various immune axes are needed to determine the pathogenic contribution of various cytokines and chemokines.

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**CONFLICT OF INTEREST**

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**REFERENCES**

