Overview of Alopecia Areata

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Alopecia areata is a complex genetic, immune-mediated disease that targets anagen hair follicles. The disease affects children and adults and is characterized by round or oval patches of hair loss, loss of all scalp hair (alopecia totalis), body hair (alopecia universalis), or ophiasis pattern hair loss. Patients may also present with patchy loss in multiple hair-bearing areas. Commonly associated diseases include asthma, allergic rhinitis, atopic dermatitis, thyroid disease, and automimmune diseases, such as thyroiditis and vitiligo. Nail abnormalities may precede, follow, or occur concurrently with hair loss activity. Alopecia areata has no known age, race, or ethnic preponderance and in contrast to other autoimmune diseases such as thyroiditis or lupus, the hair follicle does not usually sustain permanent injury and maintains its potential to regrow hair. It is estimated that alopecia areata affects between six and seven million individuals in the United States. Genes, the immune and nervous systems have all been implicated in the pathogenesis of alopecia areata. Although many treatments are available, there is still no cure. Bolstered by new scientific and translational opportunities from recently published genome-wide association studies, an ambitious treatment development program has recently been initiated by the National Alopecia Areata Foundation.

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INTRODUCTION: ETIOLOGY OF ALOPECIA AREATA

Immunology

A hallmark of active alopecia areata is the presence of peribulbar lymphocytes around the bulb region of anagen hair follicles (Alkhalifah *et al.*, 2010; Gilhar *et al.*, 1998, 2012). Killer CD8+ T cells in this infiltrate are thought to be attracted to this region by the expression of the natural killer group 2D (NKG2D) ligand. Recent studies have also demonstrated the expression of cytomegalovirus UL16-binding protein in lesional scalp of patients with active disease, providing evidence for the involvement of both innate and acquired immunity in the pathogenesis of alopecia areata (Ito *et al.*, 2008, 2012; Petukhova *et al.*, 2010; Forstbaurer *et al.*, 2012) Additional mechanisms include the loss of immune privilege in the hair follicle. (Kang *et al.*, 2010)

Transplantation studies in severe-combined immunodeficient mice have shown T cell immunity is directly involved in the disease. In recent experiments, injections of peripheral blood mononuclear cells enriched for NKG2D+ cells and activated by phytohemagglutinin/IL-2 from healthy individuals into healthy human skin transplanted onto severe-combined immunodeficient mice resulted in a hair loss pattern similar to the human alopecia areata phenotype, including hair follicle immune privilege collapse (Gilhar *et al.*, 1998, 2012). This model is believed to be the first functional evidence of the concept that NKG2D+ and/or CD56+ cells as well as the NKG2D–stimulating ligands have key roles in alopecia areata.

The nervous system

Many but not all patients describe stressful life events in relationship to the onset and progression of alopecia areata. Alterations in perifollicular innervation have been described but to date a distinct role for neurogenic inflammation in the pathogenesis of alopecia areata remains to be identified (Peters *et al.*, 2006; Cutter and Pittelkow, 2006). The expression of the neuropeptide substance P (SP) and its effects on immune cells in a C3H/HeJ mouse model for alopecia areata have been examined and the number of SP–immunoreactive nerve fibers in skin was found to be increased in evolving alopecia areata. In contrast, in more advanced stages of the disease, the number of SP–immunoreactive nerves and SP protein levels in skin were found to be decreased, and the SP–degrading enzyme neutral endopeptidase increased. These results suggest that SP, neutral endopeptidase, and NK-1R can serve as regulators in the molecular signaling network modulating inflammatory response in autoimmune hair loss such as alopecia areata. (Siebenhaar *et al*, 2007). Further support that a neuronal abnormality may be present in alopecia areata comes from the observation that both SP– and calcitonin gene–related peptide expression vary in alopecia areata scalp eccrine glands (Hordinsky *et al*, 1995). The expression of neuropeptides and neuropeptide receptors by nerves as well as immune cells provides a link between the peripheral nervous system, the central nervous system, and the skin immune system that deserves further study.

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Abbreviations: NK, natural killer; NKG2D, natural killer group 2D; SP, substance P

Genetics

Genetic complexity underlies the heterogeneity seen in alopecia areata. For instance, the concordance rate among identical twins is roughly 55%, not high enough to be considered for dominant inheritance. Family-based studies in the United States show that roughly a third of probands have a biological relative with alopecia areata. Recurrence risks of around 5–6% are estimated for the children of affected individuals (Blaumeiser *et al.*, 2006; Rodriguez *et al.*, 2010). In 2010, a genome-wide association study of 3,278 control subjects and 1,054 well-characterized cases from the Alopecia Areata Registry was published. This Registry was established in 2001 with the goal of better understanding the causes of alopecia areata as well as treatments. The results from well-characterized Registry samples revealed eight genetic loci contributing to alopecia areata such as the HLA region, the UL16-binding protein gene cluster, cytotoxic T-lymphocyte antigen 4 (CTLA4), interleukins (IL-2/IL-21, IL-2RA), and several genes that control the differentiation and maintenance of regulatory T cells. These genomic regions were also noted to be associated with other diseases such as rheumatoid arthritis and celiac disease, other autoimmune diseases with pre-existing treatments, making it possible to consider using these treatments for alopecia areata (Duvic *et al.*, 2003; Petukhova *et al.*, 2010). The key genes identified in the 2010 genome-wide association study were corroborated and additional genes identified in two subsequent genome-wide studies (Petukhova *et al.*, 2010; Forstbaurer *et al.*, 2012; Jagielska *et al.*, 2012). Taken together, these three genome-wide association studies show evidence for associations of alopecia areata with genomic regions that have a role in the immune system and/or hair follicle.

TREATMENT: CHALLENGES

There is currently no cure for alopecia areata and no universally proven therapy that induces and sustains remission (Delamere *et al.*, 2008). Many therapies are available but there continue to be very few published randomized controlled clinical trials in alopecia areata. However, the application of the Alopecia Areata Investigational Guidelines in clinical studies has recently provided some standardization (Olsen *et al.*, 1999). Current treatment choices include a variety of topical, intralesional, and systemic agents with the choice and recommendation based on disease extent, duration, associated medical conditions, and age of the patient.

TREATMENT: OPPORTUNITIES

In October 2010, a Translational Research Summit was sponsored by the National Alopecia Areata Foundation and held at Columbia University in New York City. The primary goal of this meeting was to address how to improve and fast track new treatments for alopecia areata in a coordinated, efficient, safe, and scientifically sound manner. Findings from the recent genetic studies have opened new avenues of treatment exploration based on the underlying mechanisms of alopecia areata and applying therapies already in trials or approved for other autoimmune diseases (Hordinsky, 2011). Trials are currently in progress or being initiated that take into account what we have known about mechanisms common to alopecia areata and other types of autoimmunity, T cell–related mechanisms and the IL-15 pathway or pathways downstream of the NKG2D receptor. In conjunction, other potential therapies using novel devices or medications are also in early clinical trial development to treat primarily patchy alopecia areata. These include Bimatoprost, a prostamide F2 analog and Latanoprost, a prostaglandin F2a analog (Faghihi *et al.*, 2009; Ochoa *et al.*, 2009) Finally, multicenter studies of light therapy primarily with the excimer laser are in clinical trial development (Al-Mutairi, 2009). Immune privilege-protective drugs such as FK506 and/or antagonists of hair follicle immune privilege collapse inducers remain to be studied systematically to assess the effect of restoring a collapsed immune privilege in alopecia areata patients. There is also the potential of using medications that moduate nerve and neuropeptide functions in alopecia areata (Cutter and Pittelkow, 2006). The success of any of these new approaches will be dependent on the design and execution of outstanding clinical trials. The risks and benefits of any new treatment will have to be carefully weighed, particularly in children with alopecia areata.

CONFLICT OF INTEREST

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