Treatment of Alopecia Areata with Simvastatin/Ezetimibe

Jessica Cervantes[1], Joaquin J. Jimenez[1,2], Gina M. DelCanto[2] and Antonella Tosti[1]

Alopecia areata (AA) is an autoimmune disorder characterized by T lymphocytic infiltrates around the bulbar region of hair follicles. Statins have surfaced as potential therapeutic agents for AA, partly because of their modulation of the JAK/STAT pathway. Some data indicate that statins are a possible option for acute, but not chronic, longstanding AA. Animal studies suggest that treatment with statins increases $CD4^+$/$CD25^+$/$Foxp3^+$ populations in AA-affected mice.

Journal of Investigative Dermatology Symposium Proceedings (2018) **19,** S25–S31; doi:10.1016/j.jisp.2017.10.013

INTRODUCTION

Alopecia areata (AA) is a T-lymphocyte–mediated autoimmune disorder in which inflammatory cells concentrate in and around the bulbar region of hair follicles, resulting in premature arrest of the anagen phase and abnormal major histocompatibility complex (MHC) class I and class II expression in the area of the follicular epithelium (Pratt et al., 2017).

Although the exact pathogenesis remains elusive, AA is thought to have a multifactorial etiology described as an interplay of genetic predisposition and environmental exposures. In patients with genetic susceptibility, stress, infection, and microtrauma have been documented to decrease immunosuppressive cytokines that normally maintain the immune privilege of the hair follicle (Gilhar, 2010). Breakdown immune privilege enables $CD56^+NKG2D^+$ natural killer cells to accumulate around the follicle, resulting in augmented production of substance P, calcitonin gene–related peptide, and other neuropeptides. Ultimately, this results in the accumulation of mast cells and $CD8^+NKG2D^+$ T cells around the hair follicle, leading to amplified production of TNF-α and IFN-γ, the latter of which induces expression of MHC class I and class II on the lower part of the follicular epithelium. The JAK/STAT pathway supports interferon production, potentiating the effect. Enhanced presentation of follicular autoantigens via MHC class I and II to $CD8^+$ and $CD4^+$ T cells maintains disease and contributes to loss of IP. Furthermore, reduction in regulatory T-cell (Treg) populations promotes disease (Gilhar, 2010; Pratt et al., 2017).

There is currently no cure for AA, although certain treatments can induce hair regrowth in a percentage of patients. Recently, JAK inhibitors have shown significant efficacy in inducing hair regrowth by inhibiting the JAK/STAT pathway through which inflammatory cytokines such as IL-2, IL-15, and IFN-γ function to maintain disease (Kennedy Crispin et al., 2016; Mackay-Wiggan et al., 2016). Similarly, statins have surfaced as potential therapeutic agents for AA partly because of their modulation of the JAK/STAT pathway.

Statins (Table 1) are hydroxy-methylglutaryl-coenzyme A (i.e., HMG-CoA) reductase inhibitors, commonly used for their lipid-lowering properties to lower cholesterol levels and treat cardiovascular disease, but they also possess powerful anti-inflammatory and immunomodulatory effects. By inhibiting hydroxy-methylglutaryl-coenzyme A reductase, statins inhibit the biosynthesis of various isoprenoids, which are known to act in inflammatory signaling pathways via intracellular second messenger systems (Namazi, 2004; Ulivieri and Baldari, 2014). The ability of statins to alter the imbalance of T helper type (Th) 1, Th2, and Th17 cell populations versus Treg cell populations explains their possible effects on onset and progression in autoimmune diseases including inflammatory bowel diseases, rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus. Although we have strong data on the efficacy and safety of different statins as cholesterol-lowering agents, there are no studies that compare the immunomodulatory effects of different statins (Davies et al., 2016).

Data on the efficacy of statins in autoimmune dermatological diseases are scarce, and conflicting preliminary studies suggest that treatment with simvastatin or atorvastatin can be beneficial in reducing the severity of psoriasis, but evidence is still limited (Ramessur and Gill, 2017). Agarwal et al. (2015) showed that simvastatin prevented and reversed depigmentation in the mouse model of vitiligo by inhibiting STAT-1 and reducing the number of infiltrating autoreactive CD8 T lymphocytes in the skin.

However, a small, randomized, double-blind, placebo-controlled, phase II clinical trial failed to support the use of oral simvastatin for the treatment of vitiligo (Vanderweil et al., 2017). The aim of this article is to review available literature on the use of statins and particularly of the association simvastatin /ezetimibe in AA.

The exact mechanism by which statins exert their effects on the immune system to improve AA is not yet known; current knowledge suggests multiple mechanisms (Chow, 2009).

Modulation of cytokine secretion and T-cell response

Statins have been shown to block the induction of inducible nitric oxide synthase and inhibit secretion of

[1]*University of Miami Miller School of Medicine, Department of Dermatology and Cutaneous Surgery, Miami, Florida, USA; and* [2]*University of Miami Miller School of Medicine, Department of Biochemistry and Molecular Biology, Miami, Florida, USA*

Correspondence: Antonella Tosti, Department of Dermatology and Cutaneous Surgery, University of Miami Miller School of Medicine, 1600 NW 10th Avenue, RMSB, Room 2023A, Miami, Florida 33136, USA. E-mail: ATosti@med.miami.edu

Abbreviations: AA, alopecia areata; MHC, major histocompatibility complex; Th, T helper; Treg, regulatory T cell

Table 1. List of common statins

Statin	Lipophilicity	CYP450 Pathway
Atorvastatin	Yes	CYP3A4
Fluvastatin	Yes	CYP2C9
Lovastatin	Yes	CYP3A4
Pravastatin	No	None
Pitavastatin	Yes	Glucuronidation, minor CYP2C9 and CYP3A4
Rosuvastatin	No	CYP2C, minor CYP2C19
Simvastatin	Yes	CYP3A4, CYP3A5

proinflammatory cytokines, including IFN-γ, TNF-α, IL-1β, and IL-6, which contribute to AA disease (Chow, 2009). Furthermore, certain statins have been documented to induce a Th2/Th1 bias in T helper cell populations by causing up-regulation of Th2-selective cytokine secretion (IL-4, IL-5, and IL-10) and down-regulation of Th1-selective cytokine secretion (IL-2, IL-12, IFN-γ, and TNF-α) via modulation of the JAK/STAT pathway. Specifically, through the activation of STAT6, promotion of GATA3 expression, inhibition of STAT4, and down-regulation of NF-κB and T-bet, statins induce Th2 differentiation and repress Th1 differentiation (Murphy and Reiner, 2002; Robinson and O'Garra, 2002). A few statins, including fluvastatin, promote down-regulation of both Th1- and Th2-selective cytokines (Azuma et al., 2004), whereas others such as simvastatin decrease Th1 cytokine levels without boosting Th2 function (Leung et al., 2003). Up-regulation of Foxp3+ Treg populations is also a result of statin therapy (Kim et al., 2010; Mor et al., 2006).

Inhibition of leukocyte adhesion and extravasation into target tissues

Down-regulation of adhesion molecule expression, including ICAM-1, MAC-1, and LFA-1 on leukocytes and endothelial cells and CCR5 and CXCR3 Th1-type chemokine receptors on T cells, is a documented sequela of statin therapy (Namazi, 2004; Neuhaus et al., 2002; Weitz-Schmidt et al., 2001). Additionally, inhibition of LFA-1 binding to ICAM1 via selective blockade of the lovastatin-binding site on LFA1 leads to inhibition of antigen presentation and thereby lymphocyte activation (Weitz-Schmidt et al., 2001).

Inhibition of leukocyte activation, proliferation, and differentiation

Statins inhibit the IFN-γ–induced up-regulation of MHC class II molecule expression by blocking MHC class II transactivator (i.e., CIITA) promoters pIV and pI (Chow, 2009; Kwak et al., 2000; Youssef et al., 2002). Inhibition of MHC class I expression is also a mechanism of certain statins (Kuipers et al., 2005). Furthermore, they are noted to inhibit the constitutive expression of MHC class II on B cells, activated T cells, and microglia, as well as the constitutive and IFN-γ–inducible up-regulation of co-stimulatory molecules on lymphocytes, macrophages, and endothelial cells (Chow, 2009; Kuipers et al., 2005). Inhibition of natural killer cell cytotoxicity is another likely mechanism (Lattouf et al., 2015; Namazi, 2004)

RESULTS OF LITERATURE REVIEW

Human studies

We retrieved six articles detailing the use of statins for the treatment of AA, including two case reports (Ali and Martin, 2010; Robins, 2007), three small case series (Freitas Gouveia and Trüeb, 2017; Lattouf et al., 2015; Loi et al., 2016), and an anecdotal account (Camacho, 2017) (Table 2). The first documented case (2007) involved a 54-year-old man with AA universalis and uncontrolled hyperlipidemia who achieved significant hair regrowth 1 month after combination simvastatin/ezetimibe was initiated (Robins, 2007). The patient was previously treated with simvastatin alone yet did not achieve any hair regrowth.

In a prospective pilot study (2015), 29 patients with AA involving 40–70% of the scalp were treated for 24 weeks with simvastatin/ezetimibe. Fourteen of the 19 patients who completed the full course of treatment showed evidence of hair regrowth as early as 16 weeks after treatment. Statistical analysis showed positive association between receiving therapy and stable remission ($P = 0.0400$) (Lattouf et al., 2015). However, two succeeding open studies in patients with chronic severe AA had negative results (Freitas Gouveia and Trüeb, 2017; Loi et al., 2016). More recently, Camacho (2017) reported positive results with the use of simvastatin/ezetimibe combined with dexamethasone mini-pulse over the course of 1 year for the treatment of alopecia totalis (Camacho, 2017).

Animal studies

Two animal studies were retrieved from proceedings of international conferences, both of which were performed by authors of this review (Table 3).

The simvastatin/ezetimibe combination induced hair regrowth on the C3H/HeJ mouse model of AA. In this study, 16 mice were randomized into four cohorts: one untreated, one receiving simvastatin alone (5 mg/kg, daily intraperitoneal injections), one receiving ezetimibe alone (10 mg/kg, daily intraperitoneal injections), and one receiving combination simvastatin/ezetimibe (10 mg/kg, daily intraperitoneal injections). After 3 months of treatment and 5 months of observation, results showed that both simvastatin and simvastatin/ezetimibe led to remission of AA lesions in affected mice. At 5 months after treatment discontinuation, mice were killed, and CD4, CD25, and FOXP3 markers of lymphocyte populations in the blood, spleen, and thymus were analyzed. Relative to untreated mice, all treated mice had increased proportions of $FOXP3^+$ cells within the population of Tregs sampled. Combination simvastatin/ezetimibe resulted in a relatively greater increase in $FOXP3^+$ Treg cells compared with either ezetimibe or simvastatin alone. Investigators concluded that long-term treatment with either ezetimibe, simvastatin, or combination simvastatin/ezetimibe may provide novel therapeutic avenues to diminish the autoimmune aspect of AA and promote hair regrowth (Jimenez et al., 2014, 2015).

DelCanto et al. (2015) set out to determine the efficacy of topical simvastatin on 22 female C3H/HeH retired breeders with spontaneously developed AA. Mice were equally divided into two treatment groups: 11 treated with topical simvastatin (40 mg/kg) and 11 with the vehicle. Steady