EA DV CONGRESS
BERLIN 11-14 OCTOBER 2023
EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY

Abstract N°: 4916

Exploring the therapeutic potential of DHODH inhibitor farudodstat for alopecia areata treatment in a novel ex vivo model of human hair follicle immune privilege collapse

Thomas Rouillé[1], Silvia Barbosa[1], Ana Steinhoff[1], Ilaria Piccini[1], Janin Edelkamp[1], Alexandre Kaoukhov[2], Carl Firth[2], Ferda Cevikbas[2], Marta Bertolini*[1]

[1]Monasterium Laboratory Skin and Hair Research Solutions GmbH, Münster, Germany,[2]ASLAN Pharmaceuticals, San Mateo, CA, United States

Introduction & Objectives:

Alopecia areata (AA) is an inflammatory hair disorder characterized by immune privilege (IP) collapse of the hair follicle (HF) bulb, which leads to premature transition to the catagen stage, HF dystrophy, and ultimately results in non-scarring hair loss. IP collapse, marked by elevated major histocompatibility complex (MHC) I and II expression and a reduction in MHCII+ cells, is mainly mediated by elevated IFNγ levels and a Th1-mediated inflammatory response. Interestingly, T cell proliferation, Th1-cell differentiation, and IFNγ production are dependent on the activity of the enzyme dihydroorotate dehydrogenase (DHODH) in proliferating T cells.

Materials & Methods:

Here, we established an innovative AA model in which microdissected healthy human scalp HFs were stimulated*ex vivo* with anti-CD3/CD28 antibodies to activate intra- and peri-follicular T cells via the T cell receptor (TCR) to induce key features of AA, including IP collapse. In this model, we tested whether DHODH inhibition by *farudodstat* could be beneficial for the treatment of AA.

Results:

Experimentally induced TCR activation with anti-CD3/CD28 antibodies resulted in increased numbers of proliferative T cells, which were positively stained by immune cell marker CD3 and proliferation marker Ki-67 in the HF epithelium and mesenchyme. In addition, the model yielded significant upregulation of MHC protein expression in the bulb epithelium and mesenchyme of anagen VI HFs, suggesting loss of IP induced by T cell activation. DHODH inhibition by *farudodstat* protected HFs from the increase of proliferative T cells, induction of MHC I and II proteins, and reduction of MHC II+ cells, which are IP collapse markers in AA. Importantly, DHODH inhibition did not induce cytotoxicity or catagen promotion, nor did it impact hair matrix keratinocytes proliferation or IP markers.

Conclusion:

Our preliminary results show that anti-CD3/CD28 treatment in this *ex vivo* model can successfully stimulate T cell proliferation, which subsequently induces key features of AA including upregulation of MHC I and II as markers of IP collapse. Additionally, our data suggest that *farudodstat* might protect from IP collapse and offer a novel therapeutic approach for AA, which deserves further pre-clinical investigation.