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

Abstract N°: 50

Downstream effects of IL-13Rα1 blockade on Th2-driven inflammation and Th1 immune axis activation in atopic dermatitis

Sriya V. Reddy*[1], Zachary Bordeaux[1], Ahmad Rajeh[2], Darshan Sivaloganathan[2], Hannah Cornman[2], Anusha Kambala[2], Jackson Adams[1], Carl Firth[3], Ferda Cevikbas[4], Shawn G. Kwatra[2], Madan M. Kwatra[1]

[1]Duke University Medical Center, Department of Anesthesiology, Durham, United States,[2]Johns Hopkins University, Department of Dermatology, Baltimore, United States, [3]ASLAN Pharmaceuticals, Singapore, [4]ASLAN Pharmaceuticals, United States

Introduction & Objectives:

Atopic dermatitis (AD) is an inflammatory skin disease characterized by dysregulated Th2-driven inflammation. Interleukins (IL)-4 and IL-13 are key cytokines mediating Th2-driven inflammation in AD that signal through the Type 1 receptor (composed of IL-4Ra and the common gamma chain) and Type 2 receptor (composed of IL-4Ra and IL-13Ra1). The most effective way to inhibit Th2-driven inflammation remains unknown.

Materials & Methods:

In this study, we treated peripheral blood mononuclear cells (PBMCs) isolated from 10 AD patients with either an anti-IL-4Ra antibody (R&D systems, MAB230) to block both Type 1 and 2 receptors or eblasakimab, a monoclonal antibody that binds IL-13Ra1, to block only the Type 2 receptor. We then investigated the downstream effects of blocking these receptors on cytokines involved in Th2-driven inflammation and other immune axes utilizing the Meso Scale Discovery panel from PBMC media.

Results:

We find that treatment with IL-13Ra1 blockade with eblasakimab as compared to IL-4Ra blockade resulted in lower levels of key cytokines implicated in Th2-driven inflammation, including thymus and activation-regulated chemokine (TARC; $p=0.0001$), IL-13 ($p<0.0001$), IL-4 ($p<0.0001$), and monocyte chemotactic protein-4** (MCP-4; $p<0.0001$). Furthermore, our data demonstrate that IL-13Ra1 blockade prevents subsequent expression changes of Th1 cytokines as observed with anti-IL-4Ra therapy. Specifically, treatment with eblasakimab as compared to anti-IL-4Ra therapy suppressed a paradoxical increase of Th1 cytokines, including tumor necrosis factor alpha (TNF-a; $p=0.0319$), IL-2 ($p<0.0001$), granulocyte-macrophage colony-stimulating factor (GM-CSF; $p=0.0011$), IL-12p70 ($p<0.0001$), and interferon gamma-induced protein-10 (IP-10; $p=0.0017$).

Conclusion:

These results suggest that targeting different subunits of the same molecular pathway* can lead to different downstream effects and subsequent expression of Th1- and Th2-associated cytokines. Eblasakimab may offer a differentiated therapeutic approach to treat moderate-to-severe AD with the potential to spare the Type 1 receptor and the effects seen with targeting IL-4Rα.