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], Ferda Cevikbas[3], Shawn G. Kwatra[2], Madan M. Kwatra[1]

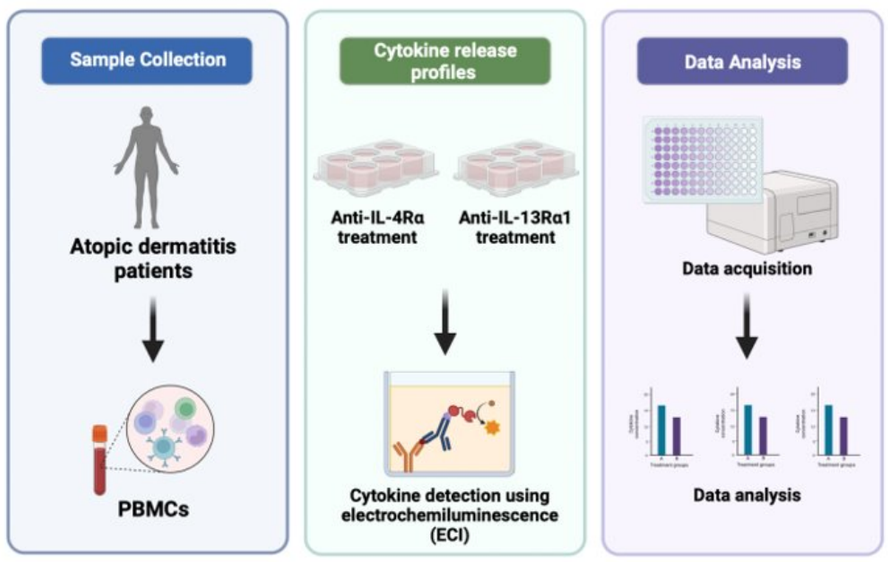
[1]Anesthesiology, Duke University School of Medicine, Durham, NC, United States.
[2]Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD, United States.
[3]ASLAN Pharmaceuticals Ltd, San Mateo, CA, United States.

INTRODUCTION

- Atopic dermatitis (AD) is a chronic inflammatory skin disease that is associated with significant pruritus[1] and is characterized by dysregulated Th2-driven inflammation.[2]
- 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-4Rα and the common γ chain) and Type 2 receptor (composed of IL-4Rα and IL-13Rα1); the IL-4/IL-13 receptor system serves a clinically validated therapeutic target for AD.[3]
- To date, therapeutics targeting this system have been or are being developed against IL-4Rα and IL-13.[4,5,6] However, IL-13Rα1 has recently garnered significant interest as a novel therapeutic target for AD.
- Eblasakimab, a fully human monoclonal antibody binds IL-13Rα1 with high affinity and blocks the signaling of IL-4 and IL-13 through the Type 2 receptor subunit IL-13Rα1 and is currently progressing through clinical trials for moderate-to-severe AD (NCT05158023).
- The most effective way to inhibit Th2-driven inflammation remains unknown.
- In this study, we aimed to understand the differentiated immunomodulatory role of eblasakimab treatment in AD compared to an anti-IL-4Rα directed antibody capable of potently inhibiting both IL-4 and IL-13 signaling.

MATERIALS AND METHODS

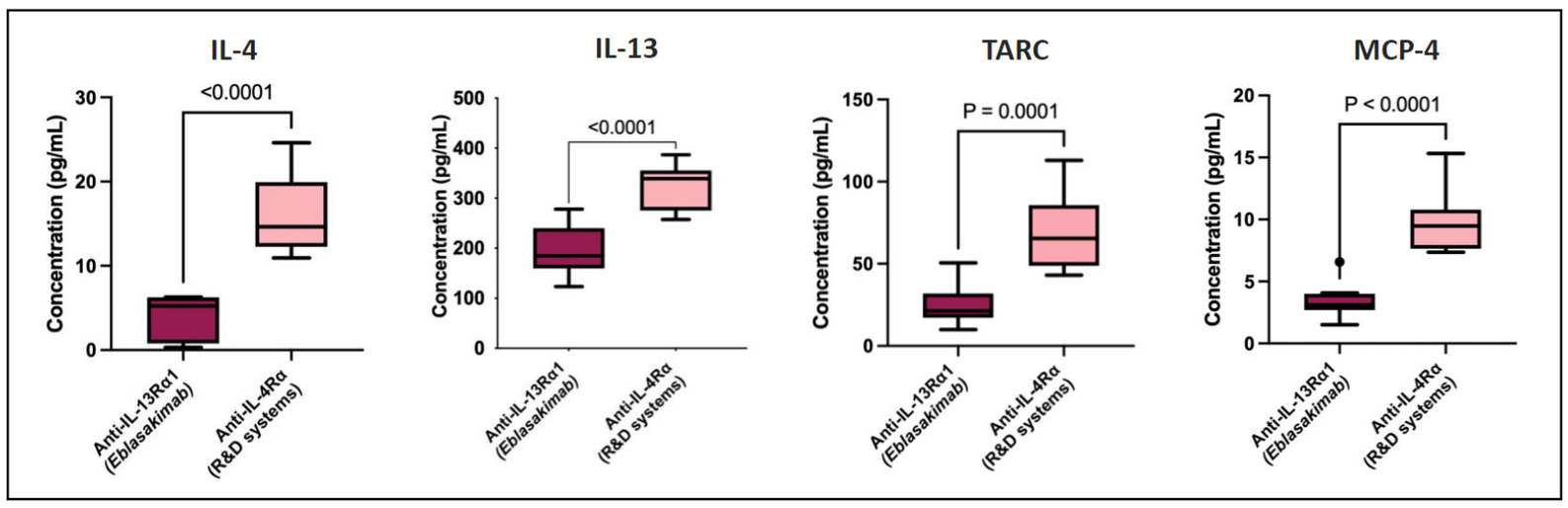
- Peripheral blood mononuclear cells (PBMCs) obtained from 10 patients with moderate-to-severe AD were treated with either 40 µg/ml anti-IL-13Rα1 (eblasakimab), which blocks IL-13 and IL-4 signaling through the Type 2 receptor,[7] or 50 µg/ml anti-IL-4Rα (R&D Systems),[8] which can block both Type 1 and Type 2 receptors.
- After 24h incubation, supernatants and cells were separated.
- The Meso Scale Discovery (MSD) platform was used to measure levels of cytokines in supernatants and analyze data.



PBMCs, peripheral blood mononuclear cells.

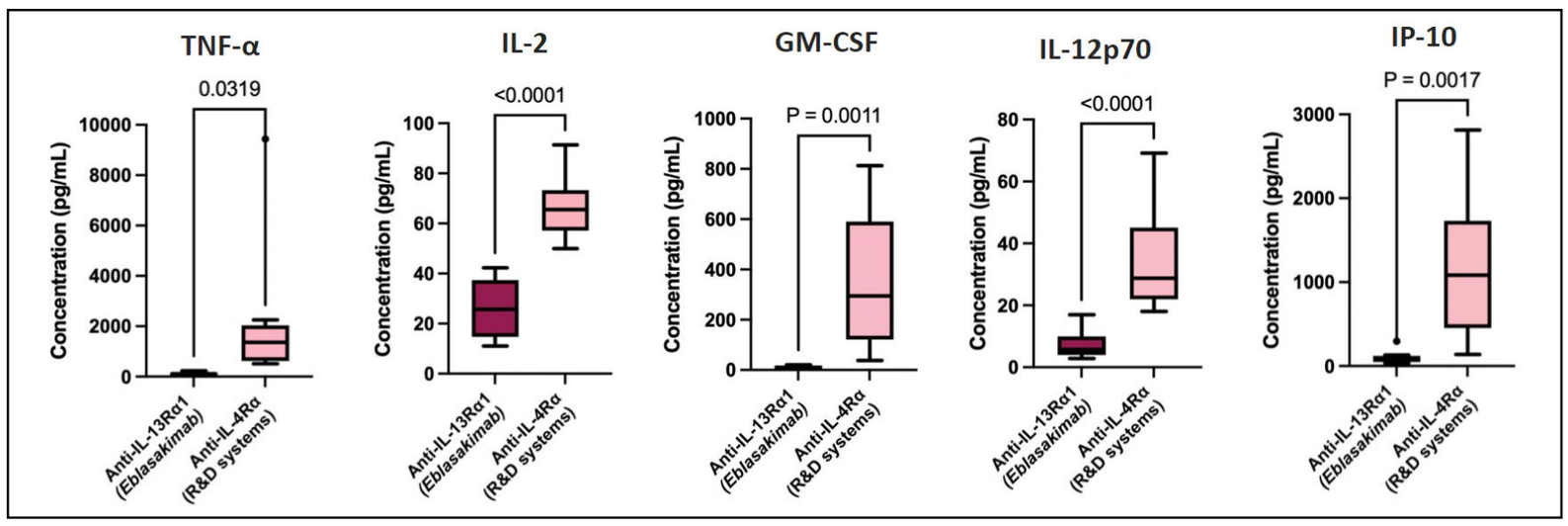
RESULTS

Figure 1. IL-13Rα1 blockade compared to IL-4Rα blockade resulted in lower levels of key cytokines implicated in Th2-driven inflammation



IL, interleukin; MCP, monocyte chemoattractant protein; TARC, thymus activation regulated chemokine.

Figure 2. IL-13Rα1 blockade compared to IL-4Rα blockade suppressed release of Th1 cytokines



GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IP, Interferon gamma-induced protein; TNF, tumor necrosis factor.

- Activated Th2 cells overproduce IL-4 and IL-13.[9] IL-13 specifically stands out as one of the main cytokines responsible for inflammation, epidermal barrier dysfunction, skin infections, fibrotic skin remodeling, and pruritus.[10,11] Moreover, levels of circulating IL-13 and IL-13 producing T-cells are increased in AD patients.[10]
- Treatment with IL-13Rα1 blockade by eblasakimab as compared to IL-4Rα blockade resulted in lower levels of key cytokines implicated in Th2-driven inflammation (**Figure 1**).
- IL-13Rα1 blockade with eblasakimab prevented subsequent expression changes of the Th1 immune response as observed with anti-IL-4Rα therapy (**Figure 2**), implicating Th1 immune response activation as a possible unwanted adverse effect.

CLINICAL SIGNIFICANCE

- These results suggest that targeting different subunits of the same molecular pathway can lead to different clinical outcomes.
- Selective blockade of the IL-13Rα1 subunit by eblasakimab may offer a differentiated therapeutic approach to treat AD by sparing the Type 1 receptor.
- This may allow for a more efficient way to reduce Type 2 inflammation without increasing levels of Th1 cytokines.

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DISCLOSURES

Dr. Shawn G. Kwatra is an advisory board member/consultant for Abbvie, ASLAN Pharmaceuticals, Arcutis Biotherapeutics, Celldex Therapeutics, Galderma, Genzada Pharmaceuticals, Incyte Corporation, Johnson & Johnson, Novartis Pharmaceuticals Corporation, Pfizer, Regeneron Pharmaceuticals, and Sanofi and has served as an investigator for Galderma, Incyte, Pfizer, and Sanofi. Dr. Ferda Cevikbas is an employee of ASLAN Pharmaceuticals.