Etrasimod, Once-Daily, Oral, Selective Sphingosine 1-Phosphate Receptor Modulator Improves Skin Inflammation in a Contact Hypersensitivity Model of Dermatitis

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Introduction

- Etrasimod (APD334) is a once-daily, orally administered, selective sphingosine 1-phosphate receptor 1 (S1P1) modulator in development for multiple immune-mediated inflammatory disorders, including an ongoing Phase 2 ADVISE trial in atopic dermatitis.

- S1P is a cell-surface G-protein-coupled receptor (GPCR) that has been shown to regulate lymphocyte egress from lymph nodes and dendritic cell trafficking.

- Upon binding to S1P1, synthetic modulators such as etrasimod act as functional antagonists by inducing and sustaining receptor internalization. This prevents cell migration along S1P gradients.

- Inducing and sustaining receptor internalization prevents cell migration along S1P gradients, allowing etrasimod to decrease effector T cell expansion into ear tissue.

- Etrasimod effectively reduced ear skin inflammation and dermatitis in the FITC-induced dermatitis mouse model.

Objective

- The goal of these preclinical studies was to establish a proof of concept for the etrasimod mechanism of action in a dermatology model. We used a fluorescein isothiocyanate (FITC)-induced dermatitis mouse model to evaluate how the reduction in circulating lymphocytes produced by etrasimod affects immune cell trafficking and the ultimate impact on skin inflammation.

Methods

Experimental Design and Treatment Groups

- Beginning on Day -1, female BALB/c mice were orally dosed daily with the indicated treatments in phosphate buffered saline (PBS). Experimental groups were based on potency determined by previous studies.

- On Days 0 and 5, mice were sensitized with 1% fluorescein isothiocyanate (FITC) in Acetone: Dibutyl phthalate (ADBP) on the hind flank skin, and subsequently challenged on the ear skin on Days 10, 11, and 12.

- On Days 10, 11, and 12, mice were sacrificed, and tissue-resident CD69+ CD4 and CD8+ T cells were counted.

- Etrasimod treatment led to a statistically significant reduction in multiple immune cell populations, including CD4+ and CD8+ T cells.

- These data encourage further study of etrasimod as a novel therapy for treating dermatitis.

- Etrasimod significantly reduced ear protein content of IL-4, IFNγ, IL-6, and TNFα in a dose-dependent manner.

- In Study 1 and Study 2, etrasimod treatment resulted in a similar dose-dependent reduction in ear thickness compared to dexamethasone.

Conclusions

- Etrasimod effectively reduced ear skin inflammation and dermatitis in the FITC-induced hypersensitivity dermatitis mouse model.

- Etrasimod reduced the trafficking of antigen-presenting dendritic cells from the skin to the lymph nodes, which correlated with a reduction of T cell activation in the lymph node.

- Etrasimod treatment led to a statistically significant reduction in multiple immune cell types in the skin, including both CD4+ and CD8+ T cells.

- Cytokine production was significantly decreased in the tissue.

- These in vivo preclinical studies support the unique mechanism of action of etrasimod, which acts upstream of treatments that specifically target cytokines within the tissue.

- Etrasimod reduced the trafficking of dendritic cells into and T cells out of lymph nodes into circulation, which produced a downstream reduction in immune cells, cytokine production, and dermatitis in the skin. These data encourage further study of etrasimod as a novel therapy for atop dermatitis.

References

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