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 1.4 (S1P1) modulator in development for multiple immune-mediated inflammatory disorders, including an ongoing Phase 2/3 ADVENT trial in psoriatic dermatitis.
- S1P1 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, resulting in lymphocyte retention within lymphoid tissue, and a reduction in peripheral blood lymphocytes available to be recruited to sites of inflammation.

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). Doses were based on potency determined by previous studies.
- On Days 4 and 5, mice were sensitized with 1.5% fluorescein thioglucose (FITC) in acetone:ethanol (99:1) on the hind flank skin, and subsequently challenged on the ear skin on Days 10, 11, and 12.

Results

Figure 1. Etrasimod Dose-Dependently Reduced Ear Histopathological Score

Figure 3. Etrasimod Reduced T Cells, CD8 T Cells, and Exocytosis in Ear Skin

Figure 5. Etrasimod Reduced Cytokine Protein in Ear Skin

- Etrasimod significantly reduced ear protein content of (A) IL-4, (B) IFNγ, (C) IL-6, and (D) TNFα in a dose-dependent manner. Data mean ± SEM.

References


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 ear skin.

- These in vivo proof-of-concept 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 atopic dermatitis.