Etrasimod, an oral, selective sphingosine 1-phosphate receptor modulator improves skin inflammation in a contact hypersensitivity model of dermatitis

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Background: Etrasimod (APD334) is a selective sphingosine 1-phosphate receptor 1,4,5 (S1P1,4,5) modulator in development for atopic dermatitis (AD). S1P1 modulates trafficking of many immune cells, including those in the skin of eczema patients.

Objective: The presented studies evaluated the effect of etrasimod on circulating and tissue immune cells and its impact on skin inflammation and cytokine production in a dermatitis mouse model.

Methods: BALB/c mice were epicutaneously sensitized with fluorescein isothiocyanate (FITC) on the hind flank on Days (D) 0 and 5, then epicutaneously FITC challenged on the ear on D10-12. From D-1 to D13, mice were dosed orally once daily with vehicle, dexamethasone (Dex), or etrasimod (1 or 3 mg/kg). Ear thickness was measured with calipers on D0, 5, 10-13. D13 analyses included histopathological analysis and scoring, complete blood count with differential, FACS analysis of ear skin and draining lymph nodes (dLN), and cytokine production in the skin.

Results: Study 1 Results: After FITC challenge, vehicle-treated mice had increased skin thickness from D11-13 and worsened histological score on D13. Histological score was a composite of dermatitis, ulceration, and presence of pustules. Vehicle-treated mice had severe dermatitis, ulceration, and all mice had many pustules. Etrasimod dose-dependently lessened ear thickening and histologic score, with the high dose achieving comparable efficacy to Dex on D13. Histologic score components of etrasimod-treated mice included a reduction of dermatitis to mild-moderate, no animals showed ulceration, and 3 of 10 mice (1 mg/kg) and 1 of 10 mice (3 mg/kg) showed many pustules. Cellular analysis revealed vehicle treated mice had increased dendritic cell trafficking to dLN and immune cell expansion in the ear skin on D13. Etrasimod treatment reduced white blood cell counts and lymphocyte frequency in the blood. In the dLN, etrasimod reduced DC influx and T cell activation. In the ear skin, the increase of T cells, B cells, and eosinophils was dose-dependently inhibited. Of note, both CLA+ and CD69+ skin-homing and resident T cells were reduced in the skin.

Study 2 Results: This study aimed to confirm study 1 and further characterize the effects of etrasimod on T cell subsets and cytokine production. After FITC challenge, similar to study 1, vehicle-treated mice had increases in skin thickness and immune cell expansion in the ear skin on D13, as well as increased tissue cytokines. Etrasimod improved ear thickening and reduced skin lymphocytes in a dose-dependent manner. Notably, etrasimod significantly reduced both CD4+ and CD8+ T cells in the ear skin, including

tissue-resident CD69+ subsets. Reductions in tissue T cells correlated with a dose-dependent reduction of tissue cytokines IL-4, IFNy, IL-6, and TNFa compared to vehicle-treated mice.

Conclusions: Etrasimod effectively reduced ear skin inflammation and dermatitis in FITC-induced hypersensitivity. Etrasimod significantly reduced the activation and expansion of immune cells after challenge in the dLN and ear skin. Etrasimod significantly reduced both skin-homing CLA+ and resident CD69+ T cells in the skin. Notably, the dose-dependent reduction of immune cells in ear skin correlated with reduced cytokine production and improvements in disease. This data encourages further study of etrasimod as a novel therapy for AD.

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