Fevipiprant, a Selective Prostaglandin D_2 Receptor 2 Antagonist, Potently Inhibits Chemotaxis and Cytokine Production by Group 2 Innate Lymphoid Cells

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Rationale

Activation of the group 2 innate lymphoid cell (ILC2) population leads to production of classical type 2 cytokines, promoting type 2 immunity. Increased ILC2 levels are found in blood and sputum of severe eosinophilic asthmatics in comparison to mild asthma patients. Such elevated ILC2 levels are hypothesized to drive the chronic eosinophilia associated with severe asthma. Prostaglandin D_2 receptor 2 (DP_2; previously known as CRTh2) is a receptor for prostaglandin D_2 (PGD_2) expressed by human ILC2s. PGD_2 binding to DP_2 induces ILC2 migration and production of type 2 cytokines such as IL-4, IL-5 and IL-13, in addition to other cytokines. Hence PGD_2 is an important activator of ILC2s through the DP_2 pathway. Fevipiprant is a potent selective DP_2 receptor antagonist which reduces airway inflammation in patients with persistent asthma and raised sputum eosinophil counts. The drug is currently in Phase III clinical development for treatment of uncontrolled asthma. Here, we report characterization of the inhibitory effects of Fevipiprant on DP_2 pathway activated ILC2 migration and cytokine release.

Methods

Lineage (CD3, CD14, CD19, CD56, CD11b, CD11c, FcεRI, and CD123)–negative, $CD45^{high}$, $CD127^{+}$, and $CRTH2^{+}$ ILC2s were isolated from mononuclear cells of blood of healthy volunteers and cultured. For chemotaxis assays, cell migration induced with PGD_2 (200 nM) in the presence of Fevipiprant was determined using the IncuCyte live cell analysis system. Protein and mRNA levels of cytokines IL-4, IL-5 and IL-13 after treatment with PGD_2 (200 nM) in the presence of Fevipiprant were measured with multiplex bead array and qPCR respectively. Negative controls DP_1 receptor agonist BW245C and DP_1 antagonist BW868C were employed to confirm the DP_2 specificity of the effect, with DP_2 antagonist TM30089 as positive control for DP_2 mediated inhibitory effects.

Results

Fevipiprant significantly inhibited PGD_2 induced ILC2 chemotaxis and cytokine production at the mRNA and protein level with low nM potency. Representative cytokine protein data from one donor is presented in Figure 1.

Conclusions

Fevipiprant is a potent inhibitor of DP_2 pathway mediated activation of ILC2s. The inhibitory potency on ILC2 migration and cytokine release is comparable with previous data generated for inhibition of PGD_2 induced cytokine release from $CD4^{+}$ Th2 cells and also with the DP_2 receptor affinity. Given the emerging important role of ILC2s in asthma, these data support further development of Fevipiprant in this indication and complement prior in vitro characterization data obtained with eosinophils and $CD4^{+}$ Th2 cells.

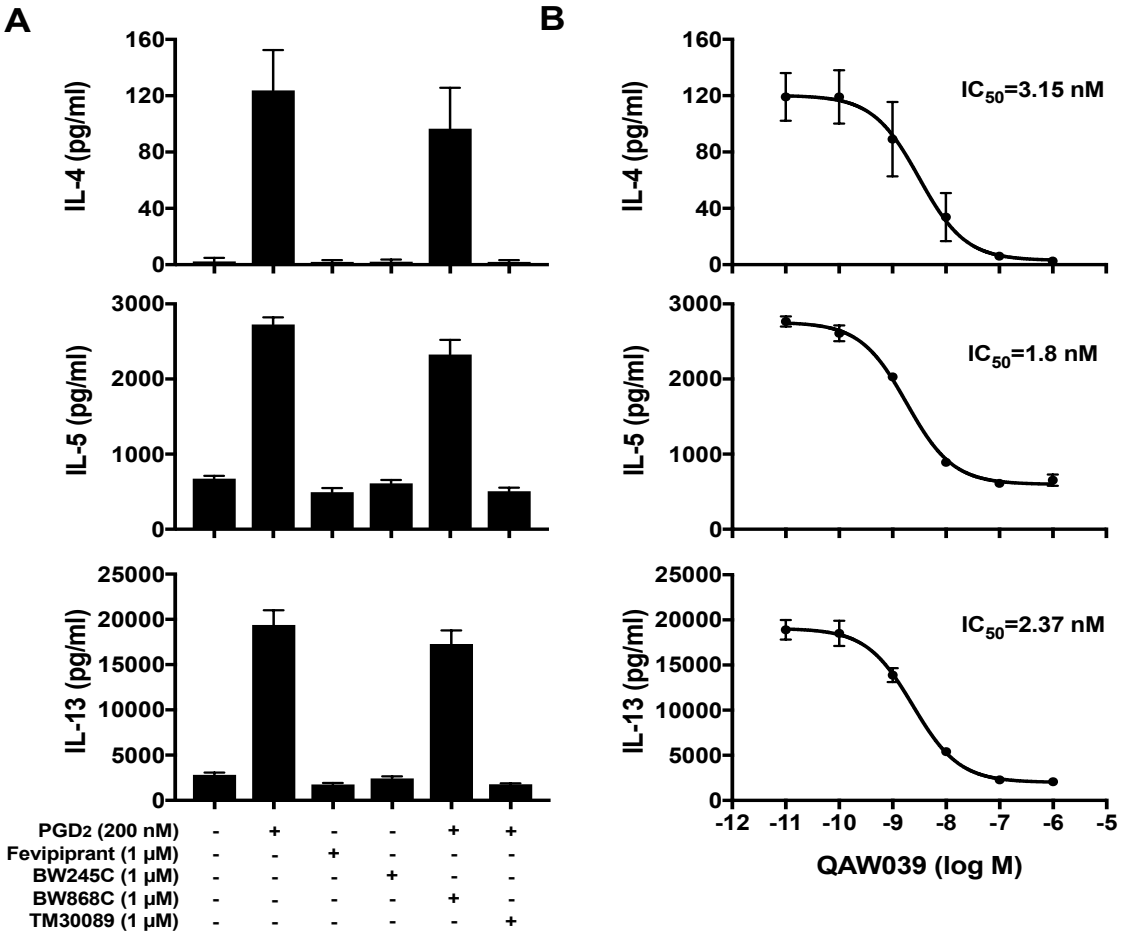

Figure 1: Fevipiprant inhibition of PGD_2 induced type-2 cytokine production. (A) Positive and negative controls for type-2 cytokine (IL-4, IL-5 and IL-13) production by ILC2s. (B) Levels of type-2 cytokines released by ILC2s after treatment with 200 nM PGD_2 in the presence of various concentrations of Fevipiprant. ILC2s were from a single healthy donor. n=3 experiments, and representative of 3 donors.