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Fevipirant inhibits prostaglandin D₂ mediated activation of group 2 innate lymphoid cells (ILC2s)

Introduction

Fevipirant is a potent selective Prostaglandin D₂ receptor 2 (DP₂) receptor antagonist which reduces eosinophilic airway inflammation in patients with persistent asthma and raised sputum eosinophil counts. Increased ILC2s are found in blood and sputum of severe eosinophilic asthmatics. They express the DP₂ receptor that mediates various cellular functions.

Aims

To comprehensively characterize the inhibitory effects of Fevipirant on DP₂ pathway-mediated cellular functions of ILC2s.

Methods

ILC2s were isolated from healthy volunteer peripheral blood and cultured. Effects on migration, cytokine production, apoptosis and adhesion molecule expression in response to PGD₂ (200 nM) in the presence of increasing concentrations of Fevipirant were determined with chemotaxis-, apoptosis-, quantitative-PCR-, ELISA- and Luminex-assays. The selectivity of Fevipirant to DP₂ in ILC2s was confirmed by using DP₁ agonist (BW245C), antagonist (BW868C) and alternative DP₂ antagonist (TM30089). Half-maximal inhibitory concentrations (IC₅₀) were calculated.

Results

Fevipirant specifically inhibited PGD₂ induced ILC2 migration (IC₅₀: 6.3nM), apoptosis suppression, cytokine and other pro-inflammatory molecule production (IC₅₀ for IL-4, IL-5, IL-8, IL-13, GM-CSF and CSF1: 0.2 to 1.96nM), and cell adhesion molecule expression (IC₅₀ for ICAM1:0.56nM, for PECAM1: 0.85nM).

Conclusions

Fevipirant is a potent inhibitor of DP₂ pathway mediated activation of ILC2s. Given the role of ILC2s in uncontrolled asthma, these data support further development of Fevipirant in this indication and its inhibitory effects on ILC2s in asthma patients.