Spotlight on fevipiprant and its potential in the treatment of asthma: evidence to date

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Abstract: Asthma is a heterogeneous disease, which may be classified into phenotypes and endotypes based on clinical characteristics and molecular mechanisms. The best described endotype of severe asthma is type 2 (T2)-high asthma, characterized by release of inflammatory cytokines by T helper 2 (T\textsubscript{h}2) cells and type 2 innate lymphoid cells (ILC2). Prostaglandin D\textsubscript{2} contributes to T2 inflammation through binding of the G-protein-coupled receptor chemottractant receptor-homologous molecule expressed on TH2 cells (CRTH2). Fevipiprant is an oral competitive antagonist of CRTH2. Early-phase trials have demonstrated safety and potential efficacy in patients with asthma, specifically, improvement in FEV\textsubscript{1} and eosinophilic airway inflammation. However, no clear biomarker identified patients who responded favorably to fevipiprant, although patients with moderate-to-severe asthma and evidence of T2 inflammation may be more likely to respond to treatment. Additional studies are needed to determine the efficacy and target population for use of this drug in patients with asthma.

Keywords: prostaglandin D\textsubscript{2}, CRTH2, biologics

Introduction

Asthma is a chronic inflammatory disease characterized by airway hyperresponsiveness and variable airflow obstruction. Asthma is a heterogeneous disease with variable clinical presentations, underlying mechanisms, and outcomes. The classification of asthma into phenotypes based on clinical characteristics and molecular endotypes based on biologic mechanisms has led to the development of targeted treatments. In particular, these treatments may improve asthma control or decrease asthma exacerbations in patients with severe, uncontrolled asthma despite treatment with inhaled or systemic corticosteroids.

The best described endotype of asthma is type 2 (T2)-high asthma, which is characterized by increased levels of T2 inflammation and occurs in approximately 50% of patients with severe asthma.\textsuperscript{1} T helper 2 (T\textsubscript{h}2) cells secrete the cytokines IL-4, IL-5, and IL-13, which define T2 inflammation. Along with T\textsubscript{h}2 cells, type 2 innate lymphoid cells (ILC2) also produce IL-5 and IL-13.\textsuperscript{2} IL-4 and IL-13 activities are linked through a shared receptor component and signaling pathway and are involved in T\textsubscript{h}2 cell differentiation and IgE synthesis by B cells.\textsuperscript{3} IL-5 induces growth, survival, and activation of eosinophils.\textsuperscript{4} Presence of eosinophils is important in determining asthma phenotypes\textsuperscript{5,6} and is a consequence of T2 inflammation. Sputum eosinophils are more strongly linked to T2 airway inflammation compared to blood eosinophils.\textsuperscript{7} The molecular pathways of T2-low asthma have not been as well established, but T helper 17 cells and neutrophils may be key mediators.\textsuperscript{8}
Prostaglandin D2 metabolism

Prostaglandin D2 (PGD2) and its receptor, chemoattractant receptor-homologous molecule expressed on T_H2 cells (CRTH2), play an important role in T2 inflammation (Figure 1). T_H2 cells stimulate IgE isotype switching in B cells, then IgE bound to mast cells binds to antigen, leading to the release of cytokines, leukotrienes, and PGD2. PGD2 is produced from the sequential metabolism of arachidonic acid by cyclooxygenase followed by PGD2 synthase. PGD2 is mainly released from mast cells, but platelets, alveolar macrophages, T_H2 cells, dendritic cells, and osteoblasts can also produce small amounts of PGD2. The effects of PGD2 are mediated by G-protein-coupled receptors. PGD2 activates two receptors: the DP (PGD) receptor and CRTH2. CRTH2 is expressed on T_H2 cells, eosinophils, basophils, and ILC2 cells. Although CRTH2 binds PGD2 with approximately equal affinity as the DP receptor, it shows little similarity to the DP receptor and is more closely related to other chemoattractant receptors.

PGD2 can function as both a pro- and anti-inflammatory mediator, depending on ligand affinity, receptor expression profile, and cellular context in which the receptor is expressed. PGD2 is responsible for allergic inflammation, likely via both the DP receptor and the CRTH2 receptor. The DP receptor is expressed on bronchial epithelial cells, and binding of mast-cell-derived PGD2 to DP in the epithelium stimulates production and release of cytokines and chemokines that recruit T_H2 lymphocytes, leading to airway inflammation, airflow obstruction, and airway hyperreactivity. PGD2 also mediates recruitment of eosinophils and basophils via the CRTH2 receptor and inhibits eosinophil apoptosis via the DP receptor. PGD2 induces rapid change in eosinophil morphology and an increase in eosinophil chemokinesis. PGD2 activation of DP has an opposite effect on basophils by inhibiting basophil migration and IgE-mediated degranulation. PGD2 is also a potent bronchoconstrictr via the thromboxane A2 (TP) receptor, although PGD2 has low affinity to the TP receptor. PGD2–CRTH2 interaction may also stimulate ILC2 migration leading to T2 inflammation in the lung.

PGD2–CRTH2 activity in asthma

PGD2 levels have been measured in patients with asthma with inconsistent results. In patients with mild asthma, levels of PGD2 in bronchoalveolar lavage (BAL) have been shown to be increased and no different compared to nonasthmatics. However, all of these studies had small numbers of patients. Patients with severe asthma had increased BAL fluid PGD2 compared to patients with mild/moderate asthma receiving inhaled corticosteroids. This finding was later confirmed in an expansion of this cohort of patients with asthma. BAL fluid PGD2 was inversely associated with lung dysfunction.
function and positively correlated with worse symptoms and a history of recent exacerbation. PGD$_2$ levels also increase in patients with asthma following allergen challenge.\textsuperscript{20,24}

Expression of the CRTH2 receptor on T cells is also different in patients with asthma compared to healthy controls. CRTH2$^+$ T cells composed only a small population of cells in BAL fluid, but there was a significantly greater percentage in patients with asthma compared to controls.\textsuperscript{21} In another study, CRTH2 mRNA levels in BAL were highest in patients with severe asthma compared to patients with mild asthma not treated with ICS and healthy controls.\textsuperscript{22} Higher BAL fluid PGD$_2$ levels and CRTH2$^+$ cell numbers were associated with poor asthma control, peripheral blood eosinophilia, and high exhaled nitric oxide (FeNO) levels. Overall, these studies suggest that increased PGD$_2$ levels and CRTH2 expression are seen in patients with more severe, T2 asthma.

**Overview of fevipiprant**

Fevipiprant (QAW039; [(2-[2-methyl-1-(4-[methylsulfonyl]-2-[trifluoromethyl]benzyl)-1H-pyrrolo(2,3-b)pyridine-3-yl]acetic acid]]) is an oral, highly selective, potent, reversible competitive antagonist of CRTH2. Fevipiprant is metabolized to an inactive acyl-glucoride metabolite. Elimination of fevipiprant occurs via hepatic metabolism as well as renal excretion.\textsuperscript{23}

**Clinical studies of fevipiprant**

A Phase I study evaluated the pharmacokinetics and safety of a range of doses of fevipiprant given as single and multiple doses in 48 healthy volunteers.\textsuperscript{26} Peak concentrations of fevipiprant were observed 1–3 hours after dosing with a half-life of approximately 18–20 hours. Fevipiprant was well tolerated, and the adverse events were similar between fevipiprant and placebo. There were no significant adverse events or death, and the most common side effects were headache and nasal congestion.

In a Phase II study, 170 patients with mild-to-moderate persistent, allergic asthma were randomized to receive fevipiprant 500 mg daily for 28 days (82 patients, 75 completed the study) or placebo (88 patients, 82 completed the study).\textsuperscript{27} There was no difference in the primary outcome, mean trough FEV$_1$, between the groups. In the predefined subgroup of patients with FEV$_1$ percent predicted <70%, there was significant improvement in trough FEV$_1$ as well as asthma control questionnaire (ACQ7) in patients treated with fevipiprant compared to placebo. In patients with high serum IgE and blood eosinophils >300/µL and patients with FeNO > median, there was a significant improvement in FEV$_1$ AUC$_{0-24}$ (the area under the effect curve from 0 to 24 hours).

In a Phase II study, Gonem et al\textsuperscript{28} randomized 61 patients with moderate-to-severe, persistent asthma and sputum eosinophilia (≥22%) to receive fevipiprant 225 mg orally twice daily or placebo for 12 weeks. The geometric mean sputum eosinophil percentage decreased from 5.4 to 1.1 in the fevipiprant group and from 4.6 to 3.9 in the placebo group. Thus, treatment with fevipiprant resulted in a significant, 3.5-fold greater decrease in sputum eosinophilia than placebo. In addition, fevipiprant reduced bronchial submucosal eosinophil numbers in bronchial biopsy samples compared to placebo. However, there was no change in blood eosinophil count. Change in mean asthma control measured by ACQ7 was not different between the groups except in the subgroup of patients with uncontrolled asthma at baseline.

In a Phase IIB study, Bateman et al\textsuperscript{29} randomized 1,058 adult patients with allergic asthma that was uncontrolled with inhaled corticosteroids to once-daily fevipiprant (9 doses ranging from 1 to 450 mg), twice-daily fevipiprant (4 doses ranging from 2 to 150 mg; 782 total patients assigned to fevipiprant), montelukast (139 patients), or placebo (137 patients). Patients were maintained on budesonide 200 µg BID during the 12-week treatment period. There was an improvement in predose FEV$_1$ with both fevipiprant and montelukast compared to placebo. There was no evidence of a higher efficacy in any predefined subgroup, including blood eosinophil count, predicted FEV$_1$, or baseline ACQ scores. Fevipiprant did not improve asthma symptom control.

In all the Phase II studies, fevipiprant had acceptable safety and tolerability. The variable efficacy of fevipiprant in these Phase II studies is likely related to differences in patient populations in terms of asthma severity, asthma control, and presence of eosinophilia. The optimal target population for fevipiprant is yet to be identified, but may be patients with severe eosinophilic asthma.\textsuperscript{30} Several biologic drugs are currently available for the treatment of severe, eosinophilic asthma including the IL-5 inhibitors mepolizumab and reslizumab, the IL-5 receptor antagonist benralizumab, and the IL-13/IL-4 inhibitor dupilumab. Because fevipiprant is orally administered, it may be an attractive alternative for patients with uncontrolled eosinophilic asthma. However, further studies are needed to determine if fevipiprant improves clinical outcomes such as symptom scores, asthma control, and exacerbation risk in addition to improving lung function and sputum eosinophilia. See Table 1 for summary of clinical trials.
Ongoing clinical studies

There are several ongoing Phase III clinical studies of fevipiprant in patients with asthma. LUSTER 1 and 2 (ClinicalTrials.gov, NCT02555683 and NCT02563067) will determine the safety of fevipiprant as well as its effect on rate of asthma exacerbations in patients with severe, uncontrolled asthma. The ZEAL1 and ZEAL2 studies (ClinicalTrials.gov, NCT03215758 and NCT03226392) will determine the efficacy and safety of fevipiprant in patients with moderate, uncontrolled asthma receiving ICS. The primary endpoint will be change from baseline in predose FEV₁ after 12 weeks. NCT03052517 is a study to assess the long-term safety of fevipiprant in patients with uncontrolled, moderate-to-severe asthma.

A number of other CRTH2 receptor antagonists have been investigated in asthma. Those studied in clinical trials include AZD1981, OC000459, setipiprant, and BI671800. In addition, AMG853 is a dual CRTH2 and DP receptor antagonist. Some studies of these agents demonstrated significant improvement in lung function and quality of life, while others showed no difference.

| Author               | Fevipiprant dose                  | Type of study | Patients                                                                 | Outcomes                                                                 | Biomarkers identifying response                        |
|----------------------|-----------------------------------|---------------|--------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------------------------------------------------|
| Erpenbeck et al (2016)²⁷ | 500 mg once daily × 28 days       | Phase II RCT  | 170 patients with mild-to-moderate asthma with a positive skin prick test to local allergens | No difference in trough FEV₁ or symptom scores                           | Improvement in trough FEV₁ in patient with baseline FEV₁ < 70% predicted |
| Gonem et al (2016)²⁸ | Fevipiprant 225 mg orally twice daily versus placebo | Single center RCT | 61 patients with moderate-to-severe asthma and sputum eosinophil count of ≥ 2% | ↓ in sputum eosinophil counts Improvement in post-bronchodilator FEV₁ | -                                                      |
| Bateman et al (2017)²⁹ | Fevipiprant once or twice daily, montelukast, or placebo × 12 weeks | Phase IIb RCT | 1058 patients with allergic asthma inadequately controlled with ICS | Improvement in FEV₁ No difference in asthma symptom control               | No difference based on blood eosinophils                  |

Abbreviations: FEV₁ – forced expiratory volume in 1 second; RCT – randomized control trial.

Conclusion

Asthma is a heterogeneous disease with a significant health care burden, especially among patients with severe, uncontrolled disease. Improved understanding of asthma phenotypes and endotypes has provided the opportunity to better tailor approaches to individual patients. Multiple biologic treatments have recently been approved by the Food and Drug Administration for the treatment of eosinophilic asthma. Fevipiprant, an oral, reversible competitive antagonist of CRTH2, has shown promise in early-phase trials in patients with asthma. Ongoing Phase III clinical studies should shed further light on the potential benefit of fevipiprant in patients with uncontrolled, moderate-to-severe asthma. Demonstrating reproducible benefit as well as defining and refining the target treatment population remains necessary for this drug to gain approval for clinical use. For now, we are left with the potential of an oral drug targeting asthma patients with severe or difficult-to-control disease.

Disclosure

The authors report no conflicts of interest in this work.

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