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NEW TREATMENTS FOR ASTHMA: FROM THE PATHOGENIC ROLE OF PROSTAGLANDIN D₂ TO THE THERAPEUTIC EFFECTS OF FEVIPIPRANT

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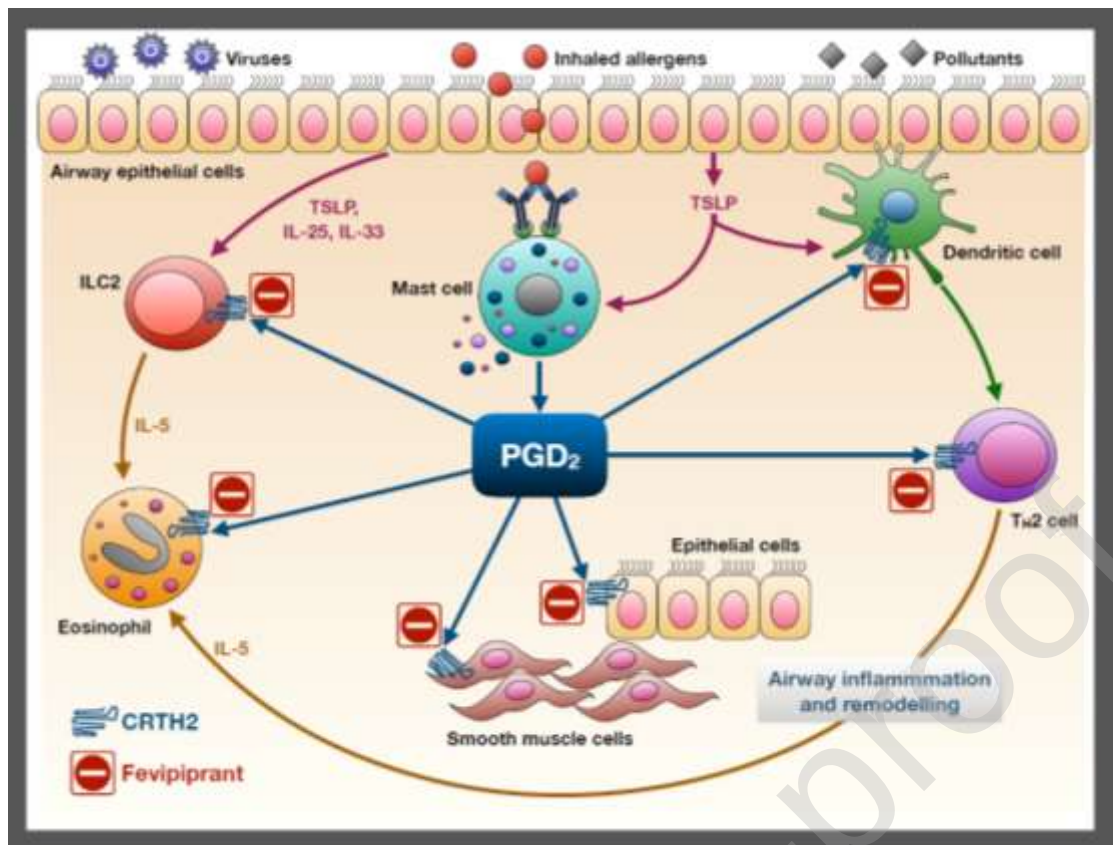
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Graphical abstract



Abstract

Prostaglandin D₂ (PGD₂) is a pleiotropic mediator, significantly involved in the pathogenesis of type 2 (T2) asthma because of its biologic actions exerted on both immune/inflammatory and airway structural cells. In particular, the pro-inflammatory and pro-remodelling effects of PGD₂ are mainly mediated by stimulation of chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). This receptor is the target of the oral competitive antagonist fevipiprant, which on the basis of recent phase II studies is emerging as a potential very promising anti-asthma drug. Indeed, fevipiprant appears to be safe and effective, especially in consideration of its ability to inhibit eosinophilic bronchial inflammation

and improve forced expiratory volume in one second (FEV₁). Further ongoing phase III trials will definitely clarify if fevipiprant can prospectively become a valid option for an efficacious add-on treatment of moderate-to-severe T2-high asthma.

Keywords: T2-high asthma, PGD₂, CRTH2, fevipiprant.

1. Introduction

Asthma is a chronic respiratory disease characterised by airway inflammation, variable airflow limitation and bronchial hyperresponsiveness, manifesting clinically as wheezing, dyspnoea, cough and chest tightness [1-3]. It is a heterogeneous disorder driven by different patho-biological mechanisms resulting in varied disease endotypes [4,5]. Patients with type-2 (T2)-high asthma (i.e. the eosinophilic endotype) demonstrate good therapeutic response to corticosteroids and biologics that target the T2 pathways (IgE, IL-5 and its receptor, IL-4/IL-13 receptor) [6,7]. Within the overall population of asthmatic subjects, however, 5-10% of patients cannot be adequately controlled and, despite an optimized inhaled treatment, experience a severe disease characterised by frequent exacerbations and refractoriness to corticosteroid therapy. In particular, severe asthma has been jointly defined by both European Respiratory Society (ERS) and American Thoracic Society (ATS) as a condition

controlled by high dosages of inhaled corticosteroids (ICS)/long-acting β_2 -adrenergic agonists (LABA) combinations, which can also require the addition of other drugs (i.e. tiotropium, leukotriene modifiers, oral corticosteroids); even worse, severe asthma might remain uncontrolled despite such heavy inhaled and systemic treatments [8]. Therefore, these patients deserve a close attention and require additional pharmacologic treatments because of their unmet medical needs [9], arising from all the problems caused by frequent unscheduled visits and accesses to emergency room, as well as by the relevant loss of school- and work-days. Such subjects with severe uncontrolled asthma are thus potential recipients of add-on biological therapies, targeting specific molecules which play a key role in the pathobiology of T2-high eosinophilic asthma [10-12]. Indeed, GINA (Global Initiative for Asthma) guidelines recommend at step five the use of a monoclonal antibody to be chosen, on the basis of patient features, among currently licensed biologic drugs [13]. The latter include anti-IgE omalizumab, anti-IL-5 mepolizumab and reslizumab, IL-5 receptor blocker benralizumab, and IL-4/IL-13 dual receptor antagonist dupilumab [14-21]. In addition to biologics, and because of the pivotal functions exerted by prostaglandin D_2 (PGD_2) in the pathogenesis of eosinophilic asthma [22,23], other new drugs which target the CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells) receptor of PGD_2 are currently being evaluated for their potential utilization in the treatment

of uncontrolled type 2 disease. In this regard, particularly promising are the results of several studies referring to the therapeutic effects of the CTRH2 antagonist fevipiprant [24-26]. Indeed, differently from each biologic drug which inhibits a specific mechanism involved in the pathobiology of T2-high asthma, fevipiprant targets a receptor widely expressed on many airway immune/inflammatory and structural cells, thus potentially interfering with the broad pathogenic circuits activated by PGD₂ and resulting in induction, development and amplification of bronchial inflammation and remodelling. Therefore, within the context of T2-high eosinophilic asthma, the therapeutic effects of fevipiprant could benefit both allergic and non allergic phenotypes, the latter occurring more often in adults and being triggered by infectious agents and/or drugs such as aspirin, rather than by aeroallergens [27].

Hence, on the basis of the above mentioned considerations, the aim of this concise review article is to outline the pathophysiologic involvement of PGD₂ in type 2 asthma, as well as to discuss the published data regarding the anti-asthma actions of fevipiprant.

2. The pathogenic role of prostaglandin D₂ in asthma

In both allergic and non allergic asthma a significant pathogenic role is played by PGD₂, which can be released by mast cells upon allergen-dependent cross-linking of adjacent IgE molecules bound to high affinity

IgE receptors (FcεRI) [28]. PGD₂ is a major product of arachidonic acid metabolism along the cyclooxygenase (COX) pathway [29]. However, COX inhibitors are not indicated for asthma treatment; even worse, in some asthmatic patients these drugs can further exacerbate their disease. Indeed, about 14% of adults with severe asthma experience a syndrome known as AERD (aspirin-exacerbated respiratory disease), characterised by a massive release of cysteinyl leukotrienes caused by COX blockade [30]. Cysteinyl leukotrienes stimulate the production of innate cytokines known as alarmins, including interleukin-25 (IL-25), interleukin-33 (IL-33) and thymic stromal lymphopoietin (TSLP). IL-33 and TSLP activate mast cells, thus inducing a paradoxical increase in PGD₂ biosynthesis, despite COX inhibition [31].

Among alarmins, TSLP is the most relevant driver of PGD₂ release from mast cells [32]. In asthmatic patients TSLP behaves as a pleiotropic mediator, secreted in large quantities by airway epithelial cells injured by several noxious agents such as allergens, cigarette smoke, airborne pollutants, bacterial, viral, and fungal infections [33]. The cellular targets of TSLP include dendritic cells, group 2 innate lymphoid cells (ILC2) and mast cells [33]. Therefore, by promoting dendritic cell-mediated differentiation of Th2 lymphocytes, as well as by inducing ILC2 activation and stimulating mast cell release of PGD₂, TSLP is significantly implicated in the pathobiology of both allergic and non allergic asthma.

PGD₂ exerts its biological effects via stimulation of two transmembrane receptor subtypes, named DP(D prostanoid)₁ and DP₂ or CRTH2, respectively [34]. The DP₁ receptor is coupled to stimulatory G-protein (Gs), thus driving adenylyl cyclase stimulation which in turn is responsible for the increase in intracellular levels of the second messenger cyclic adenosine monophosphate (cAMP), and for the subsequent activation of cAMP-dependent protein kinase A (PKA) [35]. The effects induced by DP₁ activation are predominantly non-inflammatory, i.e. eosinophil apoptosis and inhibition of cell migration [23]. On the other hand, the DP₂/CRTH2 receptor is associated with inhibitory G-protein (Gi), thus leading to a decrease in intracellular cAMP concentration and to a concomitant elevation of calcium cytosolic levels [35]. The CRTH2 receptor is expressed on several cells (Fig. 1) including Th2 lymphocytes, ILC2, eosinophils, basophils, mast cells, macrophages, dendritic cells, and airway structural cells such as bronchial epithelial cells and nasal polyp fibroblasts, whereas it does not seem to be present in human neutrophils and monocytes [25].

Several animal studies have shown that the CRTH2 receptor plays a relevant role in the pro-inflammatory cellular networks leading to airway eosinophilia. In mice, airway eosinophilia elicited by ovalbumin was significantly reduced by a potent and selective CRTH2 antagonist [36]. In Wistar rats, eosinophilic infiltration of the airways triggered by *Aspergillus*

fumigatus was almost completely abrogated by the CRTH2 antagonist OC000459 [37]. In guinea pig airways, allergen-induced eosinophilic inflammation was attenuated by the CRTH2 antagonist AM211 [38]. Another CRTH2 antagonist (MK-7246) blunted antigen-dependent bronchial eosinophilia in both monkeys and sheep [39].

With regard to human studies, the pro-inflammatory actions elicited by PGD₂ within the airways of patients with T2-high asthma appear to be also mediated by CRTH2 activation. Via stimulation of this receptor, PGD₂ promotes Th2 cell migration and dose-dependently up-regulates the production of Th2 cytokines such as IL-4, IL-5 and IL-13 [40,41]. IL-4 is essential for IgE synthesis, whilst IL-5 drives eosinophilic inflammation, and IL-13 is mostly involved in airway hyperresponsiveness and remodelling, respectively [1]. In addition to the indirect effects induced by PGD₂ on eosinophils through CRTH2-mediated up-regulation of IL-5 expression in Th2 lymphocytes, activation of this receptor at the level of eosinophils themselves also directly affects the functions of these cells. In particular, stimulation of the PGD₂/CRTH2 pathway leads to eosinophil activation including enhanced trans-endothelial migration, chemotaxis and cell shape change, as well as degranulation and release of cytotoxic proteins [42]. Furthermore, activation of the PGD₂/CRTH2 pro-inflammatory axis exerts remarkable effects on ILC2 such as increased cell migration and production of IL-4, IL-5 and IL-13 [43,44]. These actions of

PGD₂ are crucially important in the pathobiology of asthma, because ILC2 are located at a nodal crossroad point between allergen-dependent and -independent T2-high inflammatory responses of the airways. Therefore, the relevant role exerted by PGD₂ in the pathophysiology of T2-high asthma is substantiated by the above evidence referring to the stimulatory actions of this prostaglandin with regard to recruitment and activation of eosinophils, ILC2 and Th2 cells, which overexpress CRTH2 in comparison with other lymphocyte subtypes [25].

PGD₂ plays a pivotal role not only in activation of immune/inflammatory cells, but also with regard to key functions of airway structural cells [45,46]. Indeed, in mouse models of chronic bronchial inflammation PGD₂ increased mucus production by causing hyperplasia of airway epithelial goblet cells [47]. Moreover, when released from mast cells infiltrating airway smooth muscle (ASM), PGD₂ was shown to induce ASM proliferation, as well as to stimulate migration of myofibroblasts and fibrocytes to ASM layer [45].

The prominent relevance of PGD₂ in asthma pathophysiology has been further corroborated by the detection of high levels of this metabolite in bronchoalveolar lavage fluid (BALF) from allergen-challenged atopic patients and from severe asthmatics [48,49]. In particular, a 150-fold increase in BALF PGD₂ concentration was shown a few minutes after bronchial antigen challenge with *Dermatophagoides pteronyssinus* [50]. In

addition, airway allergen challenge in atopic asthmatics caused a significant increase in BALF PGD₂ levels when compared to atopic subjects without asthma [51]. Furthermore, in comparison to healthy individuals, CRTH2-positive cells were shown to be increased within submucosal airway tissues of patients with severe asthma [52]. Consistently with such findings, higher BALF levels of CRTH2 mRNA were detected in severe asthmatics when compared to either healthy control subjects or patients with mild asthma, not treated with ICS [49]. It has also been reported that high BALF concentrations of both PGD₂ and CRTH2-positive cells were associated with high levels of blood eosinophils and fractional exhaled nitric oxide (FeNO), as well as with inadequate asthma control [26].

PGD₂ also plays an important pathogenic role in viral-induced asthma exacerbations. Several viruses such as respiratory syncytial virus (RSV), rhinovirus (RV), and influenza A virus, which are frequent triggers of asthma exacerbations, are able to activate the PGD₂/CRTH2 pathway [53]. During viral replication these respiratory viruses synthesize double-stranded RNA (dsRNA) molecules that can induce innate immune responses, resulting in enhanced cytokine/chemokine production from both inflammatory cells and bronchial epithelial cells [53,54]. Moreover, viral dsRNA up-regulated PGD₂ biosynthesis in animal models of allergic asthma [53]. As a consequence, PGD₂ enhanced allergen-induced airway

eosinophilia via stimulation of CRTH2 receptor; indeed, this pro-inflammatory effect of PGD₂ was suppressed by a CRTH2 antagonist such as ramatroban [53]. In addition, in asthmatic patients viral challenge enhanced the production of PGD₂, which under these circumstances could synergize with the epithelial alarmin IL-33 to further stimulate the synthesis of type 2 cytokines (IL-4, IL-5, IL-13) [55,56]. Furthermore, in comparison with healthy controls, rhinovirus-dependent induction of PGD₂ synthesis was shown to occur at a greater extent in asthmatic subjects [56]. In this regard, the highest PGD₂ increase was detected in patients with severe uncontrolled asthma, thus suggesting a potential role for PGD₂ in contributing to the pathogenesis of virus-induced asthma exacerbations [56].

3. Targeting the PGD₂/CRTH2 pathway with fevipiprant

Among the currently developed CRTH2 antagonists, so far fevipiprant (C₁₉H₁₇F₃N₂O₄S - QAW039) represents the most extensively studied drug. Other CRTH2 antagonists that have been evaluated through phase I and II studies include ACT-129968 (Setipiprant), ADC-3680, AM211, ARRY-502, AZD1981, and BI 671800 [25]. Fevipiprant is a potent and selective antagonist of CRTH2 receptor, and this drug is orally active and suitable for once daily dosing [57,58]. In pre-clinical studies, fevipiprant has been mainly evaluated using cellular assays focusing on inflammatory and

structural airway changes which mimic the pathophysiology of asthma. Fevipiprant dissociates slowly from human CRTH2 and effectively suppresses Th2 cell synthesis of IL-4, IL-15 and IL-13 [57]. Moreover, with regard to key ILC2 functions, fevipiprant is able to effectively inhibit cell migration, aggregation, survival and cytokine (IL-4, IL-5, IL-13) production [59]. In addition to affecting the biological activities of immune-inflammatory cells such as Th2 lymphocytes and ILC2, fevipiprant can also extend its inhibitory actions on airway structural cells (Fig. 1). In particular, via competitive antagonism of CRTH2 expressed by airway smooth muscle (ASM) cells, fevipiprant decreased ASM mass in bronchial biopsies taken from asthmatic patients, and this effect was associated with a reduced recruitment of myofibroblasts and fibrocytes to ASM layer [60]. Therefore, these observations suggest that fevipiprant can potentially attenuate airway remodelling in asthma.

With regard to the safety, tolerability and efficacy of fevipiprant for asthma treatment, several phase I, II, and III studies have been performed and/or are currently ongoing [26]. A phase I evaluation referring to 48 healthy subjects demonstrated that fevipiprant was safe and well tolerated [61]. Indeed, the overall safety and tolerability profile was similar to placebo, and no serious adverse event or death occurred; the most frequent side effects were nasal congestion and headache. Upper airway symptoms, also including nasal congestion, have been reported with similar

frequencies in both placebo and fevipirant groups. Therefore, it is likely that these symptoms occur spontaneously, especially in allergic patients, and no causal relationship appears to exist between fevipirant intake and nasal congestion. With regard to pharmacokinetic aspects, peak blood levels of fevipirant were detected 1-3 hours after administration, and half-life was estimated to be about 18-20 hours [61]. Fevipirant is converted in the liver into an inactive acyl-glucoride metabolite, and drug elimination occurs via renal excretion [62].

Gonem et al. carried out a phase II trial on 61 patients with moderate-to-severe persistent asthma and high sputum eosinophil levels ($> 2\%$), who were randomly assigned to receive for 12 weeks either placebo or oral fevipirant (225 mg twice daily) [63]. In comparison with baseline sputum eosinophil counts, after 12 weeks of treatment the geometric mean of cell percentage decreased from 5.4% to 1.1% in the fevipirant group, and from 4.6% to 3.9% in the placebo arm, respectively. Hence, mean sputum eosinophil count underwent a reduction of 4.5 times during therapy with fevipirant, and only of 1.3 folds during treatment with placebo. Moreover, when compared to placebo, fevipirant decreased eosinophil numbers within the submucosal compartment of bronchial biopsy specimens. No difference was found between fevipirant and placebo in regard to their effects on respiratory symptoms evaluated by asthma control questionnaire (ACQ)7, with the exception of the patient subgroup characterised by

uncontrolled disease at baseline. Another phase II study was conducted in a larger population of subjects with mild-to-moderate persistent allergic asthma by Erpenbeck et al., who completed their evaluation in 157 patients, treated with either fevipiprant (75 subjects) or placebo (82 subjects) [64]. No difference between fevipiprant and placebo was detected in regard to their effects on trough forced expiratory volume in one second (FEV₁). However, when compared to placebo fevipiprant induced a higher FEV₁ increase in participants who had FEV₁ baseline values < 70% predicted, as well as in patients with high serum IgE concentrations, blood eosinophil counts > 300 cells/ μ L, and relatively high FeNO levels. A further phase II study was performed by Bateman et al. on 1058 patients with allergic asthma, whose disease severity was characterised by a score of the asthma control questionnaire (ACQ) > 1.5 and by low FEV₁ measures, included between 40% and 80% of individual predicted values [65]. These study subjects were randomised to receive fevipiprant (782 participants) at different once-daily or twice-daily oral dosages, oral montelukast (139 participants) at a daily dose of 10 mg, or placebo (137 participants), respectively [65]; all patients were also treated with budesonide (200 μ g twice daily). In comparison to placebo, after 12 weeks of treatment both fevipiprant and montelukast elicited significant increases in pre-dose FEV₁; in this regard, the most effective dosages of fevipiprant resulted to be 150 mg once-daily and 75 mg twice-daily. Taken together, these phase II

studies also showed that fevipirant was safe and well tolerated. In particular, the most responsive patients to the therapeutic effects of fevipirant could be subjects with severe eosinophilic asthma [66].

The positive results of the above phase II trials have prompted the design of several, currently ongoing phase III studies [25,26]. Given the important pathophysiologic role played by PGD₂/CRT2 pathway in T2-high severe asthma, these trials have been designed with the aim of assessing the efficacy and safety of two once daily dosages (150 mg and 450 mg, respectively) of fevipirant in patients with recurrent disease exacerbations, blood eosinophil counts > 250 cells/ μ L, and FEV₁ measures < 85% of individual predicted values. In particular, both LUSTER 1 and LUSTER 2 studies (ClinicalTrials.gov, NCT02555683 and NCT02563067) aim to investigate the safety and efficacy of fevipirant in patients with uncontrolled severe eosinophilic asthma. The experimental protocols of such double-blind, placebo-controlled trials focus on two daily dosages of fevipirant throughout 52 weeks of therapy. The primary endpoint regards the potential effects of fevipirant on asthma exacerbation rates. Secondary outcomes include asthma symptom control, asthma-related quality of life, and changes in pre-dose FEV₁. Pre-dose FEV₁ modification with respect to baseline, eventually induced by a 12-week treatment with fevipirant, is also the primary outcome of the multicenter, double-blind, randomized and placebo-controlled ZEAL 1 and ZEAL 2 studies (ClinicalTrials.gov,

NCT03215758 and NCT03226392), designed for patients with uncontrolled moderate asthma. Moreover, assessment of long-term safety of fevipirant, compared with placebo in subjects with moderate-to-severe asthma, is the primary endpoint of a further phase III study (ClinicalTrials.gov, NCT03052517). Other two phase III trials are evaluating the pharmacokinetics of fevipirant in patients with either hepatic (ClinicalTrials.gov, NCT03048448) or renal (ClinicalTrials.gov, NCT03087942) impairment.

4. Conclusions

Because PGD₂ is a pleiotropic mediator which in asthma pathobiology exerts relevant actions on many immune/inflammatory and airway structural cells via stimulation of CRTH2, this receptor represents a suitable molecular target for novel anti-asthma treatments. Within such a therapeutic context, fevipirant is emerging as a very interesting drug. Indeed, several phase II studies have preliminarily shown that fevipirant is characterised by a good efficacy and safety profile. If these findings will be further corroborated and extended by ongoing phase III trials, fevipirant could become a valid option for add-on therapy of difficult to control T2-high asthma. In particular, when compared to the currently available anti-

asthma biologics, fevipirant is featured by undoubted advantages such as its lower cost, and especially the oral route of administration.

Author contributions

All authors contributed to elaborate the text and to draw the figure.

Conflict of interest

The authors declare no conflict of interest.

Conflict of Interest and Authorship Conformation Form

Please check the following as appropriate:

X All authors have participated in (a) conception and design, or analysis and interpretation of the data; (b) drafting the article or revising it critically for important intellectual content; and (c) approval of the final version.

X This manuscript has not been submitted to, nor is under review at, another journal or other publishing venue.

X The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript

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Figure legend

Fig. 1 – Molecular and cellular targets of fevipiprant. PGD₂ (prostaglandin D₂) is mainly released by mast cells, but can also be produced by other cell types such as Th2 lymphocytes, eosinophils and dendritic cells. IgE and alarmins (TSLP, IL-33, IL-25) trigger mast cell secretion of PGD₂, which exerts its pleiotropic pathogenic actions in asthma by activating target cells that express CRTH2 (chemoattractant receptor-homologous molecule expressed on Th2 cells), including immune/inflammatory and structural cells such as Th2 lymphocytes, eosinophils, group 2 innate lymphoid cells (ILC2), bronchial epithelial cells and airway smooth muscle cells. PGD₂ also promotes the recruitment into inflamed tissues of dendritic cell precursors. All these effects of PGD₂ significantly contribute to potentiate the inflammatory and structural changes underlying T2-high eosinophilic asthma. Fevipiprant competitively antagonizes PGD₂-mediated stimulation of CRTH2, thus potentially inhibiting both pro-inflammatory and remodelling events in asthmatic airways.

