



Targeting lipid mediators in asthma: time for reappraisal

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Purpose of review

In the past decades, cysteinyl leukotrienes (CysLTs) and prostaglandin D₂ have been recognized as key mediators of asthma and comorbid conditions for their potent broncho-active and proinflammatory properties. However, both the development and initial positioning of small molecules targeting these lipid mediators [i.e., leukotriene-synthesis inhibitors, CysLT-antagonists, and chemoattractant receptor homologous molecule on T-helper2-cells (CRTH2) antagonists] experienced drawbacks by lacking adequate biomarkers to define potential responders.

Recent findings

New insights into the mechanisms of airway inflammation in asthma including the interaction of leukotrienes and prostanoids has uncovered potential therapeutic targets. Emerging application of biomarkers in more recent clinical studies helped identify responders to therapies targeting lipid mediators and demonstrated their clinical efficacy in distinct asthma phenotypes and endotypes.

Summary

Interest in small molecules targeting lipid mediators in asthma and related conditions is emerging. Several clinical trials evaluating the efficacy and safety of CRTH2 (Prostaglandin D₂ receptor 2) antagonists are ongoing. There is an urgent need for sensitive biomarkers to identify responders to such therapies and for monitoring of (long-term) effects. Furthermore, evaluation of effectiveness of combining different agents targeting lipid mediators or combining them with available or emerging biologics may uncover other potential benefits in certain asthma populations warranting future research.

Keywords

asthma phenotypes and endotypes, chemoattractant receptor homologous molecule on T-helper2-cells antagonists, cysteinyl leukotrienes, leukotriene receptor antagonists, prostaglandin D₂

INTRODUCTION

From the 1980s onwards, cysteinyl leukotrienes (CysLTs) have increasingly been recognized as important mediators of asthma and its comorbid conditions including allergic rhinitis and NSAID-exacerbated respiratory disease (N-ERD) [1]. When inhaled by both healthy and asthmatic individuals, CysLTs have been shown to induce key features of asthma including potent bronchospasm and airway hyperresponsiveness through direct interaction with airway smooth muscle (ASM) cells, airway edema through microvascular leakage and airway inflammation through interaction with inflammatory cells, including mast cells and eosinophils [2–7]. In addition, increased levels of CysLTs have been found in asthmatic patients both at baseline and during both modeled and spontaneous exacerbations [1]. These observations gave rise to the development of the first targeted oral therapy for asthma,

both upstream at the origin of the 5-lipoxygenase (5-LO) metabolic pathway (i.e., leukotriene synthesis inhibitors) and downstream at the CysLT1 (and CysLT2) receptor [i.e., (Cys)leukotriene receptor antagonists (LTRA)]. Initial positioning of antileukotrienes (anti-LTs, mainly LTRA) for asthma was mainly based on their efficacy confirmed by proof of mechanism studies in clinical models of asthma:

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KEY POINTS

- Cysteinyl leukotrienes possess potent bioactive and proinflammatory activities and act on several inflammatory and structural effector cells, including mast cells, eosinophils, and innate lymphoid cells, epithelial cells, airway smooth muscle cells, and endothelial cells through various affinities with the CysLT1 and CysLT2 receptors.
- CysLTs and prostaglandin D2 are involved in both allergic as nonallergic T2-driven asthma and may have an important role both as proinflammatory mediators as well as being involved in airway remodeling.
- Although CysLT1R antagonists seem to be effective in mild to moderate asthma either as monotherapy or complementary to inhaled corticosteroids, the new CRTH2 inhibitors may have a role also in more severe T2 asthma as add-on to standard therapy.
- Potential combined effects of multiple receptor blockade need to be further explored in appropriately designed clinical trials.

that is, in exercise-induced asthma, allergic asthma (with concomitant allergic rhinitis) and N-ERD [1]. Subsequent longer clinical studies helped to establish their complementary effectiveness-based on anti-inflammatory properties – as add-on to low and moderate doses of inhaled corticosteroids (ICS) [8–10].

Apart from leukotrienes, other lipid mediators, especially prostaglandin D2 (PGD2), has been considered as an important mediator of asthma and allergic rhinitis because of its bio-active properties inducing cough, bronchial obstruction (ASM constriction, vasodilation, and edema), airway hyper-responsiveness, cellular infiltration, mucin production, nasal congestion, rhinorrhea, and chemotaxis of effector cells (Th2 cells, eosinophils, basophils) [11–13]. These bioactive and proinflammatory effects are mediated through interaction with G protein coupled receptors: DP1, thromboxane receptor and chemoattractant receptor-homologous molecule expressed on Th2 cells [CRTH2 or prostaglandin D2 receptor 2 (DP2)] on Th2 lymphocytes [14]. Apart from Th2 cells, CRTH2 are also expressed on eosinophils and basophils [15] and play a role in the recruitment of these effector cells during the late phase allergic response (LAR), including the production of Th2-cytokines and IgE and therefore may be involved in the more ‘chronic inflammatory (allergic) process’ [16²²] (Fig. 1). The DP1 and CRTH2-mediated processes act synergistically: PGD2 released by mast cells may be the essential link between the early and the LAR through the recruitment and activation of the effector cells, Th2-

cells and eosinophils [14]. These observations and the subsequent evidence that the putative anti-asthma effects of the first dual thromboxane receptor/CRTH2 antagonist, ramatroban, were mainly mediated through its CRTH2-antagonistic properties resulted in the development of selective CRTH2 antagonists [17,18]. However, small molecules targeting lipid mediators and their pathways in asthma experienced drawbacks both during clinical development and their initial clinical positioning due to lacking adequate biomarkers to define potential responders [19²³].

Although more work is still needed, the new insight into the role of lipid mediators in the pathophysiology of asthma and using available predictive biomarkers have allowed the demonstration of clinical effectiveness of some small molecules targeting these lipid mediator in distinct asthma phenotypes and endotypes [20,21]. In addition, recent findings on the effects and interactions of leukotrienes and prostanoids with both inflammatory and structural cells, as well as the discovery of CRTH2 on several other cells from both the adaptive and innate immune system, revived the interest in targeting these biologically active mediators [22–24]. Ultimately, these findings suggest a potential role of these small molecules as stand-alone or combination therapy in the management of asthma.

EICOSANOIDS IN ASTHMA

Leukotrienes and prostaglandins, members of the eicosanoids family, are lipid mediators produced by cells of both the innate and adaptive immune system. These mediators possess different activities and are involved in health and disease, that is, in physiological and pathophysiological processes. Based on their bioactive and proinflammatory properties, eicosanoids are key mediators in chronic inflammatory airway diseases, including asthma and rhinitis [25] (Fig. 2).

Leukotrienes are generated through the 5-LO pathway following oxidation of arachidonic acid which is released from phospholipid membranes by phospholipase A2. The process of forming leukotriene A4 (LTA4) is induced by 5-LO and copartnered by the 5-LO-activating protein. Immune cells containing the enzymes LTA4 hydrolase and leukotriene C4 (LTC4) synthase, which is largely confined to leukocytes, are capable of converting LTA4 into either leukotriene B4 or any of the CysLTs subtypes: LTC4, leukotriene D4, and leukotriene E4 (LTE4) [26]. In chronic (allergic) inflammatory airway disease, CysLTs are mainly synthesized by activated effector cells, including mast cells, eosinophils, basophils, and innate lymphoid cells (ILCs) to

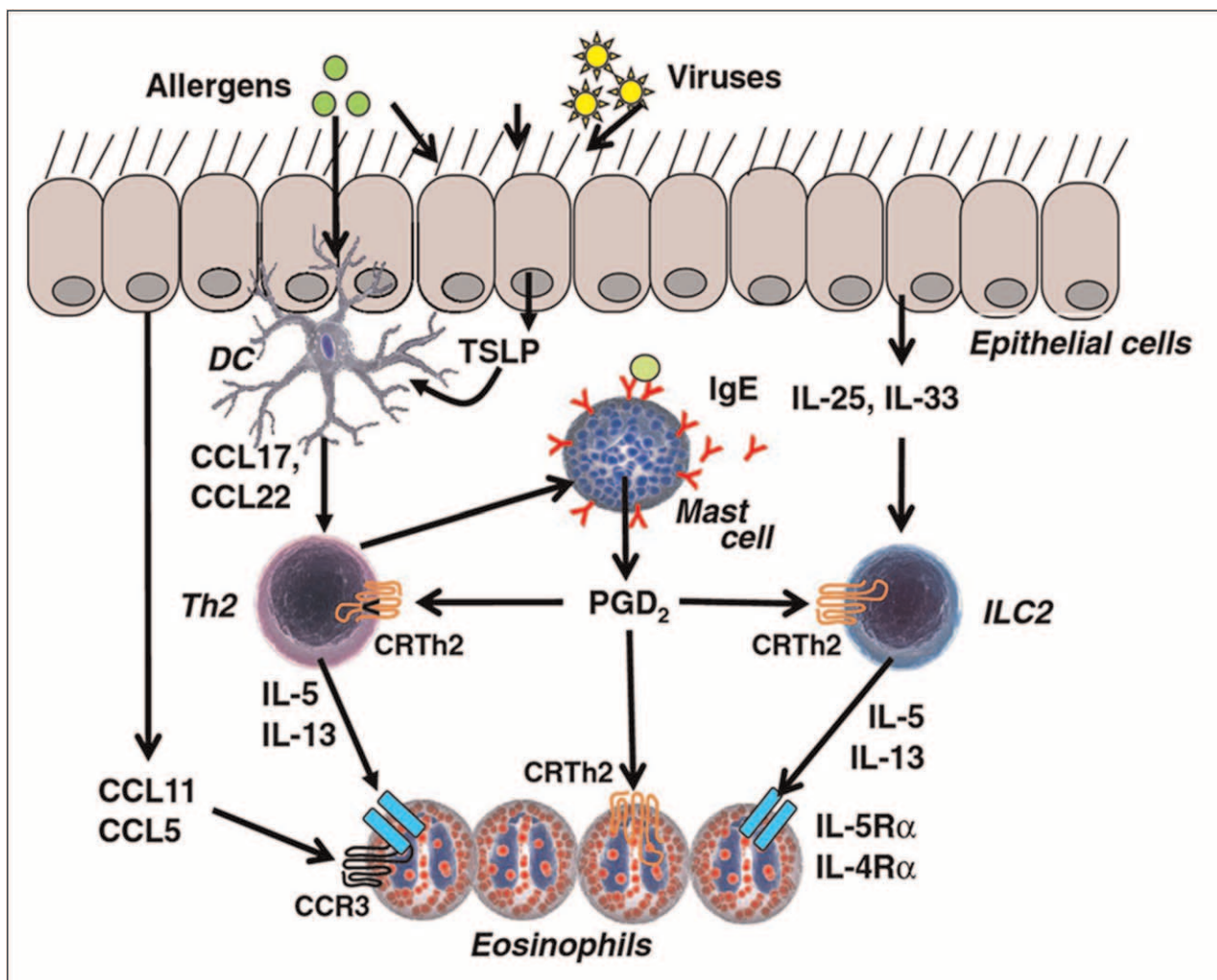


FIGURE 1. Chemoattractant receptor homologous molecule on T-helper2-cells targets in T2-airway inflammation from Barnes [16^{***}]. CCL, chemokine ligand; CCR, chemokine receptor; CRTh2, Chemoattractant receptor-homologous molecule expressed on T helper 2 cells; DC, dendritic cell; IgE, immunoglobulin E; IL, interleukin; ILC2, innate lymphoid cell 2; PGD₂, prostaglandin 2; Th2, T helper2 cell; TSLP, thymic stromal lymphopoietin.

induce chemotaxis of inflammatory cells, bronchoconstriction, mucus hypersecretion, and vascular leakage with subsequent edema of the airway wall [27]. Patients with asthma have increased levels of CysLTs [28]. CysLTs can bind either CysLT1 or CysLT2 receptors. Animal studies revealed that interaction with the CysLT1 receptor promote effector cells (i.e., Th2 and ILC2) to produce IL-4, IL-5, and IL-13 [29]. These cytokines induce bronchospasm, increased vascular permeability, and mucus hypersecretion in asthma [30]. Activating the CysLT2 receptor has been shown to promote inflammation, vascular permeability, and tissue fibrosis and has been associated with the pathophysiology of arteriosclerosis [31]. Upon inhalation, CysLTs induced airway narrowing, airway hyperresponsiveness, cough, and airway inflammation in human individuals [32]. Furthermore, studies show that

CysLTs regulate airway remodeling through release of proteolytic enzymes such as elastase and matrix metalloproteinases which may be suitable targets for future therapies in chronic asthma [33].

Prostaglandins are released from arachidonic acid by cyclooxygenase isoenzymes and possess potent proinflammatory properties. Four different prostaglandins can be formed when arachidonic acid is released from the plasma membrane by phospholipases and converted by prostanoid synthases: prostaglandin E₂, PGD₂, prostaglandin F_{2α}, and prostacyclin. Which prostaglandin is produced depends on the effector cell, each of which generates one or two dominant prostaglandins. Significantly, prostanoid synthases are mainly expressed by innate immune cells, whereas prostanoid receptors are expressed on inflammatory cells of both the innate and adaptive immune system [34], implicating that

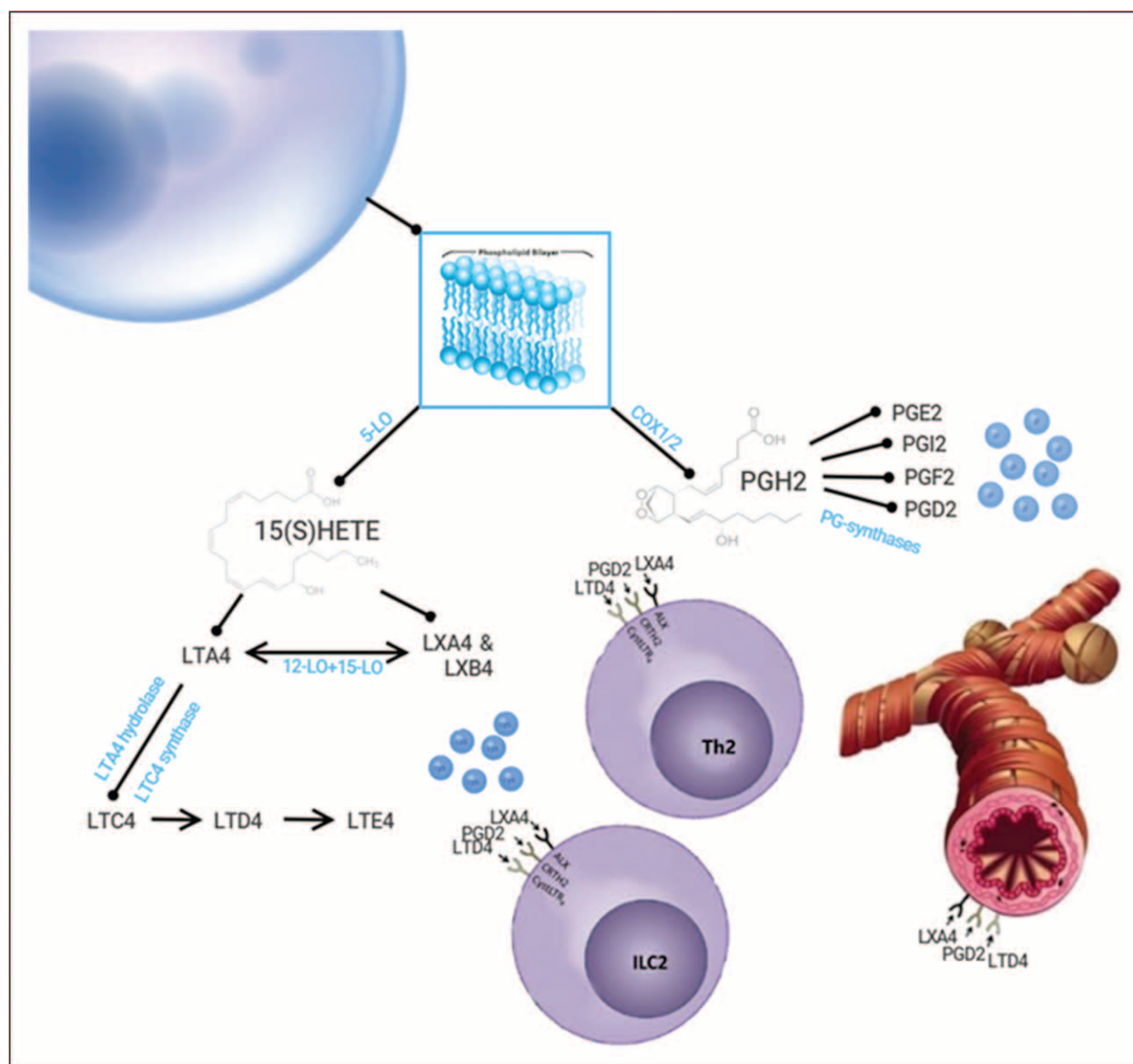


FIGURE 2. Eicosanoid pathways yielding leukotrienes and prostanoids and their interactions. COX, cyclooxygenase; ILC2, innate lymphoid cell 2; LO, lipoxygenase; LT, leukotriene; LX, lipoxin; PG, prostaglandin; Th2, T helper 2 cell.

prostaglandins act in both a paracrine and autocrine way. PGD2 is known to initiate IgE-mediated Type I acute allergic responses [35]. PGD2 acts through binding to the thromboxane receptor, PGD2b receptor 1 (DP1), and chemoattractant receptor-homologous molecule expressed on Th2 lymphocytes (CRTH2/DP2), which all mediate proinflammatory effects [35]. Studies confirm that thromboxane receptor activation mediates ASM contraction and bronchoconstriction [36,37]. DP1 activation in murine models show conflicting results on airway hyperresponsiveness as both constrictive and dilating effects on ASM were observed [38,39]. However, binding PGD2 to DP1 receptor has proinflammatory effects with subsequent recruitment of Th2

lymphocytes in animal models. CRTH2/DP2 activation leads to chemotaxis of Th2 cells, and by promoting the IgE pathway, CRTH2/DP2 receptor activation leads to more PGD2 production [40]. Furthermore, PGD2 contributes to cough [41] which was confirmed in animal models [42]. When exposing healthy individuals to PGD2 inhalation, bronchoconstriction and airway eosinophil infiltration similar to an allergic response occurred [43]. In patients with asthma, postallergen challenge PGD2 levels in bronchoalveolar lavage fluid were significantly higher compared with preallergen levels [44]. Other immune cells such as antigen-presenting dendritic cells and Th2 cells are also found to produce PGD2, suggesting a transcellular

regulating role of PGD2 in adaptive allergic immune responses [45]. Upregulation of the PGD2 pathway was found in patients with severe, poorly controlled T(h)2 high asthma [20].

Although development and testing of selective antagonists targeting lipid mediator receptors like CysLT1R antagonists (e.g., montelukast and zafirlukast) and CRTH2 receptor antagonists (e.g., fevipiprant, timapiprant) helped better understanding of the role of these mediators in the pathophysiology and the inflammatory pathways of asthma, they have also given rise to more research questions. For example, it has been demonstrated that in addition to anti-inflammatory activity of blocking the CysLTR1, antagonists also possess other CysLTR-independent anti-inflammatory properties like downregulating neutrophils, monocytes/macrophages [22], inhibiting proinflammatory cytokines/chemokines, and preventing adhesion of eosinophils [23]. Currently, CysLTR antagonists are commonly used as add-on therapy in (allergic) asthma; but the abovementioned findings suggest a broader therapeutic potential for these agents in selected patient populations. Moreover, recent studies provided more insight in the synergistic behavior of the key lipid mediators. Th2-cells have been shown to express both the CysLT1, and the CRTH2 receptor [24]. Similarly, ILC2s expresses both the CysLT1 [30] and the CRTH2 receptor [46]. Therefore, a combination of a CRTH2 and a CysLT1R antagonist may produce a synergistic blockade of both the Th2-downstream and ILC2-downstream inflammatory pathways, similar to biologics, and hence may have a more robust therapeutic potential in both allergic and nonallergic eosinophilic airway diseases. Obviously, this needs further investigation.

TARGETING LIPID MEDIATORS IN ASTHMA

Due to a lack of their positioning within guidelines in the early days, LTRA have initially been prescribed by default, often to patients with uncontrolled severe asthma. Hence, their clinical effectiveness, as observed in controlled trials, could often not be replicated in daily practice. Almost two decades later, although generally perceived to be less effective than ICS in patients with persistent asthma, their (modest) efficacy and documented safety warrants their application as an acceptable alternative in patients who have intermittent or mild asthma as monotherapy and as add-on therapies in responsive patients on other controller medication as well as in patients who may not comply or are unable to use ICS [47]. Randomized, placebo-controlled trials of LTRAs have demonstrated

improvements in lung function [forced expiratory volume in 1 second (FEV1)], symptoms, quality of life, and exacerbations in patients with asthma [48–51]. A recent meta-analysis confirmed 40% decreased risk for exacerbation and improvement in FEV1 when LTRAs were used as monotherapy [52]. In patients inadequately controlled with ICS alone, addition of LTRAs improves asthma control and lung function [9]. However, addition of a long-acting beta agonist is superior in improving lung function compared with the addition of LTRA [53]. Because LTRAs are administered as a once or twice daily pill, they may have superior compliance compared with ICS. Indeed, in a pragmatic, real world trial, LTRAs were equivalent to ICS after 2 months when used as first-line controller therapy, but adherence to LTRA was higher than to ICS [54]. However, there is marked heterogeneity in the response to LTRAs across patients, with no clearly defined biomarkers identifying responders. Urinary LTE4 is a stable metabolite of CysLTs and urinary LTE4 was found to be higher in adult patients who responded to treatment with montelukast [55], and urinary LTE4 to fractional exhaled nitric oxide ratios were associated with response to montelukast in children [56]. In contrast, in a study of aspirin-intolerant patients with asthma, urinary LTE4 did not correlate with a therapeutic response to montelukast [57]. However, patients with aspirin-intolerant asthma did show improvement in pulmonary function and asthma symptoms when treated with montelukast as well as when treated with zileuton, a 5-lipoxygenase inhibitor [58]. Some specific asthma phenotypes that may respond to antileukotriene therapy include asthma patients with signs of small airways disease [59,60], those with a strong exercise-induced component or with comorbid allergic rhinitis (either as stand alone or with antihistaminic meds) [61] and in smokers [62,63].

PGD2 receptor antagonists, also known as CRTH2 or DP2 antagonists, have recently been identified as a potential new therapy for asthma. The first proof-of-concept studies with early CRTH2 antagonists, including OC000459 and setipiprant [64,65] in unselected patients with mild-to-moderate allergic asthma, demonstrated reduction in the late response to allergen and associated markers of inflammation. In a post-hoc analysis, OC000459 (timapiprant) improved lung function and asthma control mainly in young patients with eosinophilic (≥ 250 cells/ μ l) asthma [21]. More recently, another CRTH2 antagonist, fevipiprant, demonstrated conflicting results in phase II studies. In a single center study of patients with moderate-to-severe asthma and an elevated sputum eosinophil count ($\geq 2\%$), treatment with fevipiprant significantly decreased

sputum eosinophil counts but not blood eosinophil counts [66]. In another study of patients with mild-to-moderate allergic asthma, there was no improvement in lung function with fevipiprant in the general asthma population, but it improved lung function and asthma control in patients with baseline FEV1 less than 70% [67]. Finally, in a phase IIB study of patients with asthma inadequately controlled with ICS, there was improvement in FEV1 when fevipiprant was added to low-dose ICS similar to the positive control montelukast (LTRA). However, there was no difference in response based on blood eosinophil level [68]. Currently, data from two phase III trials are awaited, assessing the safety and efficacy of fevipiprant in patients with poorly controlled asthma.

CONCLUSION

Leukotrienes and prostaglandins are lipid mediators play a major role in the pathophysiology of asthma. Although the role of CysLT1 receptor antagonists (LTRA) have thus far been limited to patients with mild disease as stand-alone medications or as add-on therapies in more severe disease, they seem to have a potential broader role in selected patient populations. The positioning of the new CRTH2 antagonists in the management of asthma is still unclear awaiting ongoing studies. If their safety and efficacy are confirmed in Phase III studies, they may have an important role in patients with uncontrolled disease ahead of biologic therapies which require parenteral administration and are much more expensive. Comparative studies with currently available asthma therapies are needed to further evaluate their role.

Furthermore, because ILC2s which have been recently demonstrated to have a vital role in T2 airway inflammation express both CysLT1 receptors [30] and CRTH2 receptors [46] the role of molecules that block such receptors may be vital in blocking their downstream inflammatory responses. By blocking airway inflammation, CRTH2 antagonists may protect both against allergic airway disease and/or more severe asthma [20,21]. Alternatively, simultaneous blockade of CysLT1 and CRTH2 receptors may show synergistic efficacy as these receptors are present on both Th2 cells and ILC2. Such effect needs to be examined in future studies.

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Conflicts of interest

Z.D. is Executive Medical Director a Director of Respiratory & Allergy at QPS-NL, a CRO conducting early phase clinical trials with biotech and pharmaceutical companies; Z.D. received in the past 36 months honoraria/consultancy fees/speaker fees from: Acucort, Aquilon, ALK, AstraZeneca, Boehringer Ingelheim, Gilead, HAL Allergy, MSD, Sanofi-Genzyme. W.A.: works as research physician for QPS-NL. N.A.H.; Research Support to Institution: AstraZeneca, Boehringer Ingelheim, GSK; Consultant/Advisory Board: AstraZeneca, Boehringer Ingelheim, GSK, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi – consultant. A.D.P. has received consulting fees from AstraZeneca.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

1. Diamant Z, Mantzouranis E, Bjermer L. Montelukast in the treatment of asthma and beyond. *Expert Rev Clin Immunol* 2009; 5:639–658.
2. Bel EH, van der Veen H, Kramps JA, *et al.* Maximal airway narrowing to inhaled leukotriene D4 in normal subjects. Comparison and interaction with methacholine. *Am Rev Respir Dis* 1987; 136:979–984.
3. Tufvesson E, Aronsson D, Bjermer L. Cysteinyl-leukotriene levels in sputum differentiate asthma from rhinitis patients with or without bronchial hyperresponsiveness. *Clin Exp Allergy* 2007; 37:1067–1073.
4. Diamant Z, Hiltermann JT, van Rensen EL, *et al.* The effect of inhaled leukotriene D4 and methacholine on sputum cell differentials in asthma. *Am J Respir Crit Care Med* 1997; 155:1247–1253.
5. Laitinen A, Lindqvist A, Halme M, *et al.* Leukotriene E(4)-induced persistent eosinophilia and airway obstruction are reversed by zafirlukast in patients with asthma. *J Allergy Clin Immunol* 2005; 115:259–265.
6. Laitinen LA, Laitinen A, Haahela T, *et al.* Leukotriene E4 and granulocytic infiltration into asthmatic airways. *Lancet* 1993; 341:989–990.
7. Diamant Z, Timmers MC, van der Veen H, *et al.* Effect of an inhaled neutral endopeptidase inhibitor, thiorphan, on airway responsiveness to leukotriene D4 in normal and asthmatic subjects. *Eur Respir J* 1994; 7:459–466.
8. Peters-Golden M, Sampson AP. Cysteinyl leukotriene interactions with other mediators and with glucocorticosteroids during airway inflammation. *J Allergy Clin Immunol* 2003; 111(1 Suppl):S37–S42; discussion S43–8.
9. Price DB, Hernandez D, Magyar P, *et al.* Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003; 58:211–216.
10. Bjermer L, Diamant Z. Current and emerging nonsteroidal anti-inflammatory therapies targeting specific mechanisms in asthma and allergy. *Treat Respir Med* 2004; 3:235–246.
11. Norman PS, Naclerio RM, Creticos PS, *et al.* Mediator release after allergic and physical nasal challenges. *Int Arch Allergy Appl Immunol* 1985; 77:57–63.
12. Wenzel SE, Westcott JY, Smith HR, Larsen GL. Spectrum of prostanoid release after bronchoalveolar allergen challenge in atopic asthmatics and in control groups. An alteration in the ratio of bronchoconstrictive to bronchoprotective mediators. *Am Rev Respir Dis* 1989; 139:450–457.
13. Shiraishi Y, Asano K, Nakajima T, *et al.* Prostaglandin D2-induced eosinophilic airway inflammation is mediated by CRTH2 receptor. *J Pharmacol Exp Ther* 2005; 312:954–960.
14. Pettipher R, Hansel TT, Armer R. Antagonism of the prostaglandin D2 receptors DP1 and CRTH2 as an approach to treat allergic diseases. *Nat Rev Drug Discov* 2007; 6:313–325.
15. Nagata K, Hirai H, Tanaka K, *et al.* CRTH2, an orphan receptor of T-helper-2-cells, is expressed on basophils and eosinophils and responds to mast cell-derived factor(s). *FEBS Lett* 1999; 459:195–199.
16. Barnes PJ. Cellular and molecular mechanisms of asthma and COPD. *Clin Sci* 2017; 131:1541–1558.
- A very insightful review on the inflammatory and molecular pathways in chronic respiratory disease.
17. Sugimoto H, Shichijo M, Iino T, *et al.* An orally bioavailable small molecule antagonist of CRTH2, ramatroban (BAY u3405), inhibits prostaglandin D2-induced eosinophil migration in vitro. *J Pharmacol Exp Ther* 2003; 305:347–352.

18. Pettipher R, Whittaker M. Update on the development of antagonists of chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2). From lead optimization to clinical proof-of-concept in asthma and allergic rhinitis. *J Med Chem* 2012; 55:2915–2931.
 19. Kupczyk M, Kuna P. Targeting the PGD2/CRTH2/DP1 signaling pathway in asthma and allergic disease: current status and future perspectives. *Drugs* 2017; 77:1281–1294.
- A very insightful and updatated review on chemoattractant receptor homologous molecule on T-helper2-cells (CRTH2)/DP2 antagonists.
20. Fajt ML, Gelhaus SL, Freeman B, *et al.* Prostaglandin D(2) pathway upregulation: relation to asthma severity, control, and TH2 inflammation. *J Allergy Clin Immunol* 2013; 131:1504–1512.
 21. Pettipher R, Hunter MG, Perkins CM, *et al.* Heightened response of eosinophilic asthmatic patients to the CRTH2 antagonist OC000459. *Allergy* 2014; 69:1223–1232.
 22. Theron AJ, Steel HC, Tintinger GR, *et al.* Cysteinyl leukotriene receptor-1 antagonists as modulators of innate immune cell function. *J Immunol Res* 2014; 2014:608930.
 23. Tintinger GR, Feldman C, Theron AJ, Anderson R. Montelukast: more than a cysteinyl leukotriene receptor antagonist? *ScientificWorldJournal* 2010; 10:2403–2413.
 24. Xue L, Fergusson J, Salimi M, *et al.* Prostaglandin D2 and leukotriene E4 synergize to stimulate diverse TH2 functions and TH2 cell/neutrophil cross-talk. *J Allergy Clin Immunol* 2015; 135:1311–1358.
 25. Holtzman MJ. Arachidonic acid metabolism. Implications of biological chemistry for lung function and disease. *Am Rev Respir Dis* 1991; 143:188–203.
 26. Lewis RA, Austen KF, Soberman RJ. Leukotrienes and other products of the 5-lipoxygenase pathway. Biochemistry and relation to pathobiology in human diseases. *N Engl J Med* 1990; 323:645–655.
 27. Peters-Golden M, Henderson WRJ. Leukotrienes. *N Engl J Med* 2007; 357:1841–1854.
 28. Arm JP. Leukotriene generation and clinical implications. *Allergy Asthma Proc* 2004; 25:37–42.
 29. Lynch KR, O'Neill GP, Liu Q, *et al.* Characterization of the human cysteinyl leukotriene CysLT1 receptor. *Nature* 1999; 399:789–793.
 30. Doherty TA, Khorram N, Lund S, *et al.* Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates TH2 cytokine production. *J Allergy Clin Immunol* 2013; 132:205–213.
 31. Beller TC, Maekawa A, Friend DS, *et al.* Targeted gene disruption reveals the role of the cysteinyl leukotriene 2 receptor in increased vascular permeability and in bleomycin-induced pulmonary fibrosis in mice. *J Biol Chem* 2004; 279:46129–46134.
 32. Adelroth E, Morris MM, Hargreave FE, O'Byrne PM. Airway responsiveness to leukotrienes C4 and D4 and to methacholine in patients with asthma and normal controls. *N Engl J Med* 1986; 315:480–484.
 33. Lagente V, Boichot E. Role of matrix metalloproteinases in the inflammatory process of respiratory diseases. *J Mol Cell Cardiol* 2010; 48:440–444.
 34. Harizi H, Gualde N. The impact of eicosanoids on the crosstalk between innate and adaptive immunity: the key roles of dendritic cells. *Tissue Antigens* 2005; 65:507–514.
 35. Herlong JL, Scott TR. Positioning prostanoids of the D and J series in the immunopathogenic scheme. *Immunol Lett* 2006; 102:121–131.
 36. Beasley RC, Featherstone RL, Church MK, *et al.* Effect of a thromboxane receptor antagonist on PGD2- and allergen-induced bronchoconstriction. *J Appl Physiol* 1989; 66:1685–1693.
 37. al Jarad N, Hui KP, Barnes N. Effects of a thromboxane receptor antagonist on prostaglandin D2 and histamine induced bronchoconstriction in man. *Br J Clin Pharmacol* 1994; 37:97–100.
 38. Matsuoka T, Hirata M, Tanaka H, *et al.* Prostaglandin D2 as a mediator of allergic asthma. *Science* 2000; 287:2013–2017.
 39. Spik I, Brenuchon C, Angeli V, *et al.* Activation of the prostaglandin D2 receptor DP2/CRTH2 increases allergic inflammation in mouse. *J Immunol* 2005; 174:3703–3708.
 40. Tanaka K, Hirai H, Takano S, *et al.* Effects of prostaglandin D2 on helper T cell functions. *Biochem Biophys Res Commun* 2004; 316:1009–1014.
 41. Doyle WJ, Boehm S, Skoner DP. Physiologic responses to intranasal dose-response challenges with histamine, methacholine, bradykinin, and prostaglandin in adult volunteers with and without nasal allergy. *J Allergy Clin Immunol* 1990; 86(6 Pt 1):924–935.
 42. Maher SA, Birrell MA, Adcock JJ, *et al.* Prostaglandin D2 and the role of the DP1, DP2 and TP receptors in the control of airway reflex events. *Eur Respir J* 2015; 45:1108–1118.
 43. Hardy CC, Robinson C, Tattersfield AE, Holgate ST. The bronchoconstrictor effect of inhaled prostaglandin D2 in normal and asthmatic men. *N Engl J Med* 1984; 311:209–213.
 44. Murray JJ, Tonnel AB, Brash AR, *et al.* Release of prostaglandin D2 into human airways during acute antigen challenge. *N Engl J Med* 1986; 315:800–804.
 45. Urade Y, Ujihara M, Horiguchi Y, *et al.* The major source of endogenous prostaglandin D2 production is likely antigen-presenting cells. Localization of glutathione-requiring prostaglandin D synthetase in histiocytes, dendritic, and Kupffer cells in various rat tissues. *J Immunol* 1989; 143:2982–2989.
 46. Xue L, Salimi M, Panse I, *et al.* Prostaglandin D2 activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on TH2 cells. *J Allergy Clin Immunol* 2014; 133:1184–1194.
 47. Chauhan BF, Ducharme FM. Antileukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane database Syst Rev* 2012; CD002314.
 48. Baumgartner RA, Martinez G, Edelman JM, *et al.* Distribution of therapeutic response in asthma control between oral montelukast and inhaled beclomethasone. *Eur Respir J* 2003; 21:123–128.
 49. Reiss TF, Chervinsky P, Dockhorn RJ, *et al.* Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. *Montelukast Clinical Research Study Group. Arch Intern Med* 1998; 158:1213–1220.
 50. Malmstrom K, Rodriguez-Gomez G, Guerra J, *et al.* Oral montelukast, inhaled beclomethasone, and placebo for chronic asthma. A randomized, controlled trial. *Montelukast/Beclomethasone Study Group. Ann Intern Med* 1999; 130:487–495.
 51. Fish JE, Kemp JP, Lockey RF, *et al.* Zafirlukast for symptomatic mild-to-moderate asthma: a 13-week multicenter study. The Zafirlukast Trialists Group. *Clin Ther* 1997; 19:675–690.
 52. Miligkos M, Bannuru RR, Alkofide H, *et al.* Leukotriene-receptor antagonists versus placebo in the treatment of asthma in adults and adolescents: a systematic review and meta-analysis. *Ann Intern Med* 2015; 163:756–767.
 53. Chauhan BF, Ducharme FM. Addition to inhaled corticosteroids of long-acting beta2-agonists versus antileukotrienes for chronic asthma. *Cochrane Database Syst Rev* 2014; CD003137.
 54. Price D, Musgrave SD, Shepstone L, *et al.* Leukotriene antagonists as first-line or add-on asthma-controller therapy. *N Engl J Med* 2011; 364:1695–1707.
 55. Cai C, Yang J, Hu S, *et al.* Relationship between urinary cysteinyl leukotriene E4 levels and clinical response to antileukotriene treatment in patients with asthma. *Lung* 2007; 185:105–112.
 56. Robinson DS, Campbell D, Barnes PJ. Addition of leukotriene antagonists to therapy in chronic persistent asthma: a randomised double-blind placebo-controlled trial. *Lancet* 2001; 357:2007–2011.
 57. Dahlen S-E, Malmstrom K, Nizankowska E, *et al.* Improvement of aspirin-intolerant asthma by montelukast, a leukotriene antagonist: a randomized, double-blind, placebo-controlled trial. *Am J Respir Crit Care Med* 2002; 165:9–14.
 58. Dahlen B, Nizankowska E, Szczeklik A, *et al.* Benefits from adding the 5-lipoxygenase inhibitor zileuton to conventional therapy in aspirin-intolerant asthmatics. *Am J Respir Crit Care Med* 1998; 157(4 Pt 1):1187–1194.
 59. Zeidler MR, Kleerup EC, Goldin JG, *et al.* Montelukast improves regional air trapping due to small airways obstruction in asthma. *Eur Respir J* 2006; 27:307–315.
 60. Nieto A, Pamies R, Oliver F, *et al.* Montelukast improves pulmonary function measured by impulse oscillometry in children with asthma (Mio study). *Respir Med* 2006; 100:1180–1185.
 61. Kim M-K, Lee SY, Park H-S, *et al.* A randomized, multicenter, double-blind, phase III study to evaluate the efficacy on allergic rhinitis and safety of a combination therapy of montelukast and levocetirizine in patients with asthma and allergic rhinitis. *Clin Ther* 2018; 40:1096–1107.e1.
 62. Price D, Popov TA, Bjerner L, *et al.* Effect of montelukast for treatment of asthma in cigarette smokers. *J Allergy Clin Immunol* 2013; 131:763–771.
 63. Lazarus SC, Chinchilli VM, Rollings NJ, *et al.* Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007; 175:783–790.
 64. Singh D, Cadden P, Hunter M, *et al.* Inhibition of the asthmatic allergen challenge response by the CRTH2 antagonist OC000459. *Eur Respir J* 2013; 41:46–52.
 65. Diamant Z, Sidharta PN, Singh D, *et al.* Setipiprant, a selective CRTH2 antagonist, reduces allergen-induced airway responses in allergic asthmatics. *Clin Exp Allergy* 2014; 44:1044–1052.
 66. Gonen S, Berair R, Singapuri A, *et al.* Fevipiprant, a prostaglandin D2 receptor 2 antagonist, in patients with persistent eosinophilic asthma: a single-centre, randomised, double-blind, parallel-group, placebo-controlled trial. *Lancet Respir Med* 2016; 4:699–707.
 67. Erpenbeck VJ, Popov TA, Miller D, *et al.* The oral CRTh2 antagonist QAW039 (fevipiprant): a phase II study in uncontrolled allergic asthma. *Pulm Pharmacol Ther* 2016; 39:54–63.
 68. Bateman ED, Guerreros AG, Brockhaus F, *et al.* Fevipiprant, an oral prostaglandin DP2 receptor (CRTh2) antagonist, in allergic asthma uncontrolled on low-dose inhaled corticosteroids. *Eur Respir J* 2017; 50; pii: 1700670. doi: 10.1183/13993003.00670-2017.
- A recent phase IIB study comparing the efficacy of fevipiprant (CRTH2 antagonist) and montelukast in patients with asthma uncontrolled on low dose inhaled corticosteroids.