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Editorial

Are emerging PGD2 antagonists a promising therapy class for treating asthma?

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1. Introduction

Until very recently, the management of asthma has centred around a handful of bronchodilators and corticosteroids developed empirically decades ago. The lack of therapeutic innovation is all the more surprising given the pressing clinical need: over 3,000 people die of asthma a year in the US alone, and ~50% of patients report exacerbations necessitating increased treatment in the last year.

That is all set to change. Respiratory medicine is entering a new era of biological therapies – treatments that selectively target specific inflammatory mediators and cellular pathways critical in disease pathophysiology. These treatments have already revolutionised patient care in rheumatology, gastroenterology, dermatology and oncology. Almost all current and emerging biologic treatments for asthma target 'type 2' inflammation and require subcutaneous or intravenous administration. However several pharmaceutical companies have recently developed inhibitors of prostaglandin D_2 (PGD_2) signalling offering an oral alternative capable of suppressing the type 2 inflammatory cascade. This editorial focuses on the rationale and efficacy of blocking PGD_2 signalling in asthma.

2. Asthma pathophysiology

Most asthma is characterised by 'type 2' inflammation, so-called because it is thought to be mediated by type 2 helper (Th2) cells and type 2 innate lymphoid cells (ILC2s) [1]. Th2 cells secrete the type 2 cytokines interleukin (IL)-4, IL-5 and IL-13, which in

turn bring about the archetypal features of asthma: IgE production, mucus hypersecretion, airway hyperreactivity, and eosinophilia (Figure 1). Based on this understanding of asthma immunology, monoclonal antibodies directed against these mediators have been developed as novel therapies, specifically anti-IgE (omalizumab), anti-IL-5 (mepolizumab, reslizumab), anti-IL-5Rα (benralizumab), anti-IL-13 (lebrikizumab, tralokinumab), and anti-IL-4Rα (dupilumab).

Meanwhile, attention has turned to describing the initiating events in the cascade of type 2 inflammation. Several candidates have subsequently been identified with the potential to stimulate Th2 cells and ILC2s to release type 2 cytokines, at least in vitro. These include IL-25, IL-33, thymic stromal lymphopoietin (TSLP) and PGD_2.

3. Prostaglandin D_2 biology

PGD_2 is a lipid inflammatory mediator produced by the sequential action of cyclo-oxygenases (particularly COX-2) and PGD_2 synthases (PGDS) – either haematopoietic PGDS in circulating haematopoietic-derived cells, or lipocalin PGDS in the brain, heart, and adipose tissue (Figure 2). Mast cells are traditionally thought to be the principal source of PGD_2 as they release vast quantities in response to IgE binding [2], but Th2 cells [3] and macrophages [4] may also produce biologically significant amounts (eosinophils and basophils can also produce PGD_2, but in concentrations roughly 1,000 times more dilute than mast cells).

PGD_2 binds the D prostanoid (DP) 1 and CRTH2 receptors. DP1 is found on a variety of cell types and has broadly anti-inflammatory effects. CRTH2, by contrast, is expressed selectively on immune cells, specifically eosinophils, basophils, Th2 cells, and type 2 innate lymphoid cells (ILC2s). Indeed, although it has long been known that PGD_2 has bronchoconstricting effects when inhaled, it was only after the relatively recent discovery of the CRTH2 receptor that a pro-inflammatory role for PGD_2 in

allergic conditions has been described. Thus following CRTH2 receptor binding *in vitro*, PGD_2 triggers chemotaxis and, in the case of ILC2s and Th2 cells, the release of the type 2 cytokines IL-4, IL-5 and IL-13 [5, 6]. CRTH2 binding is therefore hypothesised to be important in diseases characterised by type 2 inflammation, such as asthma, atopic dermatitis and allergic rhinitis.

There is good evidence that the PGD_2-CRTH2 pathway is upregulated in asthma. Both COX-2 [7] and haematopoietic PGDS [8] are more highly expressed in asthmatic lungs, suggesting a greater capacity for producing PGD_2, and there are greater numbers of $CRTH2^+$ cells [9], increasing sensitivity to PGD_2. These observations are more pronounced in patients with poor asthma control [8].

4. The case for CRTH2 antagonists

Given the pathogenic roles of IL-4, IL-5 and IL-13 in asthma, a broader treatment that suppresses all three mediators is likely to be more effective than monoclonal antibodies targeting each individually. Of the various candidates that might trigger type 2 inflammation, PGD_2-CRTH2 activation is particularly attractive as there is evidence to support it being a dominant pathway: whilst IL-25 and IL-33 can also induce type 2 cytokine release by ILC2s in vitro, their stimulatory effect is inhibited by a selective CRTH2 antagonist [6].

On a practical level, selective CRTH2 antagonists are small molecules (rather than monoclonal antibodies) and can therefore be produced relatively cheaply, stored without refrigeration, and administered orally. As with all chronic disorders, non-adherence is a major problem in asthma, and an oral alternative could improve adherence and hence efficacy. There is therefore a compelling case for clinical development of selective CRTH2 antagonists.

5. Evidence to date

There have been several trials of CRTH2 antagonists in stable asthma and in the asthmatic response to an inhaled allergen challenge, a model with good positive and excellent negative predictive value for drug efficacy (Table 1). These have universally found CRTH2 antagonists to be safe and well-tolerated, even at the highest doses. The overall results in terms of efficacy, however, have been underwhelming, with inconsistent reports of statistically significant but small (and potentially not clinically significant) improvements in lung function and quality of life measures (it is worth noting that the bronchoconstricting effects of PGD_2 are via the activity of its metabolite 11β-PGD_2α on the thromboxane receptor, so CRTH2 blockade would not be expected to affect lung function). How do we explain the lack of clinical efficacy? Much of it may come down to two aspects of clinical trial design, selection of the appropriate population and outcome measures.

Asthma is increasingly recognised as a heterogenous disease with various clinical phenotypes and molecular endotypes. Given this, it is unrealistic to expect a single drug to be a panacea for all asthmatics. The type 2 inflammatory endotype, which theoretically should respond best to CRTH2 antagonism, is only one of these endotypes, albeit the most common representing around half of all asthma. However, most clinical trials of CRTH2 antagonists have selected patients on the basis of severity (e.g. use of inhaled corticosteroids, or Forced Expiratory Volume in 1 second, FEV_1) rather than phenotype or endotype (see Table 1). It makes more sense to select participants on the basis of biomarkers of type 2 inflammation, such as blood eosinophilia or exhaled nitric oxide (FeNO) levels. Indeed, when these study participants are analysed separately, the results are more impressive. For example, there were significantly greater increases in

FEV_1 in subgroups with: elevated serum eosinophils [10]; positive skin prick tests [11]; and raised FeNO [12].

The choice of endpoints assessed may also be painting an unduly negative picture of CRTH2 antagonist efficacy in clinical trials of asthma. In particular, no trial to date has been powered to detect an effect on asthma exacerbations, an outcome responsible for the majority of morbidity and mortality in asthma and around half the healthcare costs. Moreover, type 2 inflammation is particularly prominent during exacerbations, as demonstrated both by the marked reduction in exacerbation frequency using anti-IL-5 therapies [13, 14] as well as experimentally using rhinovirus challenge models in asthma [15]. Our group has recently shown that PGD_2 also rises during asthma exacerbations, with levels correlating with increases in IL-5, IL-13, and measures of exacerbation severity [16]. It is therefore biologically plausible that CRTH2 antagonists could be particularly effective in preventing or attenuating exacerbations, whilst simultaneously having a limited effect on stable disease. Interestingly this appears to be the case for the emerging monoclonal antibody treatments, which produce only modest improvements in lung function and symptom scores in stable asthma, but crucially are effective in preventing ~40-50% of exacerbations (see Table 2).

6. Future directions

There are a number of clinical trials ongoing of CRTH2 antagonists in asthma that will address the shortcomings outlined above. These include studies that restrict inclusion to asthmatics with evidence of type 2 inflammation (NCT02560610, NCT02660489, NCT01836471) and those powered to assess an effect on exacerbations. The latter studies include those of sufficient length and size to study naturally occurring exacerbations (NCT02563067, NCT02555683), or precipitating exacerbations

following withdrawal of oral corticosteroid maintenance therapy (NCT02560610) or experimentally following rhinovirus challenge (NCT02660489).

Should the results be positive, studies comparing CRTH2 antagonists to existing treatments and other novel monoclonal antibodies targeting type 2 pathways will be required. Their cost to healthcare systems will also likely determine where they fit into existing management pathways. In addition, studies in paediatric asthma and potentially in those with other clinical phenotypes, such as aspirin-exacerbated respiratory disease (AERD), will be needed to establish benefit across the asthmatic spectrum. As is the case for other treatments targeting type 2 inflammation, the discovery of a biomarker that identifies patients most likely to benefit from CRTH2 blockade would be invaluable, particularly in those whose FeNO and serum eosinophils are suppressed by inhaled corticosteroid treatment. Nonetheless given the positive findings with CRTH2 antagonists in the subset of asthmatics with evidence of type 2 inflammation, as well as the benefit of other type 2-targeted therapies in reducing exacerbations, we believe the outstanding studies are warranted and hopeful that they yield positive results.

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Figure 1. Asthma immunology

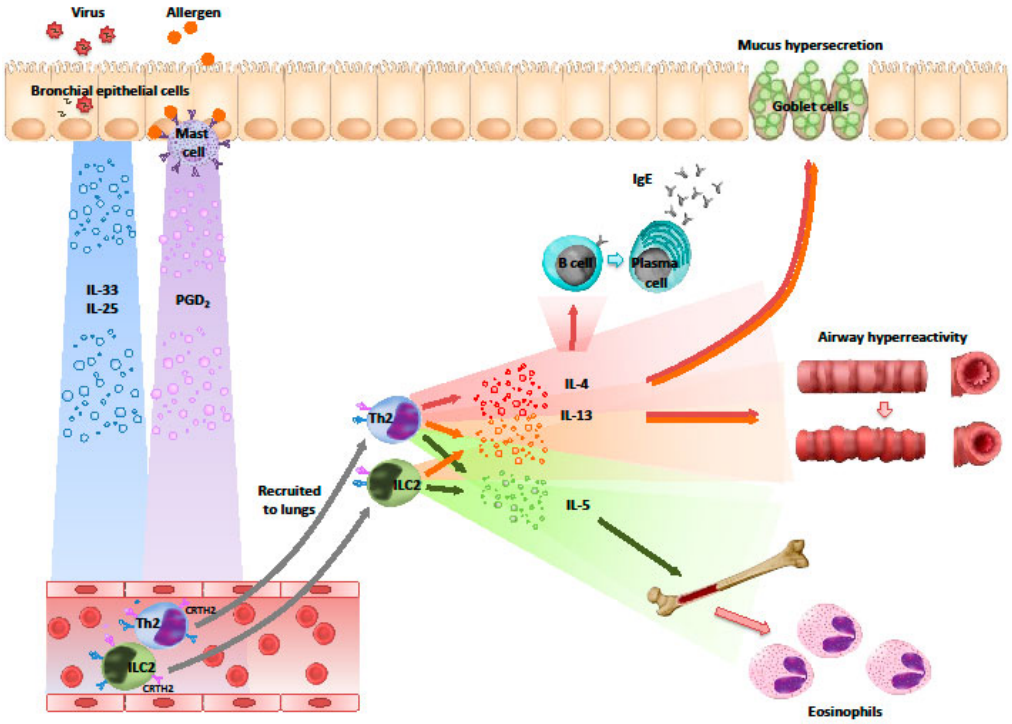

Figure 2. Prostaglandin D_2 biology

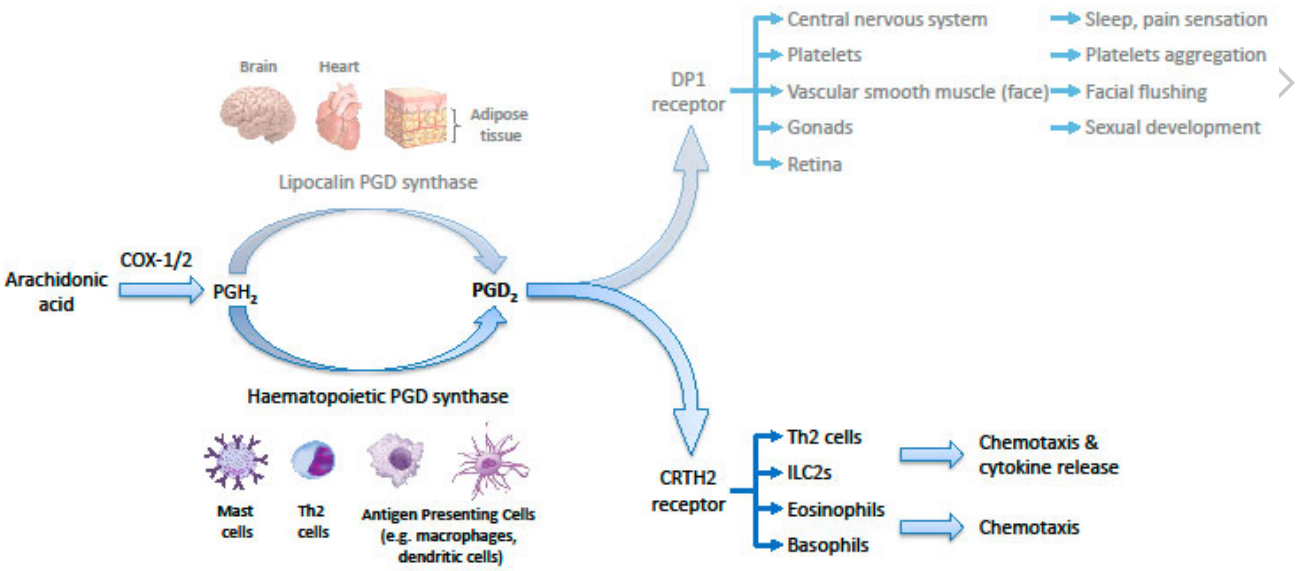

Table 1. Trials of CRTH2 antagonists in asthma.

Study	Year	Population	Intervention	Main findings
OC459				
Barnes et al	2012	ICS-free, allergic asthma *n=132*	OC459 vs Placebo	• Small but significant improvement in quality of life (AQLQ) and night time symptom scores • Small improvement in FEV_1, significant in per protocol analysis only (+9.2% vs +1.8% placebo; p=0.037)
Singh et al	2013	ICS-naïve allergic asthma FEV_1 >65% *n=16*	OC459 vs Placebo	• Effect on response to bronchial allergen challenge • Reduced late but not early asthmatic response, reduced sputum eosinophils • No effect on FEV_1, FeNO
Pettipher et al	2014	ICS-free, FEV_1 60-85% *n=476*	OC459 vs Placebo	• Small but significant improvement in FEV_1, ACQ and AQLQ • Non-significant trend towards reduced exacerbations
BI671800				
Miller et al	2012	ICS-treated, FEV_1 60-85%, ACQ ≥1.5 *n=108*	BI671800 + ICS vs Placebo + ICS	• No significant difference in trough FEV_1 or ACQ
Sutherland et al	2012	ICS-naïve, FEV_1 60-85%, ACQ ≥1.5 *n=388*	BI671800 vs ICS vs Placebo	• Small but significant improvement in FEV_1 and ACQ
Hall et al	2015	FEV_1 60-85%, ACQ ≥1.5 a) ICS-free *(n=388)* b) ICS-treated *(n=243)*	a) BI671800 vs ICS b) BI671800 + ICS vs Montelukast + ICS vs Placebo + ICS	• For (a) small significant improvement in trough FEV_1, no effect on ACQ • For (b) small significant improvement in trough FEV_1 and ACQ vs placebo + ICS but not vs montelukast + ICS
QAW039				
Gonem et al	2016	ICS-treated, ACQ ≥1.5, sputum eosinophil ≥2% *n=61*	QAW039 vs Placebo	• Significant reduction in sputum eosinophils, and small significant improvements in FEV_1 (+0.06L vs -0.10L placebo; p=0.021) and AQLQ (+0.27 vs -0.33 placebo; p=0.008) – but not ACQ • In subgroup with uncontrolled asthma at baseline, ACQ clinically and statistically significantly lower

Erpenbeck et al	2016	Atopic, FEV_1 60-85%, ACQ ≥1.5 *n=170*	QAW039 vs Placebo	• No significant differences in FEV_1 or ACQ overall (both improved if baseline FEV_1 <70%)
Bateman et al	2016	ICS-treated (low dose), FEV_1 40-80%, ACQ ≥1.5 *n=1,058*	QAW039 + ICS vs Montelukast + ICS vs Placebo + ICS	• Significant reduction in trough FEV_1 vs placebo, no effect on ACQ or AQLQ
ARRY-502				
Wenzel et al	2014	ICS-free, FEV_1 60-85%, ACQ ≥1.5 *n=184*	ARRY-502 vs Placebo	• Patients with elevated Th2 associated biomarkers (e.g. FeNO) had improved spirometry, measures of asthma control and quality of life (unspecified)
Discontinued (AMG853, ACT-129968, AZD1981)				
Busse et al	2013	ICS-treated (200-1000µg/d fluticasone), FEV_1 50-85%, ACQ ≥1.5 *n=396*	AMG853 + ICS vs Placebo + ICS	• No significant difference in ACQ, FEV_1, symptoms, exacerbations, AQLQ, serum IgE, FeNO; discontinued
Diamant et al	2014	ICS-free, house dust mite allergy, FEV_1 >70% *n=18*	Setipiprant (ACT-129968) vs Placebo	• Reduced late but not early asthmatic response • No effect on serum eosinophils, IgE, FeNO
NCT01225315 (unpublished)	2012	ISC-free, FEV_1 ≤85%, ACQ ≥1.5 *n=438*	Setipiprant (ACT-129968) vs Placebo	• Did not replicate efficacy of allergen challenge model (no details available); discontinued
NCT00758589 (unpublished)	2013	ICS-treated, FEV_1 40-85% *n=368*	AZD1981 + ICS vs Placebo + ICS	• Significant improvement in ACQ, FEV_1 only improved for middle of three doses; post-hoc analysis showed responders were atopic
NCT01197794 (unpublished)	2013	Atopic, ICS-LABA-treated, FEV_1 40-85% *n=1,144*	AZD1981 + ICS-LABA vs Placebo + ICS-LABA	• Only patients on second lowest dose demonstrated statistically significant improvement in FEV_1; discontinued