

EDITORIAL

Clinical & Experimental Allergy

Novel therapies targeting eosinophilic inflammation in asthma

This editorial discusses the findings of the paper in this issue by H. Neighbour et al. [23] pp. 508–516.

N. C. Thomson

Institute of Infection, Immunity & Inflammation, University of Glasgow, Glasgow, UK

An important goal of personalized medicine in asthma is to individualize treatment using biomarkers to predict a beneficial response and/or to identify individuals who are at risk of adverse effects. The advantage of this approach is that it increases the probability that patients are prescribed effective therapies with a favourable therapeutic risk–benefit ratio. Personalized medicine also maximizes the cost-effective use of interventions, which is important in an era when some therapies for asthma, particularly biological agents, are expensive to develop and market. One method used to stratify patients with asthma is by identifying those with eosinophilic airway inflammation, usually based on the presence of sputum or blood eosinophilia [1]. A type-2 helper T cell (Th₂) subtype of asthma is also recognized, termed Th₂-high or type-2 inflammation, where there is increased expression of cytokines such as interleukin (IL)-4, IL-5 and IL-13 [2, 3]. It has been proposed that the term ‘type-2/eosinophilic’ asthma should be used to describe this subgroup, because there is considerable overlap between eosinophilic and Th₂-high/type-2 inflammation [3]. In the future, it is hoped that by identifying specific underlying cellular and molecular biological pathways, termed endotypes of asthma [4], it will be possible to accurately select patients for specific treatments.

Considerable evidence supports targeting eosinophilia in the management of asthma and the development of new therapies for asthma. Studies in experimental mod-

els of allergic asthma and in clinical asthma implicate eosinophils as a key effector cell in the pathogenesis of asthma including airway remodelling [5–7]. An asthma phenotype associated with ‘type-2/eosinophilia’ occurs in a third to a half of adults with asthma [8], and high eosinophil counts are associated with worse clinical outcomes, particularly exacerbations [9, 10]. Corticosteroids reduce eosinophil numbers by inducing apoptosis and by preventing the potentiating effects of IL-5 and granulocyte/macrophage colony-stimulating factor (GM-CSF) on eosinophil survival. Corticosteroids are a highly effective treatment for eosinophilic asthma, mainly by reducing the risk of exacerbations [11–13]. In some patients, particularly those with severe disease, a refractory eosinophilia is present despite high-dose inhaled corticosteroids or oral corticosteroids. For those subgroups of patients, new therapies are needed to target persistent airway eosinophilia. Low molecular weight drugs and human monoclonal antibodies have been developed by the pharmaceutical industry as potential novel therapies for eosinophilic asthma [5, 14, 15]. These interventions block one or more of the specific receptors expressed on the surface of eosinophils, or antagonize ligands that activate these receptors or inhibit pro-inflammatory intercellular pathways (Fig. 1). Clinical trials have reported recently on the effects of small molecular weight drugs and human monoclonal antibodies on clinical and inflammatory outcomes in patients with eosinophilic asthma.

Inflammatory mediators including eotaxin 1-3 [CCL11, 24 and CCL26], RANTES (CCL5) and monocytes chemoattractant proteins recruit and activate eosinophils by acting on CC chemokine receptor-3 (CCR3) on the cell surface of eosinophils [5]. Studies in experimental models of allergic asthma support a potential role for antagonists of the CCR3 receptor in the treatment for eosinophilic asthma. In murine models of allergic asthma, pre-treatment with an anti-CCR3 monoclonal antibody [16, 17] or pre-treatment with a small mole-

Correspondence:

Prof. Neil C. Thomson, Institute of Infection, Immunity & Inflammation, University of Glasgow and Respiratory Medicine, Gartnavel General Hospital, Glasgow G12 0YN, UK.

E-mail: neil.thomson@glasgow.ac.uk

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ing eosinophil recruitment from the blood and bone marrow, and it is possible that the duration of treatment may have been too short to reduce airway eosinophils. Although knowledge of the half-life of eosinophils in different compartments of the body is uncertain, the authors contend that 10-day treatment should be long enough to impact on airway eosinophil numbers. Interestingly, Neighbour et al. [23] postulate that local maturation and *in situ* eosinophilopoiesis contribute to airway luminal eosinophilia in patients with moderate-to-severe asthma [26] and that this mechanism may be more important than chemokine-induced recruitment. The CCR3 antagonist had no beneficial effect on FEV₁ although there was a small improvement in PC₂₀ methacholine and ACQ scores. CCR3 receptors are expressed on airway smooth muscle [27], which may explain the beneficial effect of the CCR3 antagonist (GW766994) on airway responsiveness. This warrants further study. Taken together, these findings do not support a role for the CCR3 receptor in airway eosinophilia in asthma. It seems unlikely that the CCR3 antagonist GW766994 will be developed further as a treatment for eosinophilic asthma in patients receiving inhaled corticosteroids. Interestingly, prior treatment with the CCR3 antagonist increased the ability of oral prednisone to reduce blood eosinophilia by 47%, which may suggest a possible role for the CCR3 antagonist GW766994 in patients with severe asthma who have persistent eosinophilia despite chronic oral corticosteroid therapy.

Other small molecule drugs could potentially target eosinophilic inflammation by acting as antagonists of ligands, such as prostaglandin (PG)D₂ and cysteinyl leukotrienes, that activate surface receptors on eosinophils (Fig. 1). PGD₂ activates chemoattractant receptor-homologous molecule expressed on TH2 cells (CRTH2) receptor expressed on the surface of eosinophils, basophils and Th₂ cells, leading to chemotaxis and activation of these cells. Low molecular weight antagonists of the CRTH2 receptor reduce airway eosinophilia in experimental models of asthma [28], and so these compounds might be of value in the treatment for eosinophilic asthma. A CRTH2 receptor antagonist OC000459 attenuated the late asthmatic response after allergen challenge and the associated post-allergen increase in sputum eosinophils [29]. In patients with corticosteroid naïve moderate asthma, OC000459 produced modest improvements in symptoms and asthma quality of life after 4-week treatment, but in a subgroup of participants did not significantly reduce sputum eosinophil counts compared to placebo [30]. A small molecule dual antagonist of human DP1 and CRTH2 receptors AMG 853 when added to inhaled corticosteroid treatment did not improve symptoms, lung function or induced sputum eosinophil counts (subgroup analysis) in patients with poorly controlled moderate-to-severe asthma [31].

Neither of these latter two studies recruited patients with elevated sputum eosinophil levels at baseline, thus reducing the power to detect an effect of the CRTH2 receptor antagonist on sputum eosinophils. The cysteinyl leukotrienes, leukotriene C₄, leukotriene D₄ and leukotriene E₄ are synthesized from arachidonic acid by 5-lipoxygenase and 5-lipoxygenase-activating protein (FLAP) in inflammatory cells such as eosinophils and mast cells and act on the cys-LT₁ receptor expressed on target cells including eosinophils [32]. Chronic treatment with Cys-LT₁ receptor antagonists and 5-lipoxygenase inhibitors reduces circulating blood and induced sputum eosinophil numbers [33–35] indicating that drugs modifying the 5-lipoxygenase pathway have anti-eosinophilic activity in asthma. However, this approach is unlikely to be useful in treating severe asthma as the addition of the Cys-LT₁ receptor antagonists montelukast to existing high-dose corticosteroid therapy in subjects with severe eosinophilic asthma does not decrease blood or sputum eosinophil numbers [36].

A number of biological agents have been developed to target inflammatory pathways in asthma, including some that may play an important role in eosinophilic and/or type-2 inflammation (Fig. 1). Activation of the IL-5 receptor- α (R α) on the surface of eosinophils induces the recruitment and survival of these cells. Anti-IL-5 monoclonal antibodies under development for the treatment of asthma target eosinophils either by preventing circulating IL-5 binding to IL-5R α on the surface of eosinophils, for example mepolizumab and reslizumab, or by blocking IL-5R α , for example benralizumab. In two exploratory clinical trials, mepolizumab treatment reduced severe exacerbations in patients with refractory eosinophilic asthma and a history of recurrent severe exacerbations [37] and allowed a step-down in oral corticosteroid dose in patients with severe oral corticosteroid-dependent asthma [38]. A follow-up phase 2 study, the Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) trial undertaken in 621 patients with a history of recurrent severe asthma exacerbations and evidence of eosinophilic inflammation reported that mepolizumab infusion four weekly for 1 year reduced the risk of asthma exacerbations, but had no effect on FEV₁ and AQLQ and ACQ scores [39]. Baseline blood eosinophil count and number of exacerbations in the year before entry to the study predicted the reductions in the rate of exacerbations with mepolizumab [39]. Treatment for 12 weeks with the antibody to IL-5, reslizumab reduced sputum eosinophil and blood numbers and produced a small improvement in lung function in patients with poorly controlled asthma and sputum eosinophilia despite high-dose inhaled corticosteroids [40]. A subgroup with nasal polyps obtained greater clinical benefit

from reslizumab treatment. Benralizumab, a monoclonal antibody against IL-5R α reduces eosinophil counts in airway submucosal, sputum and peripheral blood in asthma [41] and also enhances antibody-dependent cell cytotoxicity of eosinophils [42]. In summary, anti-IL5 antibody treatment for eosinophilic asthma reduces the risk of exacerbation and decreases eosinophils, but produces only minimal improvements in lung function and indices of current symptom control. Phase 3 clinical trials are planned or underway to examine the oral corticosteroid-sparing effect and effectiveness of anti-IL-5 antibody treatment in severe eosinophilic asthma or in patients who remain uncontrolled on high doses of inhaled corticosteroids and long-acting beta₂-agonists (LABA).

Th₂ cytokines IL-4 and IL-13 activate the IL-4R α /IL-13R α 1 receptor complex expressed on resident and myeloid cells including eosinophils. Human monoclonal antibodies targeting IL-13 and/or the IL-4R α /IL-13R α 1 complex attenuate airway eosinophilia in experimental models of asthma [43, 44]. Most clinical studies have not included participants with a pre-treatment blood or sputum eosinophilia [45, 46]. One recent clinical trial, however, administered the human monoclonal antibody to IL-4R α dupilumab, what inhibits both IL-4 and IL-13 signalling, to patients with persistent, moderate-to-severe asthma and who had elevated blood or sputum eosinophil levels [47]. IL-4R α monoclonal antibody treatment reduced asthma exacerbations, improved lung function and reduced levels of some Th₂-associated inflammatory markers such as FE_{NO} when inhaled corticosteroids and LABA were stepped-down. There was no consistent reduction in blood or sputum eosinophils [47], although the interpretation of the effects of dupilumab on eosinophilic inflammation is complicated by the design of the study, which involved a step-down of inhaled corticosteroid during the dupilumab treatment period. In another study, a monoclonal antibody that neutralizes IL-13 bioactivity, IMA-638, reduced early and late allergen-induced responses, but had no effect on allergen-induced sputum eosinophils [48]. Clinical trials to date of monoclonal antibodies targeting IL-13 in chronic asthma report an improvement in selected clinical outcomes with different antibodies and in different patient populations. For example, treatment with the monoclonal antibodies lebrikizumab and tralokinumab results in modest improvements in lung function in patients taking inhaled corticosteroids [45, 46]. The improvement in lung function was larger in a subgroup of patients receiving lebrikizumab who had elevated serum periostin and FE_{NO}, biomarkers of Th₂-high inflammation [45], although lebrikizumab was ineffective in patients not taking inhaled corticosteroids [49]. At present, it is unclear whether blocking IL-13 or IL-4 attenuates tissue eosinophilia in asthma. Further

Phase 2 and Phase 3 studies are underway to examine the effectiveness of dupilumab, tralokinumab and lebrikizumab in chronic asthma although none is reported to target specifically patients with baseline eosinophilic inflammation.

Omalizumab is a humanized monoclonal antibody that binds circulating IgE antibody, preventing it from binding to its specific high-affinity IgE receptor (Fc ϵ RI) on mast cells and basophils [50]. In patients with allergic asthma, omalizumab treatment improves symptoms and reduces exacerbations [51, 52]. Omalizumab reduces bronchial, sputum and blood eosinophils [53–55], although the mechanism for this effect is uncertain. Possibilities include inhibition of IgE-dependent secretion of eosinophil-activating mediators from mast cells and basophils or inhibition of IgE-mediated stimulation of specific IgE receptors on the eosinophil surface [56]. Elevated blood eosinophils, FE_{NO} and serum periostin identified patients with allergic asthma who obtained greater reductions in exacerbation after 48 weeks of omalizumab [57]. Taken together, these studies suggest that treatment with omalizumab reduces eosinophilic airway inflammation, which may account, at least in part, for the reduction in the risk of exacerbations.

Several small molecule drugs that block intracellular signalling pathways might suppress the function of eosinophils (Fig. 1). Phosphodiesterase (PDE)₄ inhibitors have immunomodulatory effects on inflammatory cells including eosinophils [58]. PDE₄ inhibitors reduce eosinophilic inflammation in experimental animals [59] and after allergen challenge in asthma [60]. However, high doses of PDE₄ inhibitors may be necessary to treat severe asthma, and gastro-intestinal side effects may limit their use, although inhaled PDE₄ inhibitors may improve their therapeutic index [61]. Inhibition of protein kinases such as p38 mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI3K) or tyrosine kinases involved in cell signalling of pro-inflammatory cytokines may have a role in the treatment for severe asthma [62, 63]. There are no published clinical trials of protein kinase inhibitors in an eosinophilic subtype of asthma.

In conclusion, the preferred treatment option for the majority of patients with eosinophilic asthma is inhaled corticosteroids supplemented with short courses of oral corticosteroids for severe exacerbations. If patients have persistent eosinophilia and poor asthma control despite high-dose inhaled corticosteroid and LABA therapy or chronic oral corticosteroids, then poor adherence with treatment is a likely explanation in many patients [64]. If adherence is considered to be satisfactory, additional treatments are required for patients with persistent airway eosinophilia despite high-dose inhaled corticosteroids or oral corticosteroids. What treatment options may become available for these patients? Neighbour

and colleagues [23] have convincingly demonstrated that the CCR3 antagonist GW766994 does not suppress sputum eosinophilia in patients receiving inhaled corticosteroids. Possible beneficial effects of GW766994 in reducing airway hyperresponsiveness or potentiating the eosinopenic effects of oral corticosteroids require further study [23]. Several CRTH2 receptor antagonists are under development for asthma, but to date, there is no data to indicate that these compounds suppress airway eosinophils in chronic asthma. Clinical trials in patients with eosinophilic/type-2 inflammation may help determine the efficacy of CRTH2 receptor antagonists in this subgroup of asthma. Several biological agents may have a role in the treatment for persistent eosinophilic asthma, although due to their high cost, monoclonal antibodies are likely to be used only in patients with severe disease. Anti-IL-5 blockers show promise in phase 2 studies through their ability to reduce exacerbations in eosinophilic asthma. Omalizumab is effective in reducing exacerbation in allergic

asthma, possibly at least in part by suppressing eosinophilia. The efficacy of monoclonal antibodies targeting IL-13 or the IL-4R α /IL-13R α 1 receptor complex in eosinophilic asthma is unclear, although a phase 2 study undertaken in patients with eosinophilic asthma using the monoclonal antibody to IL-4R α dupilumab reduced asthma exacerbations. Future studies of biological agents under development for asthma need to establish whether specific monoclonal antibodies work in eosinophilic asthma and/or in other specific subtypes or endotypes of asthma and whether a combination of biologics or the sequential use of two or more biologics may be required for effective asthma control in some patients with severe disease. High costs may limit these latter options.

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