EDITORIAL

Anti-interleukin-13 antibody therapy for asthma: one step closer

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Current guidelines for the treatment of asthma recommend inhaled corticosteroids for all patients with persistent asthma. Despite the increasing use of these drugs, asthma remains poorly controlled in a small subset of individuals who do not respond fully to existing therapies. The medical needs of these patients have prompted a search for new medications that inhibit specific molecular targets thought to play key roles in asthma pathogenesis.

Interleukin (IL)-13 is a cytokine that represents a potential critical factor in the development and persistence of asthma. Originally discovered in 1993, IL-13 was identified by molecular cloning in activated human T-lymphocytes [1]. Subsequent *in vitro* studies have demonstrated that IL-13 has a broad range of activities, including effects upon lymphocytes (switching of immunoglobulin isotype synthesis by B-cells from immunoglobulin (Ig)M to IgE [2]), eosinophils (increased adhesion to the vascular endothelium [3] and augmentation of cell survival [4]), mast cells (proliferation and activation [5]), epithelium (increased epithelial permeability [6], and induction of goblet cell differentiation and growth [7]), fibroblasts (transformation into myofibroblasts and production of collagen [8]) and smooth muscle (diminished relaxation in response to β-agonists [9] and augmentation of contractility in response to acetylcholine [10]).

In tandem with the above *in vitro* experiments, the potential role of IL-13 in airways disease has been investigated in animal studies. Using a murine model of allergic asthma, neutralisation of IL-13 led to reversal of airway hyperresponsiveness and inflammation, while administration of IL-13 was sufficient to induce the pathophysiological features of asthma independently of IgE and eosinophils [11, 12]. These observations from an animal model have been shown to have possible relevance to asthma in humans, as IL-13 has been identified to be upregulated in the blood [13], sputum [14], bronchoalveolar lavage fluid [15] and bronchial mucosa [14] of asthmatics compared with nonasthmatic individuals.

The recent development of monoclonal antibodies directed against IL-13 is now providing clinical investigators with opportunities to better define the relevant effects of IL-13 in asthma and to determine whether IL-13 inhibition is effective in patients refractory to existing therapies. As we embark on clinical trials of these agents, a number of important questions arise. First, as IL-4 has been shown to share most activities with IL-13, and has also been identified in the sputum and bronchial tissue of patients with asthma [13], can an agent specifically aimed at IL-13 alone be effective? In the murine model of allergic airway disease, IL-13 has been shown to be more important than IL-4 for induction of airway hyperresponsiveness and chronic remodelling changes, including smooth muscle hyperplasia and subepithelial fibrosis [11, 12]. These findings may, in part, be due to considerably higher pulmonary concentrations of IL-13 than IL-4 in sensitised mice [16]. This phenomenon appears to be true in human asthma as well, as IL-13-producing cells significantly outnumber those making IL-4 [17]. Therefore, as IL-13 is probably the predominant cytokine of the two, therapies directed towards specific IL-13 antagonism may have significant therapeutic effects. Secondly, given the increasing evidence of the pathophysiological heterogeneity of asthma, are there clinical, immunological or biochemical characteristics capable of predicting a positive response to IL-13 inhibition? While the answer to this question is only partly certain, emerging data have provided us with a number of laboratory tests that correlate significantly with airway-derived IL-13 and T-helper cell (Th) type 2 inflammation. Both total serum IgE and blood eosinophils are established markers of Th2 inflammation and, therefore, might be useful as predictors of anti-IL-13 responsiveness [18]. Recently, a number of serum proteins produced by the airway epithelium, including periostin, chloride channel regulator 1 and serpin peptidase inhibitor, have all been shown to be elevated in asthmatics who have increased levels of pulmonary IL-13 and a Th2 phenotype [18]. In addition, IL-13 has been shown to regulate nitric oxide synthase and, thereby, directly control the quantities of nitric oxide that are produced and exhaled from the lungs [19]. One or more of these parameters may, therefore, serve as surrogate markers of increased IL-13 activity in the airways and help in identifying asthmatics who are most likely to benefit from anti-IL-13 treatment.

In the article by PIPER *et al.* [20] in this issue of the *European Respiratory Journal*, patients with poorly controlled asthma who were receiving high doses of inhaled glucocorticoids with or without other drugs for asthma were administered a humanised monoclonal antibody directed against IL-13 (tralokinumab) or placebo. The primary end-point of the study, the 6-item Asthma Control Questionnaire, was not significantly improved by active treatment. However, forced expiratory volume in1 s (FEV1) and supplemental β-agonist use were both significantly improved in

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patients receiving tralokinumab. A *post hoc* analysis of patients with elevated sputum IL-13 (>10 pg·mL^{-1}) at study entry had numerically higher improvements in FEV1 compared with subjects whose values were lower than these thresholds, suggesting that the presence of residual IL-13 was associated with a larger FEV1 response. However, the numbers of patients in this subgroup were too small to conduct an adequate statistical analysis.

These data bear much in common with recently published findings from a trial of lebrikizumab, another anti-IL-13 monoclonal antibody, in patients with asthma [21]. The treatment group who received lebrikizumab had a significant mean improvement in FEV1, 5.5% higher than that in patients receiving placebo. As part of the analysis, patients were identified at the onset of the trial as having serum periostin concentrations that were either higher or lower than the group median. Those with high serum periostin concentrations demonstrated larger improvements in FEV1 during treatment with lebrikizumab, while those with lower levels of periostin had FEV1 values that were not significantly different from placebo. Measurement of exhaled nitric oxide served a similar discriminatory function, as a *post hoc* analysis revealed that patients with values above the group median had larger improvements in FEV1 while receiving lebrikizumab than patients with lower levels.

These data from the trial of tralokinumab are encouraging and bring clinical investigators one step closer to the use of anti-IL-13 antibodies in patients with refractory asthma. Larger trials are eagerly awaited, both to confirm these initial findings as well as to explore what effects these drugs may have upon asthma exacerbations and patient-reported outcomes. Studies of both tralokinumab and lebrikizumab do suggest that IL-13 inhibition may be most effective in patients who have evidence of residual IL-13 activity with persistent Th2 inflammation. Determination of which diagnostic tests will be most cost-effective for assessing phenotypic status will hopefully be born out in the ensuing phase III studies of these agents.

STATEMENT OF INTEREST

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