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EXPERT OPINION

Anti-IL-4/-13 based therapy in asthma

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It is recognised that airway inflammation is key to asthma pathogenesis. Biopharmaceutical approaches have identified new therapies that target key cells and mediators that drive the inflammatory responses in the asthmatic lung. Such an approach resulted in the development of biologics targeted at inhibition of IL-4, IL-5 and IL-13. However, early clinical trials with these biologics in patients with asthma were for the most part disappointing even though they were highly effective in animal models of asthma. It is becoming apparent that significant clinical effects with anti-cytokine-based biologic therapies are more likely in carefully selected patient populations that take asthma phenotypes into account. The development of discriminatory biomarkers and genetic profiling may aid identification of such patients with asthma. This review is an update of the evidence demonstrating the effectiveness or otherwise of the targeting of the T_H2 cytokines IL-4 and IL-13 with biologics in patients with asthma.

Keywords: asthma, discriminatory biomarkers, IL-13, IL-4

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It is now generally accepted that asthma is a complex, heterogeneous mixture of syndromes that can be subdivided into several phenotypes on the basis of clinical, physiological and inflammatory markers. Such heterogeneity in symptoms can in turn result in variable responses to treatment [1]. The complex relationship between genetic determinants and environmental stimuli such as allergens and respiratory viruses represent key elements in the pathobiology of asthma. Inhaled glucocorticoids (GCs) remain the gold-standard anti-inflammatory therapy for the majority of asthmatic patients primarily reducing airway hyperreactivity and exacerbations while improving lung function and quality of life [2]. However, they have well-documented side effects and patient compliance to GC therapy remains an issue [3], while variations in the clinical response of asthmatics to inhaled GC therapy are common [4]. Furthermore, patients with severe disease and the refractory eosinophilic asthma phenotype often suffer frequent asthma exacerbations that may require intensive treatment with daily oral corticosteroids in a hospital setting with attendant side effect and quality-of-life issues [5]. Increased knowledge of the different patterns of inflammation involving diverse infiltrating and structural cell types has driven the development of biological therapies that target the cytokines important in asthma pathobiology [6]. In the case of biologics targeted at T_H2 cytokines such as IL-4, IL-5 and IL-13, a necessary prerequisite is the identification of the presence of eosinophilic inflammation in the airways to increase the likelihood of their efficacy in this asthmatic subgroup. This editorial is an update on an earlier review for this Journal [7] and is based on English-language original articles in PubMed or MedLine that reported significant clinical findings published in the last 2 years on the current status, therapeutic potential and potential problems of biologics that target IL-4 and IL-13 as asthma therapy.



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Both IL-4 and IL-13 are important in eosinophil accumulation and are key factors in IgE synthesis by B cells; they also contribute to mucus production, bronchial fibrosis and airway hyper-responsiveness in asthma [8]. Increased levels of IL-13 have been reported in the sputum and bronchial biopsies from patients with asthma which correlated with increased eosinophil numbers [9,10]. Tralokinumab (CAT-354 -MedImmune) is an injectable anti-IL-13 humanised IgG4 mAb for the potential treatment of asthma. Tralokinumab has been shown to inhibit a range of IL-13-mediated effects in preclinical studies and Phase I studies have demonstrated linear pharmacokinetics and an acceptable safety profile over the dose range tested [11,12]. A proof-of-concept study evaluated the effect of subcutaneous tralokinumab (150, 300 or 600 mg) or placebo in 194 adults with moderate-to-severe uncontrolled asthma who continued their existing controller therapy [13]. Compared with placebo, there were improvements in lung function with mean $\pm$ s.d. increases from baseline in FEV₁ of 0.16 ± 0.35 L ($p = 0.299$), 0.21 ± 0.37 L ($p = 0.102$) and 0.26 ± 0.41 L ($p = 0.041$) in the 150, 300 and 600 mg tralokinumab treatment groups, respectively. The use of short-acting β -2 agonists was also reduced with no significant improvement in ACQ-6 score. Furthermore, when a subgroup of patients were stratified into sputum IL-13-positive or negative (< 10 pg/ml), there were no differences in the response to tralokinumab. All adverse events were mild to moderate and determined not to be related to treatment with tralokinumab.

A randomised multi-centre study of the anti-IL-13 biologic lebrikizumab (Genentech/Chugai Pharmaceutical) demonstrated significantly improved lung function in patients with inadequately controlled asthma, but only in a subgroup defined on the basis of high serum levels of periostin [14]. The latter is an extracellular matrix protein that is released by airway epithelial cells stimulated with IL-13 [13] that has been shown to have potential as a systemic biomarker of airway eosinophilia in asthmatic patients [15]. At week 12, compared with baseline values, the reported FEV₁ increase was 5.5% in the whole lebrikizumab-treated group, 8.2% in the high-periostin subgroup and 1.6% (not significant) in the low-periostin subgroup. Exhaled nitric oxide also serves as a pro-inflammatory, if less specific, marker in asthma and a *post hoc* analysis revealed that lebrikizumab-treated patients with nitric oxide values above the group median exhibited larger improvements in FEV₁ than those patients with lower levels. A more recent Phase-II study recruited 212 asthma patients who were not receiving inhaled GC. Following randomisation, patients received subcutaneous placebo or lebrikizumab (125, 250, or 500 mg) monthly for 12 weeks with an 8-week follow-up period. Although there was an increase in FEV₁ in the active arm of the study, this was neither statistically or clinically significant. Periostin levels were measured in all subjects, but no meaningful increases in FEV₁ were seen in the periostin-high patients [16]. The authors concluded that although there was no improvement in lung function,

their study indicated lebrikizumab may improve disease control but that treatment with this biologic would not be superior to the use of inhaled GC in these patients.

An alternative approach to randomised clinical studies is to use inhaled allergen challenge of volunteers with atopic asthma that results in a rapid fall in FEV₁ (early response) within minutes that is reversible. In around half of subjects, this early response is followed by a subsequent fall in FEV₁ between 3 and 8 h after the initial challenge termed the late asthmatic response (LAR). This technique is reproducible, requiring relatively small subject numbers and has been extensively used as a model of allergic asthma to study mechanisms and also for screening novel therapeutics including biologics [17]. This approach was recently used in a multi-centre double-blind clinical trial in 29 subjects with mild asthma allergic to house dust mite, cat dander or ragweed who had been identified as developing LAR in response to a screening allergen challenge [18]. Compared with placebo, lebrikizumab reduced the magnitude of LAR in 49% of challenged subjects but this finding was not statistically significant. Those subjects with elevated peripheral blood eosinophils, serum IgE or periostin who were treated with lebrikizumab exhibited a greater reduction in LAR compared with subjects with lower levels of these biomarkers.

IL-4 and IL-13 share some structural similarities and they bind the IL-4R α /IL-13R α 1 receptor complex which then activates the transcription factor STAT-6 [19]. Dupilumab (SAR231893/REGN668) is a fully humanised mAb against the IL-4R α chain, a shared receptor component for IL-4 and IL-13. It pairs with not only IL-13R α 1 but also IL-2R γ . In theory, suppression of IL-4 signal transduction by dupilumab stems from blocking the IL-4R α /IL-2R γ complex as well as the IL-4R α /IL-13R α 1 complex. A multi-centre randomised, double-blind, placebo-controlled, parallel-group Phase IIA study evaluated dupilumab (300 mg administered subcutaneously for 12 week – 52 patients) or placebo (52 patients). Subjects had moderate-to-severe asthma requiring medium- to high-dose inhaled GC plus long-acting beta-agonists (LABA), with a blood eosinophil count of at least 300 cells/ μ l or a sputum eosinophil level greater than 3%. At week 2, dupilumab treatment gave significant increases from baseline in both predicted and actual FEV₁ that was maintained through to week 12 despite the instruction to subjects to discontinue their LABA therapy at week 4 and to taper and stop inhaled GC during weeks 6 – 9. Exacerbations occurred in 26 patients: 3 receiving dupilumab (6%) and 23 receiving placebo (44%) giving an 87% relative reduction in the proportion of patients experiencing medication withdrawal-induced exacerbation [20]. These encouraging findings support a significant pathogenic role for both IL-4 and IL-13 in persistent, moderate-to-severe eosinophilic asthma and targeting both cytokines appears more effective than inhibiting either alone. In contrast, the studies of lebrikizumab and tralokinumab reported improvements in lung function but not in asthma symptoms, reduced β -agonist

use or improved quality of life. Dupilumab also significantly reduced serum IgE, eotaxin-3, thymus and activation-regulated chemokine and exhaled nitric oxide, all of which associated with T_H2-driven inflammation. There have been criticisms of this trial [21] including the short study period and the way in which exacerbations were defined being based on inhaled GC/LABA withdrawal. Such a protocol does not represent 'real-world' asthma and precludes the opportunity to evaluate whether the addition of dupilumab to the standard inhaled GC/LABA controller treatment might provide an additive effect. In terms of adverse events, injection-site reactions, nasopharyngitis, nausea and headache occurred more frequently with dupilumab than placebo.

Expert opinion

Despite the availability of inhaled GC together with leukotriene antagonists, long-acting bronchodilators and the anti-IgE monoclonal antibody omalizumab; patients with GC-refractory eosinophilic asthma represent a clear and pressing unmet medical need. It is becoming increasingly accepted that variations in response to treatment are due to human asthma not being driven by a single pathological process. The development of discriminatory biomarkers and genetic profiling may identify patients with particular sub-phenotypes of asthma to guide the use of biologic therapy in carefully selected patient populations most likely to benefit. There is a great deal of interest in the development of biomarkers that do not require direct sampling of the airways. The latter would be both impractical and ethically questionable in large-scale clinical trials or in general clinical practice. The three most promising markers identified to date are serum periostin, exhaled nitric oxide and blood eosinophil counts and these should aid identification of those patients most likely to derive benefit from biologics targeted at IL-4/13, IL-5 or IgE [22]. One other important consideration is that the

placebo group in trials of biologics in asthma often exhibits a marked improvement in symptoms which may reduce the likelihood of significant findings being observed for the test compound. This phenomenon has several potential explanations including suggestibility, natural disease variability, regression to the mean or improved compliance with concomitant anti-inflammatory therapy [23]. The latter is most likely due to the close monitoring of trial subjects that ensures greater compliance in adhering to their normal anti-inflammatory therapy and does emphasise the importance of ensuring patient compliance with current GC-based therapy to control symptoms rather than moving unnecessarily to expensive biologic-based therapies. Biologics such as dupilumab that target the dual cytokines IL-4/13 represent a particularly promising approach for those patients suffering from refractory difficult to control eosinophilic asthma. Larger trials with longer duration are required to fully assess the utility of such an approach and also the long-term safety and tolerability of dupilumab and other anti-IL-4/IL-13 biologics. Dupilumab has also recently shown great promise in the treatment of another allergic disease, atopic dermatitis [24]. The innate immune response clearly plays a significant role in the inflammatory processes underlying asthma and as such provides potential therapeutic targets beyond the T_H2 pathway [25,26]. Such an approach might lead to asthma treatments that are truly disease modifying rather than the symptomatic medications currently available.

Declaration of interest

The author has no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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