



Biologics for asthma and allergy

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Purpose of review

The development of monoclonal antibody-based biologics targeted at inhibition of the Th2 cytokines interleukin-4, interleukin-5 and interleukin-13 represent potentially effective treatments for asthma and allergic diseases. This short review is based on English-language original articles in PubMed or MedLine that reported significant clinical findings on the evidence demonstrating the effectiveness or otherwise of the targeting of interleukin-4, interleukin-5 or interleukin-13 in asthma or allergic disease.

Recent findings

Asthma exhibits marked heterogeneity both clinically and at the molecular phenotypic level requiring specifically targeted treatments to block the key pathways of the disease. It is becoming apparent that significant clinical effects with anticytokine-based biologic therapies are more likely in carefully selected patient populations that take asthma phenotypes into account. Biologics aimed at interleukin-4/13, interleukin-5 or immunoglobulin E are potentially effective treatments for patients with difficult to treat allergic disease. The development of reproducible and straightforward discriminatory biomarkers may aid identification of those patients most likely to benefit from treatment with these expensive interventions.

Summary

Overall these biologics-based therapies are effective treatments for difficult to treat asthma and allergic disease with a safety profile comparable with placebo in the majority of published studies.

Keywords

allergy, asthma, interleukin-3, interleukin-3, interleukin-5

INTRODUCTION

Asthma remains a major cause of ill-health [1] leading to significant morbidity that is associated with substantial direct and indirect healthcare costs, whereas allergic diseases remains a worldwide problem, resulting in substantial morbidity and loss of quality of life in affected individuals. Increased knowledge of the different patterns of inflammation involving mediator production by diverse infiltrating and structural cell types that contribute to asthma and allergic disease pathobiology has driven the development of antibody-based biological therapies that target those cytokines important in these conditions [2]. This short review is based on English-language original articles in PubMed or MedLine that reported significant clinical findings on the current status, therapeutic potential and potential problems of biologics targeted at Th2 cytokines such as interleukin-4, interleukin-5 and interleukin-13 in the treatment of asthma and allergic disease.

INTERLEUKIN-4 AND INTERLEUKIN-13

Both interleukin-4 and interleukin-13 are key to asthma and allergic disease pathogenesis, having

important roles in the differentiation of naive T cells into Th2 effector cells together with contributing to eosinophil accumulation in addition to their vital role in immunoglobulin E (IgE) synthesis by B cells [3]. Tralokinumab (CAT-354; MedImmune, UK) and lebrikizumab (Genentech/Chugai Pharmaceutical, Novartis, US/Japan) are interleukin-13-binding humanized monoclonal antibodies (mAb) that have been shown to improve lung function and possibly reduce asthma exacerbations, but only in those patients with severe asthma with evidence of a type 2 phenotype, demonstrated by raised levels of the biomarkers serum periostin (an extracellular matrix protein released by airway epithelial cells stimulated

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KEY POINTS

- Dual targeting of cytokines such as interleukin-4/13 by biologics such as dupilumab represent a very promising approach for those patients suffering from refractive difficult to control asthma.
- Biologics aimed at interleukin-4/13, interleukin-5 or IgE are potentially effective treatments for patients with difficult to treat allergic disease.
- Overall these biologic-based treatments exhibit a safety profile comparable with placebo in the majority of published studies.

with interleukin-13 with potential as a biomarker of airway eosinophilia in asthmatic patients [4]) or elevated interleukin-13 levels in sputum [5,6]. In contrast, a recent study reported that lebrikizumab did not significantly reduce asthma exacerbations consistently in biomarker-high patients with uncontrolled asthma [7].

Dupilumab (SAR231893/REGN668) is a humanized mAb against the interleukin-4Ra chain, a shared receptor component for interleukin-4 and interleukin-13. A multicenter randomized, double-blind, placebo-controlled, parallel-group phase 2A study evaluated dupilumab in individuals with moderate-to-severe asthma 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 Forced expiratory volume in one second (FEV1) that was maintained through to week 12 despite the instruction to individuals to taper and stop inhaled glucocorticoids during weeks 6 to 9 with an 87% relative reduction in the proportion of patients experiencing medication withdrawal-induced exacerbation [8]. Dupilumab also significantly reduced serum IgE, eotaxin-3, thymus- and activation-regulated chemokine and exhaled nitric oxide, all of which associated with Th2-driven inflammation. More recently, [9[■]] the utility of dupilumab as add on therapy was evaluated in a phase-2b study that enrolled 769 patients with asthma who required treatment with medium-to-high-dose inhaled corticosteroids plus a long-acting β 2 agonist. The greatest significant improvement in FEV1 was observed in patients with baseline blood eosinophil counts of at least 300 eosinophils per microlitre at week-12 compared with placebo. In contrast to earlier studies with dupilumab and the anti-interleukin-5 biologics discussed below, similar improvement in lung function were seen in the overall population and also in the sub-group of patients with fewer than 300 eosinophils per microliter. Furthermore, compared with

placebo, significant reductions in exacerbation rates were seen in all sub-groups including the fewer than 300 eosinophils per microlitre group together with significant improvements in patient-reported asthma symptom outcomes. These findings strongly indicate that targeting both interleukin-4 and interleukin-13 can have a critical role in improving lung function, exacerbation rates and patient-reported outcomes in patients with uncontrolled persistent asthma. However, the study was of short duration with relatively small patient numbers in each group. Dupilumab has been studied in other type 2 inflammatory conditions such as atopic dermatitis, chronic sinusitis and nasal polyposis with very encouraging significant clinical outcomes reported [10,11[■],12,13]. For example, two recent phase 3 trials with identical design reported that compared with placebo, dupilumab significantly improved the symptoms of atopic dermatitis, including pruritus, and the Eczema Area and Severity Index [14[■]]. Dupilumab therefore represents a potential effective biologic-based therapy for both asthma and a number of allergic diseases.

Eosinophilic esophagitis (EoE) is a severe inflammatory condition of the esophagus clinically manifesting itself as dysphagia in both adults and children. The hallmark of EoE is a marked infiltration by eosinophils [15] and other pro-inflammatory cells including T cells, tissue mast cells, with increased expression of type 2 cytokines [16]. A recent phase 2, double-blind, randomized control trial [17] examined the safety and efficacy of a 12-week course of the anti-interleukin-13 mAb (QAX576; Novartis, Switzerland) in adult individuals with EoE in whom conventional intervention using dietary approaches or topical steroid treatment had largely failed. A 75% reduction in the number of eosinophils in the esophagus compared with baseline was achieved in 40% of patients receiving anti-interleukin-13 treatment compared with 13% of placebo patients. Although the study findings were not significant it does provide proof of principle for larger future studies of QAX576 in adults and children with EoE.

INTERLEUKIN-5

Interleukin-5 is vital for the maturation and release of eosinophils from the bone marrow and their accumulation, activation and persistence in the tissues and therefore represents a rational target to prevent or blunt eosinophil-mediated inflammation. Early clinical trials with the anti-interleukin-5 humanized mAb mepolizumab (Nucala; GlaxoSmithKline, UK) were disappointing as recruitment was based on clinical and

physiological characteristics that did not specify the presence of eosinophilic airway inflammation [18]. More recently, the focus of clinical study primary outcomes has been narrowed to asthma exacerbation rates and oral glucocorticoid-sparing effects with the critical issue of appropriate patient selection based on a simple and reliable biomarker coming to the fore. In this respect, two large, multicenter, randomized, placebo-controlled studies [Dose Ranging Efficacy And safety with Mepolizumab in severe asthma (DREAM) and Mepolizumab as Adjunctive Therapy in Patients with Severe Asthma (MENSA) – [19,20]] found that an elevated eosinophil blood count greater than 300 eosinophils/ μ l, despite concurrent treatment with high-dose glucocorticoids and regardless of patient atopic status, was sufficient to select patients who had significant reductions in symptom exacerbations following mepolizumab treatment compared with placebo. Ortega *et al.* [21] re-examined baseline blood eosinophil counts in over 1000 patients from the DREAM and MENSA studies and reported progressive exacerbation reductions with mepolizumab versus placebo as eosinophil blood counts increased, with clinically relevant outcomes observed with an eosinophil baseline count greater than 150 eosinophils/ μ l. These studies demonstrate that blood eosinophil levels are a reliable and simple biomarker for patient selection associated with positive clinical responses to mepolizumab treatment, findings supported by a meta-analysis of seven randomized placebo-controlled trials confirming that mepolizumab reduced exacerbation rates and improved the quality of life in patients with eosinophilic asthma [22], whereas a meta-analysis in patients with severe eosinophilic asthma found that mepolizumab approximately halved exacerbations requiring hospitalization and/or emergency room visits [23]. Furthermore, a systematic literature review and indirect treatment comparison [24] reported mepolizumab to be at least as effective as the IgE inhibitor omalizumab in patients with severe asthma with comparable effects on lung function together with similar tolerability profiles.

In terms of allergic disease, mepolizumab significantly modulated esophageal eosinophil counts in children with EoE [25], whereas a study in adult patients with active EoE also reported reductions in eosinophil numbers in esophageal tissues together with modulation of the expression of molecules associated with esophageal remodeling. However, symptom improvement was not significantly different from placebo [26]. Reslizumab is a potent interleukin-5 antagonist and findings from limited pilot studies suggested that it is a potentially efficacious and well tolerated treatment for EoE, eosinophilic

gastritis, hyper-eosinophilic and eosinophilic polyposis [27]. A randomized, clinical trial evaluated the safety and efficacy of reslizumab in 226 children and adolescents with EoE. All doses of reslizumab gave significant reductions in esophageal eosinophil counts but improvements in symptoms were observed in both the treatment and placebo groups [28].

CONCLUSION

There is now a great deal of interest in the identification of those patients most likely to benefit from biologics aimed at interleukin-4/13, interleukin-5 or IgE with an emphasis on those biomarkers that do not require direct sampling of the airways i.e., serum periostin, exhaled nitric oxide and blood eosinophil counts [29]. Interventions that target dual cytokines such as interleukin-4/13 by biologics such as dupilumab represent a very promising approach for those patients suffering from refractive difficult to control asthma. Several studies also suggest that dupilumab may give great benefit to patient suffering from allergic diseases such as atopic dermatitis. However, the high cost of these biologic treatments does represent a significant concern.

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Conflicts of interest

The author has no conflicts of interest.

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- of special interest
- of outstanding interest

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