



Mepolizumab-based therapy in asthma: an update

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Purpose of review

There is considerable evidence that implicates eosinophils as important effector cells in the inflammation characteristic of eosinophilic asthma. IL-5 is central to eosinophil maturation and release from the bone marrow, their subsequent accumulation, activation and persistence in the tissues. IL-5 therefore represents an attractive target to prevent or blunt eosinophil-mediated inflammation resulting in the development of humanized anti-IL-5 monoclonal antibody such as mepolizumab. This review is an update of the evidence demonstrating the effectiveness of mepolizumab treatment of patients with asthma.

Recent findings

Although early clinical trials with mepolizumab in patients with asthma gave disappointing clinical outcomes, it is becoming apparent that significant clinical effects with this biologic are more likely in carefully selected patient populations that take the eosinophilic asthma phenotype into account. A number of recent studies have reported significant effects by mepolizumab on reductions in exacerbations together with a significant glucocorticoid-sparing effect.

Summary

Mepolizumab is a potentially important and well tolerated therapy in carefully selected populations of patients with asthma.

Keywords

anti-IL-5, eosinophilic asthma, exacerbations, mepolizumab

INTRODUCTION

Asthma is a major cause of ill-health worldwide [1] and is characterized by a complex, heterogeneous mixture of syndromes that can be subdivided into several phenotypes on the basis of clinical, physiological and inflammatory markers that in turn can result in variable responses to treatment [2,3]. Inhaled glucocorticoids remain the anti-inflammatory therapy of choice for the majority of asthmatic patients primarily reducing airway hyperreactivity and exacerbations while improving lung function and quality of life [4]. However, they have well documented side-effects [5] and compliance to glucocorticoid therapy remains an issue [6] whereas variations in the clinical response of asthmatic patients to inhaled glucocorticoid therapy are common [7,8]. 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-effects, quality of life and healthcare cost issues [9]. Increased knowledge of the different patterns of inflammation involving diverse infiltrating and structural cell types [10] has driven the development of biological therapies that target the cytokines,

important in asthma pathobiology [11]. However, the realization that mechanisms other than classic allergic Th2-driven inflammation can contribute to asthma disease manifestations has complicated the picture. In the case of biologics targeted at Th2 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 [12]. This review updates on an earlier one [13] and is based on the English-language original articles in PubMed or MEDLINE that reported significant clinical findings published during the last year on the current status, therapeutic potential and potential problems of mepolizumab as asthma therapy.

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KEY POINTS

- Anti-IL-5 treatment appears effective in well defined patients with eosinophilic asthma through exacerbation prevention.
- In some studies anti-IL-5, treatment is associated with a glucocorticoid-sparing effect.
- Mepolizumab, reslizumab and benralizumab all exhibit good safety profiles.

EOSINOPHILS

Eosinophil involvement in inflammatory conditions affecting the skin, gastrointestinal tract and upper and lower airways is well documented [14]. Eosinophils are normally absent in healthy lungs but their accumulation is a well defined feature of eosinophilic asthma where they release their potent proinflammatory diverse arsenal that includes granule-derived basic proteins, lipid mediators, cytokines and chemokines. These mediators potentiate airway inflammation and contribute to lung tissue remodelling that includes airway thickening, fibrosis and angiogenesis together with a significant contribution to asthma exacerbations [15]. More recent findings emphasize the immunomodulatory functions of eosinophils and their role they play in promoting homeostasis [16]. For example, in addition to their role as degranulating effector cells, eosinophils have the capacity to act as antigen-presenting cells resulting in T-cell proliferation and activation thereby propagating inflammatory responses [17].

It is long established that the TH2-derived cytokine IL-5 is crucial to bone marrow development of eosinophils; it enhances their extravasation, activation, secretion and prolonged survival in the tissues through apoptosis inhibition [18]. These potent effects led to the development of humanized anti-IL-5 monoclonal antibody (mAb) such as mepolizumab [19], reslizumab [20] or benralizumab, a mAb against the human IL-5R α [21,22].

MEPOLIZUMAB

Early clinical trials with the anti-IL-5 humanized mAb mepolizumab (GlaxoSmithKline, Brentford, UK) in patients with mild-to-severe asthma reported disappointing results as participants were recruited on the basis of clinical and physiological characteristics that did not specify the presence of eosinophilic airway inflammation [16]. Two proof-of-concept, randomized, double-blind, placebo-controlled, parallel-group studies [23,24] in patients who manifested eosinophilic asthma demonstrated that mepolizumab not only reduced eosinophil

numbers in the blood and sputum but also resulted in a significant reduction in asthma exacerbations. These findings were confirmed in a larger multicentre randomized placebo-controlled study (DREAM – Dose Ranging Efficacy And safety with Mepolizumab in severe asthma) [25] of 616 patients with poorly controlled asthma with two or more asthma exacerbations requiring oral glucocorticoid treatment in the preceding year. Compared with placebo, mepolizumab reduced the rate of clinically significant asthma exacerbations but there were no consistent improvements in symptoms or lung function. Such a marked dissociation between clinical and functional measurements and exacerbations suggests that they represent different aspects of the disease, with separate underlying pathophysiology. One interesting aspect was the use of a peripheral blood eosinophil count of more than $0.3 \times 10^9/l$ for study inclusion. The use of a peripheral blood eosinophilia is an important step forward as it simplifies the identification of asthmatic patients likely to respond to mepolizumab, rather than the use of a sputum eosinophilia, a technique only available in highly specialized centres requiring a high degree of technical and interpretative expertise. A meta-analysis on seven randomized placebo-controlled trials examined the effect of intravenous infusion of mepolizumab on clinical outcomes in patients with asthma found that this biologic reduced the risk of exacerbations and improved the quality of life in patients with eosinophilic asthma, but no significant improvements in lung function outcomes were observed [26]. In a more recent randomized placebo-controlled study, patients with recurrent asthma exacerbations and evidence of eosinophilic inflammation who were treated with high-dose inhaled steroid treatment received mepolizumab (75-mg intravenously dose or 100-mg subcutaneously) or placebo. As in earlier studies there were significant reductions in exacerbations in both the subcutaneous group and the intravenous group (32%) compared with placebo. Of interest was the fact that the exacerbation rate among the patients recruited to this study was considered high at a mean of 3.6 per year, suggesting that inhaled glucocorticoids and long-acting bronchodilators had not been optimized [27]. Although the rate of exacerbations declined by approximately 50% in the placebo treatment group, the decline in exacerbation rate was significantly greater in both mepolizumab treatment groups (1.75 exacerbations per year with placebo; 0.93 per year with 75-mg intravenous mepolizumab and 0.81 per year with 100-mg subcutaneous mepolizumab). This observation does emphasize that even in well characterized asthma patients poor adherence to therapy

most commonly leads to loss of symptom control [9], providing one explanation for the improvement in symptoms seen in the placebo group in this and other trials with biologics.

Bel *et al.* [28[■]] conducted a double-blind trial that looked at the effect of subcutaneous mepolizumab (100 mg every 4 weeks for 20 weeks) compared with placebo on reduction in oral glucocorticoid dose in 135 patients with severe eosinophilic asthma who required daily oral glucocorticoid therapy to maintain asthma control. There was a significant glucocorticoid-sparing effect of 50% in the mepolizumab group compared with placebo, together with reductions in exacerbations and improved asthma symptom control. However, the proportion of patients who had a reduction in glucocorticoid dose (54%) was lower than in an earlier study [25] in which higher doses of mepolizumab (750 mg) given intravenously resulted in an 87% glucocorticoid dose reduction in all of the patients in the active study arm. A larger study examined the effect of 75 mg intravenous mepolizumab or 100 mg subcutaneous mepolizumab on exacerbation rates in 576 patients with evidence of eosinophilic inflammation despite receiving high doses of inhaled glucocorticoids. Compared with placebo intravenous mepolizumab reduced exacerbation rates by 47% compared with a 53% reduction in those receiving subcutaneous mepolizumab [29[■]]. The authors also reported a modest mean increase in baseline forced expiratory volume in 1 s (FEV1) of 100 ml in the treatment groups compared with placebo. Significant improvements in markers of asthma control as assessed by the St George's Respiratory Questionnaire were seen together with a near-significant improvement in the Asthma Control Questionnaire scores. Table 1 [28[■],29[■]] summarizes the main findings of both studies.

OTHER ANTI-IL-5 mAb

Other anti-IL-5 mAb include reslizumab (Cinquil; Teva Pharmaceuticals, Petah Tikva, Israel; formerly SCH-55700) and benralizumab (AstraZeneca, Cambridge, UK) a humanized afucosylated IgG1 κ mAb

indicated for the potential treatment of asthma that binds to a distinct epitope within the extracellular domain of recombinant human IL-5R α [20–22]. Several recent studies [30–32] suggest that both reslizumab and benralizumab are also effective in reducing exacerbations in patients with eosinophilic asthma, signifying that efficacy is associated with efficiently targeting IL-5 or IL-5 receptor bearing cells rather than being confined to a given biologic.

SAFETY

Mepolizumab has now been studied in several randomized placebo-controlled clinical trials. The majority of these reported adverse events that were either not clinically relevant or that were not attributable to treatment [33[■]]. In the more recent studies researchers blinded for the treatment did report more adverse events for mepolizumab (30%) than for placebo (18%) [28[■]] whereas Ortega *et al.* [29[■]] reported a similar safety profile to that of placebo. Benralizumab has been characterized by a favourable safety profile whereas more studies are required for reslizumab to support its safety profile. Overall, anti-IL-5 treatment appears to have an acceptable safety record for clinical use [33[■]].

CONCLUSION

Despite the availability of inhaled glucocorticoids together with leukotriene antagonists, long-acting bronchodilators and the anti-IgE monoclonal antibody omalizumab, patients with glucocorticoid-refractory eosinophilic asthma represent a clear and pressing unmet medical need. The development of discriminatory biomarkers and genetic profiling may identify patients with particular subphenotypes of asthma to guide the use of biologic therapy in carefully selected patient populations most likely to benefit. However, issues remain with regard to the cost of these biologics, determination of the most effective biomarkers to select responsive patients and whether treatment with mepolizumab and other biologics should be confined to specialist asthma centres [19]. Although treatment with mepolizumab and other biologics have obvious cost

Table 1. Primary findings of the studies

Study	Number/period	Clinical endpoints	Biomarkers	Safety profile
Bel <i>et al.</i> [28 [■]] (phase III)	135/32 weeks	Significant glucocorticoid-sparing effect with reductions in exacerbations with improved asthma symptom control	Significant reductions in blood and sputum eosinophils	Similar safety profile to placebo
Ortega <i>et al.</i> [29 [■]] (phase III)	576/20 weeks	Significant reduction in exacerbation rate, with improved FEV1 and quality of life (AQLQ)	Significant reductions in blood and sputum eosinophils	Similar safety profile to placebo

AQLQ, Asthma Quality of Life Questionnaire; FEV1, forced expiratory volume in 1 s.

implications, patients with severe eosinophilic asthma account for the majority of the asthma-related healthcare costs together with significant quality-of-life issues due in part due to the side-effects of high-dose systemic glucocorticoid treatment. These patients are likely to be greatly benefited from drugs that can control asthma exacerbations with minimal side-effects and the prevention of frequent hospitalization of these patients may justify the relatively high cost of biologic-based therapy [33[■]]. Another important consideration is that the placebo group in trials of biologics in asthma often exhibit a marked improvement in symptoms, which may reduce the likelihood of significant findings being observed for the test compound most likely as a result of the close monitoring of participants under trial ensuring greater compliance in adherence to their normal anti-inflammatory therapy. Furthermore, the use of currently available therapies guided by sputum cell counts leads to substantial reductions in exacerbations, decreases that are clinically comparable to those reported for biologic therapies [34]. This does emphasize the importance of first ensuring patient compliance and correct inhaler technique with current glucocorticoid-based therapy to control symptoms rather than moving unnecessarily to expensive biologic-based therapies. Dual targeting of IL-4/13 by biologics such as dupilumab [35] appears very promising, but large trials with longer duration in carefully selected patients are required to fully assess the utility of such an approach. Increased understanding of the role that the innate immune response plays in asthma also provided potential therapeutic targets beyond the Th2 pathway [36,37]. Such an approach may lead to asthma treatments that are truly disease modifying rather than the symptomatic medications currently available.

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Conflicts of interest

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- of outstanding interest

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