

EXPERT OPINION

1. Introduction
2. Mepolizumab
3. Other anti-IL-5 strategies in asthma
4. Mepolizumab for other eosinophilic diseases
5. Expert opinion

Mepolizumab treatment for asthma

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Introduction: Five percent of asthmatics have severe symptoms despite high doses of inhaled (ICS) or additional oral corticosteroids (OCS): these patients have high morbidity, risk for asthma death, and account for half of asthma healthcare spending. A subgroup (20 – 40%) of these has persistent airway eosinophilia and frequent exacerbations. Mepolizumab is a humanized monoclonal antibody that blocks binding of the key cytokine implicated specifically in eosinophil maturation and survival, interleukin-5, to its receptor.

Areas covered: Pharmacology, Phase I/IIa and Phase II/III studies of mepolizumab for asthma. Mepolizumab depleted blood and sputum eosinophils and partially reduced airway and bone marrow eosinophils. It also reduced airway remodeling. In unselected patients with moderate/severe asthma there was no clinically significant effect on lung function, but a trend to reduced exacerbation rates. When patients were selected for persistent sputum eosinophilia despite high-dose ICS/OCS, and frequent exacerbations, mepolizumab reduced exacerbations by 50%.

Expert opinion: Mepolizumab can reduce exacerbation rates in the severe asthma cohort who have eosinophilic airway inflammation despite corticosteroid treatment. This may be 30% of severe asthmatics and represents a new and important treatment option. Further studies need to confirm efficacy and indications for asthma (and other eosinophilic airway disease), and to examine clinical consequences of reducing remodeling.

Keywords: asthma, exacerbation, interleukin-5, mepolizumab

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1. Introduction

1.1 Asthma

Asthma is a chronic inflammatory airway disease characterized by airway hyper-responsiveness (AHR) and intermittent and reversible airflow obstruction, leading to symptoms of cough, wheeze, and breathlessness [1]. Current definitions depend on physiological measurement of lung function with documentation of reversible airway narrowing. It affects around 8.6% of the adult population in Europe [2]. It accounts for £0.75 billion per year in direct health care costs in the UK [3]. A large proportion of asthmatics are well served by current treatments including inhaled corticosteroids, long-acting bronchodilators and leukotriene modifiers. However, an important group of some 3 – 5% of asthmatics have severe symptoms and frequent exacerbations despite use of maximal therapy and may require constant or frequent oral corticosteroid treatment with attendant long-term side effects [4]. This “refractory asthma” group represents an important unmet need both in terms of morbidity and mortality (up to 1000 deaths per year from asthma in the UK), and in terms of health care costs as this subgroup accounts for roughly 50% of total expenditure [4].

Recent analysis of clinical, physiological, and pathological features has led to the concept of asthma being a heterogeneous disease. Cluster analysis identified several

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Box 1. Drug summary.

Drug name	Mepolizumab
Phase	IIb/III
Indication	Severe asthma with persistent airway eosinophilia despite ICS and/or OCS and frequent exacerbations
Pharmacology	IgG1 κ humanized monoclonal antibody. Blocks binding of interleukin-5 to its receptor
Route of administration	Intravenous
Pivotal trials	
Flood-Page <i>et al.</i> [26]	Phase III DBPC study in 362 patients with mod/severe asthma despite high-dose ICS: placebo versus 250 mg versus 750 mg mepolizumab every 4 weeks for 3 months. Small change in primary outcome (morning PEF) at 250 mg but not 750 mg dose. Trend to reduced exacerbation rate at high dose
Haldar <i>et al.</i> [27]	Phase IIb DBPC study of 61 patients with persistent asthma symptoms despite high-dose ICS and in some OCS, at least 3% eosinophils in induced sputum in the last 2 years, and at least two exacerbations requiring OCS in the last year. One year study of placebo (32 patients) versus monthly injections of 750 mg mepolizumab. Exacerbations were 57 in the mepolizumab group and 109 in the placebo patients (odds ratio 0.57, interquartile range 0.32 – 0.92, $p = 0.02$). Inclusion criteria met by around 30% of severe asthmatics at this site
Nair <i>et al.</i> [28]	Phase IIb DBPC study of 20 patients with sputum eosinophilia of at least 3%, requiring OCS for asthma. Actively treated patients received 5 monthly infusions of 750 mg mepolizumab. There were 12 exacerbations in the placebo group and one in the mepolizumab group ($p = 0.008$). Inclusion criteria met by 3% of severe asthmatics at this site

clusters or subtypes of asthma which seems generally applicable across several populations [5,6]. Broadly speaking these include:

- early onset disease associated with IgE to common allergens (atopic asthma), much of which responds well to current treatments,
- a group of obese, later onset, largely female asthmatics with relatively little evidence of airway inflammation,
- a group of late-onset asthmatics with persistent eosinophilic airway inflammation and less atopy but frequent exacerbations,
- a smaller group of asthmatics with very variable airway obstruction but minimal airway inflammation

Less information is available from children, but similar patterns seem to prevail [7].

1.2 Immunology of asthma

Over the last 25 years, there has been an increasing understanding about immunological and inflammatory mechanisms in asthma. Cluster analysis, together with the advent of specific biological therapies aimed at specific targets in the immunopathological pathways of asthma, has led to the concept of targeting specific biological interventions to specific subgroups in asthma. Asthma has been characterized as involving IgE interaction with allergen in atopic disease, and possibly even in non-atopic asthma, as well as eosinophilic airway inflammation especially in exacerbations [1]. These processes were linked to Th2-type inflammation.

Th2 cytokines produced by T cells drive IgE (interleukin [IL]-4, IL-9 and IL-13), eosinophilia (IL-5, IL-3 and GM-CSF) and AHR (IL-13) [8]. Recent data suggest that a proportion of asthmatics may not have active Th2-type airway inflammation and that other immunological subtypes may exist [9].

Eosinophils have been associated with asthma since they were described by Ehrlich. Airway eosinophil numbers and activation status and measures of the specific pro-eosinophilic cytokine IL-5 have been correlated with AHR, symptoms and provoked asthma models [10]. Corticosteroids, the most effective anti-inflammatory treatment for asthma, reduce IL-5 expression and airway eosinophilia in most patients, although 3 – 5% remain symptomatic (see above) [11]. Indeed, experimental treatment protocols based on adjusting corticosteroid dose guided by sputum eosinophil numbers improved asthma control and reduced exacerbation rates [12]. These data, together with encouraging results from rodent and primate asthma models, lead to development of Mepolizumab, a humanized anti-IL-5 antibody for the treatment of asthma (see Box 1).

1.3 Biologics for asthma

The only licensed biologic to date for asthma is Omalizumab (Xolair), a humanized monoclonal antibody that blocks interaction between IgE and its receptor [13]. This treatment has shown efficacy in reducing exacerbation frequency in severe atopic asthma, and may also have a steroid-sparing effect (allowing reductions in oral steroid requirements). At present it is limited to those with atopic asthma with frequent

exacerbations requiring hospital admission or oral steroid therapy who have a total serum IgE within a set window. Anti-TNF therapies showed some initial positive results but these were not confirmed and there are concerns about adverse events [14,15]. Anti-IL-13 (lebrikizumab) shows promising effects in around 50% of relatively severe asthmatics [16]. The IL-13-induced protein periostin may act as a serum marker for these “Th2-high” patients who respond well to Lebrikizumab [16]. In addition to mepolizumab, a similar anti-IL-5 monoclonal antibody (reslizumab) was developed in parallel [17,18]. More recently, an anti-IL-5R α antibody (benralizumab), which depletes cells expressing the IL-5 receptor (predominantly eosinophils and basophils), has entered Phase II studies [19].

2. Mepolizumab

2.1 Chemistry

Mepolizumab is a fully humanized monoclonal antibody (IgG1 κ) to human interleukin-5 produced in Chinese hamster ovary cells. It blocks binding of human IL-5 to the alpha chain of the IL-5 receptor [20].

2.2 Pharmacodynamics and pharmacokinetics

At doses of 0.05 – 10 mg/kg the mean initial half-life was 2 days and terminal phase $t_{1/2}$ 20 days, with plasma clearance of 0.064 – 0.163 mL/h/kg, a volume of distribution of 49 – 93 mL/kg and bioavailability of 64 – 75% from subcutaneous injection, and 81% from intramuscular injection. At doses used in clinical studies it led to a greater than 85% reduction in peripheral blood eosinophils with an IC₅₀ of around 0.45 μ g/mL [20].

2.3 Clinical efficacy in asthma: Phase I/II

2.3.1 Does Mepolizumab deplete eosinophils?

Since eosinophilic airway inflammation is characteristic of asthma, Phase I studies in healthy non-asthmatic subjects may not be informative. Initial studies with mepolizumab are summarized in Table 1. These showed rapid, prolonged roughly 10-fold reductions in both blood and sputum eosinophils [21-25]. However, reductions in both bronchial mucosal tissue and bone marrow were less, at around 50%. There were no significant reductions in eosinophil precursor numbers in bone marrow or airway tissue (Table 1). Markers of airway remodeling were reduced after mepolizumab treatment, as were airway eosinophils expressing TGF β [25]. In these small Phase II studies there were no significant changes in lung function, AHR, or allergen challenge parameters.

Thus these Phase I/II studies suggested that mepolizumab did indeed reduce eosinophilia in asthma, albeit with different relative efficacy in different tissue compartments. Which is most relevant to clinical expression of different aspects of asthma (AHR, symptoms, exacerbations) is uncertain. They also raised the possibility of a relatively mepolizumab “resistant” tissue population. In addition, one

study suggested a potential role for eosinophils in airway remodeling which was reduced by mepolizumab treatment. Most of these studies were of patients with mild asthma not taking regular inhaled or oral corticosteroids. In addition, they were relatively short-term studies, and did not select for patients with baseline eosinophilia (which was quite variable).

2.3.2 Is Mepolizumab clinically effective in asthma?

Since both inhaled and oral corticosteroids reduce IL-5 expression and eosinophilia in blood, sputum and tissue in asthmatics, the key question for mepolizumab is whether it adds any clinical benefit for patients with persistent symptoms despite corticosteroid treatment.

In a 3-month Phase III DBPC multicenter study, mepolizumab at two doses by intravenous infusion given every 4 weeks (250 and 750 mg) was compared to placebo in 362 asthma patients with persistent symptoms despite prescribed treatment with up to 1000 μ g/day of beclometasone equivalent of inhaled corticosteroid [26]. Primary endpoint was morning peak flow. This was significantly improved in the 250 mg mepolizumab group compared to placebo, but the change was small (13.5 l/min, $p = 0.039$) and there was no significant change in the 750 mg mepolizumab group. There were no significant changes for active treatment compared to placebo for FEV1, symptom scores, rescue short-acting beta agonist use, quality of life scores, or exacerbation rates. There was a trend for reduction in grade 2 and 3 exacerbations (requiring oral corticosteroids or hospital visit) for the patients treated with the 750 mg dose compared to placebo ($p = 0.065$) but numbers were very small (4 vs 2). Blood eosinophils fell as in previous studies and there were significant reductions in sputum eosinophils in the 32 patients for whom samples were available. Pharmacokinetic studies showed a mean mepolizumab concentration in plasma of 22.2 (SD 9.1) ng/mL after the third dose of 250 mg and 51.2 (19.5) ng/mL for the 750 mg dose, and confirmed a terminal half-life for the drug of 21 days.

Of note this study did not select for patients with persistent eosinophilia despite inhaled corticosteroid treatment. Seventeen out of 32 of the patients studied by sputum induction had baseline sputum eosinophilia ($> 3\%$). In addition, there was an improvement in symptoms and other measures of asthma control in the placebo group, presumably due to regression to the mean in patients selected for current asthma symptoms. The authors concluded that mepolizumab did not improve asthma control in the study population.

With increasing emphasis on subgroups of asthma, particularly severe asthma, a clear question was whether there exists a subgroup of patients with asthma symptoms despite inhaled or oral corticosteroid treatment with persistent eosinophilia for whom mepolizumab might be clinically effective. In addition, studies highlighting the potential for reducing exacerbation frequency by control of sputum eosinophils raised exacerbation rates as perhaps the most relevant outcome

Table 1. Phase I-II studies of mepolizumab in asthma.

Study	Study design	Outcomes
Leckie <i>et al.</i> [20]	DBPC mild asthma (SABA only) 8 placebo, 8 2.5 mg/kg 8 10 mg/kg Single dose i.v. Allergen challenge (AgCh)	5 – 10x decrease in blood eos (10 mg dose) no change in AHR before or after AgCh no change in late asthmatic response
Buttner [21]	DBPC mod asthma (on ICS) 8 placebo, 8 250 mg, 8 750 mg 3 doses i.v. at intervals of 4 weeks	7 fold decrease in blood eos or both doses persisted for 12 weeks after last dose significant fall in serum ECP
Flood-Page x2 Menzies-Gow [22-24]	DBPC mild asthma (SABA only) 12 placebo, 12 3 × 750 mg 4 weekly i.v. Bronchoscopy, bone marrow	Median 100% fall in blood eos (from $0.27 \times 10^9/L$) BAL eos fell 79%, bronchial mucosa eos 55%, bone marrow eos 52%. No change in blood basophils, FEV1 or AHR eo myelocytes fell 37%, metamyelocytes 44% no change in eoCFU in BM, or CD34 ⁺ /IL5R α + cells in bronchial biopsies reduced tenascin, lumiican and procollagen III in biopsies after mepolizumab and decreased TGF β + eosinophils in biopsies

measure (rather than measures of airflow obstruction or symptoms) for mepolizumab [12]. In 2009 two important proof of concept studies were published in the same issue of the New England Journal of Medicine.

Haldar and co-workers from Leicester UK studied 61 asthmatic patients (confirmed by documented PEF variability, greater than 15% increase in FEV1 to inhaled bronchodilators, or methacholine PC20 of less than 8 mg/mL). Patient were aged over 18, with symptoms despite high-dose inhaled corticosteroids (equivalent to at least 1000 μ g/day beclometasone), at least two exacerbations requiring oral steroid treatment in the last year, and sputum eosinophilia of more than 3% on at least one occasion in the last 2 years [27]. Smokers were excluded. These patients were selected from a tertiary asthma clinic serving a total population of around 4 million. In a DBPC trial 29 patients received monthly infusions of 750 mg mepolizumab for 12 months, and 32 placebo infusions. The primary outcome was rate of severe exacerbation (defined as loss of asthma control requiring oral corticosteroids for at least 5 days). The mean age was 48 for active and 50 for placebo treatment, 68% of all subjects were atopic, and mean baseline post-bronchodilator FEV1 predicted was 78.1 and 77.6% predicted respectively. Fifty-seven and 53% required regular oral prednisolone (at a mean dose of 9 and 10 mg respectively). The mean number of severe exacerbations over 50 weeks was 2.0 for mepolizumab-treated patients and 3.4 for placebo (a median relative risk of exacerbation of 0.57, interquartile range 0.32 – 0.92, $p = 0.02$). There were 57 exacerbations in the mepolizumab group, versus 109 with placebo, and 31% of mepolizumab-treated patients were exacerbation free for the year of the study, compared to 16% of the placebo group. There were three admissions to hospital for asthma in the mepolizumab group and 11 for placebo, and mean length of stay was 12 days versus 48.

There was a small but statistically significant improvement in quality of life. Measured by the AQLQ score there was an increase of 0.55 with active treatment versus 0.19 for total

score, with a mean difference between treatments of 0.35 (IQR 0.08 – 0.62, $p = 0.02$). There were no significant differences for symptoms, measured by visual analog score, asthma control questionnaire, post-bronchodilator FEV1 or AHR, measured by methacholine PC20. The study protocol included a 2-week course of oral prednisolone at 0.5 mg/kg (maximum dose 40 mg/day) before the first dose of study medication and at the end of 50 weeks treatment: the response to oral corticosteroids was not significantly altered by treatment.

The study included assessment of inflammatory markers including blood and sputum eosinophils at regular intervals and at exacerbation, and exhaled nitric oxide (FeNO). Bronchoscopy with bronchoalveolar lavage (BAL) and bronchial biopsies was performed in a subgroup of 14 patients (11 for BAL), of these 8 for biopsy and 7 for BAL had paired before and after treatment samples after mepolizumab treatment. After mepolizumab treatment, blood eosinophils were reduced 6.6-fold, sputum eosinophils 7.1-fold, bronchial biopsy eosinophils 2.1-fold, and BAL eosinophils 8.2-fold. There was no significant effect of treatment on FeNO. Of the exacerbations for which sputum was obtained, more than 3% eosinophils were present in 59% of placebo-treated patients and 36% of mepolizumab treated patients, $p = 0.04$.

CT scans were obtained before and after treatment for 26 patients in each treatment group. These were performed after the 2-week course of prednisolone to minimize airway edema and inflammation, and were used to assess airway wall thickness as a surrogate for airway remodeling. There was a significant between-group difference for change from baseline airway wall area.

The study reported by Nair and colleagues from Hamilton, Canada, included 20 asthmatic patients (documented spontaneous or bronchodilator reversibility of FEV1 of at least 15% or AHR of 4 mg/ml methacholine PC20 in the last 8 years). Of these, 18 had sputum eosinophilia of at least 3% despite treatment (for at least 4 weeks) with oral prednisolone at a dose of 5 – 25 mg/day in addition to high-dose inhaled

corticosteroids (at least 2000 µg/day BDP equivalent) [28]. These strict selection criteria meant that less than 3% of the 800 patients in this regional severe asthma clinic were eligible. The DBPC study involved five infusions of 750 mg mepolizumab at given every 4 weeks. After the first 4 weeks, the oral prednisolone dose was reduced at a rate depending on the baseline. The primary endpoints were exacerbation rate (defined as an increase in SABA use of 4 puffs per day, 2 consecutive days of nocturnal waking, fall in FEV1 of 15% of more from baseline or increase of 2 points or more in investigator assessed cough score) and mean reduction in prednisolone dose (as percentage maximal possible according to the algorithm used). Exacerbations were treated with 30 mg prednisolone daily for 7 days, and antibiotics were given if induced sputum was neutrophilic. The mean post-bronchodilator FEV1 % predicted was 67% for the 9 patients receiving mepolizumab, and 74% for the 11 treated with placebo, and these patients had mean age of 56 and 58 respectively, and 3/9 and 4/11 were atopic. The median baseline prednisolone dose was 10 mg/day.

Over the 5 months of the study there were 12 exacerbations in 10 of the placebo patients (9 associated with sputum eosinophilia), and 1 exacerbation in the mepolizumab group (no eosinophilia): the difference was significant at $p = 0.008$ by Fisher's exact test. One patient was withdrawn due to an adverse event (which was due to cardiac failure not judged related to the study drug). The mean reduction in prednisolone was 83.8% (SD 33.4%) of the maximal possible, compared to 47.7% (40.5) for placebo-treated patients: this represents a reduction in mean daily dose from 11.9 to 3.9 mg for mepolizumab and 10.7 to 6.4 mg for placebo ($p = 0.11$). Mepolizumab treatment was associated with a significant, though modest, improvement in FEV1 from a mean of 2.0 ± 0.9 to 2.4 ± 1.1 L with no change in the placebo group, and a significant fall in the ACQ score from 1.9 ± 0.8 to 1.2 ± 0.8 . The baseline sputum eosinophil percentage was significantly higher in the mepolizumab group compared to placebo and fell eightfold after treatment, whilst blood eosinophils fell over 10-fold.

In summary, these two studies suggested that mepolizumab significantly reduced exacerbation rates in severe asthmatics with persistent symptoms and frequent exacerbations, and persistent airway (sputum) eosinophilia despite high dose inhaled (and in the second study oral) corticosteroid treatment. The reductions in exacerbation rates from the Halder study are shown in Figure 1.

2.3.3 Safety and tolerability

Mepolizumab has been safe in the studies reported for asthma, with one record of development of a maculopapular rash leading to discontinuation of the drug. Where they are mentioned, antibodies to mepolizumab were not detected. The drug was given by monthly intravenous infusion in all reported studies in asthma. This appears to have been well tolerated.

3. Other anti-IL-5 strategies in asthma

Reslizumab is an IgG4 κ humanized monoclonal antibody to human IL-5 which is similar to mepolizumab. An initial dose-finding study of various doses and placebo in 32 asthmatics with symptoms despite high-dose inhaled corticosteroids showed a dose-dependent reduction in blood eosinophils and a non-significant trend to improved FEV1 at one dose [16]. The drug was well tolerated. A more recent 15-week DBPC study of 106 patients with persistent asthma symptoms despite high-dose inhaled corticosteroids and induced-sputum eosinophilia of 3% or more at baseline, showed a trend for improvement in the primary outcome ACQ (mean change -0.7 for active treatment versus -0.3 for placebo, $p = 0.054$) [17]. There was a significant improvement in FEV1 of 0.18 L (6%) in actively treated patients (versus -0.08 L for placebo). During the study there were 4 exacerbations in the Reslizumab group (8%) and 10 in the placebo group (19%, $p = 0.085$). Thus the more limited data for this drug also suggest that anti-IL-5 treatment may reduce exacerbation rates in those with persistent airway eosinophilia.

A newer approach is a monoclonal antibody termed Bendralizumab which is a fucosylated antibody targeting the IL-5R α chain: this antibody depletes IL-5R α -bearing cells (eosinophils and basophils). To date Phase I studies show long-lasting reductions in blood eosinophils in asthmatic volunteers, and an abstract suggests efficacy in reducing exacerbations [29].

4. Mepolizumab for other eosinophilic diseases

Mepolizumab has also been studied in nasal polyposis [30], atopic dermatitis [31], eosinophilic esophagitis [32], Churg Strauss syndrome [33] and hyper-eosinophilic syndromes [34], with variable clinical success. Although a pivotal DBPC study in HES patients lacking the FIP1LI-PDGFR α gene showed an oral corticosteroid-sparing effect, the European Medicines agency withdrew approval for this indication in 2009 for lack of evidence for long-term efficacy other than a reduction in steroid dose [35].

5. Expert opinion

Current trial evidence does suggest that in selected asthma patients with persistent symptoms and frequent exacerbations despite high-dose inhaled corticosteroid treatment, and airway eosinophilia, mepolizumab can significantly reduce exacerbation rates. Although it requires monthly infusions, the medication appears safe and well tolerated.

The major unmet need in asthma is for patients whose asthma is not controlled despite high-dose inhaled steroids and other controller therapy, or who require long-term oral corticosteroids. Key targets for new therapies are symptom control, improved lung function, reduced requirement for

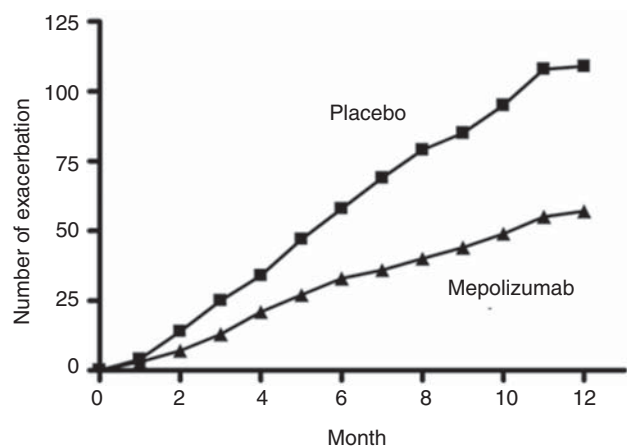


Figure 1. Effect of mepolizumab on exacerbations for patients with persistent airway eosinophils despite treatment with high-dose ICS and/or oral CS. Rate of exacerbations for mepolizumab (n = 29) and placebo [32] treated patients in the study of Haldar *et al.* [27]. Redrawn with permission.

oral corticosteroids, and reduced exacerbation rates. In addition, there is a belief that long-term uncontrolled asthma may accelerate decline in lung function which in turn may lead to fixed airflow obstruction (presumably via airway remodeling). Mepolizumab has clear potential to at least halve exacerbation rates in selected patients, without significant effects on symptoms or lung function and minimal steroid-sparing effect. There is also a suggestion that mepolizumab may reduce airway remodeling which could be beneficial in the long term.

Questions remain for mepolizumab. Most importantly, which patients might benefit, what proportion of asthmatics (or severe asthmatics) do they represent, and how are they to be identified? Other questions include whether there is the potential to prevent accelerated loss of lung function over time (if this is important clinically), and where mepolizumab fits with other biologics (either currently available or in trials). In addition, there are no currently published data for children with asthma. Without answers to these points it will be difficult to perform the cost-benefit analysis important to the company, providers, and ultimately, the patients.

5.1 Who would benefit from mepolizumab treatment for asthma?

In an editorial accompanying the two NEJM papers of 2009, Dr Sally Wenzel pointed out that the proportion of asthmatics fall into the selection criteria for the two studies was small. She estimated the persistently eosinophilic form of late-onset asthma accounts for 2% of severe asthmatics [36]: around 1000 individuals in the UK. Is the target population for mepolizumab really that limited? The study by Nair identified 18 oral corticosteroid-dependent asthmatics with

sputum eosinophilia over two years from their clinic population of 800 (just over 2%). However, the Leicester group comment that their criteria included 30% of their refractory asthma population. They also stated that one-third of patients showing best lung function improvement with a 2-week course of prednisolone, but least minimal current bronchodilator reversibility responded best to mepolizumab [37]. Looking at cluster analysis of refractory asthma patients, the Leicester group identified 68 out of 187 (36%) with persistent eosinophilic inflammation and frequent exacerbation, whilst Miranda *et al.* identified 19 of 80 (24%) patients with late-onset eosinophilic asthma [5,38].

A clear (and unstated) issue is correct diagnosis and adherence with treatment. Even in tertiary clinics rates of misdiagnosis and non-adherence are significant: these issues must be addressed by systematic assessment and quantifiable and robust measures of adherence before prescribing expensive biologics [39].

Another important point is how to identify eosinophilic asthma. The published studies used induced sputum: this is not available in all centers and does not necessarily reflect tissue eosinophilia. Which compartment for eosinophil measurement most accurately predicts responders to mepolizumab is unknown. Clearly if blood eosinophil counts or eosinophil cationic protein concentration could substitute for the need for sputum eosinophilia it would simplify selection and monitoring of patients. Nonetheless, there is no reason why sputum induction should not be established in regional severe asthma clinics.

Is there a long-term benefit in terms of airway remodeling? Although it is fashionable to assume that unchecked airway remodeling can lead to increased rate of decline in lung function over time and/or fixed airflow obstruction, this is not proven. Long-term data for mepolizumab will be required. In addition, the Leicester group point out that there are patients with eosinophilic airway disease who do not fit current criteria or pure asthma or COPD diagnosis [27]: whether (and how) they will benefit from mepolizumab remains to be studied.

On balance, my opinion is that a substantial proportion of patients with refractory asthma might benefit from mepolizumab: this certainly warrants further investigation.

5.2 Where would mepolizumab fit with other biologics, who would prescribe, and where will we be in 5 years?

The only currently licensed biologic for severe asthma is omalizumab which blocks interaction of IgE with its receptor [13]. There is probably little overlap between the early-onset allergic asthma patients for whom omalizumab is indicated and those with late-onset, eosinophilic disease who might respond to mepolizumab, although formal analysis is required. Other IL-5-directed therapies (reslizumab and brenalizumab) are potential direct competitors. In particular brenalizumab appears to have a long period of action and

may deplete tissue eosinophils more effectively than mepolizumab, although data for bendralizumab are limited. Up to 36% of exacerbations in the patients treated with mepolizumab in the Leicester study were eosinophilic, and bronchial mucosal eosinophils seem relatively resistant to mepolizumab. If this is due to down-regulation of IL-5R α and hence IL-5 dependence, this population will also not be accessible to bendralizumab. Further studies are required! Lebrikizumab is an anti-IL-13 monoclonal antibody which showed efficacy for lung function in “Th2 high” asthma [15]; whether this agent reduces exacerbation rates remains to be established and how the “target patients” overlap with those who might benefit from mepolizumab remains to be studied.

Clearly cost will be an important determinant of whether this Mepolizumab is approved for therapy by health care providers if it gets to the stage of being licensed. A conservative estimate based on UK direct health care costs for asthma and the data from the Haldar study would suggest savings of around £6000 per patient treated, largely from reduction in days spent in hospital, assuming £300 per day inpatient stay and £150 per outpatient exacerbation [40].

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