

Mepolizumab for severe eosinophilic asthma

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Evaluation of: Pavord ID, Korn S, Howarth P *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 380(9842), 651–659 (2012).

In this large (616 patients), double-blind, placebo-controlled, dose-ranging study of mepolizumab (a monoclonal antibody that blocks IL-5 binding to its receptor), patients were given placebo, 75-, 250- or 750-mg mepolizumab by intravenous infusion every 4 weeks for 1 year. Exacerbation rates at all doses were 50% less than those in the placebo group. There were no changes in any other asthma measures (symptoms, quality of life or lung function). This may be a useful advance for a subgroup of severe asthma with frequent exacerbations and persistent eosinophilia, which may be about half of severe asthmatics. More information on patient selection and cost–benefit will be required.

KEYWORDS: asthma • eosinophil • mepolizumab • severe asthma

Asthma affects around 6% of the UK population, and the 5% of asthmatics with severe refractory disease are said to consume 50% of health spending on asthma [101]. Refractory asthma has been defined as those with continued symptoms or exacerbations despite high-dose inhaled corticosteroids and other controller therapy (step 4 of guidelines), or those requiring additional long-term oral corticosteroids to control disease (step 5) [1]. These patients are at risk of dying from their asthma (the UK has a rate of 1000–1200 asthma deaths/year, higher than in much of Europe), and run considerable risk of morbidity from asthma and steroid-related side effects. Thus there is a clear need for improved delivery of care or new therapy.

Of note, systematic evaluation of patients with difficult-to-control asthma has identified non-adherence, incorrect diagnosis and psychological factors as important determinants of morbidity. Identifying ‘true’ refractory asthma is a vital, often neglected, aspect in trials of novel, potentially expensive therapy [2]. As many as 30% of severe asthmatics prescribed with long-term oral corticosteroids are not taking this treatment, and figures for inhaled therapy are comparable [3,4].

Recent studies have suggested that there are subtypes of asthma, defined by clustering of clinical characteristics or analysis of airway inflammation [5–7]. Of note, although asthma has been

thought of as a disease characterized by eosinophilic airway inflammation driven by Th2-type T cells [8], this may not be the case for a substantial minority of asthmatics. Cluster analysis identified around 50% of severe asthmatics with persistent airway eosinophilia despite treatment, and gene-expression studies suggested that 50% of mild-to-moderate asthmatics had Th2-driven airway inflammation [5–7]. As specific anti-inflammatory therapies have been developed for asthma that target features of airway inflammation, it has become clear that it will be important to have biomarkers to accurately identify who will benefit from each treatment and optimize cost–benefit.

Eosinophils have long been associated with asthma, particularly disease exacerbations and the cytokine IL-5 is a specific factor (produced largely from Th2 T cells) involved in the development and survival of eosinophils in the airway [8]. A study using sputum eosinophil counts to guide steroid dosing improved asthma control with reduced exacerbation rates [9]. Therefore, development of a monoclonal antibody therapy to block IL-5 and, thus, eosinophilia was an attractive concept for asthma treatment. Initially, two companies developed antibodies: mepolizumab from GlaxoSmithKline (GSK) and reslizumab from Teva Pharmaceuticals with Schering Plough. Initial human studies

of mepolizumab were disappointing with no effect on allergen-induced airway narrowing or irritability (airway hyper-responsiveness [AHR]), despite reduced blood and sputum eosinophils in mild asthma [10], and no effect on airway narrowing, asthma symptoms or AHR, despite a reduction greater than 50% in airway eosinophils in bronchoscopic studies [11]. Furthermore, a large study of moderate asthmatics with symptoms despite inhaled corticosteroids showed no benefit in terms of symptoms or lung function [12]. There was, however, a nonsignificant trend to reduction in exacerbation rates at the highest dose (750 mg) of mepolizumab [12]. In a study of reslizumab for severe asthmatics with persistent sputum eosinophilia, there was a trend for improved asthma quality of life (AQLQ) scores, a small but significant improvement in lung function (forced expiratory volume in 1 s), and a trend to reduced exacerbation rates [13]. Two proof-of-concept studies showed that targeted use of mepolizumab in asthmatics with persistent airway eosinophilia (>3% sputum eosinophils) and frequent exacerbations, despite step 4/5-level treatment, significantly reduced exacerbation rates (by ~50%) with the ability to reduce oral steroid dose in one small study [14–16]. However, there were no significant effects on any other asthma outcomes.

In August 2012, a large, double-blind, placebo-controlled, dose-ranging study was published examining the ability of different doses of mepolizumab to reduce the risk of asthma exacerbations in asthmatics aged 12–74 years with persistent airway eosinophilia and frequent exacerbations, despite step 4/5-level treatment [17]. That report is reviewed here, along with implications and broader context for biologic treatment for severe refractory asthma.

Summary of methods & results

Pavord *et al.* reported a GSK-sponsored double-blind, placebo-controlled, dose-ranging study conducted in 81 centers in 13 countries [17]. Patients were aged 12–74 years and met widely agreed diagnostic criteria for asthma. They had a history of two or more asthma exacerbations requiring oral corticosteroids in the last year. Criteria for eosinophilic airway disease were looser than in previous studies and are shown in Box 1. Patients were randomized 1:1:1:1 to intravenous infusion every 4 weeks for 1 year of placebo, 75, 250 or 750 mg of mepolizumab in 100 ml saline. The primary outcome was the rate of clinically significant asthma exacerbations (defined as worsening of asthma requiring oral corticosteroids for 3 or more days, admission or visit to the emergency department, corroborated by peak flow instability, increased use

of rescue medication, nocturnal symptoms or increased symptom scores for at least 2 of 3 successive days).

Of the 616 patients who received treatment, 520 completed treatment. All doses of mepolizumab reduced exacerbation rates significantly (ratio to placebo: 0.48–0.61), with no apparent dose responses. In addition, all doses reduced time to first exacerbation, and rate of exacerbations requiring admission or emergency department visit (although it is not clear if this reduction was statistically significant). However, mepolizumab had no effect on asthma symptoms, quality-of-life scores or lung function. Blood eosinophils fell by over 95% for all three doses of mepolizumab, and in the small subgroup ($n = 94$) who had sputum induction, there was a dose-related fall in sputum eosinophilia (ratio to placebo value 0.68, 0.35 and 0.12, respectively, for 75, 250 and 750 mg mepolizumab). The fraction of exhaled nitric oxide (FeNO) did not change significantly with any dose of mepolizumab. There were no serious treatment-related side effects. The authors concluded that “mepolizumab is a potentially important advance because it seems to be a safe and effective treatment option for the subgroup of patients with eosinophilic asthma and might allow safe withdrawal of oral corticosteroids.”

Expert commentary

This large dose-ranging trial offers encouraging efficacy in reducing asthma exacerbation rates in an eosinophilic subgroup of severe asthmatic patients. Apart from the anti-IgE monoclonal antibody (omalizumab), there has been no significant advance in therapy for this group for many years. However, there are questions to be addressed before this medication reaches clinical use.

First, the lack of dose–response for the primary outcome (exacerbation rates) seems surprising. One aim in a dose-ranging study is to determine the optimal dose. What would be the dose of mepolizumab for confirmatory Phase III studies? As in previous studies [10,12], there was a clear dose–response relationship between mepolizumab dose and reduction in sputum eosinophils (although not blood eosinophils). How do eosinophils cause exacerbations of asthma, if indeed they do? In previous studies, an effect of mepolizumab treatment was seen on airway remodeling in asthma [14,18]. These changes in epithelium, smooth muscle and extracellular matrix may contribute to AHR as well as the development of fixed airflow obstruction. Whether such changes occur at a dose of 75 mg per month is as unknown as their true clinical significance.

Second, although at first sight this trial is indeed a dream in that it uses biomarkers to target an effective therapy to a defined subgroup of severe asthmatics, criteria for patient selection need clarification and, perhaps, simplification. The obvious marker for those with eosinophilic asthma is airway eosinophils. However, sputum eosinophilia was only used in 94 out of 616 patients here. It can be used successfully in severe asthma but requires trained, experienced operators and interpreters, and is not available even in many tertiary severe asthma centers. There is a debate about whether it is the ‘gold standard’ or whether that should be bronchial biopsy: they may not measure the same thing [19,20]. Neither

Box 1. Criteria for inclusion as ‘eosinophilic asthma’ for the DREAM study.

- At entry or in the previous year:
 - Sputum eosinophilia of >3% (94 out of 616 had sputum examined)
 - FeNO of >50 ppb
 - Peripheral blood eosinophil count of $>0.3 \times 10^9/l$
 - Prompt deterioration in asthma control upon 25% or less reduction in inhaled or oral corticosteroids

FeNO: Fraction of exhaled nitric oxide.
Data taken from [17].

is a useful 'routine' biomarker, and although one could argue that mepolizumab treatment for severe asthma should be initiated only in specialized tertiary centers where setting up sputum eosinophil assessment could (and should) be done, this is not the case for smaller 'spoke' units managing fewer patients. What else might be used as a biomarker to select and monitor patients? Blood eosinophils are easily monitored and perform reasonably well. It is difficult to explain why other criteria were included here: data on FeNO correlating with eosinophilic airway inflammation are variable, and the criterion of a "prompt deterioration of asthma control after a 25% or more reduction in regular maintenance inhaled or oral corticosteroids" is not justified or validated here. The geometric mean blood eosinophil counts and FeNO were $0.23\text{--}0.28 \times 10^9/\text{l}$ and 29.2–33.7 ppb, both considerably below the inclusion cutoffs of $0.3 \times 10^9/\text{l}$ and 50 ppb, respectively. It would be of interest to know how many in each inclusion group there were and whether outcomes varied. FeNO did not change with mepolizumab treatment, which does not support a link with eosinophilia.

The issue of biomarkers was recently addressed in the BOBCAT study [21]. In a study of 67 patients with symptoms, despite level 4 asthma treatment (similar to those in the DREAM study), sputum and bronchial biopsy, eosinophilia was compared with blood eosinophils, serum total IgE, the 'Th2'-associated protein periostin (see below), the chitinase YKL40 and FeNO. Of 59 subjects with full data, 36 had sputum eosinophilia of >3% and 30 had biopsy eosinophil counts of >22/mm² (these were not concordant). The biomarkers most associated with airway eosinophilia (sputum and/or biopsy) were serum periostin and FeNO. Blood eosinophilia and serum IgE performed less well and YKL40 was not associated with eosinophils. However, despite claims in that study and elsewhere that periostin and FeNO are useful biomarkers, although these had quite good positive-predictive values of 93 and 94% at the cutoff set, their negative-predictive values were poor at 37 and 32% due to low sensitivity. Thus, we do not have an adequate validated biomarker (other than possibly sputum eosinophils) for selecting patients for mepolizumab treatment. This will need to be addressed. This is a problem for other potentially expensive therapies for severe asthma. Periostin is an epithelial cell-derived protein induced by IL-13 and has been suggested as a marker for 'Th2 asthma'. A study of anti-IL-13 monoclonal antibody (lebrikizumab) in severe asthma suggested improvement in lung function in moderately severe asthmatics, with larger increases in those with 'high' serum periostin [22]. However, use of periostin as a biomarker to guide patient selection has not been validated. Although omalizumab (anti-IgE) treatment has been licensed for severe asthma for some time and shows reductions in exacerbation rates not dissimilar to those for mepolizumab, trials were not performed in the most severe patients [23]. Use is currently in those within a set total serum IgE range, although there is no data to say whether this defines treatment responders. For bronchial thermoplasty, a treatment that showed benefit in several controlled trials, there is also no clear way to select patients [24]. This disconnect between aspiration and reality for stratified medicine for severe asthma needs to be addressed if potentially useful treatments are not to fall by the wayside.

Third, it is widely recognized and, indeed, stated in guidelines that nonadherence with treatment is common in severe asthma and must be thoroughly assessed [1]. In the DREAM study, those with a "history of poor treatment adherence" were excluded, but there is no mention of whether serum prednisolone and cortisol were measured, nor whether prescription issuing records were checked. Expensive monoclonal antibody therapy should not be a substitute for inhaled or oral corticosteroids for the nonadherent. In addition, adjusting steroid dosing according to sputum eosinophil counts reduced exacerbation rates and improved AHR when compared with 'standard management' [9]. Would mepolizumab have additional benefit to such a strategy?

Finally and partly related to the previous points, is the issue of cost. In the UK, the NICE recently put out for discussion a revised guidance on omalizumab, suggesting it is not cost effective for severe asthma [102]. Although there are too many deaths from asthma, it is a mercifully rare outcome. There was one asthma death in the DREAM study (in a patient on active medication). For health economists, it will be important to develop appropriate costing tools for asthma and other chronic diseases that fully take into account the devastating long-term impact. It will also be important for researchers to address these in their efficacy studies. We do not know the price that GSK will set for mepolizumab. However, for all such monoclonal antibodies, it may be difficult to reach a price acceptable to increasingly demanding authorities. Of note, although exacerbation rates were reduced with mepolizumab, other asthma outcomes such as symptoms measured by the Asthma Control Questionnaire, lung function (by forced expiratory volume in 1 s) and quality of life (AQLQ) did not change. It seems a little surprising that quality of life did not change if patients have fewer exacerbations: either day-to-day features such as breathlessness, poor sleep, steroid side effects and so on impact more than a few days of increased medication or the AQLQ is insensitive to exacerbations. It will be informative to ask patients with severe asthma what would constitute significant improvement for them: it may not be reduced exacerbation rates.

Five-year view

Severe asthma management is changing. Large collaborative groups such as EUBIOPRED [25], the UK BTS Registry [26] and SARP [6] in the USA should allow development of biomarkers to define subgroups of asthma and target new therapies. However, we need to be clear that 'endotypes' of asthma are real and not just final common pathways from reductionist murine models: for this, we need 'gold standard' airway sampling. We need better biostatistical analysis of data. Eosinophil-directed treatment for reducing exacerbations for severe asthma is, probably, to advance further in the next 5 years. Newer antibodies including bendralizumab (which binds the IL-5 receptor α chain and depletes cells bearing this receptor by antibody-mediated cell killing) may compete with mepolizumab [27]. The relative roles of treatments aimed at IgE, IL-5 and IL-13 should become clearer. In addition, we should begin to identify targets for 'non-Th2' asthma and virally induced asthma attacks.

Financial & competing interests disclosure

D Robinson has consulted for Genentech-Roche on anti-IL-13 for severe asthma. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial

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Key issues

- Asthma affects 4.5 million individuals in the UK, and 5% of asthmatics have severe symptoms despite current treatments and account for 50% of asthma health spending.
- Taking less than prescribed treatment is a frequent cause of poor response.
- Different subtypes of severe asthma have been defined, including up to half with uncontrolled eosinophilic airway inflammation and frequent asthma attacks.
- A monoclonal antibody against IL-5, a cytokine controlling eosinophil development and survival, reduced exacerbation rates when targeted to asthmatics with persistent sputum eosinophilia, despite treatment in proof-of-concept studies.
- In this larger, 1-year dose-ranging study, three doses – 75, 250 and 750 mg of mepolizumab or placebo – were given every 4 weeks by intravenous infusion in asthmatics with severe disease, frequent exacerbations and probable airway eosinophilia.
- All three doses significantly reduced the primary outcome measure (rate of exacerbation) by around 50%.
- Markers to select patients need better definition.
- More information is needed on the optimal dose.
- Cost-effectiveness is an issue with monoclonal antibody treatment for severe asthma.
- Anti-IL-5 receptor, anti-IL-13 and anti-IgE may be competitors.

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