Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies

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Summary

Background Findings from previous studies showed that mepolizumab significantly reduces the rate of exacerbations in patients with severe eosinophilic asthma. To assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab we did a secondary analysis of data from two studies, stratifying patients by different baseline blood eosinophil thresholds.

Methods We did a post-hoc analysis of data, which was completed on Sept 25, 2015, from two randomised, double-blind, placebo-controlled studies of at least 32 weeks duration (NCT01000506 [DREAM] and NCT01691521 [MENSA]) done between 2009 and 2014. In these studies, mepolizumab (DREAM: 75 mg, 250 mg, or 750 mg intravenously; MENSA: 75 mg intravenously or 100 mg subcutaneously) versus placebo was given at 4-week intervals in addition to standard care (high-dose inhaled corticosteroids plus ≥1 additional controller with or without daily oral corticosteroids) to patients aged 12 years or older with a clinical diagnosis of asthma, a history of at least two exacerbations in the previous year that required systemic corticosteroid treatment, and evidence of eosinophilic airway inflammation. The primary endpoint in both studies was the annual rate of clinically significant exacerbations (defined as worsening of asthma that required the use of systemic corticosteroids, or admission to hospital, or an emergency-room visit, or a combination of these occurrences). In our analysis, the primary outcome was the annualised rate of exacerbations in patients stratified by baseline eosinophil counts (≥150 cells per μL, ≥300 cells per μL, ≥400 cells per μL, and ≥500 cells per μL) and baseline blood eosinophil ranges (<150 cells per μL, ≥150 cells per μL to <300 cells per μL, ≥300 cells per μL to <500 cells per μL, and ≥500 cells per μL). We based our analysis on the intention-to-treat populations of the two original studies, and all mepolizumab doses were combined for analysis.

Findings Of 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1·91 with placebo to 1·01 with mepolizumab (47% reduction; rate ratio [RR] 0·53, 95% CI 0·44–0·62; p<0·0001). The exacerbation rate reduction with mepolizumab versus placebo increased progressively from 52%; 0·48, 0·39–0·58) in patients with a baseline blood eosinophil count of at least 150 cells per μL to 70%; 0·30, 0·23–0·40]) in patients with a baseline count of at least 500 cells per μL. At a baseline count less than 150 cells per μL, predicted efficacy of mepolizumab was reduced.

Interpretation Our analysis has shown a close relationship between baseline blood eosinophil count and clinical efficacy of mepolizumab in patients with severe eosinophilic asthma and a history of exacerbations. We noted clinically relevant reductions in exacerbation frequency in patients with a count of 150 cells per μL or more at baseline. The use of this baseline biomarker will help to select patients who are likely to achieve important asthma outcomes with mepolizumab.

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Introduction

Asthma is a heterogeneous condition, which includes several clinical phenotypes that differ in severity, natural history, and response to therapy.[1] One well defined pattern of disease in patients with severe asthma is characterised by persistent eosinophilic airway inflammation, as indicated by eosinophil counts of at least 150 cells per μL in blood, or more than 2% in sputum, or both.[2,3] Eosinophils normally make up fewer than 5% of leucocytes in the blood,[4] but their production is increased in response to inflammation.[5] Eosinophils are recruited from the bloodstream to areas of inflammation by cytokines such as interleukin-5 and members of the eotaxin family of chemokines.[5] Studies using specific inhibitors of this process have shown an association between eosinophils and the pathogenesis of asthma exacerbations.[6,7]

Prospective clinical studies of monoclonal antibodies inhibiting interleukin-5 have shown that baseline blood eosinophil count is predictive of response to treatment.[8,9] However, there are differences in the blood eosinophil thresholds used in clinical trials among the various biologicals targeting the interleukin-5 pathway.[9–11] Moreover, little is known about the relationship between blood eosinophil count and the effect of treatment on other important asthma-related outcomes, such as lung function, asthma symptoms, and quality of life.

Research in context

Evidence before this study

Eosinophils are inflammatory cells associated with airway inflammation in asthma, and represent an important biomarker for identification of patients with eosinophilic asthma. We searched PubMed on Nov 26, 2015, for English-language articles with the terms "asthma", "anti-interleukin-5", and "eosinophil" in the title or abstract. Our search yielded 26 results, which included a meta-analysis of randomised placebo-controlled trials of mepolizumab in patients with asthma. On the basis of our systematic review of the literature, mepolizumab appears to be the only interleukin-5 monoclonal antibody using a blood eosinophil threshold of at least 150 cells per µL at baseline in asthma clinical trials.

Added value of this study

To our knowledge, this is the first analysis to systematically assess the clinical effects of mepolizumab in patients with different thresholds of blood eosinophil counts at baseline. This approach used counts obtained at baseline from more than 1000 patients participating in two large-scale, randomised placebo-controlled trials of mepolizumab. Our analysis provides further evidence that blood eosinophils are a robust marker for selecting patients that would benefit from specific treatments and are also associated with the response to anti-interleukin-5 therapies such as mepolizumab.

Implications of all the available evidence

Clinical trials of other interleukin-5 inhibitors in development (ie, reslizumab and benralizumab) have used different blood eosinophil thresholds at baseline when investigating the effect of interleukin-5 inhibition on clinical outcomes, and confusion has arisen about the best cutoff point. We provide evidence from a large patient population with severe eosinophilic asthma that supports the value of blood eosinophil counts as a biomarker to guide therapy, and to provide guidance on the probable effect of that therapy in patients with severe asthma.

Findings from two large studies (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma [DREAM; NCT01000506][8] and MEpolizumab as adjuNctive therapy in patients with Severe Asthma [MENSA; NCT01691521][9]) have shown reductions in asthma exacerbation rates after treatment with mepolizumab compared with placebo in patients with severe eosinophilic asthma. Modelling analysis in the DREAM study identified blood eosinophils as a predictor of treatment response to mepolizumab;[8] patients were then selected in the subsequent MENSA study on the basis of this criterion.[9]

This report describes the results of our secondary post-hoc analysis of data from these two randomised studies, which aims to provide a more robust and clinically informative analysis of the relationship between baseline blood eosinophil counts and efficacy outcomes after treatment with mepolizumab.

Methods

Included studies and patients

Criteria used for the inclusion of studies in this analysis were: placebo-controlled studies of mepolizumab in patients with severe eosinophilic asthma; duration of the study at least 32 weeks; maintenance corticosteroid use kept constant; and analysis of blood samples at a central laboratory. On the basis of these criteria, we included data from DREAM[8] and MENSA done between 2009 and 2014.[9] The protocol for the analysis is available from the GSK Clinical Study Register (number 204664).[12]

Enrolment criteria for the studies have been previously published.[8,9] Briefly, patients were aged at least 12 years; required to have had a clinical diagnosis of asthma; had a history of at least two exacerbations requiring systemic corticosteroid treatment in the previous year, and met the American Thoracic Society criteria for refractory asthma.[13] For DREAM, patients had evidence of eosinophilic inflammation at study entry or within the previous year, as shown by one or more of the following criteria: (1) a sputum eosinophil count of at least 3%, (2) fractional exhaled nitric oxide (FE_{NO}) of at least 50 parts per billion, (3) an asthma-related peripheral blood eosinophil count of at least 300 cells per µL, or (4) a prompt deterioration in asthma control after at least 25% reduction in regular maintenance inhaled corticosteroids or oral corticosteroids. In MENSA, eosinophilic inflammation was defined as a blood eosinophil count of at least 150 cells per µL at screening or at least 300 cells per µL at some time during the previous year. Study-related blood eosinophil counts were done by a central laboratory from samples obtained in the morning. The original protocols were approved by local or study research ethics committees, and done in accordance with good clinical practice guidelines and the Declaration of Helsinki.

Treatments

Patients in DREAM were randomly assigned to one of three different doses (75 mg, 250 mg, or 750 mg) of intravenous mepolizumab or matched placebo at 4-week intervals for 52 weeks.[8] Patients in MENSA were randomly assigned to mepolizumab, administered as either a 75 mg intravenous dose or a 100 mg subcutaneous dose, or matched placebo for 32 weeks in a double-dummy design.[9]

Outcomes

The primary outcome for both studies was the annualised rate of clinically significant exacerbations, expressed as mean exacerbations per person per year. An exacerbation was defined as worsening of asthma that required the