Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma

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Background: Studies show that mepolizumab can reduce the frequency of clinically significant exacerbations in patients with severe eosinophilic asthma, compared with placebo. However, important events such as hospitalizations and emergency room visits are rare and difficult to characterize in single studies.
Objective: We sought to compare hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for at least 24 weeks.
Methods: This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement. PubMed and the GSK Clinical Study Register were searched for suitable studies. The primary end points were the rate of exacerbations requiring hospitalization and the rate of exacerbations requiring hospitalization/emergency room visit. The proportion of patients with 1 or more event was also assessed. All mepolizumab doses were combined and individual patient-level data were analyzed.
Results: Four studies (n = 1388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30-0.80; $P = .004$) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33-0.73; $P < .001$) versus placebo. Significant reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively.
Conclusions: Mepolizumab approximately halved exacerbations requiring hospitalization and/or emergency room visits compared with placebo in patients with severe eosinophilic asthma. This treatment addresses a key outcome in a patient population with a high unmet need (GSK Study 204664). (J Allergy Clin Immunol 2017;139:1167-75.)

Key words: *Antiasthmatic agents, exacerbation, emergency service, hospital, IL-5, mepolizumab, severe eosinophilic asthma, meta-analysis*

Severe asthma is a heterogeneous disease comprising several diverse phenotypic subgroups.[1,2] One subgroup is characterized by increased blood and sputum eosinophil counts.[3,4] Typically, these patients have frequent exacerbations and suboptimal asthma control despite intensive use of guideline-directed asthma therapies, including the use of maintenance systemic corticosteroids in many patients.[1] Asthma exacerbations are often of sufficient severity to require hospitalization or a visit to the emergency room,[5,6] accounting for a large proportion of asthma-related morbidity, mortality, and health care costs.[7-11] The prevention of severe asthma exacerbations is therefore a major goal of asthma management.[8]

Mepolizumab is a humanized mAb against IL-5, which primarily inhibits eosinophilic inflammation,[12,13] and has been shown to decrease sputum and blood eosinophil levels in patients with severe eosinophilic asthma.[3,14,15] To date, all the randomized, placebo-controlled studies of mepolizumab in this patient population have reported a reduction compared with placebo in the frequency of *clinically significant exacerbations*, defined as worsening of asthma that required use of/increased use of systemic corticosteroids.[3,15-18] Although this definition includes exacerbations that require hospitalization and/or a visit to the emergency room, the sample sizes of individual studies were insufficient for assessing these relatively infrequent events. The aim of this meta-analysis was therefore to assess the rate of exacerbations requiring hospitalization or an emergency room visit in clinical studies of mepolizumab compared with placebo in patients with severe eosinophilic asthma.

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The meta-analysis (study ID 204664) and studies in this meta-analysis (MEA112997 [NCT01000506], MEA115588 [NCT01691521], MEA115575 [NCT01691508], and CRT110184 [ISRCTN75169762]) were funded by GSK (study no. 204644). Medical writing support by Fishawack Indicia Ltd was also funded by GSK.

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Abbreviations used
IV: Intravenous
OCS: Oral corticosteroid
SC: Subcutaneous

METHODS

This meta-analysis was conducted according to Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement,[19] including search strategy, selection criteria, data extraction, and data analysis based on a defined review protocol (GSK etrack no. 204664[20]).

Identification of eligible studies

Studies eligible for inclusion were any randomized study comparing mepolizumab with placebo in patients with severe eosinophilic asthma of at least 24 weeks duration that involved at least 6 doses of the study drug. Studies were identified using a search strategy on PubMed of ("clinical trial"[Publication Type]) AND (mepolizumab[Title]) AND (asthma[Title]) and a search of completed studies on the GSK clinical trial register of "mepolizumab" and "asthma." Clinicaltrials.gov was also searched to find any completed, unpublished studies that met the inclusion criteria. These searches were carried out in May 2015.

Data extraction and outcome measures

Individual patient-level data were obtained from the GSK clinical trial databases and from the relevant investigating centers. Data used in these studies included study design, patient population, follow-up period for exacerbations, study drug and dose, number of hospitalizations, and number of emergency room visits. The intent-to-treat population was analyzed, and comprised all randomized patients who received 1 or more dose of study medication. Asthma exacerbations reported from the start of treatment until completion of the study or up to withdrawal (but less than 4 weeks after the last dose of study medication) were included in the analysis. Asthma exacerbations separated by less than 7 days were considered a continuation of the same exacerbation.[21] Hospitalization included intensive care unit admission and intubation.

The primary end points of this meta-analysis were (1) annual rate of exacerbations requiring hospitalization and (2) annual rate of exacerbations requiring a hospitalization and/or an emergency room visit. The proportion of patients with 1 or more exacerbation requiring hospitalization, the proportion of patients with 1 or more exacerbation requiring hospitalization/emergency room visit, and time to first exacerbation requiring hospitalization and hospitalization and/or emergency room visit were also assessed. Because previous studies have shown similar reductions in exacerbations based on a 10-fold dose range of mepolizumab or by a route of administration (intravenous [IV] vs subcutaneous [SC]),[3,17] all mepolizumab doses were combined for analysis and compared with placebo. In addition, a prespecified sensitivity analysis was carried out using only comparable doses of mepolizumab (75 mg IV and 100 mg SC).

Statistical analysis

The meta-analysis was conducted using SAS version 9.3 (SAS Institute, Cary, NC). The number of exacerbations requiring hospitalization/emergency room visit and the number of exacerbations requiring hospitalization were assumed to follow a negative binomial distribution.[22] Meta-analysis of relative rates of exacerbations was performed using the inverse variance fixed effects method to combine estimated rate ratios and standard errors from each individual study. Meta-analysis of relative risks for the proportion of patients with at least 1 exacerbation was performed using Mantel-Haenszel methods. Kaplan-Meier curves of time to first exacerbation were constructed using a weighted average of the curves for the individual studies, with Mantel-Haenszel weights for each study.[23] All outcomes were reported with 95% CIs. Statistical heterogeneity was tested with the I^2 statistic, with $I^2 \leq 50\%$ indicating no significant heterogeneity.[24]

RESULTS

Description of studies

A summary of the mepolizumab studies identified through the search strategy is provided in Fig 1 and in Table E1 in this article's Online Repository at www.jacionline.org. A total of 12 potentially eligible articles were identified after removal of duplicates.[3,15-18,25-31] Four studies were identified as meeting the inclusion criteria: DREAM (NCT01000506),[3] MENSA (NCT01691521),[17] SIRIUS (NCT01691508),[16] and the 2009 study by Haldar et al[15] (ISRCTN75169762). The study by Nair et al[18] was excluded because the treatment period was less than 24 weeks and included 5 administrations of the study drug rather than the 6 required to meet the prespecified inclusion criteria. Furthermore, there were no exacerbations requiring hospitalization or an emergency room visit reported in this study, and, therefore, inclusion of this study would not affect the results. SIRIUS could not be included in the analysis of rates of exacerbation requiring hospitalization because there were no exacerbations requiring hospitalization in the mepolizumab arm of the study, therefore no variability could be associated with the rate reduction for this study. Similarly, Haldar et al's 2009 study could not be included in the analysis of hospitalization/emergency room visit rates because data were not available for emergency room visits. The sensitivity analysis excluded the SIRIUS study because it was primarily an oral-sparing study and excluded Haldar et al's 2009 study because the study included only the 750 mg IV dose.

Most of the inclusion criteria for DREAM, MENSA, SIRIUS, and Haldar et al's 2009 study were similar (Table E1), with the following differences of note: Haldar et al[15] included only adults (18 years or older), whereas DREAM, MENSA, and SIRIUS included patients 12 years or older; DREAM, MENSA, and Haldar et al[15] included only those patients who had 2 or more exacerbations requiring corticosteroid treatment in the previous year, whereas SIRIUS required the use of maintenance oral corticosteroids (OCSs); definition of eosinophilic asthma in DREAM was not confined to peripheral blood eosinophil levels; Haldar et al[15] used sputum eosinophils to define eosinophilic asthma. Patients in all 4 studies met the American Thoracic Society definition of severe asthma,[4] requiring treatment with high-dose inhaled corticosteroids plus a second controller therapy to prevent it from becoming uncontrolled or which remains uncontrolled despite this therapy.

Across all studies, 1388 patients received either mepolizumab intravenously (75 mg, 250 mg, or 750 mg), mepolizumab subcutaneously (100 mg), or placebo approximately every 4 weeks in addition to their baseline standard of care (which included high-dose inhaled corticosteroids and additional asthma control medications). Baseline demographic characteristics of the patients in these studies are described in Table I. The mean age of the patients in each study was approximately 50 years, with a mean asthma duration of 17 to 24 years. Baseline blood eosinophil counts were similar across all studies (with geometric means ranging from 230 to 350 cells/μL), and the mean number of severe exacerbations in the previous year ranged between 2.9 and 5.5. Overall, 36% of patients were on maintenance OCS at the start of the studies. Lung function,