Original Article

Evaluation of Potential Continuation Rules for Mepolizumab Treatment of Severe Eosinophilic Asthma

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What is already known about this topic? The early identification of patients likely to receive long-term benefit from treatment is important to minimize unnecessary treatment, but this identification must avoid selecting less severe patients and discontinuing patients benefiting from treatment.

What does this article add to our knowledge? This analysis provides a method for assessing continuation rules that measure the impact of the rules while controlling for placebo responses. There was no evidence of a reliable rule predicting long-term exacerbation reduction from mepolizumab.

How does this study impact current management guidelines? This analysis shows no evidence that any continuation rule adds value to established initiation criteria for mepolizumab treatment, which include a history of exacerbations and appropriate blood eosinophil count in patients with severe eosinophilic asthma.

BACKGROUND: Mepolizumab significantly reduces exacerbations in patients with severe eosinophilic asthma. The early identification of patients likely to receive long-term benefit from treatment could ensure effective resource allocation.
OBJECTIVE: To assess potential continuation rules for mepolizumab in addition to initiation criteria defined as 2 or more exacerbations in the previous year and blood eosinophil counts of 150 cells/μL or more at initiation or 300 cells/μL or more in the previous year.
METHODS: This *post hoc* analysis included data from 2 randomized, double-blind, placebo-controlled studies (NCT01000506 and NCT01691521) of mepolizumab in patients with severe eosinophilic asthma (N = 1,192). Rules based on blood eosinophils, physician-rated response to treatment, FEV_1, Asthma Control Questionnaire (ACQ-5) score, and exacerbation reduction were assessed at week 16. To assess these rules, 2 key metrics accounting for the effects observed in the placebo arm were developed.
RESULTS: Patients not meeting continuation rules based on physician-rated response, FEV_1, and the ACQ-5 score still derived long-term benefit from mepolizumab. Nearly all patients failing to reduce blood eosinophils had counts of 150 cells/μL or less at baseline. For exacerbations, assessment after 16 weeks was potentially premature for predicting future exacerbations.
CONCLUSION: There was no evidence of a reliable physician-rated response, ACQ-5 score, or lung function–based continuation rule. The added value of changes in blood eosinophils at week 16 over baseline was marginal. Initiation criteria for mepolizumab treatment provide the best method for assessing patient benefit from mepolizumab treatment, and treatment continuation should be reviewed on the basis of a predefined reduction in long-term exacerbation frequency and/or oral corticosteroid dose. **(J Allergy Clin Immunol Pract 2017;■:■-■)**

Key words: *Severe asthma; Anti–IL-5; mAb; Continuation; Response*

Mepolizumab is a first-in-class anti–IL-5 mAb used as add-on therapy for the treatment of severe eosinophilic asthma. Previous studies have shown significantly reduced exacerbation rates for

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This analysis and the primary studies (NCT01000506/NCT01691521) were funded by GlaxoSmithKline (GSK). Editorial support by Fishawack Indicia Ltd was funded by (GSK).
Conflicts of interest: N. B. Gunsoy, S. M. Cockle, S. W. Yancey, O. N. Keene, E. S. Bradford, and F. C. Albers are employed by and have stock/stock options in GlaxoSmithKline (GSK). I. D. Pavord has honoraria for speaking at sponsored meetings from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim and GSK; and advisory board honoraria from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Genentech, GSK, Novartis, Regeneron, Roche and Teva.
Received for publication January 6, 2017; revised November 8, 2017; accepted for publication November 15, 2017.
Available online ■■
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2213-2198

https://doi.org/10.1016/j.jaip.2017.11.026

Abbreviations used
ACQ-5- 5-item Asthma Control Questionnaire
IV- Intravenous
PARR- Placebo-adjusted rate ratio
RR- Rate ratio
RRNC- Rate ratio for noncontinuers
SC- Subcutaneous

mepolizumab compared with optimized standard of care plus placebo.[1,2]

For mAb treatments, there is a desire to identify markers that could be used as a continuation rule after treatment initiation to identify patients likely to receive benefit from ongoing treatment. This is important to ensure the benefit-risk balance in treated patients and effective allocation of limited health care resources.

The mepolizumab clinical development program endeavored to develop and validate markers that would effectively identify patients likely to respond to treatment before treatment initiation. Although several baseline characteristics were found to predict treatment benefit in Dose Ranging Efficacy And Safety with Mepolizumab in Severe Asthma (DREAM),[1] meeting specific blood eosinophil thresholds before treatment initiation was identified as the most predictive biomarker of response to mepolizumab in patients with severe eosinophilic asthma and 2 or more exacerbations in the previous 12 months despite high-dose inhaled corticosteroids and additional controller(s). Criteria of 150 cells/μL or more at initiation or 300 cells/μL or more in the previous 12 months were shown to select patients most likely to receive benefit from mepolizumab therapy. These predictive thresholds were confirmed in the subsequent Efficacy and Safety Study of Mepolizumab Adjunctive Therapy in Subjects with Severe Uncontrolled Refractory Asthma (MENSA) study.[2]

An alternative or potential adjunct to this approach is to use a posttreatment continuation rule to identify patients unlikely to receive therapeutic benefit with continued treatment. A continuation rule should ensure that patients who continue treatment are receiving benefit from the introduction of the rule beyond that observed among patients on placebo, and that patients who should stop treatment are not receiving treatment benefit compared with patients on placebo who do not meet the rule. Because the primary aim of mepolizumab treatment is to reduce the frequency of exacerbations, an evaluation of long-term treatment response should be based on exacerbations. This *post hoc* analysis assessed to what extent clinical markers and biomarkers measured 16 weeks after treatment initiation meet the criteria for an appropriate continuation rule.

METHODS

Included studies

Studies included in this analysis were DREAM (GSK/ClinicalTrials.gov identifier: MEA112997/NCT01000506)[1] and MENSA (GSK/ClinicalTrials.gov identifier: MEA115588/NCT01691521).[2] Inclusion criteria for DREAM and MENSA are summarized in this article's Online Repository at www.jaci-inpractice.org.[1,2] The rate of clinically significant exacerbations was the primary end point for both studies.

Patients

Patients from the intent-to-treat populations of DREAM and MENSA were included in this *post hoc* analysis if they had a blood eosinophil count of 150 cells/μL or more at screening or 300 cells/μL or more in the past year; had continued on treatment after the week 16 visit; and had sufficient data for evaluation of a continuation rule. Patients assigned to the 100-mg subcutaneous (SC) or the 75-mg intravenous (IV) doses from either study were included in the analysis because the 2 doses give comparable pharmacokinetic exposure. Mepolizumab 75-mg IV and 100-mg SC doses were combined for analysis in MENSA.

Outcomes assessed to define continuation rules

Patients were classified according to whether they met a potential continuation rule based on values recorded at week 16, which are as follows:

1. *Blood eosinophils:* Change from baseline blood eosinophils, expressed as the ratio at week 16 and baseline, was selected because of the mechanism of action of mepolizumab. Absolute change was not considered because of dependencies with baseline count. Thresholds considered were a reduction of 20% or more, 40% or more, 60% or more, and 80% or more.
2. *Physician-rated response to treatment:* Physicians were asked to assess patients' response to treatment at week 16. The measure comprised 7 levels (significantly improved, moderately improved, mildly improved, no change, mildly worse, moderately worse, and significantly worse) and is closest to the Global Evaluation of Treatment Effectiveness, used in omalizumab studies.[3,4] The thresholds considered were moderately to significantly improved as well as any improvement (ie, mildly to significantly improved).
3. *Asthma control:* The Asthma Control Questionnaire (ACQ-5) was administered at baseline and each following visit. The minimum important difference for this questionnaire is 0.5.[5] An improvement of 0.5 or more points from baseline was therefore considered.
4. *Lung function:* Pulmonary function was evaluated at baseline and each following visit. A widely accepted threshold indicative of a meaningful improvement was not available. Therefore, thresholds considered were an improvement of 80 mL or more and 10% or more from baseline in prebronchodilator FEV_1.
5. *Exacerbations:* No change or a reduction in annualized frequency of exacerbations from baseline to week 16 compared with the previous year was considered.

Continuation rule assessment

The rate of clinically significant exacerbations after assessment (week 16) to end of study (week 32 for MENSA, week 52 for DREAM) was used as the long-term outcome to assess continuation rules.

Two measures were used to assess the performance of a potential continuation rule: the placebo-adjusted rate ratio (PARR) and the rate ratio for noncontinuers (RRNC) (Figure 1). A practical example comparing these measures to previously used measures is presented in this article's Online Repository at www.jaci-inpractice.org.

The PARR is the ratio of the effect of the continuation rule with mepolizumab compared with placebo. It provides a metric for the performance of the continuation rule among patients on mepolizumab that is adjusted for the impact of the continuation rule among patients on placebo; a value less than 1 indicates specific treatment-associated benefit (Figure 1). This placebo adjustment avoids selection of a rule that discontinues patients more likely to exacerbate regardless of treatment. A PARR of 0.8 or less was considered indicative of a potentially useful continuation rule, where patients meeting the rule show a reduction of 20% or more in