

“Knowing When to Hold’em and When to Fold’em” with Biological Treatments of Asthma



William W. Busse, MD *Madison, Wis*

In the song *The Gambler*, by Don Schlitz, Kenny Rogers advises, “You’ve got to know when to hold’em, know when to fold’em.” Although the practice of medicine is not akin to “The Gambler,” there is an expanding need to have predictive probabilities of treatments to form a foundation of evidence-based medicine and rules of continuation. In the treatment of severe asthma with an expanding availability and administration of biologics, the need for early “rules of continuation” will be essential to most accurately determine whether a newly selected treatment is effective, that is, hold’em, or ineffective, that is, fold’em. Current Food and Drug Administration–approved biologics for severe asthma have demonstrated efficacy in preventing adverse disease outcomes, exacerbations, in appropriately and carefully selected populations of patients. From clinical trial data, physicians generally know who are the most appropriate candidates to receive biologics for treatment of refractory asthma. However, the next step in this treatment process, an early determination of “responders” and “nonresponders,” is far from clear at present.

To a large extent, this lack of early guidance to treatment responsiveness is based on the primary indication for the use of biologics in severe asthma—a prevention of exacerbations. Targeting the prevention of exacerbations in severe asthma is clinically and economically sound, because these events are the greatest contributors to morbidity and health care costs. However, it will often require at least a year of treatment to determine whether the prescribed biologic has had an effect on asthma exacerbations. This is a long time to wait to determine whether an intervention is effective, particularly given the inherent costs of biologics and possible associated risks. Furthermore, the occurrence of an exacerbation during treatment does not mean that the intervention is not effective, because many of the patients appropriately selected for a biologic have previously experienced multiple such events on an annual basis. On the

basis of these clinical circumstances and unmet management needs, both prescribing physicians and recipient patients would benefit from reliable and early indications that a specific biological intervention will lead to long-term benefit. Validated continuation rules will meet these needs.

The article by Gunsoy et al¹ in this issue of *Journal of Allergy and Clinical Immunology: In Practice*, “Evaluation of potential continuation rules for mepolizumab treatment of severe eosinophilic asthma,” is an important and early attempt to address this issue, but also points to perplexities and possible shortcomings with the use of existing conventional assessment tools to achieve this goal. To fully appreciate the significance of their efforts to identify early continuation rules for the use of the anti-IL-5 mAb, mepolizumab, in the treatment of severe eosinophilic asthma, it is important to first frame the relevance of their investigation.

The persistence of significant eosinophilia, in the peripheral blood, sputum, or both, in the presence of ongoing treatment with high-dose inhaled corticosteroids or systemic corticosteroids is a biomarker for the risk of asthma exacerbations.^{2,3} Furthermore, during asthma exacerbations, there is often an increase in airway eosinophils. An enhanced generation of IL-5 is associated with exacerbations and likely contributes to enhanced eosinophilic inflammation and subsequent loss of asthma control.⁴ Consequently, targeting IL-5, or its receptor, with currently available biological treatments, mepolizumab, reslizumab, and benralizumab, is a sound scientific premise and has proven to be clinically effective in appropriately identified populations with sustained elevations of peripheral blood eosinophils.^{5–8} Anti-IL-5–directed treatments prevent asthma exacerbations by approximately 50%, and also reduce symptoms, improve lung functions, and eliminate the need for systemic corticosteroids. Despite these highly significant benefits over conventional asthma therapy, the current experiences also mean that 50% of treated patients may not respond to an inhibition of IL-5 and its effects. As we continue to move toward precision treatment of asthma, a major component of success in this effort will be an early detection of who is a “responder.”

To evaluate the possibility that “continuation rules” can be developed for mepolizumab, Gunsoy et al¹ used 2 major mepolizumab clinical trials, DREAM (Dose Ranging Efficacy And safety with Mepolizumab in severe asthma)⁵ and MENSA (MEpolizumab as adjuNctive therapy in patients with Severe Asthma),⁷ to test this approach. In both studies, a primary outcome was prevention of an asthma exacerbation, defined as the need for systemic corticosteroids to gain disease control. In DREAM,⁵ subjects received 1 of 3 intravenous doses of mepolizumab—75 mg, 250 mg, or 750 mg every 4 weeks for a year or placebo. In MENSA,⁶ treatment included mepolizumab, either 75 mg intravenously or 100 mg subcutaneously every week, or placebo for 32 weeks. Given a demonstrated equivalency of the

Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wis

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Corresponding author: William W. Busse, MD, University of Wisconsin Hospitals and Clinics, 600 Highland Ave, Madison, WI 53792. E-mail: wwb@medicine.wisc.edu.

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75 mg intravenous (IV) dose and 100 mg subcutaneous dose in MENSA,⁶ only those subjects receiving the 75 mg IV dose in DREAM⁵ were part of the current evaluation by Gunsoy et al.¹ Both the 75 mg IV dose and 100 mg subcutaneous dose treatments led to an approximate 50% reduction in exacerbations over placebo.

With the data from MENSA and DREAM, Gunsoy et al¹ selected 5 assessments, which were made at 16 weeks of treatment, to develop continuation rules: (1) changes in blood eosinophils (with different cutoff points of reduction: $\geq 20\%$, $\geq 40\%$, $\geq 60\%$, and $\geq 80\%$), (2) a global physician response evaluation, (3) improved asthma control (a ≥ 0.5 point improvement on the Asthma Control Questionnaire [ACQ]), (4) improvements in lung function (≥ 80 mL and $\geq 10\%$ from baseline prebronchodilator values), and (5) reductions in exacerbations. To assess the predictive effectiveness of the continuation rules that had been determined at 16 weeks of treatment, these assessments were evaluated in relation to rates of clinically significant exacerbations made at the end of each study: 32 weeks in MENSA and 52 weeks in DREAM.

Importantly, from my perspective, the authors used 2 determinants to evaluate their continuation rules: the placebo-adjusted rate ratio (PARR) and the rate ratio for the noncontinued group (RRNC). As noted, these assessments were made at 16 weeks of treatment and their predictive values evaluated in relationship to effects on exacerbations at the completion of MENSA and DREAM. PARR is the ratio of the effect of the continuation rule with mepolizumab compared with placebo and serves as a predictive metric to support the benefit of continuing mepolizumab. A PARR value of 0.8 or less was used as a predictive continuation rule to reflect 20% or more reduction in exacerbation and represents a treatment-associated benefit. RRNC was the ratio of exacerbation rates among patients *not* meeting the continuation rules on mepolizumab and placebo. An RRNC close to 1 (investigators used ≥ 0.8) was felt to indicate situations where patients on mepolizumab not meeting the continuation rule would have the same outcomes to patients on placebo not meeting the rule, and therefore support the prediction of not benefiting from continuing treatment. Thus, there is an assessment of the continuation rules for those meeting the rule and continuing, as well as those *not* meeting the rule and of having stopped treatment.

Table III of their article provides an overall summary of the predictive value of their continuation rules taking into account both the PARR and RRNC. Overall, the continuation rules did not provide a predictive assessment of the response to mepolizumab at 16 weeks of treatment. A strength of the article was the use of the 2 studies—DREAM and MENSA—each serving as a validation of the accuracy of the predictability of the continuation rules in relation to numerous potential assessment outcomes considered. As also noted in Table III, there was a consistent and universal lack of benefit of their continuation rules when physician-rated response to treatment, ACQ-5 score, and prebronchodilator FEV₁ were tested. In MENSA, however, decreases in blood eosinophils, at all levels of reduction, were found as useful continuation rules—but not in DREAM. In contrast, when changes in exacerbations were noted at 16 weeks, the continuation rules were predictive in DREAM, but not in MENSA. A review of the patient characteristics and outcomes of the 2 studies did not establish a readily apparent basis for discrepancies in predictive effectiveness of the continuation rules.

The investigators' approach and analyses were comprehensive, but, in the end, not informative, likely indicating both the complexity of identifying informative assessments to establish continuation rules and possible limits with currently available or used parameters.

Where do the findings of Gunsoy et al¹ leave clinicians who have started biologic treatment in an appropriate at-risk patient, that is, not controlled with high-dose inhaled corticosteroids plus another controller and with continued exacerbations and a persistently elevated eosinophil count? As the authors point out, experience with continuation rules with other biologics has been associated with limited degrees of success. Bousquet et al⁹ tried to determine whether pretreatment patient baseline information would be predictive of a response to omalizumab in subjects with severe asthma. A wide variety of parameters were evaluated but what emerged as being predictive of responsiveness at 16 weeks of treatment was Global Evaluation of Treatment Effectiveness (GETE), a general overall clinical assessment that included a physician's global assessment of asthma control. GETE was based on a composite assessment of patient interviews, review of recent medical history, spirometry, symptoms, rescue medication, and peak expiratory flow. The composite assessment was graded over 5 levels from marked improvement to no improvement. Predictive responses were found in those treated patients who had been assessed to have marked improvement or complete control. The use of GETE, despite its broad assessment, had a predictive value at 16 weeks of omalizumab treatment, but does not have quantitative specificity. In preliminary communications, associations between early improvements in lung function have been noted with reslizumab to predict the likelihood of preventing future exacerbations.¹⁰ An appeal of improved lung function as a predictor for exacerbation prevention is its quantitative end point. Thus, continuation rules remain a hope more than a guidance at present.

As the use of anti-IL-5-directed treatment in asthma increases, so will the need and benefit for informative and validated continuation rules. What other relevant assessments might be considered in the development of informative and predictive continuation rules?

A recent publication by Mukherjee et al¹¹ from McMasters has, in a very limited patient set, presented evidence that evaluations of the benefit of anti-IL-5 treatments may be informative if assessments of the biologics' effects on target organ responses, such as airway eosinophils, are used. Their article presents the results of an evaluation of 10 prednisone-dependent patients with asthma who had been first treated with a fixed 100 mg dose of mepolizumab for a year. Following a year of treatment, the 10 subjects underwent a 12-month washout followed by weight-adjusted treatment with IV dosages of reslizumab for an additional year. Both mepolizumab and reslizumab led to improvements in FEV₁, but reslizumab treatment also significantly improved ACQ-5 measures of asthma control. The improvement in both the FEV₁ and ACQ-5 score was considered, by the authors, to represent a "responder" even though effects on exacerbations were not included in their evaluation. Both mepolizumab and reslizumab, as expected, reduced peripheral blood eosinophils, the primary outcome, and there was no differential effect with the 2 biologics. The investigators also obtained sputum to evaluate effects of the individual treatments on airway eosinophil numbers and their biology, including determinations of the eosinophil granule protein, eosinophil

peroxidase, which may reflect not only the presence of airway eosinophils but also a state of activation. Sputum eosinophil peroxidase did not change with mepolizumab but was reduced with reslizumab. The number of subjects studied was small and these data cannot be considered conclusive, but raise the possibility that a more precise assessment of eosinophil involvement, or contribution, in airway inflammation should include not only this cell's presence but also its inflammatory biology, which may presumably be more related to airway dysfunction. Sputum measures were not made early in the course of treatment and cannot, at present, be an assessment for inclusion in continuation rules. Future research will, however, guide us in this effort.

As we march toward an application of precision medicine to more effectively control severe asthma with potentially effective biologics, it is apparent from the work of Gunsoy et al¹ that assessment tools, possibly outside of the currently available biomarkers, will be needed to formulate reliable continuation rules. Although Gunsoy et al¹ carefully applied both PARR and RRNC continuation rules to determine a predictive index, it is also apparent that more specific assessments are needed and might include measures of airway markers that are relevant to actions of a biologic on asthma. Like in poker, we would like to know when to "hold and when to fold" by an early assessment with biologic treatments, but achieving a highly desired and effective predictive end point will need, in my opinion, to be extended beyond our currently considered assessment end points.

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