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New Biologics for Severe Asthma: What Patients, What Agents, What Results, at What Cost?

“New Biologics for Severe Asthma: What Patients, What Agents, What Results, at What Cost?” was the title of a well-attended symposium initiated by the editor of the *New England Journal of Medicine* at the recent meeting of the European Respiratory Society in Paris. Physicians treating patients with asthma need guidance on how to best manage severe disease and what drugs are the most appropriate in chronic care. Although this generally applies to all therapeutic measures, the further development of biologics requires a proper, patient-centered approach that is economically responsible. This discussion is not new, and since the introduction of antibodies targeting IgE, investigators have searched for a clinically applicable rule to identify patients who would benefit from this treatment, and for indicators to estimate how long such a costly treatment should last. One approach that has been used, the Global Evaluation of Effectiveness scale (1), largely relies on subjective impressions of treatment success by the physician and the patient.

Major efforts to further unravel the mechanisms of severe asthma have been undertaken and have delivered a wide range of new drug targets, such as IL-5, the transcription factor GATA-3, IL-4, IL-13, TSLP (thymic stromal lymphopoietin), and the prostaglandin DP2 (CRTH2) receptor (2). Among these, the cytokine IL-5 and its receptor are the most advanced and have yielded a number of drugs that are now available for clinical use. They are finding their way into clinical practice and owing to their efficacy will be used globally and not only in specialized centers.

A recent expert consensus statement aims to provide guidance regarding the use of these new classes of drugs, and suggests that in patients with severe eosinophilic asthma, biologics should be tried for at least 4 months before a decision is made to continue treatment for a year (3). The remaining principal problem in assessing the efficacy of the available antibodies, however, lies in the lack of validated assessment tools and reliable biomarkers of treatment success. The level of IgE in patients is not related to disease severity, and a change under therapy is not indicative of treatment outcome.

For the new anti-IL-5 monoclonals, serum eosinophils are predictors of success above a threshold, but there are still nonresponders despite high eosinophil levels, and a change in eosinophilia does not allow for any judgment regarding the length of treatment.

In a study presented in this issue of the *Journal*, Bateman and colleagues (pp. 489–495) examined data from two clinical trials for the anti-IL-5 monoclonal antibody reslizumab (4), which was used as an add-on maintenance treatment for patients with uncontrolled asthma and eosinophilia (5). The two trials recruited patients ≥ 18 years of age who met Global Initiative for Asthma 4 or 5 criteria and received intravenous reslizumab. The authors developed an algorithm based on clinical indicators to predict response at 52 weeks.

A mathematical model was constructed based on the change from baseline to 16 weeks in the Asthma Control Questionnaire (ACQ) and Asthma Quality of Life Questionnaire, lung function, and number of asthma exacerbations during the year before enrollment and the first 16 weeks of treatment. The 16-week data were used to evaluate the algorithm’s ability to predict outcomes at 52 weeks. The algorithm predicted that 276 patients would be classified as responders, and in 248 (89.9%) the prediction was correct. However, for the 26 patients predicted to be nonresponders, this was only correct in 50.0% of the cases, and 19 patients remained indeterminate. The authors describe a 95.4–95.5% sensitivity and 40.6–54.1% specificity, adding a rather sophisticated jackknife resampling and cross-study validation confirming the robustness of the algorithm; however, this approach may not be obvious to the nonaficionado of biostatistics and requires profound in-depth knowledge. The authors conclude that the algorithm allows prediction at 16 weeks of treatment of the response to reslizumab at 52 weeks, but is actually not suitable for predicting nonresponders.

This study clearly addresses a relevant issue, and the authors are to be commended for their approach to guide clinical decision-making regarding these novel and expensive compounds. The study follows earlier attempts to predict clinical outcomes in asthma and other chronic pulmonary diseases under treatments, and Bateman and colleagues previously identified clinical factors associated with an increased risk for severe asthma exacerbations based on another

large dataset from three clinical studies (6). They identified five dominant predictors, namely, the Global Initiative for Asthma treatment step, mean daily number of reliever inhalations, FEV₁, ACQ-5 score, and body mass index, and used them to develop a risk score for exacerbations. Similar methods for predicting outcomes are used in rheumatoid arthritis, and disease activity scores have been tested to predict radiographic progression (7).

In interpreting the new data presented by Bateman and colleagues, we need to consider that the criteria of most suggested algorithms use data from clinical trials with defined inclusion and exclusion criteria and a careful study design. The authors frankly confirm that in their study, the criteria for defining the three outcomes were based on the observed association between early improvement in lung function and asthma control observed with reslizumab and the annual rate of asthma exacerbations (8). This highlights one of the potential circular problems of the current approaches: the criteria were developed in studies based on “early improvement in lung function and asthma control,” and are now used to identify “early responders.” The authors also acknowledge that their algorithm is “by necessity” arbitrary but based on widely used clinical thresholds. However, the applied criteria defining a patient as a nonresponder in this trial is quite different from the definition of response used in some clinical studies. Additionally, although the definition of a clinical asthma exacerbation (CAE) was determined by the studies from which the model derivation data were obtained, the classification of “worsening of lung function or asthma symptoms requiring a doubling of the ICS [inhaled corticosteroid] dose” as a CAE could also be questioned. Such events may have less clinical relevance than those requiring treatment with systemic corticosteroids, particularly in severe asthma.

Notably, the suggested algorithm explicitly does not put a specific weight on the parameters, but rather considers all four to be of equivalent importance, which might be a limitation of the study as prevention of asthma exacerbations and reduction of oral corticosteroid load is typically considered the major clinical benefit. Also, the authors did not attempt to assess the value of their algorithm for reducing the risk of asthma exacerbations alone. That being said, however, treatment with biologics achieves significant improvements in a variety of clinical endpoints that are important to both patients and payers.

A 16-week time point was reported to be chosen because responses to asthma treatment tend to plateau by then (9). However, data obtained with anti-IgE may well differ from those obtained with anti-IL-5, and the clinical responses have very different time courses. Maybe it would be worthwhile to extend the analysis of the algorithm to several time points. The term “early responders” may seem arbitrary for an assessment after 4 months of therapy, considering that the consensus statement by Buhl and colleagues postulates that treatment with biologics should be stopped or switched after 4 months when there is no or an intermediate clinical response, following a “traffic light” system (3). Perhaps the term “early identification” should be used for the identification of responders directly at the beginning of treatment or in the first few weeks from a clinical standpoint. The implementation of standardized methods for assessing clinical data early in treatment, which would be less provider dependent than the current methods of assessment, might result in a higher quality of care across patient groups.

The criteria used for the definition of responders and nonresponders may seem complex and include parameters such as those specified in ACQ-6 and the Asthma Quality of Life

Questionnaire, which are not widely used clinically, raising a question as to how such assessment tools can be implemented. At present, it seems advisable to restrict the use of novel biologics to specialized centers because these drugs are costly, and the added burden of performing labor-intensive assessments can only be justified if they provide objective input regarding treatment (dis)continuation decisions. Ultimately, and with time, such complex tools will need to be replaced with validated, easy-to-use assessments that capture the patient’s perspective and health status. The hope remains that biologics will eventually be affordable for the global medical community, and that such treatments will be tested in broader populations and earlier in the course of disease.

Although the reported sensitivity of 95% is impressive, the specificity is likely too low to render the algorithm ready for use to stop treatment with reslizumab. An earlier report by Gunsoy and colleagues suggested that changes in lung function and ACQ-6 scores at 16 weeks are not useful for predicting future reductions in asthma exacerbations in patients being treated with another anti-IL-5 antibody (10), and improvements in CAE rates cannot be clinically assessed before a full year has elapsed. This means that although a positive response to treatment may be predicted with a high degree of certainty with the presented algorithm, the potentially more important prediction of long-term nonresponders remains problematic. Bateman and colleagues very modestly and correctly concede this shortcoming of the proposed approach, which deserves applause.

The research and modeling proposed by Bateman and colleagues are clearly the right way forward to guide clinical care with novel drugs in an increasingly fierce economical setting. In its current iteration, the algorithm might add (unfortunately) little to routine practice, as it will not change the need for a 12-month trial of treatment in patients with severe asthma, and this would ideally be the outcome of such a prediction model. This, however, would be the basis for real cost savings for healthcare systems worldwide, considering that global sales of the anti-IgE antibody omalizumab alone totaled around 1.9 billion U.S. dollars in 2017. In the end, the accuracy and utility of such an algorithm will also still require prospective examination in a real-world patient population, and outside the world of clinical trials. ■

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Ezrin in Asthma: A First Step to Early Biomarkers of Airway Epithelial Dysfunction

The airway epithelium has gained significant traction in recent years as a major site of disease origin, perpetuation, or resolution in lung diseases such as asthma, chronic obstructive pulmonary disease, bronchiolitis obliterans syndrome, or idiopathic pulmonary fibrosis. Previously underappreciated, the diversity of epithelial cell types in the airways significantly contributes to homeostasis of the lung's inner surface (entirely represented by epithelial cells). Airway epithelial cell dysfunction has been detected in most, if not all, chronic lung diseases. Importantly, our knowledge about the lung epithelium continuously increases with the availability of novel technologies, and in particular single-cell RNA sequencing approaches, which have uncovered previously unknown cell types in the lung, such as the recently described ionocyte (1).

Despite this wealth of knowledge on airway epithelial cell phenotypes, we are currently unable to easily detect or monitor airway epithelial cell viability/dysfunction in minimally invasive liquid biopsies, such as exhaled breath condensate (EBC), serum, or urine. It is reasonable to hypothesize that we could intervene in lung disease pathogenesis and progression more efficiently if we were able to detect early biomarkers of epithelial cell dysfunction in the abovementioned biosamples.

This is the truly exciting finding that Jia and colleagues report in this issue of the *Journal* (pp. 496–507) (2). The authors sought to measure ezrin, a member of the ERM (ezrin/radixin/moesin) family of membrane cytoskeletal proteins, in BAL fluid (BALF) in mice, and EBC and serum in humans with asthma. Using a moderately sized asthma single-center cohort ($n = 61$), and an OVA (ovalbumin)-induced animal model of asthma, the authors explore the relationship between ezrin abundance (which the authors suggest is present in airway epithelial cell-derived exosomes) and clinical parameters of asthma severity. Protein measurements of ezrin detected a surprisingly tight correlation between ezrin and lung function, independent of the origin of the liquid biosample used

to measure ezrin (e.g., EBC, serum in humans, or BALF in mice). In other words, the authors were able to detect a physiologically secreted ERM protein, ezrin, in all liquid biosamples investigated. High levels of ezrin in EBC and serum correlated with normal lung function, whereas a decline in lung function (FEV_1 , $FEV_1\%$ predicted, or FEV_1/FVC) correlated with decreased ezrin levels. The authors went on to show that ezrin is contained in exosomes secreted by cultured airway epithelial cells, and that IL-13 is a key factor inhibiting ezrin secretion in a JAK2 (janus kinase 2)-dependent manner. Knockdown of ezrin resulted in increased epithelial permeability, which the authors argue could be an early event in IL-13-driven asthma. Although exosome secretion to EBC and BALF seems logical given ezrin expression in airway epithelial cells, it will be informative to investigate how and why ezrin levels are detected in serum, and whether these are truly derived from airway epithelial cells.

At this point, most readers will ask, What is ezrin, and what is its normal cellular function? Ezrin is a protein with a molecular mass of 80 kD, which was initially identified as a substrate for the epidermal growth factor receptor protein-tyrosine kinase and as a structural component of the microvillus cytoskeleton in chicken intestinal epithelial cells and other actin-containing surface structures (3, 4). Ezrin is a critical member of the ERM family of proteins and acts at the cytoplasmic surface of cellular membranes by linking plasma membrane proteins to the cortical actin cytoskeleton. This function is essential for cell–cell and cell–substrate adhesion, cell morphology, and polarity, as well as the formation and maintenance of actin-based cell surface structures (5, 6). Of note, ezrin remains inactive in the cytoplasm and exerts its crucial regulatory role in plasma membrane-based processes through direct interactions with membrane proteins, such as the hyaluronan receptor CD44 (7) or cytoplasmic adaptor proteins, such as ezrin-binding protein EBP50 (8) via a dynamic phosphorylation and dephosphorylation process.

In 2001, Laoukili and colleagues first reported that IL-13 downregulates the expression of ezrin and interferes with its apical localization to alter epithelial cell polarization and ciliated cell differentiation in human nasal epithelial spheroid cultures (9).

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