The authors say that "a recent pragmatic trial of omalizumab demonstrated similar benefits in T2-high and -low patients (AEC $<$300 or $\geq$300 cells/μl and fractional exhaled nitric oxide [F_{ENO}] $<$25 or $\geq$25 ppb)." However, we think that describing the patient population of this study as type 2 (T2)-high and -low patients may cause confusion because we should not evaluate the atopic asthma (in which asthma is clinically allergen driven) independently from T2-high asthma. Allergic (atopic) asthma is also part of the T2-high asthma (2). The authors of the study have already described the patient groups as high-biomarker subgroups and low-biomarker subgroups, not T2 high and low (2).

Another point the authors have mentioned is that omalizumab has no biomarker that has been useful for predicting or monitoring response. However, some potential predictors of good response to omalizumab have been recommended in the GINA (Global Initiative for Asthma) severe asthma guidelines such as blood eosinophils $\geq$ 260/μl, F_{ENO} $\geq$ 20 ppb, childhood-onset asthma, and clinical history suggesting allergen-driven symptoms (3).

In conclusion, current biologics for T2-high severe asthma should be chosen wisely according to some logical recommendations, which can be made at this time on the basis of the mechanisms of the action of the drugs and the underlying pathophysiology of various asthma phenotypes, until validated biomarkers are detected for the selection of biologics. ■

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Reply to Yilmaz

From the Authors:

We thank Dr. Yilmaz for the thoughtful comments in his letter to the editor regarding our review, "Role of Biologics in Asthma" (1).

Dr. Yilmaz makes an important point when discussing atopic asthma as a type 2 (T2)-high condition. The PROSPERO (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab) study we referenced demonstrates similar benefits of omalizumab in patients with both high and low absolute blood eosinophil counts and fractional exhaled nitric oxide levels (2). Although these are important biomarkers of T2 inflammation, allergic (atopic) asthma is also driven by T2 inflammation, and thus it is better to describe these subgroups of allergic asthma as high- and lower-biomarker groups rather than T2-high and -low groups. The important takeaway point from the PROSPERO trial was that patients who were deemed candidates for omalizumab in a real-world setting responded irrespective of their biomarker profile, and thus omalizumab should be considered in patients with allergic asthma regardless of the biomarker levels. However, if the patients have asthma that is severe enough to require high-dose maintenance corticosteroids, anti-IgE therapy is unlikely to be effective even if the patients are atopic (3), implying that IgE may not be the main driver of symptoms in those patients.

The recently updated 2019 GINA (Global Initiative for Asthma) guidelines (4) do suggest that blood eosinophils $\geq$ 260/μl, fractional exhaled nitric oxide $\geq$ 20 ppb, allergen-driven symptoms, and childhood-onset asthma may be predictors of response to anti-IgE therapy. As noted in our review, although retrospective analyses have suggested that patients with high biomarker profiles treated with omalizumab may have a greater reduction in exacerbation rates (5), this difference may be a result of the higher rate of exacerbation in the high biomarker group. Future studies that prospectively evaluate factors that predict response to omalizumab and other biologics are paramount in the era of precision medicine. ■

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Biomarkers of Right Ventricular–Pulmonary Coupling in Chronic Obstructive Pulmonary Disease

To the Editor:

Stockley and colleagues, authors of the state-of-the-art review of biomarkers of chronic obstructive pulmonary disease (COPD), are to be commended for identifying the need for a strategic change in approach to COPD biomarkers (1). It should be highlighted that a concomitant focus on biomarkers of right ventricular (RV)–pulmonary coupling is essential for comprehensive assessment and management of this systemic disease.

Prognostically significant alterations in RV shape and function have been described across the spectrum of COPD (2). However, COPD is a complex and heterogeneous disease, and RV–pulmonary interactions are variable. For instance, cor pulmonale is a well-known phenotype of RV dilation and failure in some patients with COPD, whereas cor pulmonale parvus (i.e., lower RV volumes without significant alterations in RV mass and ejection fraction) has been described in contemporary COPD (3). Washko and colleagues, in a recent publication in this journal, eloquently demonstrated that COPD subphenotyping using computed tomography measure of distal pulmonary arterial vascular morphology correlated with RV phenotype (4). Right intraventricular and right and left interventricular dyssynchrony, as assessed by strain echocardiography, have been associated with COPD and have been shown to improve with pulmonary rehabilitation (5). In patients with COPD and a pulmonary vascular phenotype associated with more severe pulmonary hypertension, biomarkers of RV–pulmonary arterial coupling would be important. The significance and need for bedside biomarkers of RV–pulmonary arterial coupling is increasingly being recognized across the breadth of cardiopulmonary disease processes (6).

A paradigm shift in biomarkers for COPD needs to incorporate assessment of RV–pulmonary coupling to better endotype the disease, assess pulmonary therapeutic targets for RV preservation, and serve as novel endpoints for clinical investigation. Refining, validating, and promoting the use of biomarkers of RV–pulmonary coupling in COPD derived from widely available imaging modalities of computed tomography and echocardiography may have the potential to yield the most dividends. ■

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