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Reply to Liao *et al.*

From the Authors:

We read with interest the letter from Liao and colleagues, who performed a retrospective study of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine responses and found no differences in patients with severe asthma on biologics compared with controls, whereas we, in Runnstrom and colleagues, showed reduced vaccine responses in patients treated with biologic therapies for asthma (1). There are several reasons why our conclusions may have differed. Our study evaluated patients with severe asthma on biologic therapies compared with healthy control subjects. In contrast, Liao and colleagues studied only patients with diseases from the pulmonary clinic, which included the following: patients with asthma on biologic therapies, patients with asthma not on biologic therapies, patients with nonasthma pulmonary diseases, and "disease controls" who had been to their respiratory clinic but did not have a pulmonary diagnosis. Ultimately, the two studies asked different questions, which likely led to different conclusions. We asked if there were differences between patients with asthma on biologics compared with healthy control subjects, and Liao and colleagues asked if vaccine responses were different among patients with asthma on biologics compared with patients with other diseases.

Another major difference between the two studies was the time when the vaccine titers were examined. Studies have shown that antibody responses wane significantly after SARS-CoV-2 mRNA vaccination, up to 90% in the first 6 months, which makes it critical to correlate antibody responses with time after vaccination (2, 3). In the study by Liao and colleagues, they evaluated vaccine responses retrospectively between 1 month and almost 1 year (29–296 d) after the second dose, which was an extremely broad range; thus, they may not have been able to distinguish differences among their groups. Furthermore, the mean day after the second dose was earlier in patients with asthma on biologics (150 d) than in the others (178, 186, and 186 d), which may have also confounded the results.
Our prospective study focused on a smaller time-period (the first 3 months) after the second vaccination and even narrowed the window to three time points, 25–49, 50–74, and 75–99 days, to demonstrate differences. Given the rapid decline in titers over time, the broad range of time in the study by Liao and colleagues may have concluded no differences as patients with asthma on biologic therapies were evaluated earlier when vaccine titers may have been higher.

Overall, Liao and colleagues studied more patients and control subjects ($N = 139$ vs. $N = 84$), but the numbers of patients with asthma on biologics were only 21 subjects in their study compared with Runnstrom and colleagues with 48 patients on biologics. This small sample size in Liao and colleagues may not have had sufficient power to detect differences among these groups. In addition, we found it interesting that half of their controls had antibody titers at or below the protective threshold (154 BAU/ml). Thus, the wide range of days after vaccination and small sample size may have limited the ability to detect differences.

Finally, the type of vaccines administered may have affected their conclusions. Studies have shown that vaccine titers after Pfizer-BioNTech BNT162b2 compared with Moderna mRNA-1273 were demonstrably lower (4, 5). Interestingly, in Liao and colleagues, only 43% of the patients with asthma on biologics compared with nearly all (83%) of the control subjects with nonpulmonary disease received the Pfizer vaccine, which may have led to a lower antibody response in that group. In our study, the vaccines were more closely matched, albeit not perfectly (Pfizer in 71% of the biologic group vs. 58% of the controls).

Several studies have shown a lack of vaccine antibody impairment in patients with asthma on benralizumab or patients with atopic dermatitis on dupilumab, but these studies only compared diseased patient populations on or off biologics without a healthy adult comparison and only assessed the response 4 weeks after vaccination (6, 7). Although most studies evaluating vaccine responses in patients with asthma studied children or live vaccines, studies have found that after 23-valent pneumococcal vaccination, patients with asthma had a decreased change in antibody titer (8) and lower rate of seroconversion (9) compared with healthy control subjects. Another study found a nonsignificant trend toward reduced humoral immune response and statistically significant reduced cell-mediated immune response among adults with asthma compared with healthy control subjects after influenza vaccination (10). In addition, among patients with asthma, high-dose inhaled corticosteroid use has been associated with lower vaccine response (11), something that is frequently used in patients with severe asthma. Therefore, understanding differences of vaccine responses in diseased populations compared with healthy adults was

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critical to provide recommendations of boosters until more studies evaluating these populations were available. Because our study did not include patients with severe asthma who were not on biologics, the reduced responses we observed may have been owing to disease or treatments and not necessarily from the biologics alone.

In all, there may have been no differences in vaccine responses among the four diseased cohorts in Liao and colleagues owing to the limitations of patient populations, timing of the vaccine titers, and the types of the vaccines administered. Thus, understanding the kinetics of protective immunity over time in these diseased cohorts is critical. Nonetheless, Liao and colleagues performed a valuable study, and together with the findings in the study by Runnstrom and colleagues, we emphasize the importance of repeat boosters for patients with severe asthma whether they are on biologics, have pulmonary disease, or have other chronic illnesses. That said, it is essential that we continue to study these vulnerable patients with the emergence of new SARS-CoV-2 variants after the primary vaccine series and repeat boosters to appreciate the initial responses and durability of protective immunity. ■

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Martin C. Runnstrom, M.D.
F. Eun-Hyung Lee, M.D.*
Department of Medicine
Emory University
Atlanta, Georgia

ORCID ID: 0000-0002-6133-5942 (F. E.-H.L.).

*Corresponding author (e-mail: f.e.lee@emory.edu).

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The Need for a CYFRA 21-1 Cutoff Value to Predict Clinical Progression of IPF in Clinical Practice

To the Editor:

We read with much interest the article by Molyneaux and colleagues on the concentrations of CYFRA 21–1 in patients with idiopathic pulmonary fibrosis published online in your prestigious journal (1). The authors found that the serum concentration of CYFRA 21–1 is significantly higher in patients with idiopathic pulmonary fibrosis than in a healthy population and that it can predict disease progression and overall mortality in idiopathic pulmonary fibrosis patients, suggesting the potential usefulness of serum CYFRA 21–1 as a diagnostic and prognostic biomarker (1). Unfortunately, a specific cutoff value of CYFRA 21–1 was not defined in the study to use as a reference in clinical practice. Although the mean CYFRA 21–1 values were statistically different between healthy subjects and patients with idiopathic pulmonary fibrosis, most data from healthy subjects appear to overlap those from patients with idiopathic pulmonary fibrosis, making it difficult to determine a cutoff value for distinguishing both groups (1). The receiver operating characteristic curve analysis has been used in previous studies to define the most appropriate cutoff value of serum CYFRA 21–1 to differentiate benign from malignant disease, advanced from early cancer clinical stage, and squamous cell from small cell carcinoma (2, 3). Cutoffs of serum CYFRA 21–1 calculated from receiver operating characteristic curves were also useful for diagnosing preeclampsia and endometriosis and predicting response to therapy and prognosis in patients with cancer (3–6). These previous observations suggest that receiver operating characteristic curve analysis of serum CYFRA 21–1 concentration in subjects from the PROFILE (Prospective Observation of Fibrosis in the Lung Clinical Endpoints) study could also provide a cutoff value to diagnose the disease and predict clinical outcomes in idiopathic pulmonary fibrosis. We believe that if the authors can provide the cutoff value of serum CYFRA 21–1 for diagnosing and predicting clinical progression in idiopathic

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