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SARS-CoV-2 mRNA Vaccine Antibody Response in Patients with Asthma Receiving Biologic Therapy: A Real-World Analysis

To the Editor:

Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused significant morbidity and mortality worldwide, the development of vaccines has controlled the ongoing global crisis. However, vaccine effectiveness may be diminished in patients with chronic underlying conditions or using certain immunomodulatory medications (1). Biologic therapies such as benralizumab, mepolizumab, and dupilumab have revolutionized care and improved outcomes in severe asthma. However, there have been concerns that antibody responses to mRNA vaccines could be blunted in patients with asthma treated with biologics. Runnstrom and colleagues (2) reported that patients with severe asthma or atopic dermatitis on biologic therapies have lower antibody concentrations after SARS-CoV-2 mRNA vaccination than healthy adults and that these differences persist for at least 3 months. However, these results differed from previous studies of other vaccines (e.g., tetravalent influenza, meningococcal, or tetanus vaccination) that did not show different antibody responses 4 weeks after vaccination (3, 4) in patients with asthma treated with biologics versus no biologic treatment. A recent study also suggested that dupilumab did not affect yellow fever vaccine response (5). These conflicting results raise concerns about impaired effectiveness of mRNA vaccination against SARS-CoV-2 in the context of asthma biologic use and make it difficult for physicians to advise patients with asthma about optimal therapy to treat severe asthma.

To address this question, we used real-world data from our respiratory specialty clinic to compare the antibody response to two or three doses of SARS-CoV-2 mRNA vaccines between patients with asthma who were treated with biologics and other patient groups. Using the National Jewish Health electronic medical records research database, we identified patients who had a spike IgG antibody test ordered after the second or third dose of SARS-CoV-2 mRNA vaccine as part of routine clinical care by individual physicians evaluating vaccine immunity or by patient request between December 16, 2020, and February 17, 2022. Anti–SARS-CoV-2 QuantiVac ELISA (EUROIMMUN) detecting IgG to spike protein recombinant S1 domain, a surrogate for neutralizing antibodies to

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Table 1. Characteristics of the Study Population after the Second Dose (*N* = 139) and Patient Groups

Characteristics	Asthma with Anti–IL-4/13 or Anti–IL-5 (*N* = *21*)	Asthma without Biologics (*N* = *43*)	Pulmonary Diseases (*N* = *46*)	No Pulmonary Diseases (*N* = *29*)
Age, mean (SD), yr	59 (14)	65 (14)	65 (16)	64 (13)
Sex, *n* (%)				
Female	15 (71)	31 (72)	33 (72)	16 (55)
Male	6 (29)	12 (28)	13 (28)	13 (45)
Vaccine type				
mRNA-1273 (Moderna)	12 (57)	22 (51)	18 (39)	5 (17)
NT162b2 (Pfizer-BioNTech)	9 (43)	21 (49)	28 (61)	24 (83)
Days of BAU/ml measurement (after second dose), mean (SD)	150 (52)	178 (44)	186 (51)	186 (63)
BAU/ml measurement				
BAU/ml, mean (SD)	439 (423)	330 (388)	435 (429)	355 (410)
BAU/ml < 100, *n* (%)	5 (24)	15 (35)	10 (22)	9 (31)
BAU/ml < 154, *n* (%)	7 (33)	22 (51)	15 (33)	15 (52)
BAU/ml < 200, *n* (%)	9 (43)	23 (53)	20 (43)	15 (52)
Hypertension, *n* (%)	7 (33)	10 (23)	9 (20)	3 (10)
Diabetes, *n* (%)	2 (10)	4 (9)	2 (4)	0 (0)
Congestive heart failure, *n* (%)	0 (0)	1 (2)	2 (4)	1 (3)
Renal diseases, *n* (%)	2 (10)	1 (2)	1 (2)	0 (0)
Rheumatic diseases, *n* (%)	0 (0)	3 (7)	6 (13)	2 (7)
Systemic corticosteroids, *n* (%)	11 (52)	9 (21)	9 (20)	5 (17)

Definition of abbreviation: BAU = binding antibody units.

coronavirus disease (COVID-19) vaccine, was used in our clinical laboratory, and binding antibody unit (BAU) per milliliter was reported (reported range, 3.2–1,216). BAU from EUROIMMUN assays has been correlated with other commercial assays reporting receptor binding dominant (6), and 154 BAU/ml was suggested as a mean protective threshold (7). Asthma and other medical conditions were from physician diagnosis. We excluded patients with a prior history of COVID-19 or significant immunosuppression

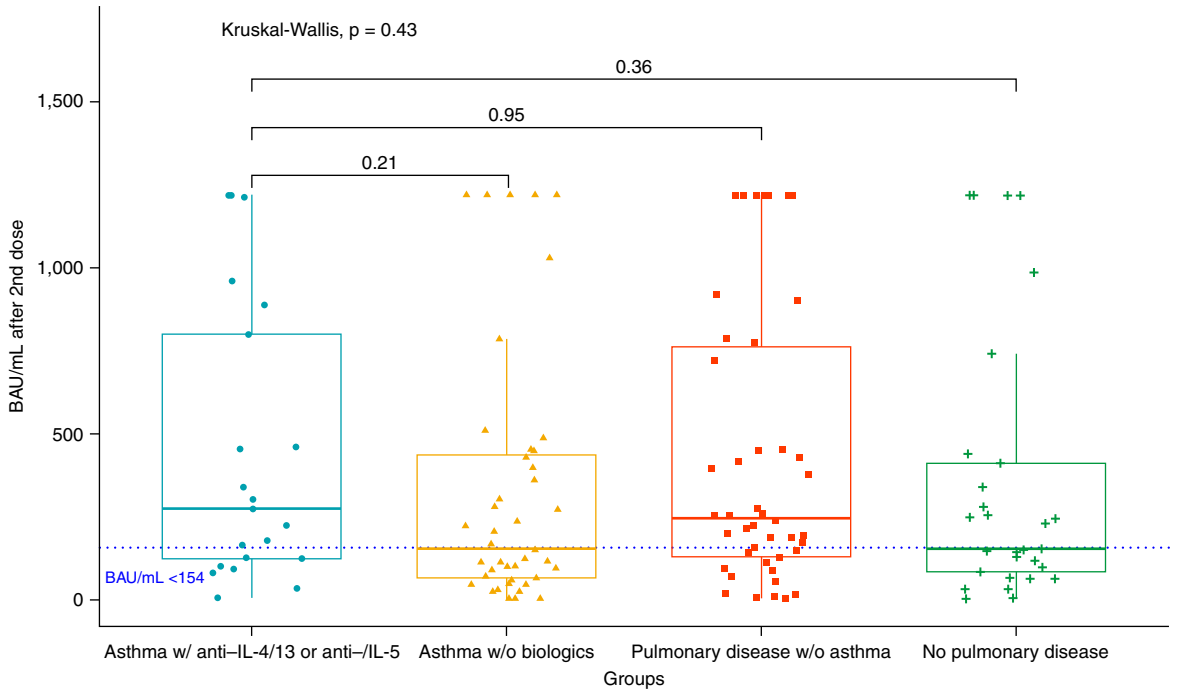

Figure 1. BAU/ml measurement after two doses of severe acute respiratory syndrome coronavirus 2 mRNA vaccine among groups. Box and scatter plot along with *P* values among groups was presented. The dotted line is BAU/ml at 154 thresholds (7). BAU = binding antibody unit; w/ = with; w/o = without.

(e.g., azathioprine, methotrexate, mycophenolate mofetil, etc.), except for corticosteroids. Patients using biologics other than benralizumab, mepolizumab, or dupilumab were also excluded. The subjects were divided into four groups for comparison: *1*) patients with asthma treated with biologics (anti-IL4/13 or anti-IL5); *2*) patients with asthma without biologic use; *3*) patients with pulmonary diseases other than asthma, and *4*) patients without pulmonary diseases. A Kruskal-Wallis test was used to compare the BAU/ml among groups. We further categorized the BAU/ml using thresholds (7) of 100,154 and 200 and performed chi-square testing to compare percentages of low BAU/ml with each threshold across groups. To minimize confounding by age, gender, comorbidities (hypertension, diabetes, pulmonary diseases, congestive heart failure, and renal and rheumatic diseases with definition described in the previous study [1]), systemic corticosteroid use, vaccine type (mRNA-1273 vs. BNT162b2), or days of measurement from the last dose, we used propensity score nearest neighbor matching method (8) to match each patient with asthma treated with biologics (case) with three controls drawn from the remaining cohort (1:3 ratio) and then used Wilcoxon test to compare these two groups. We analyzed BAU/ml measured after the second and third doses, respectively.

We identified 139 patients (mean age, 64 years; 68% female, after excluding 81 patients with a history of COVID-19 and 106 patients with significant immunosuppression [19 methotrexate/leflunomide, 62 mycophenolate mofetil/azathioprine/sirolimus/tacrolimus, 25 biologics other than anti-IL4/13 or anti-IL5, 4 JAK inhibitor, and 14 anti–TNF-α (tumor necrosis factor α) inhibitors; some patients take multiple immunosuppressants]) who received two doses of mRNA vaccines and had antibody testing between second and third dose (Table 1). BNT162b2 (Pfizer-BioNTech) was administered to 59% of the patients, and 41% received mRNA-1273 (Moderna). BAU/ml was measured at a mean (SD) of 178 (52) days, range, 29–296 days, after second dose vaccination. There was no significant difference in BAU/ml among all four patient groups ($P = 0.43$) (Figure 1). There was no significant difference in the percentage of patients with low BAU/ml using thresholds (7) of 100, 154, or 200 among different patient groups ($P = 0.53$, 0.18, and 0.73, respectively). Comparing patients with asthma treated with anti-IL4/13 or anti-IL5 biologics with matched control patients using propensity score method for covariates, there was no significant difference in basic characteristics between the case and matched control patients (P values ranged from 0.06 to 1, except the case group had more asthma, 100% vs. 68% as expected), and we found no significant difference in BAU/ml ($P = 0.17$). Adding two patients with asthma treated with anti-IgE into the analysis yielded similar results. The same statistical approach was applied to an additional 42 patients (6 patients with asthma treated with anti-IL4/13 or anti-IL5, 13 nonbiologic patients with asthma, 17 patients with pulmonary diseases, and 6 patients without pulmonary diseases) who had BAU/ml measurement after a third vaccine dose (mean age, 63 years; 52% female; mean days of BAU/ml measurement, 50). Similarly, there was no significant difference in BAU/ml across patient groups.

Our study demonstrated that in a real-world setting, patients treated with asthma biologics had no significant difference in antibody response to mRNA vaccines compared with other patient groups after either two or three vaccine doses. This conclusion remains valid after controlling for multiple comorbidities and systemic corticosteroid use. These data should be very reassuring to patients with asthma and physicians who may be concerned about the potential for asthma biologics to impair COVID-19 vaccine response. Our study data differ from the results reported by Runnstrom and colleagues (2), probably owing to the uncontrolled confounding in their study population for age, comorbidities, and corticosteroid use, a concern also raised by those authors. Another potential explanation is that the authors compared with "healthy controls", whereas in our study, we compared with "disease controls." To address this concern, we used the propensity score method to control for those potential confounders including comorbidities and observed no significant difference in vaccine response in patients with asthma using biologics. Whereas our previous work indicates that patients with comorbidities such as interstitial lung disease and congestive heart failure may have impaired antibody responses (1), our work here does not support the notion that patients with asthma treated with biologics have a higher risk for impaired antibody-mediated immune response to mRNA vaccine than other patient populations without significant immunosuppression. Thus, our data suggest that interrupting biologics in this population may not be warranted. As antibody response is not the sole determinant of vaccine effectiveness, this report should stimulate further studies of immunologic response in patients with asthma treated with biologics, including evaluation of T-cell response and longitudinal protection in vulnerable populations, to inform recommendations regarding the timing of boosters. Limitations in our study include too small of a sample size to examine the antibody response after the third dose and the lack of healthy controls; this is to be expected in real-world data analysis in which the study population is drawn from clinic patients. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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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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