

## Reduced COVID-19 Vaccine Response in Patients Treated with Biologic Therapies for Asthma

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**To the Editor:**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines confer great protection against symptomatic and severe coronavirus disease 2019 (COVID-19) in healthy adults, but little is known for specialized patient populations despite billions of doses given worldwide. Asthma is one of the most common chronic respiratory diseases and affects approximately 25 million people in the United States alone. There are currently six US Food and Drug Administration (FDA) approved biologic therapies for the treatment of asthma, with some that target cytokines critical for asthma pathogenesis, but inhibition of these cytokines may also negatively affect B cell to plasma cell differentiation, somatic hypermutation in the germinal centers, and long-lived plasma cell generation and maintenance potentially through eosinophil depletion<sup>1-3</sup>. Despite animal studies showing decreased vaccine-induced humoral immunity without these cytokines<sup>4,5</sup>, there is a paucity of literature available in this patient population following SARS-CoV-2 vaccination.

Two prior studies have evaluated short term vaccine response in patients treated with biologic therapies approved for asthma. The first study enrolled patients with moderate or severe asthma who were treated with benralizumab or placebo and given the tetravalent influenza vaccine. They found similar antibody response 4 weeks after vaccination in the treated group compared to placebo<sup>6</sup>. Another study evaluated patients with moderate or severe atopic dermatitis treated with dupilumab or placebo and found that both groups had similar antibody response 4 weeks after meningococcal or tetanus vaccination<sup>7</sup>. Neither of these studies evaluated durability of the antibody response beyond 4 weeks. In addition, since neither study compared responses to healthy adults, it is not clear if patients with asthma or atopic dermatitis indeed have similar vaccine responses to healthy adults that made up the majority of patients in the original SARS-CoV-2 vaccine trials. Therefore, it is unclear if patients with severe asthma

and atopic dermatitis on biologic therapies have adequate and durable humoral immune response after vaccination to SARS-CoV-2.

To address these questions, we conducted a prospective observational trial from February 2021 to September 2021 with adults who had severe asthma or atopic dermatitis treated with benralizumab (interleukin [IL] 5 receptor antagonist), mepolizumab (IL-5 antagonist) or dupilumab (IL-4 receptor  $\alpha$  antagonist). Patients had received one of the SARS-CoV-2 messenger ribonucleic acid (mRNA) vaccines, Pfizer-BioNTech or Moderna. Blood samples were taken from 41 patients on dupilumab (57% treated for severe asthma, 37% for atopic dermatitis, 3% for both severe asthma and atopic dermatitis and 3% for Hyper Immunoglobulin E syndrome), 23 patients on benralizumab, and 9 patients on mepolizumab for a total of 73 patients in addition to 39 healthy adults. After excluding patients with a prior history of COVID-19 or significant immunosuppression, the final cohort included 107 samples from 48 patients (average age 53 years, 60% women; 30 patients on dupilumab, 12 patients on benralizumab and 6 patients on mepolizumab), in addition to 107 samples from 36 healthy controls (average age 36 years, 72% women). Samples were analyzed for specific SARS-CoV-2 antigen reactivities (wild-type [WT] and Delta variant receptor binding domain [RBD], S1, S2, N-terminus binding domain, Nucleocapsid, and ORF3a) with a high-throughput multiplex Luminex assay<sup>8</sup>.

Patients on biologic therapies had lower Immunoglobulin G (IgG) levels to the WT SARS-CoV-2 RBD compared to healthy adults (average median fluorescence intensity [MFI] 105,950 and 160,584, respectively; p-value 0.0001; Figure 1) on days 25-49 after the second vaccine dose. At the later time point, antibody levels for patients on biologic therapies remained significantly lower compared to healthy adults (average MFI 67,535 and 100,519, respectively; p-value 0.012), at approximately 67% of the healthy adult's antibody levels. Similar results were seen for other SARS-CoV-2 antigens, including Delta variant RBD and Spike protein S1.

These data demonstrate that patients with severe asthma or atopic dermatitis on biologic therapies have lower antibody levels after SARS-CoV-2 mRNA vaccination compared to healthy adults and that these differences persist for at least three months. The question remains whether the lower antibody levels in our specialized patient population are an effect of the biologic therapies, or if it is a combination of confounding factors such as higher average age in the treatment group compared to controls, more comorbid conditions, and greater number of medications used in our treatment group compared to healthy controls. Although patients on high dose oral corticosteroids were excluded (defined as a daily dose of >10 mg of oral prednisone, or other corticosteroid equivalent), we raise the issue whether the frequent use of high dose inhaled corticosteroids which are routinely taken in patients with severe asthma<sup>9</sup> may have also confounded these results. As there is evidence that lower vaccine-specific titers afford less protection against COVID-19<sup>10</sup>, clinicians and patients should consider earlier or more frequent booster vaccinations in these patients who may unknowingly remain at high risk for severe disease.

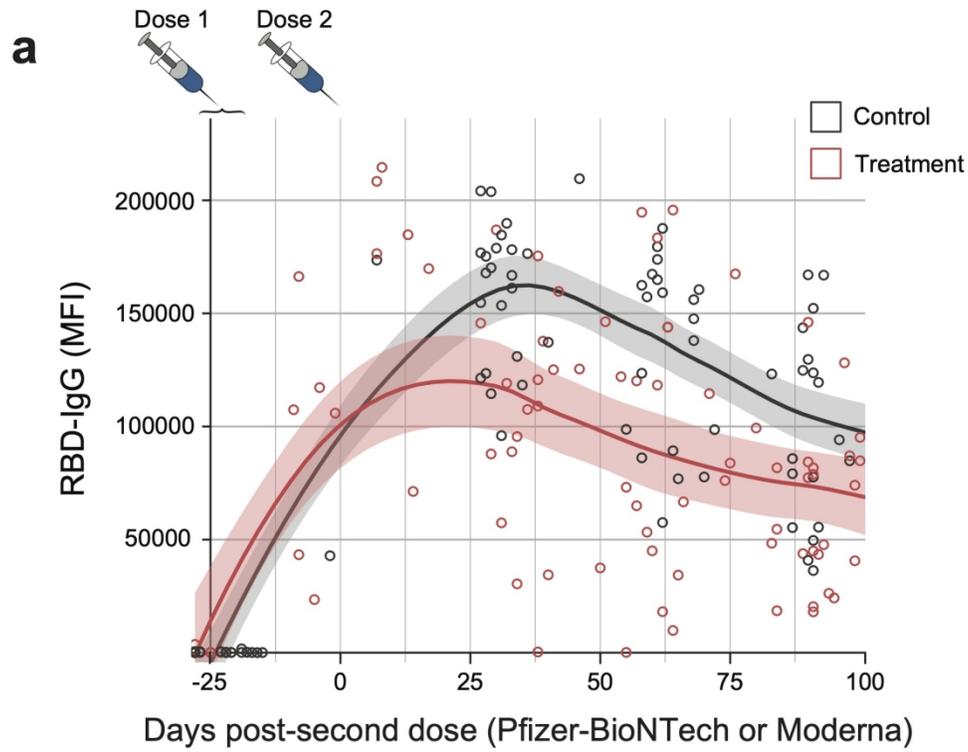
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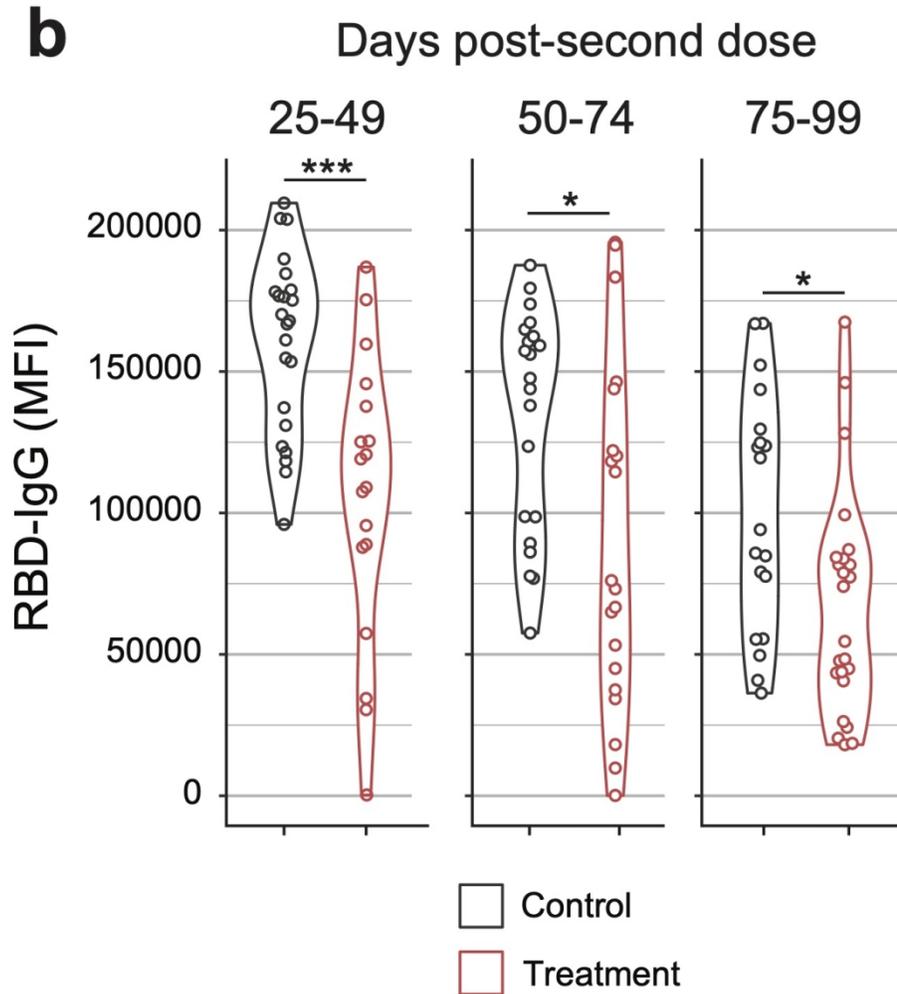
## Figure Legends

**Figure 1 A)** Time after dose 2 of the SARS-CoV-2 mRNA vaccination and IgG titer to WT SARS-CoV-2 RBD. Shaded area indicates 95% confidence interval. Treatment group includes all patients on benralizumab, dupilumab and mepolizumab. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; mRNA, messenger ribonucleic acid; IgG, Immunoglobulin G; WT, wild-type; RBD, receptor-binding domain; MFI, median fluorescence intensity. **B)** IgG to WT SARS-CoV-2 RBD on days 25-49, 50-74 and 75-99 after dose 2 of the SARS-CoV-2 mRNA vaccine. Treatment group includes all patients on benralizumab, dupilumab and mepolizumab. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; mRNA, messenger ribonucleic acid; IgG, Immunoglobulin G; WT, wild-type; RBD, receptor-binding domain; MFI, median fluorescence intensity. \*\*\*, P value 0.0001; \*, P value <0.012.



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IgG to WT SARS-CoV-2 RBD on days 25-49, 50-74 and 75-99 after dose 2 of the SARS-CoV-2 mRNA vaccine. Treatment group includes all patients on benralizumab, dupilumab and mepolizumab. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; mRNA, messenger ribonucleic acid; IgG, Immunoglobulin G; WT, wild-type; RBD, receptor-binding domain; MFI, median fluorescence intensity. \*\*\*, P value 0.0001; \*, P value <0.012

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