

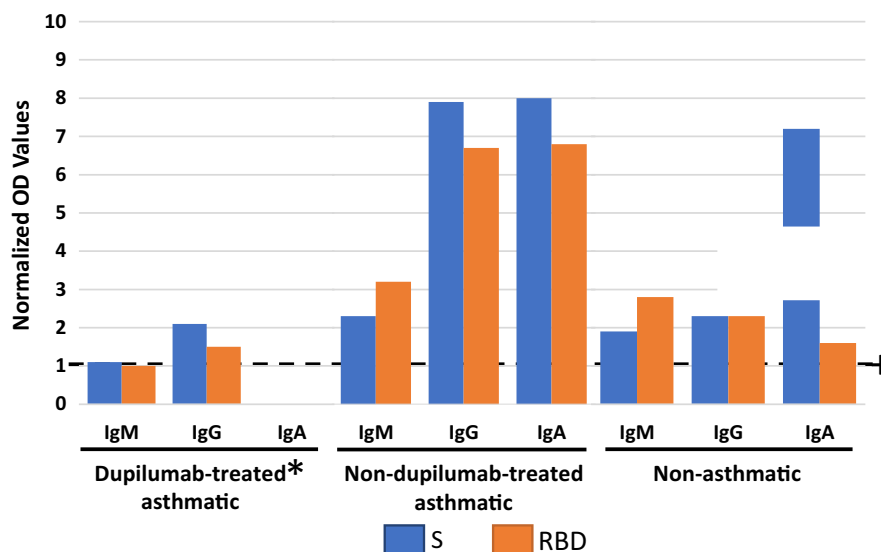
# Dupilumab, severe asthma airway responses, and SARS-CoV-2 serology

To the Editor,

There is paucity of data on immune responses to COVID-19 in severe asthmatics treated with biologics. Recent guidelines recommend continuing these agents (as clinically indicated) to maintain asthma control. Supporting this claim, Lommatzsch demonstrated that omalizumab could safely be continued during active COVID-19 infection in a patient with allergic asthma.<sup>1</sup> There are other reports that treatment with benralizumab<sup>2</sup> and dupilumab<sup>3</sup> are not associated with significant negative impact. We had similar experience in a young patient with severe asthma who had previously been treated with dupilumab. However, her immunoglobulin responses to the virus were modest compared to two other patients who had not previously been exposed to dupilumab. We speculate if interruption of IL-4 receptor signaling may prolong the development of antibody responses to SARS-CoV-2.

A 23-year-old female, who had predominant IL-4/IL-13-driven disease (characterized by atopy, severe airway hyperresponsiveness with PC<sub>20</sub> methacholine 0.08 mg/mL, mucus hypersecretion,

sputum and blood eosinophilia, and FeNO of 74ppb), noticed significant improvement in asthma control (ACQ-5:1.0, 26% improvement in FEV<sub>1</sub>) after receiving dupilumab (600 mg loading dose followed by 300 mg every 2 weeks, subcutaneously) from September-December of 2019 (NCT03884842; clinicaltrials.gov). In mid-March of 2020 (3 months after the last dose of dupilumab), she tested positive by PCR of a nasopharyngeal (NP) swab for SARS-CoV-2. Her asthma was uncontrolled (ACQ-5:4.4) but her blood eosinophil ( $0.1 \times 10^9/L$ ) and lymphocyte ( $1.7 \times 10^9/L$ ) counts were normal. Sputum and spirometry were not examined. She remained on high doses of inhaled corticosteroids (800 µg mometasone) and formoterol, and her ACQ-5 gradually improved over the following 8 weeks to 3.0. Blood eosinophils went up to  $1.4 \times 10^9/L$ , but sputum eosinophils were normal at 1%, FeNO was 15ppb and FEV<sub>1</sub> was 2.2L (70% predicted). However, 9 weeks after her onset of symptoms, the virus was still detectable by PCR from her NP swab. There was insufficient viral load to attempt viral culture.



**FIGURE 1** Serum antibodies against SARS-CoV-2 in dupilumab-treated asthmatic and in two nondupilumab-treated patients (one of whom was on inhaled steroid and the other steroid-naïve nonasthmatic). The level of detection was determined using the optical density (OD) of pre-COVID sera. Levels of antibody are determined for each antibody/antigen combination by determining a cutoff value (optical density + 2 standard deviations for pre-COVID plasma), and optical density values are divided by this cutoff value. Levels above one are considered positive (dashed line). Dupilumab-treated patient remained PCR positive for 9 wk, while the nondupilumab-treated patients tested negative between 4 and 5 wk

We examined some potential mechanisms (using archived sputum samples collected before and immediately after treatment with dupilumab) to investigate whether dupilumab may have contributed to the infection (by modulating *ACE2* or *TMPRSS2* expression) and the prolonged viral detection (by modulating anti-SARS-CoV-2 antibody levels). *ACE2* could not be detected in her sputum samples but *TMPRSS2* expression had increased fourfold (by RT-PCR normalized to *GAPDH* housekeeping gene, using validated primers from Bio-Rad, CA, USA). It is plausible that the high dose of inhaled steroids decreased *ACE2* expression<sup>4</sup> but probably did not affect *TMPRSS2* expression that facilitated the infection. Inhaled steroids also probably prevented significant asthma deterioration and respiratory distress. Indeed, dexamethasone was demonstrated to improve COVID-19 outcomes in hospitalized patients.<sup>5</sup> Additionally, serum antibodies (IgA, IgM, and IgG) to two SARS-CoV-2 antigens, the Spike-protein (S) and receptor-binding-domain (RBD), were measured using an ELISA to purified recombinant proteins as previously described<sup>6</sup> in our index patient and two other control patients who developed the infection (an asthmatic on inhaled steroid only (fluticasone 500µg daily) and a steroid-naïve nonasthmatic). In comparison with two control patients, the dupilumab-treated patient had blunted IgG and IgM and absent IgA antibodies to two SARS-CoV-2 antigens, the Spike-protein and receptor-binding-domain (Figure 1). It is unclear if previous treatment with dupilumab may have led to a less robust antibody response or reduced class switching, although this has not been observed with T-cell-dependent and T-cell-independent humoral immune responses to tetanus and meningococcal vaccines.<sup>7</sup> Lastly, our index patient had relative eosinopenia at the time of diagnosis, which has been associated with increased symptoms and a longer disease course, whereas high blood eosinophils are associated with COVID-19 recovery.<sup>8</sup>




In conclusion, we suggest that while dupilumab, when used along with glucocorticosteroids for asthma may be safe during SARS-CoV-2 pandemic, further research is necessary to understand its effect on the sero-immune responses to the virus, and whether it may prolong the time to recover from the infection.

## KEYWORDS

asthma, dupilumab, SARS-CoV-2

## CONFLICT OF INTEREST

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