

## Review

# COVID-19, Severe Asthma and Omalizumab Therapy: A Case-Based Inquiry into Associations, Management, and the Possibility of a Better Outcome

Sadi Can Sönmez<sup>1</sup>, Zeynep Büşra Kısakürek<sup>1</sup>, Ayşe Bilge Ozturk<sup>2</sup>, Süda Tekin<sup>3</sup><sup>1</sup>School of Medicine, Koç University, Istanbul, Turkey<sup>2</sup>Department of Allergy and Immunology, Koç University, School of Medicine, Istanbul, Turkey<sup>3</sup>Department of Infectious Diseases, Koç University, School of Medicine, Istanbul, Turkey

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## Abstract

Recent developments in research have put forward claims on the protective effect of allergic diseases—especially allergic airway inflammation including allergic asthma—against the COVID-19 pandemic. This was first suggested by the underrepresentation of asthma patients in some cohorts and was later investigated by angiotensin-converting enzyme II (ACEII) receptor expression studies. Controversial data on this matter persists and continue to be a challenge for clinicians when it comes to managing allergic diseases during the pandemic. We present in this study a thorough review of related findings so far and our own experience with 2 severe asthma patients who presented with atypical symptoms. Interestingly, both patients were administered anti-IgE therapy prior to the initial positive polymerase chain reaction (PCR) results for COVID-19 and showed no symptoms of severe respiratory disease during the infection unlike what we know from other viral respiratory illnesses. Stemming from that, we wanted to combine the perspectives of allergists and infectious disease specialists to address certain concerns in the management of allergic diseases, such as biologicals, in the light of current guidelines. We have also pointed out certain gaps in clinical and molecular level research, such as the lack of phenotypical subgroup analysis among ill asthma patients and the lack of data concerning the molecular effects of biologicals on viral infection.

**KEYWORDS:** COVID-19, severe asthma, omalizumab, anti-Ig-E, T helper 2-mediated inflammation

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## INTRODUCTION

Since the very beginning of the COVID-19 pandemic, research was focused on foreseeing the outcomes and choosing the timing of appropriate interventions to change them. It has proved to be a very challenging task as the infection led to a diverse variety of prognoses in different populations with different comorbidities.<sup>1</sup> In that sense, asthma as a prevalent representative of allergic diseases seems to have a complex relationship with the current outbreak. From what we know so far, allergic airway diseases can be triggered by respiratory pathogens, which leads to persistent airway symptoms even after the clearance of the infection.<sup>2</sup> To give a solid example from influenza, people with asthma tend to develop asthmatic exacerbations and recover late from the virus. Current evidence suggests that this might not be the entire picture with COVID-19.<sup>2</sup>

Asthma to this day is listed with other pulmonary diseases as a comorbid risk factor for severe outcomes. This was first questioned because of the underrepresentation of asthma among patients hospitalized with severe disease in different cohorts around the world.<sup>3,4</sup> It seemed as if asthma had some sort of a protective role that led to lower percentages of asthmatics in ICUs than the estimated prevalence of asthma in that population. However, new data emerging from other centers (United Kingdom and United States of America) reported the exact opposite of this and suggest that asthma continues to be a risk factor.<sup>5</sup> They argue that the underrepresentation in certain centers is because the individuals with asthma in some locations could have maximized personal protective measures, thanks to the successful propaganda on pandemic control. This also means good adherence to medications and possibly good control of symptoms even before the spread of infection in those regions.

In addition to that, the use of biological modulators in people with asthma is a major concern as to whether they are detrimental, neutral, or actually beneficial. In our recent report, we have shown that 25% of the allergists in Turkey discontinued biological therapy in asthma patients without any symptoms or clinical signs of COVID-19, while the current European Academy of Allergy and Clinical Immunology (EAACI) statement recommends continuing biologicals for the treatment of asthma during COVID-19.<sup>6,7</sup> The commonly used monoclonal anti-IgE and anti-IL-5 antibodies can actually provide a more solid control of the allergic disease, allowing the immune system to consolidate resources adequately against the viral load. However, since they mainly act on T helper 2 (Th2)-driven cytokines and processes, more cellular research is required to determine their exact standpoint in the face of infections.

**Corresponding author:** Ayşe Bilge Ozturk, e-mail: aysebilgeozturk@yahoo.com

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In light of all these new findings that sometimes seem to contradict one another, asthma management during the pandemic has become a more complex, yet important, issue. It has been reported that many allergists have postponed biological therapies and oral steroids for their patients indefinitely during the pandemic, going against international suggestions.<sup>6</sup> This might mean exposing those individuals to a greater risk of poor outcomes as good control seems to be a key element in the interaction between asthma and COVID-19. We, therefore, present our own experience with 2 cases of severe asthma under biological therapy and would like to review current research and guidelines on this matter. We find it important to discuss this issue to cover both the asthmatic individuals and the general population by providing new insights into research and data analysis.

### Case 1

A 31-year-old female patient was diagnosed with asthma 2 years ago. She was admitted to the emergency department with shortness of breath due to having attacks 5 times within the last 1 year despite her medications. Her asthma could be first categorized as “difficult to manage” as she had been using different inhaled medications on and off without benefit. We rearranged her prescription and agreed on full compliance with the regimen. Her current medications included regular use of inhaled corticosteroids and long-acting beta-agonists (LABA) (Symbicort® forte 2 × 1/day). However, even after following a short-term oral corticosteroid (OCS) plan in addition to step 4 controllers, her symptomatic response was not satisfactory. She also reported nighttime symptoms which awakened her. Her complaints also pointed toward a postnasal drip syndrome. On her allergy panel, we detected grass pollen and *Dermatogoides pteronyssinus* allergies.

Therefore, we decided to follow a step-up approach and categorized her under severe asthma. We then initiated monthly treatment with omalizumab as an add-on in February 2018. In the follow-up appointments, we noted that her symptoms abated and were eventually under full control.

Three days after she received the 29th dose of her monthly omalizumab regimen, she came to our hospital with

### MAIN POINTS

- COVID-19 can have a unique interaction with asthma due to factors such as, but not limited to, T helper 2 (Th2) inclination, modulator treatments, and angiotensin-converting enzyme II (ACEII) receptors and can ultimately yield favorable results in certain patient groups such as those presented here.
- Despite ambivalent data on biologicals, full control of asthma symptoms prior to and during the infection seems to be a key element, and physicians must, therefore, refrain from step-up or step-down strategies unless the patient's situation requires.
- There is a pressing need for varied subgroup analyses for different asthma phenotypes, treatment types and durations, severity, and level of control in future patient cohorts.

suspected case of COVID-19 after one of her coworkers tested positive. She had excessive fatigue as the presenting and sole symptom. Her diagnosis was confirmed by a positive PCR test for SARS-CoV-2 despite her clear chest computed tomography (CT). In accordance with the national protocols and WHO guidelines, she was informed about the progression and treatment of the disease and was sent home for self-quarantine.<sup>8</sup> We suggested pausing omalizumab treatment but educated the patient about continuing her inhaled regimens for asthma control.

During this period, she suffered from muscle pain that was localized to her back, hoarseness of her voice, mild coughing, and severe nasal congestion. She had no asthma exacerbation and did not need frequent relievers or OCS. She did not apply for any further medical care. Her COVID-19 treatment included Plaquenil for 5 days. After her symptoms receded, we confirmed her recovery by a negative PCR after the 10th day of COVID-19 symptoms. She was then permitted to work, and her omalizumab treatment was reinitialized for the next month 20 days after a negative PCR test.

### Case 2

A 46-year-old man was diagnosed with asthma 10 years ago. His medications were Symbicort® forte 2 × 1/day and Spiriva® 1 × 1/day. He used them appropriately, but nevertheless, his symptoms were not relieved completely. He suffered from prolonged exhalation, wheezing, and shortness of breath despite his medications. In further allergy investigations, his skin prick test was positive for tree pollen and *Aspergillus fumigatus*, and his total IgE level was 318 IU. OCS treatment also provided only temporary relief and did not provide full abatement.

He fulfilled the criteria for severe asthma due to his uncontrolled symptoms, and we decided to administer monthly omalizumab injections starting from April 2017. This new regimen provided him with complete relief.

During the 2nd year of his monthly omalizumab treatment, he came to our hospital in September 2020 because of newly developed dry cough. His diagnosis was confirmed by a positive PCR test for COVID-19 after 20th day of the last omalizumab treatment dose, although his chest CT did not show any signs of viral infection. On his physical examination, wheezing was detected bilaterally. His omalizumab treatment was suspended. The progress of the disease was explained to him, and he was sent home for self-quarantine. During this time, no other symptom was detected, and his asthma stayed under control. His COVID-19 medications included Plaquenil for 5 days, and there was no need for additional regimens. We confirmed his recovery by a negative PCR test after the 10th day of COVID-19 symptoms. His routine treatment with monthly omalizumab was continued after his symptoms disappeared and after 45th day of PCR negativity.

### DISCUSSION

The 2 cases we presented can be considered similar as they both have received anti-IgE therapy as part of the Global Initiative for Asthma (GINA) step 5 management guidelines.<sup>9</sup>

It was only after initiation of this therapy that their symptoms could be controlled. It is important to note that they have been receiving this treatment until the detection of PCR positivity for COVID-19. The biologic therapy was then postponed until they fully recovered from COVID-19.<sup>7</sup>

We had 35 severe asthma patients in our clinic and 17 of them were receiving either omalizumab or mepolizumab therapy. Only 4 of them had COVID-19 disease during the pandemic and it was mild. Two of them were on biological therapy. None of these 4 COVID-positive patients reported an asthma exacerbation during their self-quarantine period. Adding to that, the cases we present are also good examples of the borderline presentations of COVID-19, lacking symptoms like fever and shortness of breath which used to be fundamental in diagnostics. They also pose a difficulty in differentiating asthmatic symptoms from the viral presentation as coughing and nasal congestion are also seen in rhinitis or mild asthma. At this point, self-vigilance and COVID-positive contact history seem to be crucial in early diagnosis. Additionally, using multiple diagnostic procedures as a combined approach seems to be the most effective treatment strategy. Singular approaches might come up as false negative or not reveal specific viral pathology as in the CT results of our patients.

It might be proposed here that the reason why some of the canonical respiratory symptoms are lacking is because of the unique interaction of allergic mechanisms and the viral entrance via the angiotensin-converting enzyme II (ACEII) receptor. Inhaled corticosteroids, biological, and other asthma controllers—which these patients have been using consistently—could also have modified the cellular environment of the airways and the presentation of the COVID-19 disease.

The similar courses that these 2 cases followed made us revisit some questions which have proved to be challenging for both allergists and infectious disease specialists worldwide. We believe it is important to address them to clarify the modified gold standards of asthma management during the COVID-19 pandemic.

### **Overall, Does Asthma Increase COVID-19 Risk or Worsen the Outcome?**

It is impossible to give a concise answer to this question as many variables are still missing from what seems to resemble less of a linear equation each day.

The most profound support for the protective effect of allergic asthma was put forward by the ACEII receptor expression studies.<sup>10</sup> It is now well established that the ACEII receptor levels, which the virus uses to enter the cell, are critical in determining the viral load. When the expression levels in asthmatics were checked, they were found to be lower than the general population. A detailed summary of the mechanisms suggested can be found in Figure 1. Although the transmembrane serine protease 2 (TMPRSS2)—which the virus uses to facilitate its entry—levels were found to be increased in individuals with asthma, the cumulative effect is claimed to be determined by the ACEII levels.<sup>10</sup> This could be in some ways attributed to the Th2 inclination in the cellular

environment in people with atopic diseases. Ultimately, this might provide a more suitable environment for immune cells to mount an appropriate response.

However, this might sound counterintuitive to some extent since we also know that Th2-driven responses suppress Th1 responses that constitute the main arsenal against viral pathogens.<sup>11</sup> Especially in asthmatic patients, this is shown by decreased Interferon Beta (IFN-B) levels, lower rates of apoptosis of infected cells, increased eosinophilic airway remodeling, and higher neutrophilic load, which can worsen respiratory symptoms.<sup>12</sup>

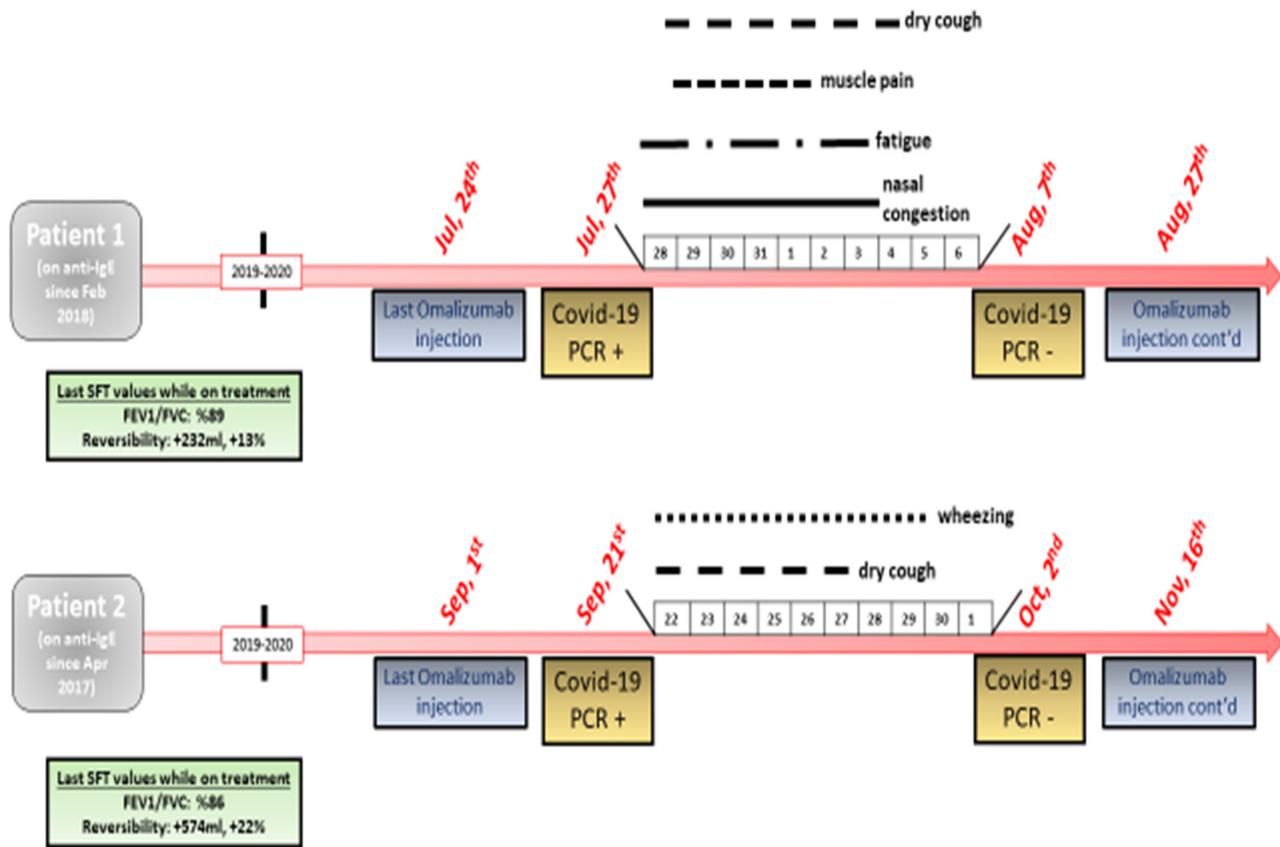
In a recent meta-analysis of 107,983 patients with COVID-19, asthmatic individuals—especially young and obese—were found to be more at risk for intubation, but ultimately had a better prognosis when compared to non-asthmatic individuals.<sup>13</sup> However, the majority of other studies have highlighted that asthma patients, in general, may not be at risk for severe COVID-19, which may be due to a potential protective effect of type 2 inflammation.<sup>14-16</sup> From the earliest observations, it has appeared that the course of COVID-19 is heterogeneous, varying from asymptomatic infection to severe pneumonia. Although results remain controversial, at this time, asthma does not appear to positively or negatively affect the outcomes of COVID-19.<sup>17</sup>

Several risk factors for poor outcome of COVID-19 have been identified, including sex (male), older age, diabetes, cardiovascular disease, and obesity.<sup>1</sup> Cases 1 and 2 were relatively young for having a worse prognosis, and there were no asthma comorbid conditions, such as bronchiectasis or obesity or any other risk factors, such as diabetes or cardiovascular disease. It is, therefore, important to underline that young age and the absence of additional risk factors on their own—especially for our cases—are important determinants of a better outcome and need differentiation from the effect of asthma.

In particular, the beneficial effects of inhaled corticosteroids and their downregulating effect on ACEII receptors along with interference with viral assembly were reported.<sup>18,19</sup> Certain cohort studies could demonstrate a significant effect only on certain age groups—older than 50 years of age—when compared to individuals not using inhaled corticosteroids.<sup>20</sup> Nevertheless, we know from prior global experiences with viruses that well-controlled asthma patients are less susceptible to exacerbations during acute infections.<sup>2,12</sup> Th2 high inflammation, inhaled steroid use, ACE receptor gene downregulation, and good asthma control may all have an impact on better outcomes of COVID-19 patients with asthma.

### **When Should a Person with Asthma Go Through Diagnostic Testing for COVID-19, Given the Lack of Symptoms?**

As seen in our cases, these individuals have been receiving immune modulators varying from inhaled corticosteroids to biologicals for long periods of time. This might have altered their airway responses. Apart from its interaction with the virus and being either a risk or a benefactor, it is considerable to assume that these individuals are responding differently to airway pathogens.



**Figure 1.** Brief timeline and summary of symptoms. The timelines are depicted in parallel to draw similarities between the courses of the 2 cases. The lines represent the persistence of symptoms on a daily basis. Both patient 1 (F, 31 years) and patient 2 (M, 46 years) presented to our clinic 2 years ago with severe asthma symptoms that didn't respond to step 4 regimens. After consecutive anti-IgE injections, they had no asthma attacks with only mild symptoms when the pandemic began. Their most recent renal function test (RFT) values are included in the diagram. As discussed later, performing routine RFT was avoided during the pandemic. A step-down approach was also not preferred for the same reason. Patient 1 developed a dry cough as the presenting symptom whereas patient 1 had very bleak symptoms that included nasal congestion primarily. Laboratory confirmation could be achieved with only polymerase chain reaction (PCR) testing as computerized tomography (CT) scans revealed no viral pathology in both patients. During the course of the disease, there was no exacerbation, ER admission, worsening symptoms such as shortness of breath and fever, ICU need, or increased reliever use. It is important to also note that both patients had received their biological treatment close to their initial PCR positivity. After the resolution of symptoms, we documented PCR negativity on the 10th day of infection in both patients. Subsequently, the anti-IgE therapy was continued without any change in the status of asthma.

From what we could learn from COVID-19 so far, it tends to dry up the mucosa and leads to coughing and other lower respiratory symptoms, including shortness of breath. Patients with asthma may not show this progression or display them irrespective of order. In that case, we should educate our patients about other symptoms of viral infection, such as, but not limited to, muscle pain, hoarseness, fatigue, and congestion, as presented here. Accessibility to testing is also crucial since one modality can turn up negative whereas the other might not. Patients should also keep track of positivity in close relatives, friends, and coworkers. This increases the chance that the current symptom is actually related to COVID-19.

**How a Person with Asthma and COVID-19 Should Be Managed at Home if Symptoms are Mild?**

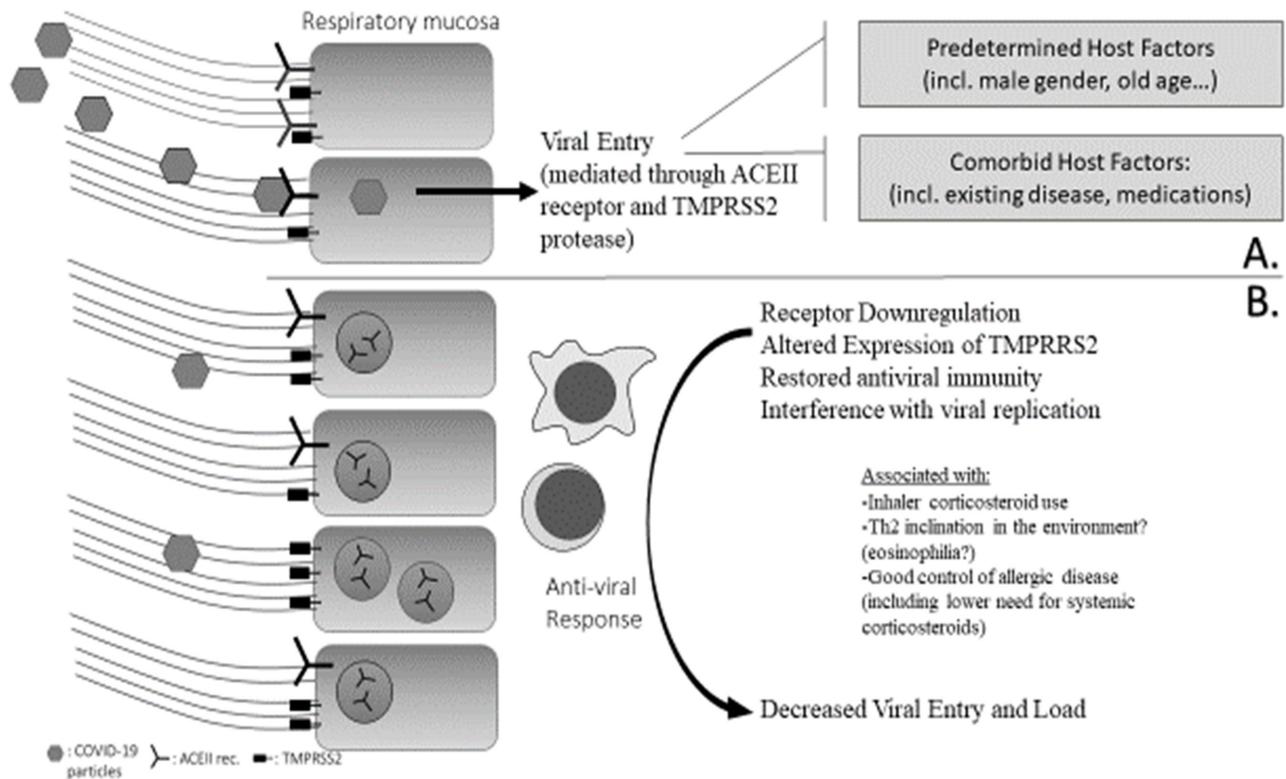
In Turkey, according to the latest state guidelines, patients with mild symptoms during COVID-19 were advised/obligated to apply self-quarantine measures.<sup>8</sup> We also complied with those rules and used telemedicine options to assess our patient's symptoms and well-being. They were educated on the conditions in which they should seek further medical help and which medical centers can provide such aid. As per the guidelines, patients should continue all their current

controllers and relievers when needed. Only biologicals are discontinued for the duration of COVID-19 positivity, shown by PCR.<sup>7</sup>

Patients should be stratified according to their severity, and mild cases should refrain from hospital exposure and could rather receive medical counsel via telehealth opportunities instead. These can include e-mails, text messages, or applications. Nebulizers can be used in home settings if adequate ventilation of the room and isolation can be provided for the patient. If not, however, it should be avoided to decrease infectivity. If the patient reports any worsening of symptoms, which might include exacerbations or persistence of the symptoms without improvement, he or she should be admitted to designated centers. Allergists can then prefer to arrange a visit, having met all the criteria for personal protection and containment of the patient. Patients, therefore, should report their symptoms and severity to the physician in good order.

**What About Biologicals? How Safe are they During the Pandemic?**

Guidelines suggest the continuation of biologicals during the pandemic unless the patient tests positive for COVID-19 as



**Figure 2.** Representation of factors associated with a viral entry that may determine outcome and factors proposed to be protective in atopic/asthmatic individuals. (A) Among the mechanisms identified in the search for novel antivirals, angiotensin-converting enzyme II (ACEII) receptors and transmembrane serine protease 2 (TMPRSS2) hold great significance as they mediate viral entry into respiratory cells. Large cohorts and genetic profiling enabled us to establish certain risk factors related to these entities in the general population. It is anticipated that either with predetermined (i.e., male gender) or acquired (i.e., cardiovascular diseases) comorbidities, COVID can progress much faster into poor outcomes. However, the interaction doesn't seem to line up with the logic of a linear equation as certain comorbid diseases actually cause downregulation of ACEII receptors. This causes equivocity among the risk factors and protective entities.<sup>9</sup> (B) As presented in this report, new evidence has emerged to assert that some mechanisms could actually be protective. Due to a lack of asthmatics among international cohorts of severe COVID-19 patients, several theories on this mechanism have been proposed. Receptor downregulation, which counteracts the protease upregulation, seems to be one of the well-established factors at play here. Propositions on this include a protective effect of T helper 2 (Th2) inclination in the environment, inhaled corticosteroids affecting both the receptors and the virus itself, and good control of the allergic disease. Further research is fundamental as Th2 immunity is also known to suppress antiviral responses and cause catastrophic cytokine storms via IL-6.<sup>9</sup>

there has been no reported direct adversity in using biologicals during the pandemic.<sup>7</sup> Reports so far about their effect on the outcome are equivocal as there have been certain retrospective database reviews that pointed toward a worse outcome for patients on biologicals.<sup>21</sup> It is important to note that these studies are not exclusively specific about whether the patient stopped or continued biological use once the infection is established by laboratory testing. On the other hand, there have been also reports about their safety even though the patient is positive, but those included only a small group of cases to arrive at a clear conclusion on biological use for now.<sup>7,22-24</sup>

It might seem counterintuitive to suppress the immune system specifically with targeted therapies like anti-IgE or anti-IL-5, but as discussed earlier, good control seems to be more important in the treatment of COVID severity. Effects of Th2 inclination in the environment and whether it is protective only if kept under control by external modulators, like biologicals, are also unclear at this point. That is why biologicals should be seen as more of a modulator and organizer instead of a total suppressor. The same also applies to short-term OCS as evidence suggests.<sup>7,22-24</sup> The 2 cases we present here can, therefore, mean that favorable asthma control with

biological treatment is the most important factor in continuing biologicals in asthma patients after getting negative test results for COVID-19.

At this point, it is safe to say that allergists should focus on full patient compliance with asthma controllers that provide maximal relief. As in our cases and the ones found in the literature, good control of asthma symptoms seems to be the key to managing COVID-19 regardless of asthma severity. They, therefore, should not follow step-down strategies as this might cause harm rather than a benefit. Treatment of patients on biologicals targeting type 2 inflammation in allergic disease should be continued in non-infected individuals. In case of an infection, withholding the treatment is recommended until recovery.<sup>7</sup> Our cases had mild COVID infection, and treating severe asthma with omalizumab seemed to protect them against severe COVID-19 infection. Summary of changes in asthma management in the clinic and workflow for patients who contracted COVID-19 is given in Figure 2.

If modulation of Th2 immunity is found to be key in achieving better outcomes with COVID-19, application of such

a strategy in other susceptible groups—other than allergic patients—is also another question the scientific community can try to answer.

## CONCLUSION

There is conflicting data available now about the incidence of asthma—especially allergic asthma—in the face of COVID-19 in certain cohorts, case reports, and expression studies. This can actually mean the discovery of something unique about *Coronaviridae* or viral infections in general.

However, in order to substantiate our claims, we require deeper subgroup analyses of patient pools to include asthma phenotypes, severity, control, and the treatments received. This can lay the foundation for studies at a molecular level that yield solid results in primary cultures.

After that, we would not only be able to determine the variables in this complex interaction but also identify a new possible drug target, “the Th2 processes.” This will be especially beneficial for not only asthma patients but also other individuals.

Apart from that, maintaining good control of asthma patients during the pandemic is crucial. Physicians should not follow step-down strategies and continue necessary regimens, including biologicals, to maintain control. As seen in our patients, to maintain control seems to be a very strong predictor of a milder disease course and outcome.

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