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Case report

Impact of omalizumab therapy on the course of COVID-19 in a patient with severe asthma: A case report

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Abstract

Introduction: Various risk factors have been attributed to coronavirus disease 19 (COVID-19) severity. Omalizumab as an immunoglobulin E blocker that enhances anti-viral immunity might be a potential cytokine storm trigger.

Aim: Our goal was to investigate if the treatment with omalizumab due to severe asthma is a risk factor of severe COVID-19 pneumonia and if severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can trigger asthma exacerbation.

Case study: We report the case of a 65-year-old patient with severe allergic asthma receiving treatment with omalizumab for last 8 months with good results, who in December 2020 was infected with SARS-CoV-2. The patient was not vaccinated against COVID-19 (no vaccine was available at that time), and had comorbidities.

Results and discussion: COVID-19 course of presented patient was asymptomatic and resolved quickly without the need for hospitalization or asthma exacerbation. There was a slightly worse score on the asthma control questionnaire after COVID-19 resolution (2.1 point vs. 1.5 points) and a threefold increase in eosinophil counts (660 cell/μL vs. 230 cell/μL). However, no wheezing or deterioration in pulmonary function tests were found. A computed tomography of the chest revealed only minor densities of pulmonary parenchyma and thickened walls of bronchi.

Conclusions: Omalizumab used in the treatment of severe allergic asthma proved to be safe and beneficial for the course of COVID-19 in the case reported. Simultaneously, SARS-CoV-2 was not a factor for asthma exacerbation.

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1. INTRODUCTION

The novel coronavirus disease of 2019 (COVID-19) is currently the greatest healthcare challenge in the world. The course of COVID-19 is variable and heterogeneous, varying from asymptomatic infection to severe pneumonia.[1,2] There is some evidence that patients with allergic asthma are protected from severe COVID-19 due to low expression of angiotensin-converting enzyme 2 (ACE2) in bronchial epithelial cells, used by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to enter cells.[3] However, the T helper cell type 2 (Th2) milieu with increased immunoglobulin E (IgE) level and expression of the high-affinity IgE receptor (FcεRI) on plasmacytoid dendritic cells (pDCs) were found to be inversely related to pDC interferon (IFN) production in response to viral infection.[4] As IFNs play an important role in the primary defense against respiratory viruses by limiting the viral spread, impaired IFN synthesis makes allergic individuals more prone to viral infections, which are often a trigger for asthma exacerbation.[5] This has been confirmed for influenza and human rhinovirus. Downregulated expression of toll-like receptor 9 (TLR-9) on pDCs, which is responsible for viral RNA recognition, and decreased production of IFN lambda in asthmatics with IgE allergy correlated with the severity of viral-induced asthma exacerbation.[6,7] On the other hand, in a mouse model of SARS-CoV-2 infection, the absent or low IFN response was beneficial in preventing monocyte and macrophage lung infiltration, cytokine storm and abnormal T-cell response manifested by hyper-inflammation, observed in the later phase.[8] Eosinophilic inflammation in the respiratory tract of asthmatics and an increased number of circulating eosinophils have been also supposed to be helpful for anti-SARS-CoV-2 response. Eosinophil cationic protein and eosinophil derived neurotoxin are enzymes that neutralize the virus.[9] All this was reflected in the research results. A systemic review and meta-analysis of 131 studies in 40 different countries found that asthma is not a risk factor for worsening COVID-19 and poor prognosis.[10] Nevertheless, in the beginning of the COVID-19 pandemic, there was concern about patients with severe asthma being treated with biologics, including omalizumab. This anti-IgE humanized monoclonal antibody that blocks the type 2 pathway by sequestering free IgE and inhibiting inflammatory cells, including eosinophils, reduces asthma exacerbation and improves the antiviral response associated with promoting IFN production.[11] It remains unclear whether this restored antiviral response is balanced or excessive, or whether an immune hyperactivity or a failure to resolve the inflammatory response underlies severe cases of COVID-19. The first reports showed mild COVID-19 courses in patients with severe asthma under omalizumab therapy.[12] However, there are also some data, which reflected the opposite conclusion.[13] Currently, guidelines recommend asthma patients continue their biological therapy in case of a mild to moderate COVID-19 course and consider extending the dosing interval or discontinuing treatment in severe courses.[14,15] Nevertheless, more research is needed to evaluate the antiviral and immunomodulatory effects of biologics used in severe asthma patients who have contracted SARS-CoV-2, especially considering that SARS-CoV-2 changes rapidly due to mutations.

2. AIM

Our goal was to determine the impact of omalizumab therapy on the course of COVID-19 and asses the risk of asthma exacerbation in case of SARS-CoV-2 infection.

3. CASE STUDY

Here, we report the case of SARS-CoV-2 infection in a 65-year-old man with severe asthma treated with omalizumab (600 mg per month). The patient has suffered from early onset allergic asthma with house dust mite allergy for 40 years, which had become severe in the last 2 years before taking the biologic. As comorbidities, he had chronic sinusitis, perennial allergic rhinitis, hypertension, and psoriasis. His body mass index of 28 kg/m^2 indicated he was overweight. He has been treated with a fixed combination of inhaled corticosteroids at high doses (fluticasone propionate and ciclesonide), long-acting β2-agonist (formoterol), long-acting muscarinic agonist (tiotropium), nasal steroid (mometasone), and antihistamine (rupatadine). Despite this, his asthma was uncontrolled. Since April 2020, omalizumab therapy has been initiated. In result, asthma control improved. On December 21, 2020, 1 day before the scheduled omalizumab administration, he tested positive for SARS-CoV-2 in the polymerase chain reaction (PCR) test without any symptoms of COVID-19. He was not vaccinated, since the vaccine was unavailable at that time. A few days before, his wife developed moderate COVID-19, proven by the PCR test, however without the need for hospitalization. Due to the asymptomatic course of COVID-19 and lack of asthma exacerbation, he was isolated at home together with his wife. His treatment regimen did not change. Of note, due to hypertension, he was on an angiotensin-converting-enzyme inhibitor, quinapril. On January 12, 2021, after the end of isolation, he was assessed in our unit due to planned administration of the next dose of omalizumab. He remained free of COVID-19 related symptoms, nevertheless, he complained of deterioration in exercise tolerance and breathlessness for the last week, which he tried to control using a short-acting β2-agonist (1–2 doses daily). The peak expiratory flow (PEF) was comparable with the result obtained in November 2020 (3.68 L/s vs. 3.74 L/s). He had a slightly worse score (2.1 points vs. 1.5 points) in the asthma control questionnaire (ACQ). The quality of life assessed in the mini asthma quality of life questionnaire (miniAQLQ) was 4.8 points vs. 4.4 points. On physical examination, no wheezing was found. Laboratory tests revealed an over threefold increase of interleukin 6 (22.7 pg/mL), vitamin D deficiency (16.6 ng/mL) and an increase of eosinophil count from 230 cells/μL to 660 cells/μL

Table 1. Laboratory parameters before and after COVID-19.

Laboratory parameters	Standard	Before COVID-19 10.07.2020	After COVID-19 12.01.2021
Leukocytes, cells/μL	4000–10000	8440	11040*
Erythrocytes, cells/μL	4.5–5.5 × 10^6	4.74 × x 10^6	4.61 × 10^6
Hemoglobin, g/dL	14–18	15.4	15.3
Eosinophils, cells/μL	0–600	230	660*
Neutrophils, cells/μL	2500–6000	6840	6760*
Lymphocytes, cells/μL	1500–3500	2060	2650
Platelets, cells/μL	140–440 × 10^3	334 × 10^3	262 × 10^3
Interleukin-6, pg/mL	0–5.9	–	22.7*
Ferritin, μg/L	20–290	–	110
Fibrinogen, g/L	2–4.39	–	3.6
D-dimer, μg/mL	<0.5	–	0.5
CRP, mg/L	0.2–5	2.5	7*
Procalcitonin, ng/mL	<0.05	–	0.02
LDH, U/L	125–220	–	179
Vitamin D, ng/mL	30–100	–	16.6*
AST, U/L	5–34	23	16
ALT, U/L	0–55	23	16
GGTP, U/L	12–64	–	53
Total protein, g/dL	6.4–8.3	–	6.9
Creatinine, mg/dL	0.73–1.18	1.07	0.84
BNP, pg/mL	0–125	–	7.4

Comments: – undefined result; * abnormal result; CRP – C-reactive protein; LDH – lactate dehydrogenase; AST – aspartate aminotransferase; ALT – alanine aminotransferase; GGTP – gamma-glutamyl transferase; BNP – b-type natriuretic peptide.

(Table 1). A high-resolution chest CT scan revealed slight densities of pulmonary parenchyma without consolidation and areas of ground-glass opacity. Thickened walls of the bronchi were visible. Due to the lack of contraindications, omalizumab was administered. One week later, he was negative for SARS-CoV-2 in the PCR test. Additionally, at the check-up, he reported clinical improvement. Exercise dyspnea considerably decreased. He did not need reliever medications. Spirometry revealed a very severe airway obstruction – forced expiratory volume in the first second (FEV1) 1.16 L (33%), forced vital capacity (FVC) 2.67 L (59%), FEV1/FVC 43% – as previously noted, and only a small decrease in FEV1 (160 mL, 4 %) compared to results before infection. PEF value was stable (3.70 L/s vs. 3.68 L/s).

4. DISCUSSION

Factors influencing the severity of COVID-19 are still being studied. It has been hypothesized that omalizumab, which breaks the negative link between IgE and IFN-α, might induce excessive IFN response and lead to a cytokine storm and severe COVID-19.[14] Meanwhile, available publications pointed to the opposite result.[16–18] Among them, Lommatzsch et al.[16] reported a case of COVID-19 without pneumonia and asthma exacerbation in a patient treated with omalizumab that could safely be continued during active COVID-19. Rial et al.[18] had a similar observation. Of the 545 severe asthma patients under biological therapy, 14 were treated with omalizumab, and only 1 of them had to be hospitalized and admitted to the Intensive Care Unit (ICU).[18] Moreover, there were no significant differences in terms of COVID-19 severity, ICU admissions and mortality between patients with severe asthma treated with biologics and mild/moderate asthma patients without biological treatment.[18] Only Eger et al.[13] demonstrated higher mortality, and more severe courses of COVID-19 associated with exacerbation of asthma and the necessity of mechanical ventilation. However, there were only 2 patients and both had comorbidities such as diabetes mellitus, obesity, and cardiovascular disease that could have influenced of COVID-19 course.[13]

In the case presented, the patient overcame the SARS-CoV-2 infection without hospitalization, antiviral treatment, and oxygen therapy. He was asymptomatic, and it was likely due to good control of asthma and comorbidities. Medicines such as ciclesonide and formoterol in addition to the treatment of asthma have additionally been shown to mitigate lung inflammation in COVID-19 by increasing lymphocyte count and inhibiting SARS-CoV-2 replication.[19,20] This was closely related to the reduced expression of ACE2 and transmembrane protease serine 2 (TMPRSS2).[21] Additionally, correct and stable blood pressure is predictive of a better prognosis.[22] In the case presented, these conditions were provided by quinapril, an angiotensin converting enzyme inhibitor (ACEI). Despite initial concerns that ACEI or angiotensin receptor blockers (ARB) by increasing ACE2 concentration may increase the susceptibility to COVID-19 infection and its severity, this has not been proven.[23] The asymptomatic COVID-19 course in our patient also contradicts this. ACEIs in COVID-19 are seen as harmless and potentially reducing mortality, but data on beneficial effects are inconclusive.[23] However, for this patient, omalizumab was of the greatest importance for asthma control and effective antiviral response. This monoclonal antibody by, blocking free IgE makes the formation of IgE–FcεRI/IgE–FcεRII complexes and cross-linking impossible. This causes a reduction in the number of surface-exposed FcεRI receptors located on pDC, as well as on mast cells and basophils. It stabilizes cells, protects from degranulation and IgE-mediated allergic reaction resulted in better asthma control and decreased risk of exacerbation.[11] Moreover, since low FcεRI expression on pDC correlates with high TLR-9 expression, RNA viruses are better recognized.[4] This increases pDC IFN production and enhances the antiviral response, also against SARS-CoV-2, ensuring better viral clearance, as probably was the case in the patient under study.[7,24] How important IFN is in SARS-CoV-2 clearance was demonstrated by Davoudi-Monfared et al.[25] They showed that early antiviral therapy with subcutaneous injection of IFN-β-1a was effective in the treatment of severe COVID-19, increasing discharge rate and decreasing fatalities.[25] On the other hand, patients with inborn immunodeficiency in IFN-I pathways related to TLR-3 defects and/or nuclear factor-κβ (NFKB) mutation, as well as with present neutralizing au-

toantibodies to IFNs, had life-threating COVID-19 pneumonia.[26,27] All of this highlights the beneficial effect of omalizumab in the course of COVID-19, which is enhanced by its anti-inflammatory properties. Omalizumab protects from the degranulation of mast cells and prevents the release of pro-inflammatory mediators and cytokines (i.e. IL-1β, IL-6 and tumor necrosis factor alpha i TNF-α) involved in COVID-19 hyper-inflammation.[28] Its inhibitory effect was also observed in case of neutrophils, which together with macrophages play a key role in COVID-19-related acute lung injury.[28]

The issue of eosinopenia is also interesting, as it was found to be characteristic of patients newly infected with SARS-CoV-2, and a persistent case was a hallmark of severe COVID-19 and higher mortality.[29] Hence, there have been doubts about the use of omalizumab, known to induce eosinophil apoptosis.[11] However, there is evidence that eosinopenia induced by anti-IL-5/IL-5R therapy (mepolizumab/benralizumab) did not influence COVID-19.[30] In turn, patients with eosinophil-related diseases do not have an altered course of COVID-19.[31] In our patient, eosinophil count at the beginning of SARS-CoV-2 infection was not determined, but a threefold increase was noted after COVID-19 resolution compared to results before infection. One of the reasons the increased eosinophil count might be the delay in omalizumab administration that resulted in asthma deterioration. However, due to the lack of need to use systemic corticosteroids, the stable value of PEF and parameters of spirometry, the recovery process from COVID-19 seems to be more likely.[32] In addition, despite omalizumab therapy the eosinophil count before COVID-19 was quite high (230 cell/μL). This number, hypothetically further reduced at the time of SARS-CoV-2 infection, was still sufficient to ensure an asymptomatic COVID-19 course. This confirms the safety of omalizumab therapy or suggests no importance of eosinophil counts in the evolution of COVID-19. Interestingly, Gao et al.[22] suggested that not eosinophil counts but decreased eosinophil expression of the chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2) and/or increased checkpoint inhibitor programmed death ligand-1 (PDL1) represent a risk factor for severe COVID-19.

6. CONCLUSION

1. Treatment with omalizumab preceding SARS-CoV-2 infection was beneficial for the course of COVID-19, as it conditioned good asthma control and improved antiviral immunity, ensuring the asymptomatic course of the disease.
2. Concerns about omalizumab inducing excessive antiviral (IFN-related) response, favoring severe COVID-19, were not confirmed.
3. There was also no evidence of impaired immune response to SARS-CoV-2.
4. No asthma exacerbation was noted, and the temporal loss of asthma control was due to mandatory isolation and delay of omalizumab administration.
5. Omalizumab treatment of asthmatics in asymptomatic/mild COVID-19 cases should be continued.
6. Efforts should be made to increase omalizumab self-administration at home.

Conflict of interest

None declared.

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Ethics

Written informed consent was obtained from the patient for his anonymized information to be published in this article.

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