Original article

Safety of biological therapy in children and adolescents with severe asthma during the COVID-19 pandemic: a case series

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Abstract. *Background and aim:* It is still unclear whether patients with severe asthma are at greater risk of developing severe COVID-19, particularly pediatric allergic patients under biologic therapy. Studies targeting pediatric patients are currently limited; thus, this study aims to assess the clinical characteristics of young patients with severe asthma under biological therapies during the COVID-19 pandemic. *Methods:* We collected data from February 2020 to April 2021. Patients with severe asthma treated with biological therapies (omalizumab and mepolizumab) have been enrolled. We described demographic data, clinical features, therapies, comorbidities, and laboratory findings for each patient. For patients who got COVID-19, we also described the severity of the disease, the need for hospitalization, and specific therapy. *Results:* A total of 14 patients were included in the study, 11 (78.6%) of them under treatment with omalizumab and 3 (21.6%) with mepolizumab. We identified four patients (28.6%) who tested positive for SARS-CoV-2. Two patients treated with mepolizumab had an asymptomatic disease, and two patients treated with omalizumab had mild disease. Only one patient with mild COVID-19 required hospitalization and specific therapy because of severe obesity. *Conclusions:* No differences regarding the SARS-CoV-2 infection have been found between the two treatments groups. Furthermore, any poor outcome has been observed, confirming the safety of biological therapies. The limited number of patients enrolled and the lack of a control group did not establish a significant risk for infections for these patients. (www.actabiomedica.it).

Keywords: Asthma, Biological therapy, Children, COVID-19, Mepolizumab, Omalizumab, SARS-CoV-2 infection.

Introduction

On March 11th, 2020, the World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) pandemic, caused by a new coronavirus named severe acute respiratory syndrome 2 (SARS-CoV-2) (1,2). Italy was the first European Country involved in the pandemic (3,4).

Respiratory viral infections, including SARS-CoV-2, are a significant cause of morbidity and exacerbations of asthma (5). Although chronic lung diseases are known as a potential risk factor for COVID-19 related complications, it was recently reported that young patients with well-controlled asthma did not demonstrate a more severe SARS-CoV-2 infection because of a low expression of angiotensin-converting enzyme 2 (ACE2) in bronchial epithelium cells (6,7). Currently, data about biological treatment in the COVID-19 pandemic are still lacking, especially in the pediatric asthmatic population (8,9). Therefore,

this study aims to assess the clinical and functional characteristics of children and adolescents with severe asthma under biological therapies (omalizumab and mepolizumab) during the COVID-19 pandemic.

Methods

We conducted a retrospective observational study, collecting data from February 2020 to April 2021.

All patients with severe asthma treated with biological therapies were included. Diagnosis of severe or uncontrolled asthma was made according to GINA 2020 guidelines (https://ginasthma.org/wp-content/uploads/2020/04/Main-pocket-guide_2020_04_03-final-wms.pdf). All asthmatic children and adolescents were followed at the Pediatric Clinic in Pavia. For each patient, we collected demographic data (age, sex), asthma-related comorbidities (obesity, allergic rhinitis, chronic rhinosinusitis with nasal polyposis, atopic dermatitis, anaphylaxis, Widal syndrome, allergic bronchopulmonary aspergillosis, and gastroesophageal reflux disease). According to GINA guidelines, asthma control was assessed using the lung function test (FEV1), the dosage of inhaled corticosteroids, and hospitalizations/year (10). We collected fractional exhaled nitric oxide (FeNO) values, total serum IgE, and blood eosinophil count. Furthermore, for patients who tested positive for SARS-CoV-2, we reported disease severity (according to the WHO classification), the need for hospitalization, and specific therapy for COVID-19.

All data were extracted from electronic medical records (Fenix™, Software). Every patient identifier (name and surname) was replaced with a specific numeric code. Statistical analysis was performed through GraphPad Prism 9.3.0, and statistical significance was set at $p<0.05$. This study was approved by the Ethical Committee (protocol number: 34401/2020). All enrolled patients provided written informed consent.

Results

Fourteen patients with severe asthma followed at the Pediatric Clinic in Pavia were included in the study. Eleven (78.6%) patients were treated with omalizumab and 3 (21.6%) with mepolizumab.

Eight (57%) patients were males, of these seven were treated with omalizumab and 1 with mepolizumab.

Demographic features of enrolled patients are summarized in Table 1.

Comorbidities

No significant differences were found between the two groups. The mean BMI was 23.9±7.5 kg/m^2. Two patients presented severe obesity (BMI > 30 kg/m^2) and were equally distributed among the two treatment groups. No patients treated with mepolizumab were affected by allergic rhinitis, atopic dermatitis, allergic bronchopulmonary aspergillosis (ABPA), or gastroesophageal reflux disease (GERD). On the contrary, these comorbidities were found in 46%, 3%, and 1% of patients treated with omalizumab, respectively. Chronic rhinosinusitis with nasal polyposis (CRSwNP) was found in three (21%) patients, one of them treated with omalizumab. Only one patient treated with mepolizumab was affected by Widal syndrome. Comorbidities are summarized in Table 2.

Table 1. Demographic features of enrolled patients.

Demographic features	Total (n = 14)	Omalizumab (n = 11)	Mepolizumab (n = 3)	p value
Male, *n (%)*	8 (57.0)	7 (64.0)	1 (33.0)	0.53
Age, *mean (min - max)*	14.3 (7 - 25)	12.3 (7 - 20)	23.7 (23 - 25)	*0.0008*
Age distribution				
6 - 12 years, *n (%)*	6 (43.0)	6 (55.0)	0	0.21
12 - 18 years, *n (%)*	4 (29.0)	4 (36.0)	0	0.51
> 18 years, *n (%)*	4 (29.0)	1 (9.0)	3 (100.0)	*0.01*

Table 2. Asthma-related comorbidities.

Comorbidities	Total (n = 14)	Omalizumab (n = 11)	Mepolizumab (n = 3)	p value
BMI, *mean ± SD*	23.9 ± 7.5	22.7 ± 5.1	28.0 ± 14.1	0.30
Obesity,* *n (%)*	2 (14.0)	1 (9.0)	1 (33.0)	0.40
Allergic rhinitis, *n (%)*	5 (36.0)	5 (46.0)	0	0.26
Atopic dermatitis, *n (%)*	3 (21.0)	3 (27.0)	0	>0.99
CRSwNP, *n (%)*	3 (21.0)	1 (9.0)	2 (67.0)	>0.99
Anaphylaxis, *n (%)*	1 (7.0)	0	1 (33.0)	>0.99
Widal Syndrome, *n (%*)	1 (7.0)	0	1 (33.0)	>0.99
ABPA, *n (%)*	1 (7.0)	1 (7.0)	0	>0.99
GERD, *n (%)*	1 (7.0)	1 (7.0)	0	>0.99

*BMI > 30 kg/m^2; ABPA, Allergic Bronchopulmonary Aspergillosis; BMI, body mass index; CRSwNP, Chronic Rhinosinusitis with Nasal Polyposis; GERD, Gastroesophageal Reflux Disease; SD, standard deviation.

Asthma control and biomarkers

Overall, most patients had well-controlled asthma (64%). All patients treated with mepolizumab had well-controlled asthma. Four patients treated with omalizumab had partially controlled asthma and one uncontrolled asthma. Six (43%) patients had more than two exacerbations/year that required hospitalization in two cases. Six (43%) patients were on a high dose of inhaled steroids combined with omalizumab therapy. The mean value of FeNO was 41.0 ± 8.7 ppb.The mean value of total serum IgE was 1,239.4 ± 868.2 KU/L, which was higher in patients treated with omalizumab. The mean value of blood eosinophils was 0.48 ± 0.3 x10^3 cells/uL; 79% of enrolled children and adolescents had more than 150 eosinophils/uL. The asthma control assessment and biomarkers are shown in Table 3 and Table 4.

Table 3. Assessment of asthma control.

Asthma control	Total (n = 14)	Omalizumab (n = 11)	Mepolizumab (n = 3)	p value
GINA control				
uncontrolled, *n (%*)	1 (7.0)	1 (9.0)	0	>0.99
partly controlled, *n (%)*	4 (29.0)	4 (36.0)	0	0.51
well controlled, *n (%)*	9 (64.0)	6 (55.0)	3 (100.0)	0.25
FEV1, *mean ± SD*	88.1 ± 18.7	87.4 ± 21.2	90.7 ± 4.0	0.80
ICS high dosage, *n (%)*	6 (43.0)	6 (55.0)	0	0.20
2 exacerbations/year, *n (%)*	6 (43.0)	5 (45.0)	1 (33.0)	>0.99
Hospitalization/year, *n (%)*	2 (14.0)	2 (18.0)	0	>0.99

SD, standard deviation.

Table 4 Biomarkers of asthma.

Biomarkers	Total (n = 14)	Omalizumab (n = 11)	Mepolizumab (n = 3)	p value
FeNO, *mean ± SD*	41.0 ± 8.7	45.0 ± 92.0	17 ± 1	0.41
Total serum IgE, *mean ± SD*	1,239.4 ± 868.2	1,399.8 ± 865.5	651.3 ± 702.9	0.20
Eosinophils, *mean ± SD*	0.48 ± 0.3	0.54 ± 0.35	0.29 ± 0.22	0.30
Eosinophils > 150, *n (%)*	11 (79.0)	9 (82.0)	2 (67.0)	>0.99

SD, standard deviation.

COVID-19 patients

In our cohort, four (28.6%) patients tested positive for SARS-CoV-2; 3 (75%) were female and one male. Two of them were treated with omalizumab and two with mepolizumab. Any patients younger than 14 years tested positive for SARS-CoV-2. Two patients with COVID-19 were obese, and one of them required the administration of specific anti-SARS-CoV-2 monoclonal therapy. COVID-19 presented with mild symptoms (fever, cough, headache, and fatigue) in two (50%) patients; the other two (50%) patients were asymptomatic. The clinical features of these patients are summarized in Table 5.

Discussion

This study reported the experience of a tertiary pediatric center, highlighting the safety of biological therapy for severe asthma during the COVID-19 pandemic. In our cohort, about 30% of children and adolescents had COVID-19. Two patients treated with omalizumab developed a mild disease that required the administration of specific monoclonal antibodies in one case. The other patients were asymptomatic and treated with mepolizumab. These results align with the recent literature, suggesting that well-controlled asthma does not increase the risk of severe COVID-19, probably for the lower expression of ACE-2 receptors in respiratory epithelial cells (8,11). Asthma therapy is crucial in reducing lung type 2 inflammation. The use of inhaled steroids does not increase SARS-CoV-2 susceptibility. An *in vitro* study demonstrated that inhaled corticosteroid suppresses the replication of coronaviruses, including SARS-CoV-2, in cultured cells (12). As reported in another observational study, biological therapy for severe asthma may also have a protective role against more severe COVID-19 (13). Atopic patients generally show low level of interferon-gamma (INF-γ) produced by mononucleate, dendritic, and bronchial epithelium cells. INF-γ is a crucial mediator of immune defense against respiratory viruses (14). It is widely known that omalizumab, the anti-IgE monoclonal antibody, increases the production of INF-γ then the defense against respiratory viruses (15). Moreover, it was reported that omalizumab also reduces pro-inflammatory cytokines, such as IL-33, IL-6, IL-1β, and TNF-α (16). The PROSE (Preventative Omalizumab or Step-up Therapy for Severe Fall Exacerbations) study demonstrated a decreased

Table 5. Clinical features of asthmatic patients with COVID-19.

COVID-19 patients	Total (n = 4)	Omalizumab (n = 2)	Mepolizumab (n = 2)	p value
Male, *n (%)*	1 (25.0)	0	1 (50.0)	>0.99
Age, *mean (min - max)*	19.0 (14 - 23)	15.0 (14 - 16)	23.0	*0.01*
Age distribution				
6 - 12 years, *n (%)*	0	0	0	-
12 - 18 years, *n (%)*	2 (50.0)	2 (100.0)	0	0.33
> 18 years, *n (%)*	2 (50.0)	0	2 (100.0)	0.33
Uncontrolled asthma, *n (%)*	1 (25.0)	1 (50.0)	0	>0.99
Comorbidities, *n (%)*	2 (50.0)	2 (100.0) [§]	0	0.33
Obesity, *n (%)*	2 (50.0)	2 (100.0)	0	0.33
Hospitalization, *n (%)*	1 (25.0)	1 (50.0)	0	>0.99
Asymptomatic COVID-19, *n (%)*	2 (50.0)	0	2 (100.0)	0.33
Severe COVID-19, *n (%)*	0	0	0	-
Mild COVID-19, *n (%)*	2 (50.0)	2 (100.0)	0	0.33
Moderate COVID-19, *n (%)*	0	0	0	-
COVID-19 therapy, *n (%)* [°]	1 (25.0)	1 (50.0)	0	>0.99

[§]Obesity, [°]Therapy with monoclonal antibody

duration of respiratory virus infections, viral shedding, and risk of illnesses in asthmatic children (15).

Lindsey et al. reported that patients treated with biologics are not at significant risk for severe SARS-CoV-2 infection (17). Licari et al. published an Italian multicenter survey reporting data on the safe use of biological therapies in allergic children and adolescents during the first months of the COVID-19 pandemic (9). From February to April 2020, in 20 Italian pediatric centers, 308 children and adolescents (mean age 12.8 years, 161 males) were treated with biologics for chronic allergic diseases (asthma, chronic spontaneous urticaria, atopic dermatitis). 1% of these patients had COVID-19 with mild symptoms that did not require hospitalization (9). According to current guidelines, nobody experienced a worsening of their underlying allergic disease or stopped the biological therapy (18,19).

For these reasons, the GINA guidelines recommend continuing asthma control medications, including inhaled corticosteroids (ICS) during the COVID-19 outbreak (20). EAACI (European Academy of Allergy and Clinical Immunology) members also suggested continuing biological therapies in patients with severe asthma and initiating them in all patients who can benefit from limiting asthma exacerbations and oral steroids (21). The Italian Pediatric Allergy and Immunology Society (SIAIP) stated that biologics should be discontinued in the case of COVID-19 (18).

On the other hand, EAACI pediatric position paper suggested that patients with severe or uncontrolled asthma may have a higher risk of developing severe COVID-19 (22). However, there is no clear evidence that patients with asthma are at increased risk of contracting the disease and developing a poor outcome (23). One of the first Chinese case studies reported a prevalence of asthma corresponding to 0.9% in patients hospitalized for COVID-19, significantly lower than in the general population, which prevalence is 6.4% (24). Conversely, studies conducted in the United States showed a high rate of asthma in children and adults with COVID-19 than previously reported in China and Europe (25). Izquierdo et al. analyzed an extensive series of 71,182 patients with asthma founding only 1,006 (1.41%) cases of COVID-19 (26). However, the lower prevalence of asthma among COVID-19 cases could result from methodological biases due to overestimating or underestimating the asthma diagnosis. In addition, there is a high risk of not diagnosing COVID-19 disease, particularly in children. Mild disease in this population could be confused with asthma exacerbations (27). A British study analyzed data from a large case series of 17 million adults, including 10,926 deaths due to COVID-19, reporting that asthma was significant comorbidity in SARS-CoV-2 infection and death-related (28). However, the pediatric population was not included in this broad analysis. In a South Korean study, the authors noted that patients with allergic rhinitis and asthma had lower hospitalization rates, suggesting that allergic disease may have a potential protective effect (29). In an Italian survey of 198 children, Tosca et al. reported no significant difference between allergic and non-allergic patients concerning the hospitalization rate, pneumonia, and oxygen therapy prevalence due to COVID-19 (30). A paradoxical phenomenon reported is that asthmatic exacerbation decreases during the COVID-19 pandemic, probably due to less exposure to outdoor aeroallergens, reduced pollution with the lockdown, fewer viral triggers due to school closure (31). In a survey proposed by the Pediatric Assembly of the European Respiratory Society (ERS), only a tiny minority of SARS-CoV-2-infected children presented with an asthma exacerbation, and only five patients were admitted to PICU (30).

This study has several limitations. First, the relatively limited number of children and adolescents with severe asthma treated with biologics did not allow us to generalize these results. Moreover, the absence of a control group did not establish if asthmatic patients are at significant risk for infections. However, this study confirms the safety of biological therapy for severe asthma also during the SARS-CoV-2 infection.

Conclusions

This study evaluated the clinical and functional evolution of young asthmatic patients during the COVID-19 pandemic. Concerning the severity of COVID-19, we did not find differences between patients treated with omalizumab and mepolizumab.

All infected patients develop mild or asymptomatic COVID-19. The relatively limited number of enrolled patients did not generalize these results. More extensive further pediatric studies are needed to characterize these clinical aspects and confirm these results.

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Conflict of Interest: Each author declares that they have no commercial associations that might pose a conflict of interest in connection with the submitted article

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