

Biologic Use in Allergic and Asthmatic Children and Adolescents During the COVID-19 Pandemic

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Background: Biologics are the cornerstone of therapy in children and adolescents with severe or uncontrolled allergic diseases, such as asthma, atopic dermatitis, and chronic urticaria. Since the World Health Organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection a pandemic in March 2020, some scientific societies have released statements on the use of biologics in allergic children and adolescents.

Materials and Methods: Given the very limited data in Italy on use of biological therapies in allergic children and adolescents during the coronavirus disease 2019 (COVID-19) pandemic, a multicenter observational nationwide survey was conducted to collect this information. The 11-question survey was designed to determine (1) the number of allergic children and adolescents treated with omalizumab, mepolizumab, or dupilumab for asthma, atopic dermatitis, and chronic urticaria; (2) the number of these patients who developed COVID-19; and (3) severity of COVID-19 symptoms. Twenty pediatric centers participated, and data were collected from February to April 2020.

Results: Three hundred eight children and adolescents (mean age 12.8 years, 161 males) were treated with biologics. Only 3 subjects (1%) who had been treated with omalizumab experienced paucisymptomatic COVID-19, but those symptoms promptly resolved. Of the 9 patients treated with mepolizumab, none had COVID-19 or asthma exacerbations. Of the 6 asthmatic subjects and 7 patients with chronic urticaria treated with dupilumab, none had COVID-19. Also, there was no worsening of the underlying disease.

Conclusion: These very preliminary outcomes suggest that continuing biologics seem to be safe. Therefore, biologics could be continued in patients with severe allergic diseases, but withheld once contracted COVID-19.

Keywords: asthma, COVID-19, biologics, children, adolescents

Introduction

THE CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC) has recognized moderate-to-severe asthma as a risk factor for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, such as coronavirus disease 2019 (COVID-19).¹ This assumption derived from evidence that asthma exacerbations are commonly triggered by respiratory viral infections, mainly in children.² Also, it has been consistently shown that asthma is a risk factor for severe Middle Eastern respiratory syndrome caused by a coronavirus.³ With this background, the CDC released in-

formation stating that people with moderate-to-severe asthma might be at higher risk of becoming very sick from COVID-19 as compared with healthy people.¹ CDC advised asthmatic patients that COVID-19 can affect their respiratory tract (nose, throat, and lungs), cause an asthma attack, and possibly lead to pneumonia and acute respiratory disease. The agency also recommended a series of rules for patients with moderate-severe asthma, leading doctors to consider asthma a risk factor for severe COVID-19.

Among hospitalized COVID-19 patients, however, asthma or allergies seem to be rare comorbidities. A preliminary Chinese study investigated 140 hospitalized patients for

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COVID-19, and none of them had asthma or allergies.⁴ Another Chinese study consistently reported an asthma prevalence of 0.9% in 548 COVID-19 inpatients, significantly lower than in the general Wuhan adult population, which is an estimated 6.4%.⁵ Our experience in Pavia, Italy, has confirmed the low prevalence of COVID-19 in children.⁶ Moreover, we initially reported that the prevalence of asthma and allergic diseases, in children admitted to 2 large teaching hospitals through April 4, 2020, was very low as only 2 (5%) subjects had allergy and 1 (2.5%) had asthma.⁷ Therefore, it seems that allergy and asthma comorbidities are unusual in children and adolescents with COVID-19.⁷

These outcomes could suggest that having an allergy might be a protective factor for coronavirus infections.⁸ In youth, asthma is mostly characterized by type 2 inflammation.⁹ To further support the protective role exerted by allergy, a very recent study provided evidence that allergic sensitization was inversely related to angiotensin converting enzyme 2 (ACE2) expression. In addition, allergen natural exposure and challenge significantly reduced ACE2 expression.¹⁰ As a result, allergic patients underexpress ACE2 on airways and could be less prone to suffer from COVID-19.

In contrast, eosinopenia has been associated with poor COVID-19 prognosis.¹¹ A Chinese study reported that upon hospital admission, 69 (81.2%) patients with COVID-19, who ultimately died, had very low eosinophil levels.¹² The authors speculated that the reduced eosinophil count was not related to glucocorticoid use, performed in 65 (94%) patients, but rather to CD8 T cell depletion and eosinophil consumption caused by SARS-CoV-2. Although eosinophil cationic protein, eosinophil-derived neurotoxin, and eosinophil-derived enzymes can neutralize the virus, eosinopenia could explain a higher SARS-CoV-2 load that, in turn, overconsumes eosinophils. In this regard, a recent review discussed the eosinophil response to COVID-19.¹³ Eosinophils orchestrate the immune response to a respiratory virus, releasing cytotoxic proteins, increasing nitric oxide, producing type 1-associated cytokines, mainly interleukin (IL)-12 and IFN- γ , and recruiting CD8 T lymphocytes. Eosinophils clear viral load, thereby promoting recovery from viral infections. Allergic patients usually present with eosinophilia, so, in theory, it could be protective against SARS-CoV-2.

Personal experience with the impact of COVID-19 on eosinophils

To determine whether eosinophilia might have a protective function, we cite our very recent study, which compared children and adolescents with COVID-19 with allergic children and adolescents without COVID-19.¹⁴ The records of 2 hub hospitals in northern Italy were analyzed. A group of 120 allergic children and adolescents (mean age 11.9 years, 67 males) who were regularly followed and had controlled respiratory symptoms was compared with a group of 52 children and adolescents (mean age 6.2 years, 24 males) who were hospitalized for COVID-19. In the group of COVID-19 patients, only 2 subjects were allergic. Regarding the eosinophil count, allergic patients had higher values than COVID-19 inpatients (median values: 423 and 112 cells/ μ L, respectively), as shown in Fig. 1.

These data could suggest that a high eosinophil count could reduce the susceptibility to COVID-19.

It is worth exploring this hypothesis in patients with severe asthma, as treatment typically includes biologics.¹⁵ The first biologic treatment for asthma was omalizumab, an anti-IgE monoclonal antibody. As type 2 severe asthma is a very frequent endotype, mepolizumab, an anti-IL-5, has been proposed,¹⁶ but this class of therapy depletes eosinophils. Consequently, mepolizumab could, in theory, promote viral infections, potentially inducing eosinopenia. In our practice, 5 patients (mean age 22.4 years, 3 males), currently treated with mepolizumab for at least 12 months, had 319 eosinophils/ μ L (median value) as reported in Fig. 1. In this very limited group of asthmatic patients, an α -IL-5 biologic did not completely stop eosinophilopoiesis. Asthmatic patients were well controlled and the rate of asthma exacerbations was significantly reduced in the last year. Notably, none of them suffered from COVID-19.

FIG. 1. Blood eosinophil count in children and adolescents with allergic diseases, in patients treated with biologic anti-IL-5, and in pediatric patients with COVID-19. Data are expressed as median (segment in the boxplot) and interquartile range. COVID-19, coronavirus disease 2019; IL, interleukin.

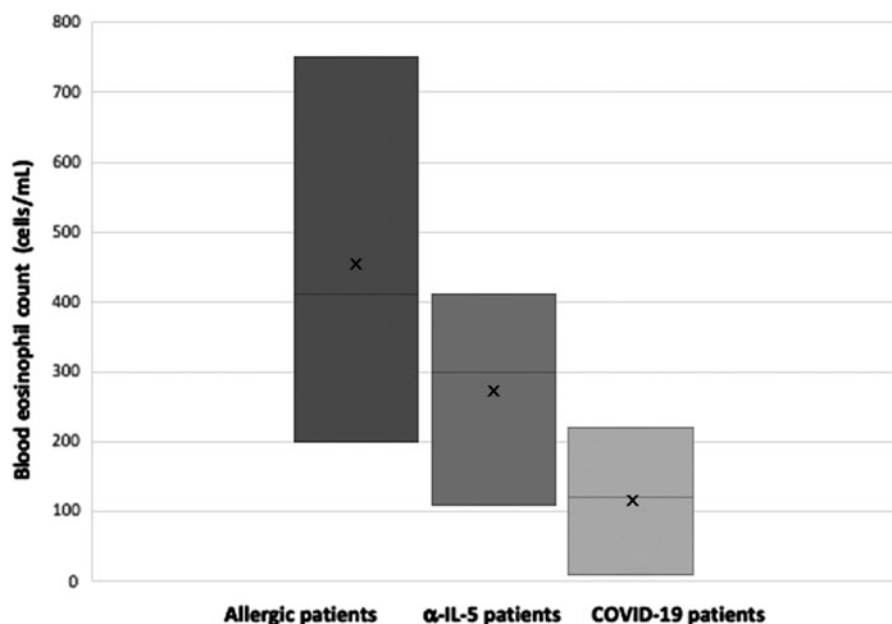


TABLE 1. SURVEY SENT TO ITALIAN PEDIATRIC CENTERS ($n=20$) AND RESPONSES

Questions	Responses
(1) How many children and adolescents are currently treated with omalizumab for asthma?	236
(2) How many children and adolescents are currently treated with omalizumab for chronic spontaneous urticaria?	50
(3) Among children and adolescents treated with omalizumab, how many patients suffered from COVID-19?	3/286 (1%)
(4) Among children and adolescents treated with omalizumab, how many patients with COVID-19 faced an exacerbation of their underlying disease?	0/286
(5) How many children and adolescents are currently treated with mepolizumab for asthma?	9
(6) Among children and adolescents treated with mepolizumab, how many patients suffered from COVID-19?	0/9
(7) Among children and adolescents treated with mepolizumab, how many patients with COVID-19 faced an exacerbation of their underlying disease?	0/9
(8) How many children and adolescents are currently treated with dupilumab for asthma?	6
(9) How many children and adolescents are currently treated with dupilumab for atopic dermatitis?	7
(10) Among children and adolescents treated with dupilumab, how many patients suffered from COVID-19?	0/13
(11) Among children and adolescents treated with dupilumab, how many patients with COVID-19 faced an exacerbation of their underlying disease?	0/13

COVID-19, coronavirus disease 2019.

Materials and Methods

To expand these very limited records, we conducted a multicenter observational nationwide survey to collect data on biological therapies in allergic children and adolescents during the COVID-19 pandemic in Italy.

A survey of 11 questions was used to investigate (1) the number of allergic children and adolescents treated with biologics (omalizumab, mepolizumab, or dupilumab) for asthma, atopic dermatitis, and chronic urticaria; (2) the number of these patients who developed COVID-19; and (3) the severity of COVID-19 symptoms (Table 1).

The Italian Society of Pediatric Allergy and Immunology (Società Italiana di Allergologia ed Immunologia Pediatrica-SIAIP) submitted the survey to 20 leading Italian pediatric hospitals, and data were collected from February to May 2020. The referring doctor at each hospital completed the questionnaire. IRB of the Istituto Giannina Gaslini, Genoa, Italy; code number: 22253/2017; in the context of the Italian Project “Control’ Asma” promoted by the Italian Society of Paediatric Allergy and Immunology.

Results

The pooled data showed that 308 children and adolescents (mean age 12.8 years, 161 males) were treated with biologics. In particular, 236 asthmatic patients and 50 patients with chronic urticaria were treated with omalizumab. Three of the 236 asthmatic patients (1%) suffered from paucisymptomatic COVID-19, which promptly resolved without hospitalization. Notably, nobody experienced worsening of the underlying disease. These patients stopped omalizumab until the nasopharyngeal swab for SARS-CoV-2 tested negative. Of the 9 patients treated with mepolizumab, none had COVID-19 or asthma exacerbations. Finally, 6 asthmatic subjects and 7 patients with chronic urticaria were treated with dupilumab, and none had COVID-19, nor worsening of underlying disease. All patients continued with the biologics.

Discussion

Current international guidelines recommend strict compliance with therapies, including biologics.^{17,18} Recent

expert opinions from the European Academy of Allergy and Clinical Immunology (EAACI) members suggested continuing biological therapy in patients with severe allergic diseases, but stopping it after contracting COVID-19.¹⁹ Similarly, SIAIP stated that biologics should be continued in the treated patients, but discontinued in case of COVID-19.²⁰

The pathogenesis of SARS-CoV-2 infection is complex and only partially understood, but is known to mainly involve the T helper type 1 (Th1) and Th17 immune responses.²¹ The pathogenicity of this disease is associated with the activation of the cell inflammasome and the subsequent release of proinflammatory cytokines, especially IL-1 β , which contribute to the “inflammatory storm” responsible for the severity of clinical manifestations of COVID-19.²¹

Atopic inflammation is characterized by the Th2 inflammatory response and mediated by serum IgE in most cases. The Th2 cytokines, namely IL-4, IL-5, and IL-13, as well as IgE, play a crucial role in the allergic inflammation involved in asthma and atopic dermatitis. IgE is also implicated in chronic urticaria subsets. Biologics prescribed based on asthma and allergy phenotype and endotype represent the emerging strategy in the management of these disorders.

Our preliminary data are, to our knowledge, the first report to address the use of biologics for asthma and allergic disorders in the era of the COVID-19 pandemic. As a consequence, a direct comparison with other experiences could not be performed. Still, the current survey provides some practical information by confirming the relevance of continuing biologics in treated patients, as the rate of infection was very limited, and the underlying disease did not worsen. However, the present survey had some limitations, including the restricted number of participating institutions and the nationwide-based design. Therefore, further investigation should be performed to confirm these preliminary outcomes.

Conclusion

Our limited data suggest that continuing treatment with biologics appears to be safe, but more data are needed to

ascertain the safety of these compounds once patients contract COVID-19. As a result, biologics could be continued in patients with severe allergic diseases but withheld once contracted COVID-19.

Author Disclosure Statement

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