

REVIEW PAPER/PRACA POGLĄDOWA

## Safety of biological treatment of severe asthma during the COVID-19 pandemic

### Bezpieczeństwo leczenia biologicznego astmy ciężkiej w czasach pandemii COVID-19

Dorota Nawarycz, Rafał Pawliczak

Department of Immunopathology, Medical Faculty, Medical University of Lodz, Lodz, Poland

#### ABSTRACT

COVID-19 is an infectious disease that rapidly spread around the world and therefore is a challenge for treating chronic diseases, such as severe asthma. According to the guidelines of various health organizations, biological treatment in patients with severe asthma should be continued. The aim of this study was to evaluate the information we have gathered so far about safety of biological treatment of severe asthma during the COVID-19 pandemic. We analyzed data involving omalizumab, reslizumab, mepolizumab, benralizumab and dupilumab coming from case studies, surveys, single-center and multicenter studies, and review articles as well. The study focuses on risks of asthmatic patients' deterioration during COVID-19 and the severity of the infection itself. As a result, we learned that there is no strong evidence for asthma exacerbations in patients infected with COVID-19 while on their biological treatment course. Biological therapy can be safely used in patients with severe asthma, as long as all the precautions and the individual evaluation are provided.

#### KEY WORDS

COVID-19, severe asthma, biological treatment, biological therapy, safety.

#### STRESZCZENIE

COVID-19 jest chorobą zakaźną, która szybko rozprzestrzeniła się na cały świat i stanowi wyzwanie w leczeniu chorób przewlekłych, takich jak astma ciężka. Według wielu organizacji zajmujących się zdrowiem terapia biologiczna u pacjentów z astmą ciężką powinna być kontynuowana. Celem tego badania jest ocena informacji, które udało się do tej pory zebrać na temat bezpieczeństwa leczenia ciężkiej astmy w czasach pandemii COVID-19. Autorzy przeanalizowali dane dotyczące omalizumabu, reslizumabu, mepolizumabu, benralizumabu oraz dupilumabu, które pochodzą z opisów przypadków, badań ankietowych, badań jedno- i wielośrodkowych, a także z artykułów przeglądowych. Tematyka badania skupia się na ryzyku pogorszenia u pacjentów z astmą podczas COVID-19 oraz ciężkości infekcji. Autorzy doszli do wniosku, że nie ma silnych dowodów na ryzyko zaostrzenia astmy u pacjentów zakażonych COVID-19, będących jednocześnie podczas cyklu terapii biologicznej. Leczenie biologiczne może być bezpiecznie stosowane u pacjentów z astmą ciężką tak długo, jak wszystkie środki ostrożności oraz ocena indywidualna są zastosowane.

**SŁOWA KLUCZOWE**

COVID-19, astma ciężka, leczenie biologiczne, terapia biologiczna, bezpieczeństwo.

**ADDRESS FOR CORRESPONDENCE**

Prof. Rafał Pawliczak MD, PhD, Department of Immunopathology, Division of Allergology, Immunology and Dermatology, Faculty of Biomedical Sciences and Postgraduate Training, Medical University of Lodz, 7/9 Zeligowskiego St, Building 2, Room 177, 90-752 Lodz, Poland, phone: +48 42 272 52 75, +48 42 272 52 76, fax: +48 42 272 52 75, e-mail: rafal.pawliczak@csk.umed.lodz.pl

**INTRODUCTION**

COVID-19 is an infectious disease that rapidly spread around the world and therefore is a challenge for treating chronic diseases, such as severe asthma [1, 2]. According to guidelines of various health organizations, biological treatment in patients with severe asthma should be continued [3–6]. However, there is still not enough evidence for safety of biological treatment in patients with severe asthma, who suffer from COVID-19 infection. There are some concerns about asthmatic exacerbations and severity of COVID-19 in patients undergoing their biological treatment course. In this study, we analyzed available data, to elucidate this problem. Currently, there are five biological drugs that are used to control severe asthma: omalizumab, reslizumab, mepolizumab, benralizumab and dupilumab [2, 7]. In general, biological treatment is considered safe, but the data from long-term clinical trials are limited to 1 or 2 years of follow-up [8–10]. The paper is divided into three sections: case studies, surveys, cohort and other studies.

We searched the PubMed database for the phrases “severe asthma COVID-19”, “biological treatment of severe asthma” and “biological treatment asthma” that were published until 18<sup>th</sup> June 2021. The results on the topic were accepted for review regardless of the paper type – we analyzed case studies, surveys, reviews, single-center and multicenter studies as well.

**CASE STUDIES**

Omalizumab is a recombinant humanized anti-IgE monoclonal antibody that is often used to control severe asthma [2]. In June 2020, Lommatsch *et al.* reported a case study of a 52-year-old patient, who was diagnosed with no other chronic disorder. He survived the infection of COVID-19 with no asthmatic exacerbation [11].

Reslizumab is a monoclonal antibody directed against interleukin-5 (IL-5) [2]. The authors did not find any single case study reporting usage of this medication during the COVID-19 pandemic.

Mepolizumab is also a monoclonal antibody directed against interleukin-5 (IL-5) and has a long-term safety profile [2]. Azim *et al.* presented a series of four case studies, 3 of which involve asthmatic patients. All of them experienced asthma exacerbation and required hospitalization. One needed ventilatory support – this patient was reported to have significant risk factors of severe infection [12]. Another case study describes a 55-year-old woman who recovered well from SARS-CoV-2 infection. Notably, this patient had elevated liver enzymes before the course of biological treatment. The cause of this condition was not identified. Her liver enzymes decreased during the therapy [13].

Benralizumab is a humanized afucosylated monoclonal antibody against IL-5 $\alpha$  receptor (IL-5R $\alpha$ ) that induces eosinophil apoptosis involving natural killer cells, which further induces peripheral blood eosinophil depletion [2]. García-Moguel *et al.* presented two case studies in patients on benralizumab therapy; both recovered from the disease and both of them presented signs of mild infection. The first patient was discharged on the fourth day of admission and a week later was asymptomatic. The second patient presented comorbidities, e.g. obesity. He requested a voluntary discharge and after that he continued therapy under the supervision of his primary care physician. One week later, symptoms of COVID-19 subsided. In these two cases the need for intubation was not reported [14].

Dupilumab is a humanized monoclonal antibody directed against the  $\alpha$ -chain of the IL-4 receptor (IL-4R $\alpha$ ), which is shared by both IL-4 and IL-13 – this drug is able to inhibit the signaling of both ILs [2]. A case study by Bhalla *et al.* describes a 23-year-old woman who noticed a significant improvement in asthma control after receiving dupilumab. Three months after the last dose of dupilumab, she tested positive by PCR for SARS-CoV-2. Her asthma was uncontrolled but she gradually improved over the following 8 weeks. However, 9 weeks after the onset of symptoms, the virus was still detectable by PCR [15].

## SURVEYS

An Italian survey performed by Matucci *et al.* comes from six different asthma centers. It included 473 patients who were receiving Step-5 treatment according to the GINA guidelines. Included patients had been receiving omalizumab, mepolizumab, benralizumab or dupilumab. Four of them with symptoms of COVID-19 tested positive. Three patients were receiving omalizumab, and one was receiving benralizumab. All of them presented good control of asthma symptoms before SARS-CoV-2 infection. Three of them temporarily suspended the therapy. Two patients required hospital admission due to the severity of symptoms. All of them clinically recovered. The authors suggest that their survey might be biased due to lack of systematic testing for COVID-19 [16].

The second survey (Tanno *et al.*) was an international questionnaire for the allergic community. The authors gathered data from 635 participants from 78 countries of all continents. Allergists with long-term professional experience were asked 24 questions. The survey demonstrated that the majority of the allergy community does not have a solid statement about official recommendations regarding the continuation of biological treatment, despite the access to the recent data available on medical databases [17].

Another Italian survey questioned clinicians of the Italian Registry of Severe Asthma (IRSA). It involved 558 subjects, 7 of which were confirmed with COVID-19. The authors noted that the hospitalization rate in COVID-19 patients with severe asthma was not significantly different from the general population. Moreover, Antonicelli *et al.* did not observe a statistically significant difference of COVID-19 frequency in groups of patients under biological treatment and those who were only on high doses of inhaled corticosteroids and long-acting  $\beta$ -agonist (ICS-LABA). The results suggest no increased risk of COVID-19 infection in both groups [18].

A large Dutch paper describes COVID-19 cases which were identified through a prospective survey performed between March and April 2020 among all severe asthma specialists from hospitals of the Dutch Severe Asthma Registry RAPSODI. This study in 634 asthmatic patients on biological treatment reported 9 cases of confirmed COVID-19. Seven patients were admitted to the hospital and 5 of them required intensive care. One patient died. There was only one diagnosis of COVID-19 in a group of patients who did not receive biological agents. Compared to the corresponding category in the general population, the study describes a poor outcome in severe asthma – Eger *et al.* suggest the results might be biased by comorbidities (mainly by overrepresentation of obese patients). The authors hypothesize that the role of biological treat-

ment itself in the occurrence of more severe symptoms of COVID-19 in their patients is uncertain [19].

Domínguez-Ortega *et al.* performed a telephone survey on 71 patients with severe asthma on biological therapy (46 omalizumab, 14 mepolizumab, 6 benralizumab, and 5 reslizumab). Seven patients had been diagnosed with COVID-19. One patient has developed pneumonia and required hospital admission for a short period of time. No asthma exacerbation or worsening of control was reported. The authors suggest that the use of biological therapy in severe asthma does not have an impact on clinical outcomes [20].

Hanon *et al.* used the Belgian Severe Asthma Registry (BSAR) to assess the differences between the risk of severe COVID-19 in patients with severe asthma on biological therapy and those who did not receive such drugs. Of 676 patients who participated in the survey the authors identified 14 subjects with COVID-19 infection confirmed by either PCR or serology. Of this group, only 5 were admitted to the hospital for a short period (from 2 to 8 days). No deaths or asthma exacerbations were reported. As a result, the authors highlight that there was no difference in the occurrence of COVID-19 between severe asthmatic patients with biological therapy and those who did not receive it. However, the study results could be biased by national restrictions on COVID-19 testing [21].

## COHORT AND OTHER STUDIES

A multicenter retrospective cohort study of 545 adult patients with severe asthma under biological treatment from 9 large hospitals belonging to the Spanish Network of Asthma was conducted between March and June 2020. 48.3% patients were treated with omalizumab, 28.2% with mepolizumab, 18.0% with benralizumab, 4.8% with reslizumab, and 0.7% with dupilumab. GINA guidelines were followed in all of the patients. Thirty-five (6.4%) subjects were diagnosed with COVID-19. Remarkably, only those who presented the symptoms were tested. Eight patients required hospitalization, two of them presented severe pneumonia. One patient with several comorbidities died. The authors conclude that biological treatment for severe uncontrolled asthma is not a risk factor for developing COVID-19 and its severity. According to this study, the type of biological drug does not cause a significant difference in the outcome [22].

Following a literature search, Patrucco *et al.* presented the data from several large studies and from international recommendations. The authors searched and compared data from PubMed, national, international recommendations and papers on severe asthmatic patients and their management during the SARS-CoV-2 pandemic. The

authors emphasize the need for proper asthma control. According to results of their study, healthcare professionals and official organizations generally agree that steroids should be used in the minimal doses required for control of the disease and biological therapy should be performed as usual [23].

A cohort of patients ( $n = 2000$ ) was admitted to COVID units of six hospitals in Italy. Electronic medical records of these patients were reviewed. Caminati *et al.* reported 42 asthmatic patients; 10 of them were diagnosed with severe asthma and only 2 received biological therapy. The study shows low prevalence of asthma in patients with COVID-19. The authors indicate the insignificant representation of patients with biological therapy for asthma, and therefore no strong evidence for safety of biological treatment could be identified [24].

Izquierdo *et al.* performed a big data analysis using the SAVANA Manager clinical platform and reviewed 71 182 patients with asthma. Eight hundred sixty-five of them were undergoing biological therapy (omalizumab  $n = 641$ , mepolizumab  $n = 308$ , benralizumab  $n = 98$ , reslizumab  $n = 26$ ) during the study period. The authors reported 20 patients with asthma under biological treatment with confirmed diagnosis of COVID-19; of these, 2 (10%) were admitted to hospital. The study indicates that despite increased severity of the symptoms from the upper respiratory tract and comorbidities in patients with severe asthma, the need for hospital admission in biologic-treated patients was relatively low. A significant difference was found when these results were compared to the frequency of hospitalizations both in the general population and in a group of patients with severe asthma without biological therapy (26% in each group). One patient under the biological therapy died; he was a 52-year-old man with several comorbidities. As a result, the authors suggest that biological therapy might even have a protective effect against severe COVID-19 infection [25].

Gaspar-Marques *et al.* reviewed papers available until February 2021 in PubMed and Google Scholar on severe asthma and COVID-19. Biological therapy in severe asthma during COVID-19 was one of their points of interest. The authors conclude that biological therapy of severe asthma does not seem to be a risk factor for infection and severity of COVID-19. It even might have a protective effect on the patients. Also, they indicate the need for more research in this field [26].

Heffler *et al.* investigated the incidence of COVID-19 cases in a large population of severe asthmatics in Italy using data from the Severe Asthma Network in Italy (SANI). The study included 1504 subjects. Twenty-one out of 26 patients with COVID-19 (confirmed or highly suspected) were on biological treatment: 15 (71%) were on anti-IL-5 inflammatory pathway (mepolizumab  $n = 13$ ;

benralizumab  $n = 2$ ) and 6 (29%) were on anti-IgE (omalizumab) treatment. The authors reported asthmatic exacerbations in 9 patients from the group with biological treatment. In this study, a difference was observed between the percentage of COVID-19 patients treated with anti-IL-5 biologic agents (71%) and the percentage of patients treated with anti-IgE (29%). Nonetheless, COVID-19 infections in asthmatic patients are relatively rare. The authors suggest that biological therapy might have an impact on the immune response [27].

## DISCUSSION

Although the evidence concerning COVID-19 is rapidly growing, we still lack information about this infection and its impact on patients with severe chronic diseases. By now, we know that asthma does not put patients at higher risk of severe COVID-19 – the prevalence of asthmatic patients in those who contracted COVID-19 is significantly lower when compared to the general population [28–30]. There is no evidence that biological agents impair the immune response [2, 23]. Moreover, studies reveal that omalizumab has some anti-viral characteristics [31, 32]. Professional organizations agree that biological therapy should not be discontinued during COVID-19 infection [3–6, 33]. The general pattern in patients with severe asthma in terms of COVID-19 should involve more biological treatment and less steroids [34]. Nevertheless, we should remember that the protection from asthma exacerbations still remains crucial. Although biological treatment shows no significant effect on the outcome of COVID-19 [18], all the decisions should be made on an individual basis [35]. As some studies show [19, 27], we cannot fully neglect the role of biological treatment in the severity of COVID-19. The question of the differences in outcome of anti-IgE and anti-IL-5 therapies still remains open. Most papers reviewed in this study indicate that biological treatment does not put patients with severe asthma at higher risk of contracting severe COVID-19 and is really helpful in preventing exacerbations. More evidence on this topic could significantly improve our knowledge on safety of biological treatment in severe asthmatic patients in the COVID-19 era.

## CONCLUSIONS

According to the presented data, we support the guidelines from professional organizations – the biological therapy should be continued. In general, it can be considered safe as long as all the precautions and individual evaluations are provided. Nevertheless, maintaining asthma under control should remain essential [23].

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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