

## COVID-19: Considerations about immune suppression and biologicals at the time of SARS-CoV-2 pandemic

Giulia Costanzo, William Cordeddu, Luchino Chessa, Stefano Del Giacco, Davide Firinu

**ORCID number:** Giulia Costanzo 0000-0003-2269-0439; William Cordeddu 0000-0003-0770-6084; Luchino Chessa 0000-0002-9474-0995; Stefano Del Giacco 0000-0002-4517-1749; Davide Firinu 0000-0002-5768-391X.

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**Giulia Costanzo, William Cordeddu, Luchino Chessa, Stefano Del Giacco, Davide Firinu,** Department of Medical Sciences and Public Health, University of Cagliari, Monserrato 09042, Cagliari, Italy

**Corresponding author:** Davide Firinu, MD, PhD, Assistant Professor, Doctor, Research Fellow, Department of Medical Sciences and Public Health, University of Cagliari, Asse Didattico "E1" Medicina, Cittadella Universitaria, Monserrato 09042, Cagliari, Italy. [davide.firinu@unica.it](mailto:davide.firinu@unica.it)

### Abstract

The extent of the profound immunological and nonimmunological responses linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is currently being investigated worldwide due to the large burden associated with death due to SARS-CoV-2 and the short-term consequences of coronavirus disease 2019 (COVID-19). It has been hypothesized that patients on immunosuppressive treatments, including biologics, may have an augmented risk of being infected by SARS-CoV-2; however, there are currently no definitive data about biological drugs and COVID-19 in immune-mediated inflammatory diseases. Current epidemiological models developed to understand how long the COVID-19 epidemic may last are not conclusive and range from sustained epidemics to complete elimination. Nevertheless, even in the best-case scenario of apparent elimination, there is concordance about a possible contagion resurgence as late as 2024. Therefore, knowledge of the impact of SARS-CoV-2 on immune-mediated diseases and among patients treated with biologicals, together with the results of novel and promising COVID-19 treatment strategies targeting the virus and the host immune response (or both), will help us to best manage our patients during this pandemic over the next few years.

**Key Words:** COVID-19; Immune-mediated diseases; Biological drugs; Targeted therapies; Cytokine storm; Immunosuppressive drugs

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**Core Tip:** The severe acute respiratory syndrome coronavirus 2 pandemic has changed health systems worldwide and the current approach to patients affected by chronic diseases such as immune-mediated disorders. To apply personalized medicine,

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knowledge of the impact of severe acute respiratory syndrome coronavirus 2 during the course of immune-mediated diseases and particularly among patients treated with biologicals, together with the results of novel coronavirus disease 2019 treatment strategies targeting the virus and the host immune response, will help us to best manage our patients during this pandemic.

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## INTRODUCTION

The extent of the profound immunological and nonimmunological responses linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is currently being investigated worldwide due to the very large death toll of the SARS-CoV-2 pandemic and the short-term consequences of coronavirus disease 2019 (COVID-19).

It is well known that patients undergoing immunosuppressive treatment may have increased morbidity and mortality related to infectious diseases. The risk varies according to age, sex, years of disease, number of comorbidities, type of drugs administered, and the number of treatment failures. This increased risk may occur due to a disease-specific alteration of cellular immunity or as a consequence of the drug used to treat the disease[1]. On the other hand, the possible risk of infections related to conventional disease-modifying anti-rheumatic drugs (DMARDs) has not been completely clarified. For instance, methotrexate may increase the infectious risk, but its beneficial effect on disease activity results in a reduction in additional risk factors for infections. Whether there is an augmented risk of pneumonia or reactivation of silent infections remains controversial[2].

Concerning the most commonly used biologic drugs, it is known that the risk of serious infection usually increases in the first 6 mo after initiating therapy; this risk is higher than that of conventional DMARDs. Emerging data also suggest that the risk of serious infections, including those leading to hospitalization, may differ among biologics[3]. The glucocorticoid dose and older age are additional predictors of the risk of serious infections in patients treated with biologics.

## CLINICAL IMPLICATIONS

There are currently no definitive data about biological drugs and COVID-19 in immune-mediated inflammatory diseases. However, we can consider data from phase III clinical trials of biologics on rates of upper respiratory infection, influenza, and serious infections[4]. These data show that, on the whole, biologics do not show major increases in infection risk compared to placebo during the course of these trials. However, as SARS-CoV-2 is a new pathogen related to high mortality and a long-term disease burden in a subset of patients, a cautious approach is warranted. Preventive withholding of biologics should be carefully weighed on the basis of the risk of exposure to SARS-CoV-2, comorbidities and the risk of increased morbidity or mortality from relapse or worsening of the disease for which the patient is being treated[4]. A systematic review and meta-analysis conducted on the few available studies so far concluded that patients with immunosuppression and immunodeficiency seem to have a trend toward an increased risk of severe COVID-19 disease; however, the differences did not reach statistical significance[5]. Major rheumatology societies now recommend the interruption of treatments only during the occurrence of documented SARS-CoV-2 infection for patients treated with DMARDs, biologicals, and small molecules[6].

Mechanistically, the pulmonary damage and acute respiratory distress syndrome due to SARS-CoV, Middle East respiratory syndrome coronavirus, and SARS-CoV-2 infections is caused by inflammatory dysregulation leading to cytokine storms and consequent lung injury[7]. Since these observations were conducted during the SARS

and Middle East respiratory syndrome outbreaks, we are aware of the high expression of interleukin (IL)-1, IL-2, IL-6, IL-12, and interferon-gamma[8], along with inappropriate complement activation in coronavirus-related pneumonia[9]; these findings have been widely confirmed to also occur in COVID-19. Specific human leukocyte antigen haplotypes have a protective effect against SARS-CoV-2 infection, while others (such as human leukocyte antigen-DRB1\*08:01) have a negative influence on the disease course[10]. Some authors divide the natural history of SARS-CoV-2 infection into different stages: early infection, pulmonary involvement, and systemic hyperinflammation, with the first phase showing a predominantly antiviral response and a second phase where the host response and organ damage mediated by inflammation is predominant[11]. A complex immune-mediated and coagulation derangement linked to thromboinflammation is a key element in this process, mediating the variety of multiple organ dysfunctions described to date[12].

Based on the abovementioned considerations, several immunomodulatory drugs have been used compassionately or in clinical trials early in the pandemic, hypothesizing that targeted interventions for immune dysregulation may change COVID-19 pneumonia outcomes. This has partially derived from previous experiences with acute respiratory distress syndrome, sepsis, and other “cytokine storm” diseases[13,14], representing a change of paradigm that has not been fully demonstrated to be safe and effective.

In patients with autoimmune or oncological diseases, Janus kinase inhibitors have been associated with an increased risk of viral and bacterial infection, probably secondary to a cytotoxic T lymphocyte-dependent mechanism and a noncytolytic cytokine-dependent mechanism mediated by inflammatory cytokines[15]. However, despite the lack of large multicenter studies, there is some evidence that patients treated with Janus kinase inhibitors do not have a higher risk of developing severe forms of COVID-19 infection[16].

Baricitinib has been proposed as a therapeutic option in COVID-19, given its activity in modulating inflammation and its ability to inhibit AP2-associated protein kinase, which mediates virus entry in cells through endocytosis, possibly resulting in a decreased viral load[17].

In a recent trial, patients with COVID-19 were assigned to receive either remdesivir (up to 10 d) and baricitinib (up to 14 d) or remdesivir plus placebo[18]. Patients who were treated with baricitinib beyond standard care showed a slightly faster median time to recovery (7 d *vs* 8 d). Moreover, patients receiving supplemental oxygen, noninvasive ventilation, or using high-flow devices at baseline (which accounted for approximately 75% of the population in both treatment groups) recovered in a median of 10 d in the combination group *vs* 18 d in the control group. Interestingly, patients receiving baricitinib did not show an increase in infectious and thrombotic complications; rather, all adverse events had a significantly lower incidence in the combination group[18]. If their safety and efficacy are confirmed, Janus kinase inhibitors could be useful in subgroups of COVID-19 pneumonia (or other manifestations of the disease) due to their short half-life, as their administration could be promptly stopped in cases of superinfection.

As far as rheumatology scientific societies are concerned, current European League Against Rheumatism recommendations suggest not stopping previous treatment with synthetic DMARDs or biologic DMARDs[19]. There is no evidence that these therapies could increase the risk of infection or adverse outcomes in COVID-19[20]. Nevertheless, in individuals with current or suspected COVID-19, the American College of Radiology recommends stopping immunosuppressants and biologics, except non-IL-6 inhibitors and Janus kinase inhibitors[21]. Focusing on rheumatologic patients on anti-tumor necrosis factor therapy, data analyzed from the rheum-COVID registry show that therapy with tumor necrosis factor blockers reduced the risk of hospitalization (odds ratio: 0.40, 95% confidence interval: 0.19-0.81) in contrast to therapy with antimalarials, which did not (odds ratio: 0.94, 95% confidence interval: 0.57-1.57)[22].

Regarding biologicals approved for allergic diseases, such as those for severe asthma, their effect is mainly focused on eosinophils and, in general, on the T-helper type 2 response. Therefore, the question to be asked is which role is involved in the T-helper type 2 response in COVID-19 infection. The evidence to date shows that, in general, there is a reduced risk of CoV-2 infection and a reduction in severity among subjects with a genetic predisposition to allergic diseases[23]. In an Italian cohort of admitted patients affected by COVID-19, asthma did not seem to be a risk factor for susceptibility to COVID-19[24].

Omalizumab, an anti-immunoglobulin E (IgE) monoclonal antibody approved for severe asthma and chronic spontaneous urticaria, has shown immunomodulatory effects mediated through the restoration of the capacity of human plasmacytoid

dendritic cells to produce interferon- $\alpha$ , increasing its antiviral activity and reducing viral-induced asthma exacerbations[25]. A recent trial investigated whether the administration of omalizumab could reduce the symptoms of an experimental infection with rhinovirus in asthmatic patients[26]. These data showed that immunoglobulin E blockade seemed to reduce lower respiratory tract symptoms. To date, there are no data on the increased severity of COVID-19 in asthmatic patients receiving omalizumab, and the Food and Drug Administration has approved omalizumab for short-term home administration during the COVID-19 outbreak to reduce hospital visits.

There are no data yet on the risk of SARS-CoV-2 infection during the use of monoclonal antibodies targeting IL-5 pathways. Therefore, in the absence of any data suggesting potential damage, it is justified to proceed with the administration of biological drugs during the COVID-19 pandemic for patients who have experienced a positive impact from them on their asthmatic symptoms and lung function[27].

Overall, to date, the available data preliminarily suggest that monoclonal antibodies currently licensed for severe asthma treatment do not impair the immunological response or outcomes in patients affected by CoV-2 infection[27]. A paper by Chhiba *et al*[28] analyzed the prevalence of asthma and comorbidities associated with asthma in both inpatients and outpatients with COVID-19[28]. They did not find that asthma was associated with an increased risk of COVID-19 hospitalization. However, biologicals used to treat severe asthma or allergic diseases may have a role in the risk of SARS-CoV-2 infection and in the course of COVID-19, potentially mediated by their steroid-sparing effect. This possibility has not been investigated.

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## CONCLUSION

Current epidemiological models developed to understand how long the COVID-19 epidemic may last range from suggestions of sustained epidemics to complete elimination. Nevertheless, even in the best-case scenario of apparent elimination, there is concordance about possible contagion resurgences as late as 2024[29,30]. Therefore, additional studies to improve our knowledge of the impact of SARS-CoV-2 on immune-mediated diseases and among patients treated with biologicals are needed. Together with the results of novel and promising COVID-19 treatment strategies targeting the virus and the host immune response (or both), they will provide optimal management for our patients in the next few years when we still need to be vigilant.

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