

## EDITORIAL

### Psoriasis, biologic therapy, and the pandemic of the 21st century

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#### Abstract

The pandemic known as coronavirus disease-19 (COVID-19) has quickly spread worldwide, with a significant impact on lives all over the world. The complexity related to the new coronavirus and the clinical syndrome it causes is not yet fully understood. The impact of COVID-19 on patients with psoriasis under biologic agents is continuously being observed in this rapidly changing pandemic. A case-by-case evaluation must be made by dermatologists, and the final decision should be discussed and decided by both the patient and the specialist. Observations reveal that immunosuppressive therapy may have

a role in the treatment of this virus, placing emphasis on the scenario of safety through maintenance of therapy with biologic agents, especially when there are no signs or symptoms related to the infection or contact with an infected patient.

**Keywords:** biologic, coronavirus, COVID-19, SARS-CoV-2, psoriasis.

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The first case of the pandemic known as coronavirus disease-19 (COVID-19) was reported to the World Health Organization (WHO) on December 31, 2019, in one metropolitan area of China called Wuhan, belonging to the province of Hubei. This syndrome, caused by the novel coronavirus known as severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) – closely similar to the coronavirus SARS-CoV-1 that caused the outbreak in 2002 and 2003 – quickly progressed and spread worldwide, with a highly significant impact on the lives of the entire world, infected or not. The 21st century has changed forever. Although the complexity related to the virus and the clinical syndrome caused by it is not yet fully understood, much information has been made available from experienced areas where its impact has been significant.<sup>1,2</sup>

The inflammatory cytokines associated with COVID-19 seem to counter themselves: on the one hand, they have an important role in an efficient immune response to the virus, whereas, on the other hand, they can be responsible for developing excessive systemic inflammation. The increased level of multiple mediators, such as interleukin (IL)-1, IL-2, IL-4, IL-5, IL-6, IL-12, IL-17, and tumor necrosis factor (TNF)- $\alpha$ , is responsible for the so-called cytokine storm effect that can culminate in acute respiratory distress syndrome, or even death.<sup>1,3</sup>

The IL-23/IL-17 axis – the main pathogenic pathway in the development of psoriasis – does not seem to be crucial for an

effective antiviral immune response in healthy individuals. In fact, observations reveal that an aberrant T-helper 17 (Th17) cell cytokines response seems to be associated with a worse prognosis in coronavirus and non-coronavirus pneumonia.<sup>3</sup> However, further data are needed to better understand this association.

At this point, we still do not understand how the syndrome caused by SARS-CoV-2 can influence patients with psoriasis under treatment with biologic agents. Whether they are more susceptible to the infection or whether they will develop a more acute and severe disease has yet to be determined. It is also unknown whether being on a biologic agent can result in a more difficult response to treatments during infection with this virus or a more prolonged course. However, data related to this subject are starting to emerge. In a recent study conducted in Northern Italy that assessed the impact of the COVID-19 pandemic on patients with chronic plaque psoriasis under treatment with biologic agents, there was no significant increase in the number of hospitalizations or deaths from SARS-CoV-2 infection in this group of patients compared to the rest of the population.<sup>4</sup>

Nevertheless, we do know, from the pivotal trials with TNF- $\alpha$ , IL-12/23, IL-23, and IL-17 blockers compared to placebo in patients with psoriasis, that there is a small increase in the risk of developing upper respiratory infections.<sup>5</sup> We do also know that by inhibiting specific mediators of the immune

response, we can control systemic inflammation – this has been observed with several biologic drugs used in the treatment of immune-mediated diseases such as psoriasis, atopic dermatitis, or inflammatory bowel disease.<sup>6</sup> This fact, together with the knowledge about the presence of the cytokine storm, was fundamental to the initiation of potential treatments with immunomodulatory drugs – adalimumab, ixekizumab, baricitinib, tocilizumab – for the treatment of COVID-19 infection.<sup>1,7,8</sup>

Thus, with the uncertainty surrounding this subject, we need to consider what we already know before can make further conclusions. The risk-to-benefit ratio must be evaluated case-by-case before making any decisions about treatment for our patients with psoriasis.<sup>9</sup>

The decision to suspend biologic agents in all patients with psoriasis, without distinction, should not be made for three main reasons. First, because it may cause flares of the disease to occur that will have a systemic impact, not only for the skin, that will affect patients' quality of life, but it may also create the possible need to visit a healthcare provider's clinic or hospital to resolve this flare – one of the most risky locations of COVID-19 spread and one that should be avoided, if at all possible. Secondly, we do not know what the impact of the infection can be with uncontrolled disease. Lastly, the suspension and then reintroduction of biologic drugs, the so-called flip-flopping (mainly with TNF inhibitors), may be responsible for the development of antibodies that could interfere with future response to the drug.<sup>10,11</sup>

In a patient with a proven symptomatic coronavirus infection, considering the information we presently have, the safest decision is to suspend the biologic agent during the COVID-19 illness and reintroduce it after its resolution. This decision is based on the fact that uncertainty reigns in this type of patient and that clinical trials that evaluated withdrawal and subsequent retreatment with biologic agents seem to demonstrate that there may be maintenance of an effective response on the skin for several weeks, with recapture of response after they are reintroduced.<sup>11</sup> Although there is the possibility of the development of antidrug antibodies (higher for TNF- $\alpha$  inhibitors), the risk-to-benefit ratio in these patients would still suggest suspending the biologic agents, under the auspices of what we know today.

In a patient with psoriasis under the treatment with a biologic drug and who has had a risk contact with a positive SARS-CoV-2 patient, a case-by-case evaluation should be made. Temporary biologic drug withdrawal should be considered, and clinicians

should look to other options available in the short term (e.g. phototherapy, topical agents, or other non-immunosuppressive therapy), as well as close monitoring of patients.<sup>12</sup> As the median incubation period is 5.1 days, with 97.5% of the patients experiencing symptoms within 11.5 days after infection,<sup>13</sup> reintroduction of the biologic agent after that period may be the safest decision.

Elderly patients and/or those with other comorbidities, such as cardiovascular disease, diabetes, or malignancy, are more susceptible to develop more acute and severe disease. They may therefore require more conservative measures and should be closely monitored.<sup>12,14</sup>

In cases of patients proposed to start therapy with biologic agents, screening for SARS-CoV-2 infection may be considered, as this is already done for other infectious agents, such as *Mycobacterium tuberculosis*, hepatitis B virus, hepatitis C virus, or human immunodeficiency virus. However, the sparsity of testing agents for asymptomatic individuals may preclude this option for the time being. In this phase, when the number of tests is limited, priority must be given to high-risk individuals, elderly patients, and/or those with several comorbidities. However, in the hope that, in the near future, the number of available tests will increase, the development and implementation of algorithms for carrying out the tests may be beneficial for clinicians.<sup>15</sup>

The discussion of the available options with the patient, explaining the pros and cons of potential management plans is of extreme importance. If the decision is to start or continue biologic therapy during this pandemic, those patients should be closely monitored for quick action in the face of a change of scenario.

We are experiencing an ever-changing health situation during this new pandemic. The rapid spread of this virus does not allow long-term, randomized, placebo-controlled clinical trials on how to manage COVID-19 infected patients receiving biologic therapy. The treatment decisions we make for our patients with psoriasis must be made rapidly taking into account our expert experience in treating patients with other viral infections – these principles may be applicable among patients with COVID-19, the new virus that has changed the way we live in the world forever. Patient safety must continue to be top priority, and joint treatment decisions must be made using the information available to us today together with new information that inundates us daily.

Stay safe.

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