Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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COVID-19 and immune-mediated inflammatory diseases: Why don't our patients get worse?

Dear Editor

We read with interest the excellent reviews about the impact of SARS-CoV-2 infection in patients with Immune-Mediated Inflammatory Diseases (IMID) [1,2]. Although at the beginning of the pandemic, physicians caring for these patients thought that they would be one of the high-risk groups most seriously beaten by COVID-19 [3], during the last months, the debate has been focused on the surprisingly lower number of IMID patients affected, and also on that they usually did not show a more ominous outcome (Supplementary Table S1) [4–35]. With some exceptions [26,33], most series shared the same message: patients with IMID do not present a greater transmission risk than the general population, and besides, they do not have higher mortality. These conclusions have also been highlighted in provisional recommendations from some international scientific societies involved in the care of IMID [36]. While awaiting more studies from larger cohorts and national IMID registries, overall, these results are encouraging and could be explained for diverse reasons. Thus, there are several factors inherent to the integral management of patients with IMID, and some others derived from the pandemic itself [37,38], which may have played a role in minimizing the unfavorable impact of SARS-CoV-2 infection in these patients (Table 1).

Epidemiological factors may have contributed to the effect of the pandemic on IMID patients. In this sense, the elderly and, especially, males have been the groups with the worst prognosis of SARS-CoV-2 infection [39]. Most IMID debut in young or middle-aged individuals and in the vast majority of IMID cohorts reported to date, the mean age of included patients was less than 60 years. Furthermore, although not always, a significant percentage of patients with IMID are females. Women, compared to men, are less susceptible to viral infections, based on different innate immunity, the presence of steroid hormones, and some other factors related to sex chromosomes [40]. Thus, the immune regulatory genes encoded by the X chromosome in females, causes lower viral load levels, lesser inflammation, and a higher concentration of neutralizing antibodies. Finally, cardiovascular diseases are more frequent in males, and subjects without cardiovascular dysfunctions infected by SARS-CoV-2 seems to have a better prognosis [39]. Another key aspect to take into account is the implementation of global preventive measures by IMID patients themselves. They have changed their health habits and applied protective measures, generally more stringent than those adopted by the general population [37]. Probably, IMID patients on biologics or immunosuppressive drugs may have self-isolate more effectively and focused on improved hygienic measures, thus limiting their own infection risk. And very importantly, these patients, specifically those receiving biological therapy, are subject to very strict control, not only concerning the prevention and treatment of cardiovascular risk factors but also the prevention of infectious diseases. In this sense, it should be noted that the majority of patients with IMID routinely follow a vaccination protocol not implemented for the general population. Although trained immunity has been described with live attenuated vaccines, it would be not surprising that repeated stimulations of the innate and acquired immune mechanisms might lead to a lower inflammatory response after SARS-CoV-2 infection [41]. Furthermore, cross-reactivity with other vaccines should not be discarded. Noteworthy, due to the movement restrictions imposed by many Governments during the most dangerous phases of the pandemic, and the need to avoid exposing IMID patients to infection, most Health Systems have implemented telemedicine programs, especially for those treated with immunosuppressive drugs or biologic agents. The implementation of telemedicine and remote patient monitoring in the COVID-19 era has been very useful and has provided a clear option for the management and follow-up of these patients [38,42]. As shown in Supplementary Table S1, most of the studies agree that those patients with active disease have a higher risk of SARS-CoV-2 infection and worse prognosis of the disease [4,8,11]. Besides, the different studies also agree on the null impact of biologic therapy on the risk of infection and mortality but point to the role of corticosteroids as a poor prognosis factor [5,11]. In fact, the use of biological therapies has been linked to a decrease in the rate of hospitalization for COVID-19 [17,22]. Furthermore, the use of non-biologic DMARDs, and especially corticosteroids, has been linked to an increased risk of hospitalization and worse prognosis [5,12,17,22]. This may be due to the strong immunosuppressive effect of corticosteroids, but especially because higher prednisone doses usually reflects uncontrolled IMID activity [17]. The mechanism of action of biological agents means that the increase in infections such as SARS-CoV-2 is not as high as one might assume. Although cytokine inhibition might be considered as 'immunosuppression' and therefore harmful, these compounds neutralize individual mediators of the inflammation cascade rather than leading to generalized immunosuppression. On the other hand, cytokine inhibitors can mitigate the hyperinflammatory state [43,44], which is part of the pathogenesis of the severe COVID-19 and contribute to a less devastating disease. Inhibition of individual cytokines does not appear to increase viral infection rates or induce a more severe course of viral infection. In fact, most ad hoc recommendations from IMID specialists do not support preemptively stopping anti-cytokine therapy if no symptoms or signs of COVID- 19 are present [45]. Finally, patients with IMID due to the tight control of their comorbidities, especially cardiovascular risk factors and osteoporosis, are treated with drugs that might have a beneficial effect on COVID-19 outcomes, such as statins [46] or vitamin D [47]. Thus, vitamin D has a key role in the function of TLR-7, the main receptor for innate immunity involved in the recognition of respiratory RNA viruses such as SARS-CoV-2 [48].

In any case, and despite the availability of limited but reassuring data, we must keep close monitoring of our IMID patients and maintain

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Table 1
Probable reasons to explain the impact of COVID-19 in patients with Immune-Mediated Inflammatory Diseases (IMID).

Differential factors of IMID	Possible explanation
Age	• The overall age of IMID patients is <60 yrs. COVID-19 is more severe in subjects >60 yrs.
Higher prevalence in women	• COVID-19 is more severe in men. • Hormonal (i.e., estrogens) and genetic (i.e., TLR-7) protective factors in women. • Cardiovascular diseases and vascular risk factors are more frequent in men.
General preventive measures	
• Protective measures to reduce the risk of infection	• Different perceptions of risk: self-isolation and social distancing.
• Vaccination protocols	• Cross-reactivity from vaccination/Trained immunity.
• Strict control of comorbidities	• Increased cardiovascular risk awareness and appropriate prophylactic measures.
Telehealth	• Limit the exposure to patients and clinicians and may also reduce the visits to the Emergency Departments.
Impact of IMID therapies	• Patients with well-controlled disease are less immunosuppressed than those with active disease. They also need fewer glucocorticoids. • Powerful anti-inflammatory drugs can lower the risk of cytokine storm.
Impact of concomitant treatments	• Patients with IMID are more likely to receive other treatments with a possible beneficial impact on the immune system such as vitamin D or statins.

TLR-7: Toll-like receptor-7.

the appropriate protective strategies. Without any doubt, one of the most useful measures for these patients is to maintain their IMID in remission or, in the worst scenario, at the lowest level of activity. On the other hand, the development of new strategies of health care, including telemedicine and the remote monitoring of disease activity have come to stay in our daily clinical practice.

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Declaration of Competing Interest

None.

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