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Novel COronaVirus Disease 2019 (COVID-19) epidemic: What are the risks for systemic sclerosis patients?

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Dear Editor,

In December 2019 in the Hubei province of China began a pandemic outbreak sustained by a novel coronavirus named Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2). The syndrome sustained by this virus has been named COronaVirus Disease 2019 (COVID-19) and respiratory illness is the dominant clinical manifestation [1]. From its onset, the virus rapidly spread in the world, leading the World Health Organization officially to declare a pandemic state on March 11, 2020, resulting in 1.812.734 confirmed cases of COVID-19, with more than 113.675 patients who died [World Health Organization. Coronavirus disease 2019 (COVID-19) Situation reports. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports, last access 14, April 2020].

To date, COVID-19 seems to have a lower mortality compared to the most important other human coronavirus syndromes (SARS-1 and MERS), but a dramatically greater spread [1]. This diffusion is favoured by infective carriers in which the virus produces no or mild flu-like syndrome during the whole duration of the disease after an incubation time (of 1–14 days). However, moderate-to-severe COVID-19 patients are very numerous and raise management concerns due to the saturation of Intensive Care Units (ICU).

Great importance in the mortality associated with coronaviruses infection has been given to the concomitant comorbidities of the patients. For COVID-19, a close correlation has been found with diabetes, hypertension, cardiovascular disease, whereas chronic obstructive lung disease, chronic liver disease and malignancies were reported in about 1–7% of patients who died [2].

Immunocompromised patients are rarely reported in SARS-1 and MERS cohorts [3–5] and mainly referred to patients with active cancer under chemotherapy (about 5–6% of patients). Particularly, the prevalence of coronaviruses infection in patients with autoimmune diseases is lacking in previous literature. This issue raises several concerns regarding the utility to continue immunosuppressive agents in this cohort of patients during outbreak [6,7]. Recently, Monti et al. [8] reported that patients with rheumatoid arthritis treated with biological DMARDs or targeted synthetic DMARDs did not seem to be at increased risk of life-threatening complications from SARS-CoV-2 compared with general population. Similarly, recent publications reported no cases of complicated SARS-CoV-2 related pneumonia in inflammatory bowel diseases, even in those patients under immunosuppressive treatment [9,10].

Whilst these figures are reassuring, the scenario could be quite different with regard to patients suffering from systemic sclerosis (SSc). SSc is a rare multifaceted autoimmune disorder characterized by inflammatory, vascular, and fibrotic processes resulting in skin fibrosis and multiple organ manifestations [11]. Lung involvement, i.e., interstitial lung disease (ILD) and pulmonary hypertension, is a common manifestation and develops in up to 75% of patients with SSc overall. To date, ILD represents the main cause of death in these patients [12]. Although at the moment the treatment of SSc is not well established, currently therapy of SSc patients focuses on immunosuppressant agents, particularly cyclophosphamide and mycophenolate mofetil. Furthermore some patients undergo conditioning immunosuppressive therapy before autologous stem cell transplantation (ASCT) [12,13]. More recently, consistent data have been published on the potential effectiveness of rituximab and anti-interleukin (IL) 6 receptor blocker tocilizumab in the improvement/stabilization of SSc ILD [13]. Since the lung disease and immunosuppression are WHO-defined risk factors for a more severe course of COVID-19, SSc patients could represent a peculiar subgroup of patients at increased risk of respiratory or life-threatening complications from SARS-CoV-2 compared with other autoimmune diseases. Very recently, Mihai et al. reported the observation of a SSc patient who developed a mild form of COVID-19, even in the presence of ILD treated with tocilizumab and type 2 diabetes mellitus [14].

More severe forms of COVID-19 are characterized by acute systemic inflammatory response and cytokine storm, which can result in injury to multiple organs. Different studies have shown that high circulatory levels of pro-inflammatory cytokines correlate with disease severity and poor prognosis during SARS-CoV2 infection [15]. Inflammation occurs to restore the homeostasis after viral infection and could be harmful if excessive. In this respect, Xu et al. [16] found an overactivation of T cells, manifested by increase of Th17 and high cytotoxicity of CD8 T cells, in the peripheral blood of a patient suffering from a severe and lethal form of COVID-19. The authors suggested that the important immune response could account for, at least in part, the severe lung immune injury in COVID-19 patients. Likewise, lymphopenia has been suggested as the result of lung sequestration of hyperactivated T-cells. In other words, inflammatory response and overaction of both T cells

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immune response in viral pneumonia could be a double-edged sword.

Although immunosuppressed SSc patients, particularly those with ILD, could be potentially more susceptible to SARS-CoV2 infection with severe clinical manifestations, the anti-inflammatory effects of immunosuppression could decrease the clinical expression of disease. Besides specific anti-IL6 effects mediated by tocilizumab, both cyclophosphamide and mycophenolate mofetil (MMF), the most commonly used drugs for the treatment of patients with progressive SSc-ILD, act as regulator of proliferation, survival and maturation of T-cells. Furthermore, MMF inhibits interleukin −17 (IL-17) production with a specific inhibition on Th17 cells [13]. Then, we can speculate that suppression of pro-inflammatory cytokines and T-cell activities by steroids and other immunosuppressive agents might be protective, even in SSc patients. Broadly speaking, there is some evidence that the use of anti-inflammatory agents, and namely of corticosteroids, may induce some improvement in the acute phase of this and other viral infections [17].

The patients with pre-existing cardiovascular disease appear to have heightened vulnerability to develop COVID-19 and tend to have more severe disease with worse clinical outcomes [18]. Cardiac involvement, due to both primary myocardiopathy and secondary to pulmonary hypertension, is common in SSc and associated with increased morbidity and mortality [19]. At the moment we do not know the impact of pre-existing scleroderma cardiac involvement on COVID-19 course.

Finally, it is highly desirable that future studies may be specifically addressed to the clinical course and outcome of COVID-19 in SSc patients under chronic immunosuppressive therapies and with pre-existing heart and pulmonary involvement.

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