Response to: 'Correspondence on 'Systemic sclerosis and the COVID-19 pandemic: World Scleroderma Foundation preliminary advice for patient management" by Snarskaya and Vasileva

We read with great interest the response from Snarskaya and Vasileva.[1] A second wave of SARS-CoV-2 infection is now a global reality[2]: since the publication of the World Scleroderma Foundation preliminary advice on the management on systemic sclerosis (SSc) patients during the first COVID-19 pandemic,[3] growing evidence has accumulated on COVID-19 affected SSc patients.[4] Up to 22 June, at the end of the first wave, 25 cases of SSc-COVID-19 were published in the literature, most of them undergoing immunosuppressant treatment with corticosteroids (CCS), conventional synthetic disease modifying antirheumatic drugs (csDMARDs) (methotrexate or mycophenolate mofetil) or biological DMARD (bDMARDs) (rituximab or tocilizumab) and with a variable outcome.[4] This heterogeneity was a limitation in understanding the possible influence of ongoing immunosuppression and the effect of administered treatments. A recent meta-analysis, including 62 studies with more than 300 000 patients with autoimmune diseases, concluded that bDMARD monotherapy was a protective factor for COVID-19-related hospitalisation and death, in particular with antitumour necrosis factor alpha, while the use of CCS, conventional-synthetic DMARDS (csDMARD) and csDMARDs/bDMARD combination exposed the patients to a higher risk.[5] A focused analysis on SSc population has described more SSc-COVID-19 cases: 1/64 patients in Crisafulli *et al*,[6] 1/168 patients in Bellan *et al*[7] and 2/526 patients in Del Papa *et al*,[8] with one of them, previously exposed to methotrexate and rituximab, with a fatal outcome.

Other major rheumatological scientific societies have released their advice for the management of adult patients affected by rheumatic diseases during the COVID-19 pandemic.[9 10] The European League against Rheumatisms (EULAR) and the American College of Rheumatology (ACR) suggested the continuation of CCS, csDMARD and bDMARD to all patients without suspected or confirmed COVID-19 infection. In addition to the same context, the ACR advised for the initiation of immunosuppressive treatment in patients with newly diagnosis or active rheumatic disease.[10] Regarding COVID-19 positive cases among patients with rheumatic conditions, the EULAR suggested to continue chronic CCS also in case of symptomatic COVID-19 infection, to evaluate the continuation of other immunosuppressive drugs (IMS) on a case-by-case basis and to adhere with local recommendations for the treatment of COVID-19 disease.[9] For SARS-CoV-2 exposed patients, the ACR recommends immunosuppressive treatments temporary interruption and to restart them on a negative test results or 2 weeks observation without symptoms. Similarly, it is suggested to stop or postpone the initiation of the immunosuppressants in case of documented or highly suspected COVID-19 disease.[10] In the literature, a case-by-case evaluation was suggested for interleukin (IL)-6 inhibitors,[10] possibly also considering Janus Kinase inhibitors.[11] Finally, the ACR suggested the restart of the immunosuppressive treatment in patients with non-complicated COVID-19 disease after 7–14 days of symptom resolution or 10–17 days after SARS-CoV-2 positive PCR test but without any symptom development.[10] Regarding more severe cases of COVID-19 disease, again, a case-by-case evaluation is strongly advised.[10]

Today, the interaction between the immunosuppressive treatments and the COVID-19 is a matter of debate, and the main actors in this scenario are, on one side, the immunosuppressants to control SSc and, on the other side, the immunosuppressive treatments targeting the COVID-19-related hyperinflammatory syndrome (eg, CCS, anticytokines such as anti-IL-1 and anti-IL-6, and JAK inhibitors).[12]

In this second pandemic wave, it may be wise to shift the therapeutic focus from the rheumatic manifestations to the potential infectious complications. In figure 1, the different clinical scenarios are presented: the case of non-exposure allows the continuation, while the exposure and/or the test/serology positivity always suggest a treatment discontinuation and a restart in due time according to the test positivity/negativity. Following the precautionary advice of EULAR and ACR, we may propose that the interruption (and not the continuation) of the immunosuppressive treatment should be discussed case-by-case, in particular regarding patients exposed to B-depleting agents. Through its direct target on CD20 positive B cells, rituximab may potentially reduce the immune response against the virus and increase the risk of reinfection.[13] Patients exposed to rituximab may benefit from a temporary interruption of other concomitant csDMARDs and/or the postponement of the next treatment cycle, with a more intensive monitoring of COVID-19-related and SSc-related manifestations. Despite the negative result of the data testing the therapeutic effect of convalescent plasma in severe COVID-19 pneumonia,[14] CD-20 depleted patients with might benefit from the use of blood-derived

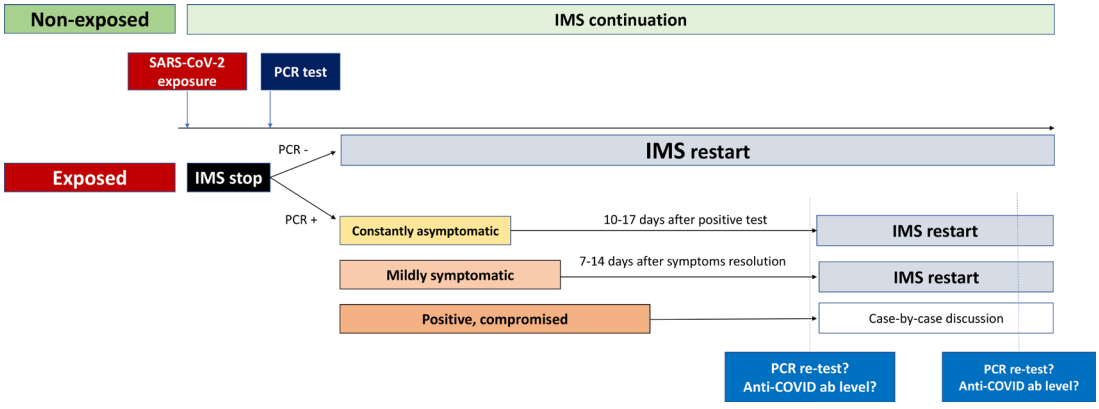

Figure 1 Algorithm for the management of immunosuppressive treatment according to SARS-CoV-2 exposure and COVID-19 disease. ab, antibodies; IMS, immunosuppressive drugs.

COVID-19 convalescent plasma, given the promising results shown in a small cohort of patients.[15]

We herein agree with the suggestions delivered from other societies and consider the possible role of PCR-retesting and anti-COVID-19 antibodies measuring before restarting IMS treatment in SSc-patients with initially positive PCR test. This preliminary consideration will be updated once data from larger initiatives, such as the EUSTAR COVID-19 registry, the EULAR COVID-19 database and the global alliance COVID-19 registry, will provide more robust evidences.

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