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LETTER

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Immunosuppressive treatment for systemic sclerosis—Therapeutic challenges during the COVID-19 pandemic

Dear Editor,

Coronavirus disease 2019 (COVID-19), caused by a recently emerged member of the coronavirus family SARS-CoV2, has created the largest public health crisis in recent years. At the time of writing this letter, the novel coronavirus has claimed more than 200,000 casualties worldwide and continues spreading at a quick pace.[1] Common symptoms of COVID-19 include fever, cough, and dyspnea. The infection may also be associated with acute respiratory distress syndrome and acute cardiac and/or renal injury with a potentially fatal outcome, especially in the population aged ≥70 years and in subjects with chronic comorbidities.[1,2]

Apart from disease-specific challenges, the universality of COVID-19 prompts the health care professionals to revisit and individualize the therapeutic approach in patients with chronic illnesses. In dermatological and rheumatological practice, systemic sclerosis (SSc) deserves particular attention because of the possibility of severe internal organ involvement and treatment regimens commonly based on immunosuppressive drugs.

Progressive interstitial lung disease (ILD) and pulmonary hypertension (PH) are common manifestations of SSc with serious implications with regard to the COVID-19 pandemic.[3] ILD and PH can deteriorate both the respiratory and cardiovascular function, which can negatively influence the overall outcome of COVID-19 in SSc individuals.

Immunosuppression was initially thought to be a risk factor of a severe course of COVID-19. However, reports considering the recipients of solid organ transplants and patients with chronic arthritis showed no such association.[4,5] Furthermore, during the previous coronavirus outbreaks caused by SARS-CoV and the Middle East respiratory syndrome (MERS)-CoV, immunosuppression was not a documented risk factor of unfavorable outcome.[5]

Immunosuppressants with the largest evidence base in SSc include methotrexate (MTX), mycophenolate mofetil (MMF), and cyclophosphamide (CYC) (Table 1).[6,7] The choice of a particular drug depends on the profile of symptoms presented by the patient and disease activity.

MTX at a dose of 10-15 mg/week is currently recommended as the first-line systemic therapy for cutaneous sclerosis in SSc.[6,7] Nevertheless, the benefits of MTX for internal organ involvement, including ILD, have not been documented.

Current guidelines suggest MMF at a dose of 1-2 g/day as the second-choice drug following MTX for progressive cutaneous sclerosis in SSc.[7] MMF additionally improves SSc-associated lung disease. Based on these observations and a favorable profile of adverse effects, MMF at a dose of 2-3 g/day may be used as first-line therapy in SSc-ILD and as maintenance therapy after CYC for severe cases.

CYC should be considered in case of severe, progressive SSc-ILD. It was also shown to improve the cutaneous symptoms of SSc. However, because of its toxicity, CYC constitutes a less favorable choice in the treatment of isolated cutaneous sclerosis and mild ILD.[6,7]

Literature data regarding the course of COVID-19 in patients treated with MTX, MMF, and CYC are lacking. However, Mohai et al have recently reported a mild course of COVID-19 in a patient with SSc and ILD who was treated with tocilizumab.[8] The authors concluded that current data suggest increased mortality of COVID-19 in individuals with higher expression of proinflammatory cytokines and suggested that anti-IL6 treatment and possibly other forms of immunosuppression could prevent the development of severe COVID-19.

Based on the presented arguments and initial recommendations of the World Scleroderma Foundation,[9] we encourage a careful, individualized approach to the management of patients with SSc during the COVID-19 pandemic. The introduction of immunosuppression (MTX/MMF/CYC) should be carefully weighed, yet in our opinion, the patients with extensive, quickly progressing cutaneous sclerosis and ILD should be treated with immunosuppressants according to the current guidelines. We also believe that immunosuppression should not be preventively discontinued because of the possible disease progression and negative influence on the long-term survival of SSc patients.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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TABLE 1 A summary of current immunosuppressive treatment for skin sclerosis and lung disease in the course of systemic sclerosis[6,7]

Drug	Dosage	Indication	Adverse effects	Comments
Methotrexate (MTX)	10-15 mg/week s.c. or p.o.	First-choice drug in SSc-associated cutaneous sclerosis	Liver toxicity, pancytopenia, teratogenicity, and possible induction of lung injury	No significant effects on internal organ manifestations were shown in the available RCTs. Higher doses may be considered, but the efficacy has not been verified to date.
Mycophenolate mofetil (MMF)	1-2 g/day p.o. for skin disease, up to 3 g/day for SSc-ILD	Second-choice drug in SSc-associated cutaneous sclerosis, milder cases of SSc-ILD	Anemia, leukopenia hematuria, fluid retention, and hypertension	Generally well-tolerated, recommended for long-term treatment of scleroderma
Cyclophosphamide (CYC)	p.o. or i.v., dosage adjusted individually dependent on the clinical condition and response	Progressive SSc-ILD, unsuccessful treatment of skin sclerosis with MTX and MMF	Bone marrow suppression, teratogenicity, gonadal failure, and hemorrhagic cystitis	The EULAR guidelines are based on favorable outcomes of two RCTS of CYC administered orally at 1-2 mg/kg/day or intravenously at 600 mg/m^2/month

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