Systemic sclerosis in the time of COVID-19

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Summary

The COVID-19 pandemic represents one of the biggest challenges of the 21st century. In addition to the general impact on society and health care system, patients with systemic sclerosis (SSc) and their physicians face specific challenges. These are related to the chronic nature of SSc, the multi-organ involvement, and the immunosuppressive treatments. Data from registries and single centre cohorts indicate that the risk to contract COVID-19 does not seem to increase importantly in SSc; conversely, severe outcome is more frequently observed in SSc compared to the general population. Vaccination is therefore highly recommended for SSc patients. Up to date, no specific recommendations are available regarding the different vaccines. Both patients and physicians should be aware that while on immunosuppressive therapy, efficacy of vaccines might be less, as antibody responses are blunted, specifically in those treated with rituximab and mycophenolate mofetil.

Introduction

The current corona virus disease pandemic (COVID-19) has had a major societal and healthcare impact worldwide, resulting in a high economic, social, and medical burden. Delays in clinical care including new consultations, follow-up assessments and treatment administration have been major challenges for many patients worldwide[1]. Standard management approaches have been modified around the world to include telemedicine and teleconsultation[2]. However, this had a substantial impact on patients affected by rheumatic diseases, including patients with systemic sclerosis (SSc)[3]. In patients with rheumatic diseases, mortality increased during the COVID-19, particularly in younger age groups where increased mortality started at the age of 35 compared to the age 55 upwards in the general population[4]. This is exemplified by an age-standardized mortality rate among people with rheumatic diseases that was 1·44 (95%CI 1·42-1·45) times higher during the pandemic than in the same months of the previous 5 years, whereas in the general population of England it was 1·38 times higher[4]. For SSc patients, the COVID-19 pandemic has had major effects on disease management in several ways. Redirection of healthcare resources towards patients with COVID-19 has reduced the capacity and resources available for complex long-term conditions such as SSc[3]. In addition, the need to reduce numbers of patients attending outpatient departments and hospital admissions has limited face-to-face interaction and resulted in remotely conducted clinic appointments via telemedicine[5]. This was a particular challenge for the routine assessment of lung and heart disease, which are normally evaluated by pulmonary function tests and echocardiography. Even performing a modified Rodnan skin score was difficult and there was increasing use of remote self-assessment approaches[6]. This had a substantial impact on clinical trials and research and may have longer-term consequences for SSc. Finally, there has been considerable direct impact, as patients with

SSc have inevitably contracted COVID-19 despite all the general and specific public health measures in place to try to shield patients and reduce transmission.

Almost two years after the beginning of the pandemic and at the beginning of the fifth wave, the gathering of large multi-centre data and widespread clinical experience is expected to provide high quality information on the risk of infection, hospitalization, severe outcome and death, measuring the impact of the pandemic on SSc patients. SSc patients with a more severe disease course and immunocompromised patients are of particular interest. In addition, international scientific initiatives may show robust evidence on the impact of COVID-19 on SSc disease course, on the development of SSc related complications and on their management. Finally, similar data on the use of the anti-SARS-CoV-2 vaccination are expected, which may provide indications for a better timing of this preventive measure. Because it is unlikely that COVID-19 infection will disappear, but more likely that we have to learn to handle it, these data will support the rheumatologist in the future care of SSc patients and in a better approach of COVID-19. With the aim of providing answers to some of these points, international initiatives are ongoing to specifically collect data on SSc-COVID cases, including the European Scleroderma Trials and Research (EUSTAR) registry, and joint efforts of the European League Against Rheumatism (EULAR) and the COVID-19 Global Rheumatology Alliance (C19-GRA)[3].

The aim of this review is to summarize the current evidence in terms of prevalence, impact, management, and vaccination of SSc patients in the time of COVID-19. References for this Review were identified through searches of PubMed with the search terms “COVID-19” and “systemic sclerosis”, from March 2020 until December 2021. Articles were also identified through searches of the authors’ own files. Only papers published in English were reviewed. The

final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

Prevalence, impact and prognosis of COVID-19 in SSc

Specific factors such as age, sex, and comorbidities have been associated with worse outcome in the general population[7]. Specifically, a recent meta-analysis, including more than 38000 hospitalized patients identified male sex (relative risk (RR) 1·3, 95%CI 1·2-1·4); age >60 years (RR 3·6, 95%CI 3·0-4·4); systemic arterial hypertension (RR=1·8, 95% CI 1·6-2·0); diabetes mellitus (RR=1·5, 95% CI 1·4-1·7) and chronic kidney disease (RR=2·5, 95% CI 2·1-3·0) as risk factors associated with COVID-19 related mortality in the general population[8]. Little is known so far on the specific impact of COVID-19 on SSc patients and of SSc specific features on long-term outcome of COVID-19 infection. To get guidance on the best practices in how to manage patients with SSc in times of the COVID-19 pandemic, it is however of key importance to understand the impact of COVID-19 on patients with SSc and their specific features. Therefore, we reviewed available data including the prevalence of COVID-19 in SSc, and SSc specific factors associated with worse outcome.

Prevalence of COVID-19 in SSc

In comparison to the general population, SSc patients and patients with rheumatic diseases overall have reported to have higher prevalence of COVID-19 in three published Italian studies. The first study included 1641 SSc patients[9] and 2994 rheumatic disease cases[10]. The prevalence of COVID-19 in these patients were 1% and 0·73% during the first wave, compared to 0·35% in the Italian general population (Italian Superior Institute of Health, reported on April 28, 2020).

The second Italian study showed that the COVID-19 prevalence in SSc patients was low in the first wave[11]. Out of 526 patients with SSc from a tertiary hospital in Milan, Italy, who were

called between 08.03.20 and 20.04.2020, two had confirmed COVID-19 and 11 were highly suggestive of COVID-19; while 513 had no signs and symptoms of COVID-19[11]. Of notice, exposure history of the patients was not captured, which is important to estimate the real prevalence of an infectious disease. Also, no population-based comparator was assessed. The cumulative prevalence of COVID-19 was assessed in a nationwide Italian SSc cohort between March 15 and April 25, 2020[12]. Out of 1636 SSc patients contacted by a telephone survey, 14 (1%) patients had COVID-19 verified by PCR test, and 47 (3%) had highly suspected COVID-19. The prevalence was compared to the population-based comparator and was found to be higher than in the general Italian population (349/100000; p=0·0010). The majority of COVID-19 infected SSc patients had clinically mild-to-moderate manifestations[12]. In this cohort, 510 (31%) had symptomatic SSc-related interstitial lung involvement (SSc-ILD). The prevalence of COVID-19 in patients with SSc associated ILD was higher than in patients without ILD (Odds ratio, OR 2·44 (95% CI 1·62-4·52), p<0·001)[12]. Whether this reflected greater awareness of risk and more testing and diagnosis, or the effect of concurrent immunomodulatory ILD treatment or the ILD manifestation itself or associated factors is unknown. Other factors also most likely affected the reported prevalence of COVID-19 in SSc. The availability of PCR tests was limited in several countries, no systematic PCR test was performed during this period, no screening was carried out? in asymptomatic patients.Lastly, patients with SSc were most likely very cautious, more than the general population, and most patients probably highly restricted their outings and visits.

Impact and prognosis of COVID-19 in SSc

There is to date little knowledge specifically on the impact of COVID-19 on SSc patients, but more on rheumatic diseases in general. In the C19 GRA registry, age, gender and comorbidities

affected mortality in patients with rheumatic diseases and COVID-19[13]. This study included also SSc patients, although they were grouped together with all other connective tissue diseases (CTDs) except for systemic lupus erythematosus (SLE). In the group of CTDs, moderate/high disease activity was significantly associated with COVID-19-related death, and rituximab treatment was associated with higher mortality compared to methotrexate[13]. Rituximab treatment was also associated with severe outcome in rheumatic disease patients in the French rheumatic disease COVID-19 cohort[6]. The cohort included 43 (4%) SSc patients of which seven (11%) were treated with rituximab. In this study, rituximab therapy was associated with severe COVID-19 outcome across all rheumatic disease patients. Notably, rituximab remained strongly associated with severe outcome even after adjustment for the main risk factors confounders. The time between last infusion of rituximab and first symptoms of COVID-19 was significantly shorter in patients who developed a severe form of COVID-19 than those with moderate or mild forms, suggesting direct drug accountability in rheumatic disease patients[6]. In the French cohort of rheumatic disease patients with COVID-19, also Mycophenolate mofetil (MMF), which is frequently used in SSc patients, especially for the treatment of ILD, was associated with severe COVID-19[14]. Associations to severe outcome in SSc patients have to date, however, not been published.

To assess the impact of COVID-19 on SSc by determining the proportion of patients with severe outcome (defined as death, ICU admission or ventilation); and to evaluate characteristics associated with severe outcome, we included all SSc patients from the EUSTAR COVID-19 registry and from C19-GRA (unpublished data). Preliminary analysis have been presented at major conferences[15]. The final results will shed important insights into SSc-specific risk factors

for severe outcome of COVID-19 infections including certain organ manifestations and SSc-specific treatments.

The pandemic also had major impact on other aspects of SSc patient care. In a study including 291 SSc patients without COVID-19, patients were asked to complete an online survey from April 13 to May 13, 2020 to assess the problems faced by patients with SSc during the pandemic, with a focus on effects on the disease, drug procurance, continuity of medical care, and prevalent fears among patients. In this study, 40·9% experienced problems directly attributable to the pandemic. Of the included patients, 38% experienced hurdles in procuring their medicines, 25% disruption in their physiotherapy sessions, 24% had difficulties and 7·2% were unable to contact their specialist[5]. The majority of patients (71·5%) feared to contract COVID-19 and 45·4% feared SSc disease flare[5]. Of all assessed patients, 55·7% preferred teleconsultations[5]. In addition, treatment strategies have been affected as well: as shown by data from the European Society for Blood and Marrow Transplantation (EBMT) register, the number of SSc patient registered with autologous stem cell transplantation was considerably lower in 2020 as compared to 2019[16]. The entire impact of the pandemic on our SSc patients including risk of a diagnostic delay and reduced routine assessments with possible missing of disease related severe lung/heart/kidney complication will first be possible to assess in the years after the pandemic.

Organ manifestations in SSc and COVID-19

It is notable that both SSc and COVID-19 are multisystem diseases with complex pathology and impact of co-morbidity[3]. Interestingly, some characteristics associated with worse outcome such as ethnicity and age are shared between the diseases, and mortality of both diseases is primarily driven by heart, lung and kidney complications. There may even be shared drivers of disease noting that IL6 receptor blockade has been reported to be beneficial in both diseases with

potential impact on lung manifestations[17,18]. Systemic vasculopathy occurs in COVID-19 and recently some of the treatments used for treating vasculopathy in SSc have been reported to be potentially beneficial in COVID-19 including iloprost[19]. Post-COVID complications such as chilblains are also a feature of CTDs and have benefited from management strategies developed more generally for digital microvascular disease[20].

COVID-19 lung disease and SSc ILD

As reported above, SSc-ILD patients with COVID-19 may have a worse outcome, emphasizing the importance to elucidate the relationship and differential diagnoses between SSc-ILD and COVID-19 lung manifestations in detail. The lung involvement of SSc and COVID-19 have several imaging similarities, which is a first hurdle in the diagnostics of COVID-19 lung in patients with SSc-ILD[21,22]. A difference is, that disease progression in COVID-19 is acute while in SSc it is frequently subacute and chronic[23]. Patients affected by COVID-19 usually present with unspecific symptoms at disease onset, such as fever, cough, fatigue, myalgia, and dyspnoea. Only 10–15% may evolve to a severe respiratory disease and of these, about 5% may evolve to respiratory failure, septic shock, and/or multiple organ dysfunction[24,25]. For this reason, an early diagnosis of lung infection and a timely treatment is mandatory to prevent progression to a critical stage of the disease, which may lead to severe outcome such as ventilation or death.

At lung level, high resolution computed tomography (HRCT) of the chest is a good[9], albeit far from perfect, tool for the detection and characterization of SARS-Co-V-2 infection and the development of COVID-19[26]. HRCT showed good sensitivity but moderate specificity to diagnose COVID-19. Thus, the role of HRCT is still evolving and has some limitations for a precise differential diagnosis between COVID-19 and other similar clinical ILD presentation in CTDs[21]. On HRCT, COVID-19 lung involvement shows involvement of the parenchyma. Single

or multiple lesions may be present, predominantly with a peripheral distribution in the middle and lower zones and in the posterior areas[27]. The most frequent lesions observed are distributed bilaterally, but with differences between the sides according to the disease progression. They range from ground glass (GGO), consolidations, pleural effusions, to GGO and reticular pattern, GGO crazy paving and eventually honeycombing.

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In clinical practice, it may be challenging to distinguish between the lung involvement of COVID-19 and ILD in an SSc patient[22], because COVID-19 pneumonia shares some HRCT features with SSc-ILD[22]. As ILD is a frequent and severe complication of SSc, current guidelines advocate screening for ILD by means of HRCT early in the disease course. (28-32). The most common imaging pattern on HRCT in SSC-ILD is non-specific interstitial pneumonia (NSIP), characterized by peripheral ground-glass opacities with an apical to basal gradient, frequently accompanied by subpleural sparing, and reticulation and traction bronchiectasisias in case of fibrotic NSIP. Several cases of COVID-19 have been described in SSc and further raised the concern about shared HRCT features[6,33,34]. The HRCT images of patients with COVID-19 pneumonia have been classified as typical, indeterminate and atypical[35]. The distribution in the upper lobes, the patchy GGO, the crazy paving and the consolidations are not frequently found in SSc-ILD and might therefore suggest a COVID-19 infection.

Clearly, HRCT findings detected in COVID-19 and SSc-ILD may reflect both diseases, having some similarities but also a consistent different evolution over time[36,37]. Recently, the comparison between SSc and COVID-19 lung involvement has shown that the HRCT differential diagnosis might be successfully achieved in practice. In particular, the presence of consolidations in the lower lobes and of fibrosis inside GGO may help in differentiating the

diseases and drive the physician toward an early diagnosis either of SSc-ILD progression or of an overlap of COVID-19 in SSc-ILD[38]. The HRCT evaluation may be performed also by the rheumatologist, but a specific expert evaluation of a radiologist is strongly recommended when an overlap of both diseases is suspected.

Recommendations to handle COVID-19 and SSc

Early in the pandemic, there was concern that patients with SSc would be especially susceptible to the disease or more likely to have a poor outcome. This was plausible due to the frequency of background cardiopulmonary or renal disease in SSc and the use of immunosuppressive drugs, which can predispose to infection. This led to SSc-specific[39], and more recently broader generic recommendations for management of COVID-19 in musculoskeletal and immunological diseases[40]. Although a substantial number of patients with SSc have contracted COVID-19, it has become apparent that, fortunately, most patients do not have a poor outcome. Whilst ongoing registry studies[41], including projects described in this article, show that SSc cases may overall have a worse outcome than the general COVID-19 population, it is also reassuring that many patients do have milder disease and make a full recovery.

Management of acute COVID-19 in SSc should largely follow the general evidence-based approach. Diagnosis should be confirmed whenever possible by a PCR antigen test for COVID-19 viral RNA and stratification according to clinical criteria[42] into non-severe, severe and critical severity groups is helpful for management. These thresholds are largely defined by need for supplemental oxygen to maintain oximetry or need for ventilatory, cardiovascular or renal support in a high dependency or intensive care ward. Current management has benefited from the large well-conducted clinical trials including the RECOVERY trial in U.K.[43]. This and other studies have already demonstrated survival benefits from dexamethasone. A total of 2104

patients were assigned to receive dexamethasone and 4321 to receive usual care, with 28-day mortality of 22·9% in the dexamethasone group and 25·7% in the usual care group (age-adjusted rate ratio, 0·83; 95%CI, 0·75 to 0·93; P<0·001). This trial also confirmed benefit from IL6 blocking agents. Thus, 4116 adults of 21 550 patients enrolled into the RECOVERY trial were included in the assessment of tocilizumab, including 3385 (82%) patients receiving systemic corticosteroids. Overall, the 28 day mortality was 31% for patients allocated tocilizumab and 35% in the 2094 patients allocated to usual care (rate ratio 0·85; 95% CI 0·76–0·94; p=0·0028)[44]. Whilst high dose steroids are generally avoided in SSc, due to risk of scleroderma renal crisis[45], the standard approach of using dexamethasone in COVID-19 pneumonitis associated with need for supplemental oxygen is appropriate as the survival advantage of steroids outweighs risk. However, blood pressure and renal function will need careful monitoring which will be in line with standard COVID-19 treatment. Tocilizumab is also standard treatment for cases of COVID-19 requiring supplemental oxygen, and the promising data for IL6R blockade in SSc-ILD supports this strategy. Trials have suggested that remdesivir can shorten hospital admission when given at an early stage, within 10 days of the onset of symptoms[46]. Monoclonal antibody therapies (casirivimab/imdevimab [Ronapreve®] and regdanvimab [Regkirona®]) are now authorised in the EU. Oral antiviral agents (e.g. molnupiravir) are also now approved by MHRA based on trial results showing benefit in preventing severe disease and hospitalisation. This follows the granting of marketing authorisations for these products by the EMA and antiviral agents are also now approved by MHRA and other Health Authorities for treatment of early COVID19 based on positive clinical trial data. These approaches may be especially valuable in high-risk cases with severe SSc that have not had adequate serological response to vaccination or are unvaccinated. Although few, if any, SSc cases have been included in these

clinical trials there is no expectation that they would not also be helpful in the context of SSc and at present all patients should be offered these important treatments that can be expected to reduce mortality in all the following waves of the pandemic. Lastly, it should be noted thattspecific SSc manifestations challenge the standard COVID-19 management, including co-existent digital vasculopathy, concurrent cardio-pulmonary or renal impairment and practical challenges of intubation and mechanical ventilation related to microstomia and restricted cranio-cervical range of movement.

Post-COVID syndrome

A further concern is the emergence of post-COVID syndrome (also known as long COVID) as an important entity. Emerging evidence and patient testimony are showing a growing number of people who contract COVID-19 cannot shake off the effects of the virus months after initially falling ill. Signs and symptoms that develop during or following an infection consistent with COVID-19, which continue for more than 12 weeks and are not explained by an alternative diagnosis are defined as post-COVID-syndrome. Symptoms are wide-ranging and fluctuating, and can include breathlessness, chronic fatigue, "brain fog", anxiety and stress[47]. Many people with post-COVID syndrome can also experience generalized pain, fatigue, persisting high temperature and psychiatric problems. Since many of these clinical features and symptoms are familiar to patients and clinicians, dealing with chronic rheumatic and musculoskeletal diseases such as SSc, it is possible that post COVID syndromes will be an additional burden for patients with SSc.

In summary, SSc and COVID-19 are both important health challenges and may have overlapping features or findings on investigation that impact on management. However, at present, SSc patients should be treated in the same way as other cases and can benefit from the increasing

number of approved therapies for both early and later stage COVID-19. Some of the adaptions to practice and new approaches that have been essential during the pandemic may be usefully incorporated into long-term practice once the pandemic subsides.

SARS-Co-V-2 vaccination in patients with systemic sclerosis

Vaccines are needed to overcome the COVID-19 pandemic and reduce the morbidity and mortality associated with SARS-Co-V-2. Rapid global efforts to develop and test vaccines have led to an unprecedented number of candidate vaccines starting clinical trials during 2020[48]. To date, the European Medicines Agency (EMA) has authorized 6 vaccines for SARS-Co-V-2, namely AZD1222, Ad26.COV2.S, mRNA-1273, BNT16b2, BBIBP-CorV and CoronaVac.

All current available SARS-Co-V-2 vaccines are non-live vaccines[49]. Three different techniques of developing these vaccines have been employed, namely vector vaccines, mRNA vaccines and inactivated virus vaccines. Of these, the first two vaccines forms are most often used. Vector vaccines are AZS1222 and Ad26.COV2.S. AZD1222 consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene, and was tested in the registration study in 11636 subjects, showing a 70·4% effectivity in preventing symptomatic COVID-19 infection[50]. Ad26.COV2.S consists of a recombinant, replication-incompetent adenovirus serotype 26 vector encoding a full length and stabilized SARS-CoV-2 and showed a 66·9% effectivity in the 43783 subjects in the phase 3 trial. The second vaccin development method is based on a messenger RNA (mRNA) vaccine platform. BNT16b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA (modRNA) encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation, which showed an effectivity of 95% in the 43548 participants of the randomized controlled trial[51]. The other mRNA vaccine is mRNA-

1273, a lipid-nanoparticle encapsulated mRNA vaccine expressing the perfusion-stabilized spike glycoprotein, with an effectivity of 94·1% in 30420 participants[48].

To assess efficacy and safety of the vaccines, data on thousands of persons are available. The majority of the subjects who received a vaccine in the context of trials experienced local reaction such as pain and swelling at the injection site, erythema or local lymphadenopathy. Systemic effects consisted of headache, fatigue, myalgia, fever and nausea[48,50-52]. However, serious adverse events occurred in less than 1% of the subjects. The very rare side effect of thrombosis in combination with thrombocytopenia that has been reported in subjects who received ChAdOx1 nCoV-19 and those who received Ad26.COV2.S; this has not changed the EMA approval to date. Long-term effects and side effects of all vaccines are to be determined during follow-up.

To date, limited information is available on possible adverse events of SARS-Co-V-2 vaccinations in patients with SSc. For patients with rheumatic diseases, there is theoretical risk for a flare related to exogenous mRNA triggering sensor recognition in dendritic cells, leading toinnate immune system activation. Stimulated dendritic cells could activate autoreactive lymphocytes but if this occurs and with what consequences has to be elucidated yet[53]. Only in the BNT162b2 phase 3 trial 118 patients with rheumatic diseases were included, but specific details are lacking[51]. In an observational study in 1377 patients with self-reported rheumatic diseases, including 14 patients with SSc, 11% reported a disease flare requiring treatment, but no severe flares after two-dose mRNA vaccine[54]. In an observational study with a two-dose regimen with BNT162b2 in 686 patients with autoimmune rheumatic diseases compared to the general population, no differences in side effects or adverse events were found and no post vaccination increase of disease activity was noted.

SARS-Co-V-2 vaccine immunogenicity can be measured by humoral IgG to spike protein or cellular T-cell reactivity via interferon-γ response to SARS-Co-V-2 peptide. Antibody responses are reported as newly positive anti-spike protein IgG (seroconversion) or by post-vaccination antibody titres. The exact role and relative contribution ofT-cell responses in generating vaccin efficacy tstill has to be elucidated but evdindece indicates that specific T-cell responses may offer protection even in the absence of humoral response[55,56]. In the above mentioned observational trial in 686 patients with BNT162b2 vaccine seroconversion was noted in 100% of the healthy controls, but only 39% of the patients treated with rituximab, 64% in MMF, 71% in abatacept, 77% in corticosteroids and 92% in MTX[57]. In a retrospective study in 89 patients treated with rituximab, a shorter duration between rituximab treatment and vaccination and lack of B-cell reconstructions are risk factors for poor humoral response on rituximab[58]. In SSc-patients at risk of severe COVID-19 infection due to their organ involvementor use of specific immunosuppressive drugs including rituximab and MMF, early treatment with the monoclonal antibodies casirivimab and imdevimab, REGEN-COV, should be considered independent of vaccination statusto prevent hospitalisation or death[59].

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Current EULAR view-points on SARS-CoV-2 vaccination

The EULAR task force based its advice on available knowledge in November 2021[60]. To date, there is no evidence that patients with rheumatic diseases suffer from higher rates of COVID-19 related mortality or intensive care admission. The demographic risk factors and comorbidities known to be associated with worse prognosis in the general population are also applicable to patients with rheumatic diseases, and no difference has been found between different rheumatic diseases. The recommendations consist of the advice to receive SARS-CoV-2 vaccination with

any of the EMA-approved vaccines. Furthermore, patients are advised to continue their treatment unchanged, taking into account that certain therapies have been associated with an increased risk of severe COVID-19[60]. However, postponing treatment with rituximab, when feasible, should be considered to improve immunogenicity[57]. Furthermore, current literature provides concerns regarding the use of rituximab, which seems to be associated with an increased risk of complications of COVID-19 and death and switching to an alternative treatment should be considered[60].

Taking all this into account, vaccination against SARS-Co-V-2 in patients with SSc is recommended. Immunosuppression should not be changed for the purpose of vaccination, but timing of vaccination is important for patients receiving rituximab. To date, there is no preference for a single vaccine, but as in the general population, long term safety aspects could change this recommendation.

Conclusion

The COVID-19 pandemic represents one of the biggest challenges of the 21st century. In addition to the general impact on society and health care system, patients with SSc and their physicians face specific challenges. These are related to the chronic nature of SSc, which implicates continuous need for health care, the multi-organ involvement which increases the risk of severe outcome of COVID-19, and the immunosuppressive treatments which might not only increase risk of severe outcome but might also affect the efficacy of vaccination.

Several ongoing international initiatives contribute to increasing insights on the impact of COVID-19 on patients with SSc. First, data from registries and single centre cohorts indicate that the risk to contract COVID-19 does not seem to increase importantly in SSc. However, based on

data from the combined EUSTAR and C19-GRA registries, severe outcome is more frequently observed in SSc compared to the general population, where reported mortality varies from 0.01% to 0.67% depending on age and sex[61]. To what extent the observed percentages reflect outcomes of COVID-19 in the general SSc-population remains to be determined, as these registries depend on active reporting by treating physicians which might induce bias towards more severe cases. However, these analyses clearly suggest that cardiopulmonary involvement, renal disease and treatment with rituximab are risk factors for severe outcome. Vaccination is therefore highly recommended for SSc patients. Up to date, no specific recommendations are available regarding the different vaccines. Both patients and physicians should be aware that the efficacy of vaccines might be less while on immunosuppressive therapy, as antibody responses are blunted, specifically in those treated with MMF, rituximab and other B-cell targeted therapies[62]. Whether these lower-than-expected antibody levels translate into less protection from COVID-19 after vaccination remains unclear, as the important T-cell mediated immunity by the vaccination has not been assessed. For the near future, potential strategies to augment vaccine immunogenicity for patients with compromised immune responses are urgently awaited, given the likelihood that COVID-19 will remain a worldwide threat in the coming years.

Management of acute COVID-19 in SSc should follow general guidelines, and with mild symptoms, immunosuppressive treatment should be continued[40]. It is important that physicians realise that COVID-19 disease and SSc share to a certain extent some manifestations including pulmonary involvement and signs of microangiopathy, which can complicate differential diagnosis. Specifically, both COVID-19 pneumonia and SSc–ILD can result in interstitial abnormalities on HRCT. However, asymmetrical lung involvement, patchy GGO, a crazy paving pattern and rapidly evolving consolidations are rare in SSc-ILD and are more frequently

observed in COVID-19 pneumonia. In our opinion, this underlines again the necessity to perform chest HRCT at diagnosis of SSc in every patient to identify presence and distribution of ILD at baseline.

Finally, the ongoing and maybe biggest challenge is to continuously provide high quality patient care for a chronic and severe condition as SSc, even in times when access to outpatient clinics and hospitals is severely limited. New initiatives that enable remote monitoring[3,63] can contribute to solve these challenges.

Declaration of interest

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