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Systemic sclerosis in the time of COVID-19

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The COVID-19 pandemic represents one of the biggest challenges of the 21st century. In addition to the general effect on society and health-care systems, patients with systemic sclerosis and their physicians face specific challenges related to the chronic nature of their disease, the involvement of multiple organs, and the use of immunosuppressive treatments. Data from registries and single centre cohorts indicate that the risk of contracting SARS-CoV-2 does not seem to increase substantially in people with systemic sclerosis; conversely, severe COVID-19 outcomes are seen more frequently in these patients than in the general population. Vaccination against SARS-CoV-2 is therefore highly recommended for patients with systemic sclerosis; however, no specific recommendations are available regarding the different vaccine platforms. Both patients and physicians should be aware that the effectiveness of vaccines might be reduced in patients taking immunosuppressive therapy, because antibody responses might be blunted, specifically in patients treated with rituximab and mycophenolate mofetil.

Introduction

The COVID-19 pandemic has had an impact on society and health care 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 approaches to patient management have been modified worldwide to include telemedicine and teleconsultation.[2] However, these changes have had an impact on patients with rheumatic diseases, including those with systemic sclerosis.[3] In a UK national database including almost 170 000 patients with rare autoimmune rheumatic diseases, mortality increased substantially in younger age groups during March and April, 2020, with increased mortality noted as early as age 35 years, compared with 55 years in the general population.[4] This increase in mortality was exemplified by an age-standardised mortality rate in 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, the mortality rate was 1·38 times higher than the average age-standardised mortality rate recorded during the same months of the previous 5 years.[4] For patients with systemic sclerosis, the COVID-19 pandemic has had an impact on disease management in several ways. Redirection of health-care resources towards patients with COVID-19 reduced the capacity and resources available for the management of complex long-term conditions such as systemic sclerosis.[3] In addition, the need to reduce numbers of patients attending outpatient departments and hospital admissions restricted face-to-face interaction and resulted in clinic appointments that were done mostly remotely via telemedicine.[5] The use of telemedicine was a particular challenge for the routine assessment of lung and heart disease, which are normally evaluated by pulmonary function tests and echocardiography.[6,7] Likewise, doing a modified Rodnan skin score was difficult via telemedicine, and there was an increased use of remote self-assessment approaches.[8] These alternative assessment approaches impact on clinical trials and research, and might have longer-term consequences for systemic sclerosis.

Almost 2 years after the beginning of the pandemic, the availability of large multicentre data and widespread clinical experience has provided high-quality information on the risk of infection, hospitalisation, severe outcomes, and death, and these data can be used to measure the effect of the pandemic on patients with systemic sclerosis. Studies of patients with systemic sclerosis who are immunocompromised or developed severe COVID-19 will help to further understand relevant risk factors. International scientific initiatives are ongoing and will provide robust evidence on the effect of COVID-19 on the disease course of systemic sclerosis and the development and management of complications related to the disease. Similarly, data on the use of the COVID-19 vaccines in patients with systemic sclerosis continue to accrue[9–11] and will provide evidence for the most appropriate timing of vaccination as a preventive measure. As it is clear that we have to learn to live with the SARS-CoV-2 virus, the data being collected during the pandemic will support rheumatologists in continuing to improve approaches to the future care of patients with systemic sclerosis. With the aim of providing answers to some of these points on COVID-19 management, international initiatives to specifically collect data on COVID-19 in people with systemic sclerosis are ongoing, 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.[3]

Little is known so far on how COVID-19 specifically impacts patients with systemic sclerosis, and how features that are specific to systemic sclerosis affect the long-term outcomes of SARS-CoV-2 infection; understanding these dynamics is of key importance to guide the best practices for the management of patients with systemic sclerosis during the COVID-19 pandemic. Therefore, we reviewed the available data, including the prevalence of COVID-19 in patients with systemic sclerosis and factors specific to systemic sclerosis associated with a worse outcome.

The current landscape

Prevalence of COVID-19 in systemic sclerosis

Patients with systemic sclerosis and patients with rheumatic diseases overall were reported to have a higher prevalence of COVID-19 than the general population in three Italian studies.[12–14] In the first study,[12] COVID-19 was reported by 4 (1%) of 438 patients with systemic sclerosis, and 25 (1·5%) of 1641 patients with rheumatic disease who were contacted for a telephone study between March 15 and April 25, 2020,[12] compared with 0·35% (349 of 100 000 population) of the general Italian population.[15]

In another study[13] of 526 patients with systemic sclerosis from a tertiary care hospital in Milan, Italy, who were contacted for a telephone survey between March 8 and April 21, 2020, two (0·4%) patients had confirmed COVID-19, and 11 patients (2·1%) had symptoms that were highly suggestive of COVID-19.[13] Of note, exposure history of the patients was not captured, which is important to estimate the real prevalence of an infectious disease, and no population-based comparator was assessed. Another study assessed the cumulative prevalence of COVID-19 in a nationwide Italian cohort of patients with systemic sclerosis between March 15 and April 25, 2020.[14] Of 1636 patients with systemic sclerosis who were contacted by a telephone survey, 14 (1%) patients had COVID-19 verified by a PCR test, and 47 (3%) patients had highly suspected COVID-19. The prevalence of COVID-19 in patients with systemic sclerosis was higher than in the general Italian population (p=0·0010).[15] The majority of patients with systemic sclerosis and COVID-19 had mild-to-moderate clinical manifestations.[14] In this cohort, 510 (31%) patients had symptomatic systemic sclerosis-associated interstitial lung disease (ILD). The prevalence of COVID-19 in patients with systemic sclerosis-associated ILD was higher than in patients without ILD (odds ratio [OR] 2·71, 95% CI 1·62–4·53, p<0·0001).[14] Whether these data reflect an increased awareness of risk and more testing and diagnosis, the effect of concurrent immunomodulatory ILD treatment, or factors associated with ILD, is unknown. Other factors are also like to have affected the reported prevalence of COVID-19 in patients with systemic sclerosis. The availability of PCR tests was restricted in many countries, systematic PCR tests were not done during this period, and generalised screening was not done in asymptomatic patients. Additionally, patients with systemic sclerosis were likely to be very cautious, more so than the general population, and most of these patients probably restricted movements and social contacts.[1]

Impact on mortality and prognosis

Specific factors such as age, sex, and comorbidities have been associated with worse COVID-19 outcomes in the general population.[16] One meta-analysis,[17] including 38 906 hospitalised patients, identified risk factors associated with COVID-19 related mortality in the general population,[17] including male sex (relative risk 1·3, 95% CI 1·2–1·4), age older than 60 years (3·6, 3·0–4·4), hypertension (1·8, 1·6–2·0), diabetes (1·5, 1·4–1·7), a history of smoking (1·3, 1·1–1·6), COPD (1·7, 1·4–2·0), and chronic kidney disease (2·5, 2·1–3·0).

Little is known specifically on the effect of COVID-19 in patients with systemic sclerosis, whereas more knowledge exists on patients with rheumatic diseases in general. Using data from the COVID-19 Global Rheumatology Alliance registry (a registry launched on March 24, 2020, in which data from patients with a pre-existing rheumatic disease and COVID-19 diagnosis are entered voluntarily by rheumatologists) factors, including increasing age, male sex, and presence of comorbidities were found to be associated with increased mortality in patients with rheumatic diseases and COVID-19.[18] This study also included patients with systemic sclerosis, although they were grouped together with all other connective tissue diseases, except for systemic lupus erythematosus.[18] In the group of patients with connective tissue diseases, those with moderate or high disease activity had higher odds of death than did patients with low disease activity or remission, and rituximab treatment was associated with higher mortality compared with methotrexate.[18] Rituximab treatment was also associated with severe outcomes in patients with rheumatic disease in the French RMD COVID-19 cohort.[19] Of the 1090 patients included in this cohort, 43 (4%) patients had systemic sclerosis, of whom seven were treated with rituximab. In this study, rituximab therapy was associated with a severe COVID-19 outcome across all patients with rheumatic diseases. Notably, rituximab remained strongly associated with severe outcomes even after adjustment for the main risk factors. The time between the last infusion of rituximab and the first symptoms of COVID-19 was significantly shorter in patients who developed severe COVID-19 than in patients with moderate or mild forms of the disease, suggesting direct drug accountability in patients with rheumatic disease.[19] Mycophenolate mofetil, which is frequently used in patients with systemic sclerosis (especially for the treatment of ILD), was also associated with severe COVID-19 in patients included in the COVID-19 Global Rheumatology Alliance registry.[18] The amount of uncertainty within the French RMD COVID-19 cohort is high, because the number of patients with systemic sclerosis who had presumed COVID-19 and were taking rituximab was rather low. Studies with large numbers of patients who have systemic sclerosis and COVID-19 and are given rituximab and mycophenolate mofetil are needed. In addition, associations of severe outcomes with treatment and risk factors specific to systemic sclerosis have not been published to date.

To assess the effect of COVID-19 on systemic sclerosis by establishing the proportion of patients with a severe outcome (defined as death, intensive care unit admission,

or ventilation) and to evaluate characteristics associated with a severe outcome, our group assessed all patients with systemic sclerosis from the EUSTAR COVID-19 registry[20] and from the COVID-19 Global Rheumatology Alliance registry (unpublished data). Preliminary analyses have been presented at major conferences,[20] and the final results will give important insights into the risk factors specific to systemic sclerosis, including organ manifestations and specific treatments, for severe outcomes of COVID-19.

Impact on the care of patients with systemic sclerosis

The pandemic also had an impact on other aspects of systemic sclerosis patient care. In an international study[5] including patients with systemic sclerosis without COVID-19, patients were asked to complete an online survey from April 13 to May 13, 2020, to assess the issues faced by patients during the pandemic, with a focus on effects on the disease, drug procurance, continuity of medical care, and prevalent fears among patients. The study was distributed worldwide using social media by various international systemic sclerosis organisations and patient communities (Scleroderma Family UK, Scleroderma Australia, Scleroderma and Functional Medicine, Limited Cutaneous Systemic Sclerosis, Worldwide Scleroderma, Scleroderma, and Scleroderma India). Of the 291 patients included in the study, 41% reported problems directly attributable to the pandemic. 38% had issues procuring their medicines (due to unspecified reasons), 25% had disruption in their physiotherapy sessions, 24% found it difficult to contact their specialist, and 7% were unable to contact their specialist.[5] Most patients (72%) had a fear of contracting COVID-19, and 45% feared systemic sclerosis disease flare.[5] Of all assessed patients, 56% preferred teleconsultations to face-to-face visits.[5] Another study assessed anxiety and depression in 435 patients with systemic sclerosis from the Scleroderma Patient-centered Intervention Network cohort before (late 2019) and during (until March, 2021) the COVID-19 pandemic.[21] Patients were mostly enrolled from France, the USA, Canada, and the UK. Mean anxiety symptom scores increased from before the pandemic to April, 2020 (standardised mean difference 0·51, 95% CI 0·37–0·64), whereas depression symptoms did not differ. Both anxiety and depression symptoms improved later in 2020, with anxiety symptoms returning to pre-pandemic levels, and depression symptoms slightly lower than before the pandemic.[21]

Treatment strategies have also been affected: as shown by data from the European Society for Blood and Marrow Transplantation register,[22] the number of systemic sclerosis patients registered with autologous stem cell transplantation was considerably lower in 2020 compared with 2019. The effect of the pandemic on patients with systemic sclerosis, including the possibility of undiagnosed lung, heart, or kidney complications related to severe disease because of diagnostic delays and reduced routine assessments, will begin to become apparent in the years after the pandemic.

COVID-19 and clinical manifestations of systemic sclerosis

Both systemic sclerosis and COVID-19 are multisystem diseases with complex pathology and comorbidity.[3] Some characteristics associated with worse outcomes, such as being Hispanic, Native American, or African American, male sex, and increasing age, are shared between the diseases, and mortality of both diseases is primarily driven by heart, lung, and kidney complications. There might even be shared contributors to disease, noting that interleukin-6 receptor (IL-6R) blockade has been reported to be beneficial in both diseases, with potential effects on lung manifestations.[23,24]

Vasculopathy

Systemic vasculopathy occurs in patients with COVID-19, and some of the treatments used for treating vasculopathy in patients with systemic sclerosis, such as iloprost, have suggested a possible benefit in the treatment of COVID-19.[25] However, more studies are warranted.[26] Post-COVID-19 complications, such as chilblains, are also a feature of connective tissue diseases and could benefit from management strategies developed more generally for digital microvascular disease.[27]

COVID-19 lung disease and systemic sclerosis ILD

Since patients with systemic sclerosis-associated ILD and COVID-19 might have worse outcomes than patients with systemic sclerosis-associated ILD who do not have COVID-19, elucidating the relationship and differential diagnoses between systemic sclerosis-ILD and COVID-19 lung manifestations in detail is important. The lung involvement characteristic of systemic sclerosis-ILD and COVID-19 have several similarities, which is the first hurdle in the diagnosis of COVID-19 lung involvement in these patients.[28,29] One difference is that disease progression in COVID-19 is acute, whereas in systemic sclerosis it is frequently subacute and chronic.[30] Patients affected by COVID-19 usually show nonspecific symptoms at disease onset, such as fever, cough, fatigue, myalgia, and dyspnoea. Only 10–15% of patients might evolve to a severe respiratory disease, of whom about 5% might evolve to respiratory failure, septic shock, or multiple organ dysfunction.[31,32] Because of the risk of symptoms evolving, an early diagnosis of lung infection and timely treatment is mandatory to prevent progression to a critical stage of the disease, which could lead to severe outcomes, such as ventilation or death.

For the lungs, high-resolution CT of the chest is a good,[33] albeit far from perfect, tool for the detection and characterisation of SARS-CoV-2 infection and for monitoring the development of COVID-19.[34]

High-resolution CT showed good sensitivity, but moderate specificity to diagnose COVID-19. Thus, the role of high-resolution CT is evolving and has some limitations for a precise differential diagnosis between COVID-19 and similar clinical ILD presentations in patients with connective tissue diseases.[28] With high-resolution CT, COVID-19 lung involvement shows involvement of the parenchyma. Single or multiple lesions might be present, predominantly with a peripheral distribution in the middle and lower zones and in the posterior areas.[35] The most frequent lesions observed are distributed bilaterally, but with differences between the sides according to the disease progression. Lesions range from ground glass opacities, consolidations, and pleural effusions, to ground glass opacities and reticular pattern, ground glass opacities with crazy paving, and eventually honeycombing. In clinical practice, distinguishing between the lung involvement of COVID-19 and ILD in a patient with systemic sclerosis might be challenging,[29] because COVID-19 pneumonia shares some high-resolution CT features with systemic sclerosis-associated ILD.[29] Because ILD is a frequent and severe complication of systemic sclerosis, current guidelines advocate screening for ILD with use of high-resolution CT early in the course of systemic sclerosis. The most common imaging pattern on high-resolution CT seen in patients with systemic sclerosis associated-ILD is nonspecific interstitial pneumonia, characterised by peripheral ground glass opacities with an apical to basal gradient, frequently accompanied by subpleural sparing, and reticulation and traction bronchiectasis in cases of fibrotic nonspecific interstitial pneumonia. Several cases of COVID-19 have been described in patients with systemic sclerosis and further raised the concern about shared high-resolution CT features.[8,36,37] The high-resolution CT images of patients with COVID-19 pneumonia have been classified as typical, indeterminate, and atypical.[38] The distribution in the upper lobes, patchy ground glass opacity, crazy paving, and consolidations are not frequently found in systemic sclerosis-associated ILD and might therefore suggest COVID-19.[36–40]

High-resolution CT findings detected in patients with COVID-19 and systemic sclerosis-associated ILD might reflect both diseases, having some similarities, but also indicate a consistently different disease evolution over time.[39,40] In the past year, the comparison between systemic sclerosis and COVID-19 lung involvement has shown that differential diagnosis by high-resolution CT might be successfully done in practice. In particular, the presence of consolidations in the lower lobes and of fibrosis inside ground glass opacities could help to differentiate the diseases and support the physician to an early diagnosis, either of systemic sclerosis-associated ILD progression or of an overlap of COVID-19 with systemic sclerosis-associated ILD.[29] The data on high-resolution CT indicate that we could differentially diagnose COVID-19 and systemic sclerosis on high-resolution CT, but it is important to note that more evidence is needed to allow a precise distinction between the two diseases. The evaluation of high-resolution CT could also be done by the rheumatologist, but a specific expert evaluation by a radiologist is strongly recommended when an overlap of both diseases is suspected.

Post-COVID syndrome

A further concern is the emergence of post-COVID-19 syndrome (also known as long COVID) as an important clinical entity. Emerging evidence and patient testimony are show that a substantial number of people who contract COVID-19 still have the effects of the virus months after first becoming ill. Signs and symptoms that develop during or after an infection consistent with COVID-19, that continue for more than 12 weeks, and are not explained by an alternative diagnosis, are defined as long COVID. Symptoms are widely ranging, fluctuate in frequency and severity, and can include breathlessness, chronic fatigue, so-called brain fog, anxiety, and stress.[41] Many people with long COVID can also have generalised pain, fatigue, a persistent high temperature, and psychiatric symptoms. Since several of the clinical features and symptoms are familiar to patients and clinicians dealing with chronic rheumatic and musculoskeletal diseases, such as systemic sclerosis, long COVID could be an additional burden for patients with these diseases.

In summary, systemic sclerosis and COVID-19 are both important health challenges and might have overlapping features or findings on investigation that affect disease management. However, at present, patients with systemic sclerosis should be treated in the same way as other people with COVID-19 and can benefit from the increasing number of approved therapies for both early-stage and late-stage COVID-19. Some of the adaptions to clinical practice and new approaches that have been essential during the pandemic could be usefully incorporated into long-term practice once the pandemic subsides.

Management of a patient with systemic sclerosis and COVID-19

Recommendations for the management of systemic sclerosis

Early in the pandemic, there was concern that patients with systemic sclerosis would be especially susceptible to COVID-19 or would be more likely than the general population to have a poor outcome. Concerns about increased susceptibility were plausible because of the frequency of background cardiopulmonary and renal disease in patients with systemic sclerosis and the use of immunosuppressive drugs, which can predispose patients to infection. These concerns led to recommendations specific to systemic sclerosis and broader recommendations for the management of

COVID-19 by both EULAR,[42,43] the American College of Rheumatology,[44] and other organisations representing patients with musculoskeletal and immunological diseases. Although many patients with systemic sclerosis have contracted SARS-CoV-2, it has become apparent that, fortunately, most patients do not have a poor outcome. Ongoing registry studies,[45] including projects described in this Review, show that patients with systemic sclerosis might have an overall worse outcome than the general COVID-19 population; however, it is also reassuring that many patients have mild disease and make a full recovery.

Management of acute COVID-19 in patients with systemic sclerosis

Management of acute COVID-19 in patients with systemic sclerosis should largely follow the general evidence-based approach. Diagnosis should be confirmed whenever possible by a PCR test for SARS-CoV-2 viral RNA, with stratification according to clinical criteria into non-severe, severe, and critical severity groups is helpful for management of patients with COVID-19.[46] These diagnosis thresholds are largely defined by the need for supplemental oxygen to maintain oximetry or the need for ventilatory, cardiovascular, or renal support in a high dependency or intensive care unit. Current management has benefited from large, well conducted clinical trials, including the RECOVERY trial in the UK.[47] This trial has shown survival benefits from dexamethasone. A total of 2104 patients in the RECOVERY trial[47] were assigned to receive dexamethasone and 4321 to receive usual care, with 28-day mortality of 23% in the dexamethasone group and 26% in the usual care group (age-adjusted rate ratio 0·83, 95% CI 0·75–0·93; p<0·001). The trial also showed benefit from IL-6 blocking agents. 4116 of 21 550 patients enrolled into the RECOVERY trial were included in the assessment of tocilizumab, including 3385 patients (82%) given systemic corticosteroids. Overall, the 28-day mortality was 31% for patients allocated tocilizumab and 35% in the 2094 patients allocated to usual care (age-adjusted rate ratio 0·85, 0·76–0·94; p=0·003).[48] Although high-dose steroids are generally avoided in patients with systemic sclerosis, because of the risk of scleroderma renal crisis,[49] the standard approach of using dexamethasone for COVID-19 pneumonitis associated with the need for supplemental oxygen is appropriate, because the survival advantage of steroids outweighs the risk. However, blood pressure and renal function should be monitored carefully in line with standard COVID-19 treatment. Tocilizumab is also standard treatment for patients with COVID-19 requiring supplemental oxygen, and the promising data for IL-6R blockade in systemic sclerosis-associated ILD supports the use of these inhibitors in patients with systemic sclerosis and COVID-19.[23] Trials have suggested that remdesivir can shorten hospital admission when given at an early stage, within 10 days of the onset of symptoms.[50] The monoclonal antibody therapies casirivimab and imdevimab (Ronapreve [Roche, Germany]), regdanvimab (Regkirona [Nuvisan, Germany]), and sotrovimab (Xevudy [GSK, Italy]) are now authorised in the EU and were granted authorisation for emergency use by the US Food and Drug Administration (FDA).[51–53] Oral antiviral agents (eg, molnupiravir) are also now approved by the Medicines and Healthcare products Regulatory Agency (MHRA) on the basis of trial results showing their benefit in preventing severe disease and hospitalisation, and for emergency use by the FDA. The approval of oral antiviral agents follows the European Medicines Agency's (EMA's) grant of marketing authorisations for these products, and antiviral agents are also now approved by MHRA and other health authorities for treatment of early COVID-19, on the basis of positive clinical trial data. The use of oral antiviral agents might be particularly beneficial in high-risk patients with severe systemic sclerosis who have not had an adequate serological response to vaccination or are unvaccinated. Although few, if any, people with systemic sclerosis have been included in clinical trials, there is no expectation that these agents would not also be helpful in the context of systemic sclerosi. At present, all patients should be offered these important treatments that can be expected to reduce mortality in future waves of the pandemic. However, it is important to note that several of the monoclonal antibody therapies have been shown to be ineffective against the omicron variant,[54,55] and authorisation by the US FDA has been modified accordingly. Effectiveness of these agents against future variants will require further studies. Specific manifestations of systemic sclerosis can challenge the standard management of COVID-19, including coexistent digital vasculopathy, concurrent cardiopulmonary or renal impairment, and practical challenges of intubation and mechanical ventilation related to microstomia and restricted craniocervical range of movement, which are challenges for intensive care management of systemic sclerosis.[56]

COVID-19 vaccination in patients with systemic sclerosis

Vaccines are needed to overcome the COVID-19 pandemic and reduce the morbidity and mortality associated with COVID-19. Rapid global efforts to develop and test vaccines led to an unprecedented number of candidate vaccines starting clinical trials during 2020.[57] Ten vaccines for COVID-19 have been approved by WHO, namely ChAdOx1 nCoV-19 (AstraZeneca; AZD1222), Ad26.COV2.S (Janssen), mRNA-1273 (Moderna; elasomeran), BNT16b2 (Pfizer-BioNtech; tozinameran), BBIBP-CorV (SinoPharm), CoronaVac (Sinovac Biotech), BBV152 (Bharat Biotech; Covaxin), Covovax (Novavax; NVX-CoV2373), Nuxaxovid (Novavax; NVX-CoV2373), and Ad5-nCoV (CanSino Biologics).[58]

All currently available COVID-19 vaccines are non-live vaccines or inactivated virus vaccines.[59,60] Three different techniques of developing COVID-19 vaccines have been used, including vector vaccines, mRNA vaccines, and inactivated virus vaccines. Of these techniques, the first vector vaccines (eg, ChAdOx1 nCoV-19 and Ad26.COV2S) and mRNA vaccines (eg, BNT16b2, mRNA-1273) are used most often. ChAdOx1 nCoV-19 consists of a replication-deficient chimpanzee adenoviral vector ChAdOx1, which contains the SARS-CoV-2 structural surface glycoprotein (spike protein; nCoV-19) gene, and was tested in a randomised, placebo controlled registration study in 11 636 patients, showing a 70% efficacy in preventing symptomatic COVID-19 infection.[61] Ad26.COV2.S consists of a recombinant, replication-incompetent adenovirus serotype 26 (Ad26) vector encoding a full length and stabilised SARS-CoV-2 spike protein, and showed a 67% effectiveness in the 19 630 patients in the phase 3 randomised, placebo controlled trial.[62] The second vaccine development method is based on an mRNA vaccine platform. BNT16b2 is a lipid nanoparticle-formulated, nucleoside-modified RNA encoding the SARS-CoV-2 full-length spike, modified by two proline mutations to lock it in the prefusion conformation, which showed an efficacy of 95% in the 43 548 participants included in the randomised controlled trial.[63] mRNA-1273 is a lipid-nanoparticle encapsulated mRNA vaccine expressing the perfusion-stabilised spike glycoprotein, with an efficacy of 94% in 30 420 patients.[57]

Most people who received a vaccine in the context of these trials had local reaction such as pain and swelling at the injection site, erythema, or local lymphadenopathy. Systemic effects included headache, fatigue, myalgia, fever, and nausea.[57,61,63,64] Notably, one systematic review showed that a third of the recipients of placebo in the COVID-19 vaccine trials reported at least one systemic adverse event after both the first and second dose.[65] This nocebo response accounts for most systemic adverse events.[65] However, serious adverse events occurred in less than 1% of the patients. A very rare side-effect of thrombosis in combination with thrombocytopenia was reported in people who received ChAdOx1 nCoV-19 or Ad26.COV2.S; the report of side-effects has thus far not changed the EMA approval. Long-term effects and side-effects of all vaccines have not yet been determined.

Information assessed in various surveys is available on the possible flares of systemic sclerosis at the time of COVID-19 vaccination in patients with rheumatic diseases.[66–68] A survey including 2860 adults with rheumatic diseases, of whom 126 had systemic sclerosis, reported that flares requiring new or increased doses of medication occurred in 4·6% of the total population.[66] A survey of 699 patients with systemic sclerosis showed that in 41 (6%) of the patients, at least one symptom of systemic sclerosis worsened after the first dose of the vaccine.[67]

COVID-19 vaccine immunogenicity can be assessed by measuring serum concentrations of IgG antibodies specific for spike protein or cellular T-cell reactivity via interferon-γ response to SARS-CoV-2 peptides. Antibody responses are reported as newly positive anti-spike protein IgG (seroconversion) or by antibody titres after vaccination. A prospective observational study in 478 patients with systemic autoimmune diseases, including 265 patients with systemic sclerosis, evaluated seroconversion after COVID-19 vaccination compared with 502 healthy people (ie, people with no systemic autoimmune diseases).[69] In the patients, antibody concentrations were significantly lower than in the control group, and patients were more likely than controls to have no detectable anti-spike antibodies (13% *vs* 3%). In another study including 264 patients with a stable inflammatory rheumatic disease, of whom 50 had systemic sclerosis, non-response was reported in 14%.[70] Furthermore, a significantly lower percentage of patients with rheumatic diseases who were taking rituximab seroconverted in both studies.[69,70] In an observational trial of 686 patients with autoimmune rheumatic diseases compared with the general population, vaccination with BNT162b2 resulted in 100% seroconversion in the control group compared with 39% of the patients treated with rituximab, 64% with mycophenolate mofetil, 71% with abatacept, 77% with corticosteroids, and 92% with methotrexate.[71] In a retrospective study of 89 patients with rheumatic diseases treated with rituximab, a shorter time period between rituximab treatment and vaccination and persistent B-cell depletion in peripheral blood were risk factors for poor humoral responses to COVID-19 vaccination.[72] A prospective study in 74 patients with rheumatic diseases treated with rituximab showed seroconversion in 39% after two doses of COVID-19 vaccine.[73] The exact role and relative contribution of T-cell responses in generating vaccine efficacy has yet to be elucidated, but evidence indicates that specific T-cell responses could offer protection, even in the absence of a humoral response.[74,75] In a prospective study in 140 patients with rheumatic diseases or glomerular diseases treated with immunosuppressants, a T-cell response after two doses of COVID-19 vaccine was found in 83% of patients, and the response was preserved in patients treated with B-cell depleting agents. In 74 patients, SARS-CoV-2 specific T-cell responses were detected in 58% of the patients after vaccination, independent of seroconversion.[73,76] Several studies have shown that, in patients with rheumatic diseases, a third dose of COVID-19 vaccine is associated with an increased humoral response;[77] as such, a third (and fourth) vaccination is advised in patients treated with immunosuppression, especially B-cell depleting agents.[77] In patients with systemic sclerosis at risk of severe COVID-19 because of organ involvement or use of specific immunosuppressive drugs, including rituximab

Search strategy and selection criteria

The aim of this Review was to summarise the current evidence in terms of prevalence, impact, management, and vaccination of patients with systemic sclerosis during COVID-19. We identified references through searches of PubMed, with the search terms "COVID-19" and "systemic sclerosis", from March 1, 2020 until March 1, 2022. We also identified articles through searches of the authors' own files. Only papers published in English were reviewed. We generated the final reference list based on originality and relevance to the broad scope of this Review.

and mycophenolate mofetil, early treatment with monoclonal antibodies (when available) should be considered, independent of vaccination status, to prevent hospitalisation or death.[78] However, some of the monoclonal antibody therapies have been shown to be ineffective against the omicron variant.[54,55]

Current EULAR recommendations on COVID-19 vaccination

The EULAR task force based its advice on knowledge available in November, 2021,[79] at which time there was no evidence that patients with rheumatic diseases had 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 COVID-19 vaccination with any of the approved vaccines. Furthermore, patients are advised to continue their treatment unchanged, taking into account that some therapies have been associated with an increased risk of severe COVID-19.[79] However, postponing treatment with rituximab, when feasible, should be considered to improve immunogenicity.[71] 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.[79] Although not yet included in the EULAR recommendations, a third COVID-19 vaccination and booster should be considered in patients treated with B-cell depleting therapy. Taking the available publications into account, vaccination against COVID-19 in patients with systemic sclerosis is recommended and immunosuppression should not be changed for the purpose of vaccination, albeit timing of vaccination is important for patients receiving rituximab. There is no preference for a particular vaccine platform, but as in the general population, long-term safety data could change this recommendation.

Conclusion

The COVID-19 pandemic is one of the biggest challenges of the 21st century. In addition to the general impact on society and health-care systems, patients with systemic sclerosis and their physicians face specific challenges. Several ongoing international initiatives contribute to increasing insights on the effect of COVID-19 on patients with systemic sclerosis. Data from registries and single centre cohorts indicate that the risk of contracting SARS-CoV-2 does not seem to increase substantially in patients with systemic sclerosis. However, severe outcomes are more frequently observed in these patients than in the general population, specifically in patients with cardiopulmonary involvement, renal disease, and those treated with rituximab. The extent to which published data reflect outcomes of COVID-19 in real-world populations of people with systemic sclerosis remains to be established, as some registries might be subject to registration bias towards more severe cases. Management of acute COVID-19 in these patients should follow general guidelines, and in those with mild symptoms, immunosuppressive treatment should be continued.[40] It is important that physicians realise that COVID-19 disease and systemic sclerosis share some manifestations to some extent, including pulmonary involvement and signs of microangiopathy, which can complicate differential diagnosis. Vaccination is highly recommended for patients with systemic sclerosis, and the data available to date support the safety and tolerability of COVID-19 vaccination in patients with systemic sclerosis in the short term. Both patients and physicians should be aware that the efficacy of vaccines might be lower in patients on immunosuppressive therapy, because antibody responses are blunted, specifically in patients treated with mycophenolate mofetil and B-cell targeted therapies.[71] Whether these lower-than-expected antibody concentrations translate into less protection from COVID-19 after vaccination remains unclear, as T-cell mediated immunity elicited by vaccination requires further study. For the near future, potential strategies to augment vaccine immunogenicity for patients with compromised immune responses are urgently awaited, because of the likelihood that COVID-19 will remain a worldwide threat in the coming years. The ongoing and perhaps biggest challenge is to continuously provide high-quality patient care for patients with chronic and severe conditions like systemic sclerosis, even when access to outpatient clinics and hospitals is severely restricted. New initiatives that enable remote monitoring can help to solve these challenges.[3,80]

Contributors

All authors contributed to the literature search, writing, and approved the final version of the Review.

Declaration of interests

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