Systemic sclerosis and the COVID-19 pandemic: World Scleroderma Foundation preliminary advice for patient management

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AbsTRACT

Due to the frequent presence of interstitial lung disease and widespread use of immunosuppressive treatment, systemic sclerosis (SSc) patients may be considered at risk for a more severe disease course and higher mortality when they develop Severe Acute Respiratory Syndrome - Coronavirus - 2 (SARS-CoV-2) virus infection. Therefore, with World Scleroderma Foundation endorsement, experts from different specialties including rheumatology, virology and clinical immunology gathered virtually to answer to the main practical clinical questions regarding SARS-CoV-2 infection coming from both patients and physicians. This preliminary advice is aligned with other national and international recommendations, adapted for SSc patients.

A novel Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection, causing the disease designated as COVID-19 principally affecting the lung at alveolar and interstitial levels, has recently emerged.[1] Among the first 41 Chinese cases described, the most frequent clinical features of COVID-19 at onset were fever (98%), cough (76%), myalgia or fatigue (44%). In addition, diarrhoea, loss of taste and smell have been reported, as well as acute cardiac injury (12.5%) in intensive care units.[1] Dyspnoea developed in 55% and lymphopenia in 63% of patients. In a population of 1014, COVID-19 suspected cases undergoing chest CT, 88% of patients had an acute interstitial lung disease (ILD) imaged as middle and lower lobe pneumonia with multi- focal ground-glass opacities with a reticular pattern, consolidation, vacuolar signs, microvascular dilation, fibrotic streaks, pleural thickening and retraction.[2] Common complications included acute lung injury (ALI) (29%).[1] In critical SARS patients, high plasma concentrations of cytokines have been associated with pulmonary inflammation and extensive lung damage.[1 3] The pathological features of COVID-19 closely resemble those seen in SARS/Middle East Respiratory Syndrome (MERS) infections, as well as the pathogenic mechanism(s) leading to ALI.[4]

In COVID-19 patients, increased IL-6 circulating levels may represent a lung immune over-reaction in the context of amplified cytokine release leading to a hyperinflammatory state,[1 5] clinically characterised by the evolution to ALI and, potentially, death.[1 3] To control inflammatory ILD and its evolution, Chinese authorities included anticytokine strategies, such as anti-IL6 therapy.[5 6] Chloroquine has shown an in-vitro antiviral effect on SARS-CoV infection and its use has been suggested against the SARS-CoV-2 strains.[7 8]

In systemic sclerosis (SSc) pathogenesis,[9] endothe- lial damage favours vascular leak fostering varying degrees of inflammation and fibrosis in the lungs, heart and other viscera.[10 11] The lung is frequently affected, developing a chronic ILD which may share some CT features with COVID-19 pneumonia,[2 11] such as ground glass, reticulation, subpleural lines, but likely not traction bronchiectasias and the even- tual honeycombing.[12] The SSc treatment relies on non-selective immunosuppressants, including agents that are cytotoxic, proapoptotic or able to inhibit cellular activation.[13–15] Among targetedt h e r a p i e s , rituximab showed promising resultsin ILD.[16] In early mild SSc-ILD with increased inflammatory reactants, tocilizumab (TCZ), an IL-6 receptor antagonist, may preserve lung function.[17–21] Hydroxychloroquine (HCQ), based on its role in reducing cellular chemo-taxis and its beneficial effects in other rheumatologic conditions, has been also used in clinical practice in SSc.[22]

SSc SARS-CoV-2-infected patients may be at risk for a severe disease course either due to under- lying ILD and/or immunosuppression. Therefore, under the World Scleroderma Foundation (WSF) umbrella, worldwide experts(r h e u m a t o l o g y, virology and clinical immunology) have provided answers to the main practical questions that physi-cians and patients may have when dealing with possibility/presence of SARS-CoV-2 infection (up to date 14 April 2020).

► ***Are SSc patients at risk to contract the infection?***

It is plausible that patients treated with immu-nosuppressive drugs and/or with severe ILD might have higher risk of developing a progressive, rapidly evolving COVID-19. Very much depends on the underlying severity of SSc-ILD and pulmonary func- tion. To prevent infection, patients with severe ILD should follow the advice of government and health authorities of their countries.

► ***Should the immunosuppressive treatment be withdrawn in SSc patients?***

While always balancing the risk/benefit ratio, we believe that patientsshould continue immunosuppression to avoid SSc relapses: any drug withdrawal should be discussed with the physician on a case-specific basis. If they develop symptoms or if someone else in the household develops COVID-19, immunosuppression should be put on hold.

► ***What are the comorbidities that may increase the likelihood of a bad outcome when infected?***

Diabetes, systemic hypertension, cardiovascular disease and other chronic lung diseases are associated with a poor outcome. Consequently, patients with these comorbidities should be closely followed, even in the early phase of the disease (before pneumonia develops). The threshold to recommend hospitalisation in these patients should be low, although symptoms, signs and baseline investigations including oximetry should guide the recommenda- tion for hospitalisation.

► ***Should all SSc patients be submitted to a test to detect SARS-CoV-2 infection?***

At the moment, testing the whole SSc population is not advised. If patients are in a high-risk population, they should follow national behavioural guidelines and seek medical advice for testing according to instructions from their local and national authorities.

► ***What to do when an SSc patient presents with acute onset of malaise, cough and fever?***

If signs and symptoms of *SARS-CoV-2* infection, like malaise, headache, diarrhoea, cough or dyspnoea appear, a diagnostic test should be performed (nasal and pharyngeal swabs). While awaiting the results, quarantine of the patient and his/her closer contacts is advised. Moreover, close follow-up should be main- tained by web-based or telephone contact. The additional value of chest CT is controversial as SSc-ILD may mask or mimic early COVID-19 lesions and studies to differentiate these two are lacking. However, if rapidly worsening dyspnoea and hypocapnic hypoxia develop, patients should be hospitalised and investi- gated with nasal swab retesting, serology and/or bronchoalveolar lavage.

► ***Should the immunosuppressive treatment be stopped in an SARS-CoV-2 positive patient?***

In real life, clinical scenarios may be heterogeneous, spanning from positive asymptomatic patients to variably severe disease. One published lcSSc patient, regularly treated with TCZ for joint and lung involvement, presented subfebrile (37.6°C) with malaise, cough, headache, unchanged bibasal lung crackles and no signifi- cant dyspnoea; her nasal swab resulted positive without developing severe ILD and the monthly treatment was postponed.[23] Looking at this case, temporary drug interruption may be advised for SSc-SARS-CoV-2-infected patients, and they should undergo vigilant monitoring of organ functions (lung, heart and kidney) to decide the best real-time therapeutic approach.

Despite lack of evidence sufficient to give precise advice, the degree of SSc-ILD and the risk of disease/progressive damage or flare versus a potential higher risk of COVID-ILD evolution should be considered. Further publications on the effects of immu- nosuppression in severe COVID-19 need to be closely monitored.

► **Should the vascular/vasoactive therapy be withdrawn in a positive patient?**

As recently suggested,[24] no change in therapy for vascular and renal involvement, in particular Angiotensin Receptor Blockers (ARB) or ACE-inhibitors, is advised. In SSc, a case-by-case evalua- tion seems corroborated by the observation of a subfebrile (37.5°) limited SSc patient who developed malaise, and cough persisting despite antibiotics (ampicillin/minocycline).Chest CTr e v e a l e d bilateral, multilobular ground-glass opacities and consolidation with a pronounced peripheral distribution. She was positive at PCR for SARS-CoV-19 but did not evolve to severe ILD. The treat- ment with ARB was continued.

► ***Might SSc patients benefit from additional supportive/preventive therapy?***

Currently, no well-controlled, well-done trials are available for the prophylactic use of chloroquine, HCQ or other adjunc- tive therapy in SSc patients. Following international preventive measures, such as wearing masks, careful hand washing, social distancing and cough hygiene is pivotal.

► ***Should SSc patients without COVID-19 symptoms avoid coming to the hospital?***

Patients should limit their visits to the hospital/clinic until the pandemic fades and the government lifts strict rules. This must be balanced against the potential of disease flare and decisions have to be made on the individual level. Telemedicine consultations are advised.

► ***What drugs may be suggested in SSc-COVID-19-infected patients?***

Antiviral therapy[6] or TCZ may be a rescue treatment in cases where COVID-19 pneumonia is bilateral and severe, due to the high possibility of a rapid evolution to an Acute Respiratory Distress Syndrome (ARDS). Chinese guidelines[6] recommend one intravenous TCZ infusion (4–8mg/kg), which can be repeated after 12hours if needed (dose not exceeding 800mg). Publica- tionsof new data need to be closely monitored and might change this advice. The presence of mycotic and/or bacterial superin- fection should be excluded prior to TCZ use; bronchoalveolar lavage may help to diagnose the disease and/or superinfection. In SSc patients already on TCZ, no additional TCZ should be given. Speculatively, TCZ may be considered in SSc-COVID-19 patientsexperiencing mild signsof infection, in addition to other ongoing treatments.[6] Despite lack of evidence, antimalarials can be administered as chloroquine 500mg two times per day for 20 days or HCQ at 200mg two times per day, from 5 to 20 days.[6 22] Outside clinical trials, WHO does not suggest the routinely use of corticosteroids for treatment of viral pneumonia[6 25–27] and corticosteroids should be carefully employed in SSc (increased risk of scleroderma renal crisis).[28] In infected hospitalised SSc patients, preventive anticoagulation is advised.[29]

ConClusions

The SARS-CoV-2 infection isa global challenge and large initiatives (https://rheum-covid.org, https://www.eular.org/eular_covid19_database.cfm) will be of great help. The WSF and European Sclero- derma Trial And Research (EUSTAR) group will launch a database dedicated to SSc-COVID-19 patients. It may be intuitive to suspect that immunosuppressed patients may be prone to a more severe infection but currently this remains controversial.[30]

In conclusion, SSc patients are a great challenge for the physi- cian to achieve an effective protective strategy or, when infected, to optimise a real-time treatment as suggested by the rapidly evolving guidelines.

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REFERENCES

1 Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395:497–506.
2 Ai T, Yang Z, Hou H, Zhan C, et al. Correlation of chest CT and RT-PCRtesting in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology 2020:200642.
3 He L, Ding Y, Zhang Q, et al. Expression of elevated levels of pro-inflammatory cytokines in SARS-CoV-infected ACE2+ cells in SARSpatients: relation to the acute lung injury and pathogenesis of SARS. JPathol 2006;210:288–97.
4 Xu Z, Shi L, Wang Y, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020;8:420–2.
5 Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033–4.
6 Diagnosis and treatment protocol for novel coronavirus pneumonia (trial version 7) 2020. (Released by National Health Commission & State Administration of Traditional Chinese Medicine on March 3, 2020).
7 Multicenter Collaboration Group of Department of Science and Technology of Guangdong Province and Health Commission of Guangdong Province for chloroquine in the treatment of novel coronavirus pneumonia. [Expert consensus on chloroquine phosphate for the treatment of novel coronavirus pneumonia]. Zhonghua Jie He He Hu Xi Za Zhi 2020;43:E019.
8 Savarino A, Di Trani L, Donatelli I, et al. New insights into the antiviral effects of chloroquine. Lancet Infect Dis 2006;6:67–9.
9 Varga J, Trojanowska M, Kuwana M. Pathogenesis of systemic sclerosis: recent insights of molecular and cellular mechanisms and therapeutic opportunities. JScleroderma Relat Disord 2017;2:137–52.
10 Bruni C, Frech T, Manetti M, et al. Vascular leaking, a pivotal and early pathogenetic event in systemic sclerosis: should the door be closed? Front Immunol 2018;9:9.
11 Nihtyanova SI, Denton CP. Pathogenesis of systemic sclerosis associated interstitial lung disease. JScleroderma Relat Disord 2020;5:6–16.
12 PignoneA, Matucci-Cerinic M, LombardiA, et al. High resolution computed tomography in systemic sclerosis. real diagnostic utilities in the assessment of pulmonary involvement and comparison with other modalities of lung investigation. Clin Rheumatol 1992;11:465–72.
13 Kowal-Bielecka O, Fransen J, Avouac J, et al. Update of EULARrecommendations for the treatment of systemic sclerosis. Ann Rheum Dis 2017;76:1327–39.
14 Hoffmann-Vold A-M, Maher TM, Philpot EE, et al. The identification and management of interstitial lung disease in systemic sclerosis: evidence-based European consensus statements. Lancet Rheumatol 2020;2:e71–83.
15 Roofeh D, Distler O, AllanoreY, et al. Treatment of systemic sclerosis–associated interstitial lung disease: lessons from clinical trials. JScleroderma Relat Disord 2020;5:61–71.
16 Elhai M, Boubaya M, Distler O, et al. Outcomes of patients with systemic sclerosis treated with rituximab in contemporary practice: a prospective cohort study. Ann Rheum Dis 2019;78:979–87.
17 Tanaka T, Narazaki M. Interleukin-6 inhibition in inflammatory diseases: results achieved and tasks to accomplish. JScleroderma Relat Disord 2017;2:S20–8.
18 Khanna D, JahreisA, Furst DE. Tocilizumab treatment of patients with systemic sclerosis: clinical data. JScleroderma Relat Disord 2017;2:S29–35.
19 Khanna D, Denton CP, JahreisA, et al. Safety and efficacy of subcutaneous tocilizumab in adults with systemic sclerosis (faSScinate): a phase 2, randomised, controlled trial. Lancet 2016;387:2630–40.
20 Kawaguchi Y. Contribution of interleukin-6 to the pathogenesis of systemic sclerosis. J Scleroderma Relat Disord 2017;2:S6–12.
21 Choy E, Rose-John S. Interleukin-6 as a multifunctional regulator: inflammation, immune response, and fibrosis. J Scleroderma Relat Disord 2017;2:S1–5.
22 Bruni C, Praino E, Guiducci S, et al. Hydroxychloroquine and joint involvement in systemic sclerosis: preliminary beneficial results from a retrospective case-control series of an EUSTARcenter. Joint Bone Spine 2017;84:747–8.
23 Mihai C, Dobrota R, Schröder M, et al. COVID-19 in a patient with systemic sclerosis treated with tocilizumab for SSc-ILD. Ann Rheum Dis 2020;79:668–9.
24 Vaduganathan M, Vardeny O, Michel T, et al. Renin-Angiotensin-Aldosterone system inhibitors in patients with Covid-19. N Engl JMed 2020. doi:10.1056/NEJMsr2005760. [Epub ahead of print: 30 Mar 2020].
25 Zhou W, Liu Y, Tian D, et al. Potential benefits of precise corticosteroids therapy for severe 2019-nCoV pneumonia. Signal Transduct Target Ther 2020;5:18.
26 Russell CD, Millar JE, Baillie JK. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. Lancet 2020;395:473–5.
27 World Health Organization. Clinical management of severe acute respiratory infection(SARI) when COVID-19 disease is suspected. Available: https://www.who.int/docs/default-source/coronaviruse/clinical-management-of-novel-cov.pdf; [Accessed 6 Apr 2020].
28 Steen VD, Medsger TA. Case-control study of corticosteroids and other drugs that either precipitate or protect from the development of scleroderma renal crisis. Arthritis Rheum 1998;41:1613–9.
29 Zhang Y, Xiao M, Zhang S, et al. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. N Engl JMed 2020. doi:10.1056/NEJMc2007575. [Epub ahead of print: 08 Apr 2020].
30 D'Antiga L. Coronaviruses and immunosuppressed patients. The facts during the third epidemic. Liver Transpl 2020;20. doi:10.1002/lt.25756. [Epub ahead of print: 20 Mar 2020].