

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

Marco Matucci-Cerinic,<sup>1</sup> Cosimo Bruni ,<sup>1</sup> Yannick Allanore,<sup>2</sup> Massimo Clementi,<sup>3,4</sup> Lorenzo Dagna,<sup>5,6</sup> Nemanja S Damjanov,<sup>7</sup> Amato de Paulis,<sup>8</sup> Christopher P Denton ,<sup>9</sup> Oliver Distler ,<sup>10</sup> David Fox,<sup>11</sup> Daniel E Furst,<sup>1,12,13</sup> Dinesh Khanna ,<sup>11</sup> Thomas Krieg,<sup>14</sup> Masataka Kuwana ,<sup>15</sup> Eun Bong Lee ,<sup>16</sup> Mengtao Li ,<sup>17</sup> Shiv Pillai,<sup>18</sup> Yukai Wang ,<sup>19</sup> Xiaofeng Zeng,<sup>20</sup> Gloria Taliani<sup>21</sup>

**Handling editor** Josef S Smolen

For numbered affiliations see end of article.

## Correspondence to

Marco Matucci-Cerinic, Experimental and Clinical Medicine, Division of Rheumatology, Università degli Studi di Firenze, Firenze 50139, Italy; marco.matuccicerinic@unifi.it

MM-C and CB contributed equally.

MM-C and CB are joint first authors.

Received 24 March 2020  
Revised 15 April 2020  
Accepted 16 April 2020  
Published Online First  
29 April 2020



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**To cite:** Matucci-Cerinic M, Bruni C, Allanore Y, et al. *Ann Rheum Dis* 2020;**79**:724–726.

## 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.<sup>1</sup> 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.<sup>1</sup> 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 multifocal ground-glass opacities with a reticular pattern, consolidation, vacuolar signs, microvascular dilation, fibrotic streaks, pleural thickening and retraction.<sup>2</sup> Common complications included acute lung injury (ALI) (29%).<sup>1</sup> In critical SARS patients, high plasma concentrations of cytokines have been associated with pulmonary inflammation and extensive lung damage.<sup>1,3</sup> 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.<sup>4</sup>

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,<sup>1,5</sup> clinically characterised by the evolution to ALI and, potentially, death.<sup>1,3</sup> To

control inflammatory ILD and its evolution, Chinese authorities included anticytokine strategies, such as anti-IL6 therapy.<sup>5,6</sup> Chloroquine has shown an in-vitro antiviral effect on SARS-CoV infection and its use has been suggested against the SARS-CoV-2 strains.<sup>7,8</sup>

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

SSc SARS-CoV-2-infected patients may be at risk for a severe disease course either due to underlying ILD and/or immunosuppression. Therefore, under the World Scleroderma Foundation (WSF) umbrella, worldwide experts (rheumatology, virology and clinical immunology) have provided answers to the main practical questions that physicians 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 immunosuppressive 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 function. 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 patients should 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 recommendation 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 maintained 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 investigated 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 significant dyspnoea; her nasal swab resulted positive without developing severe ILD and the monthly treatment was postponed.<sup>23</sup> 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 immunosuppression in severe COVID-19 need to be closely monitored.

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

As recently suggested,<sup>24</sup> 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 evaluation seems corroborated by the observation of a subfebrile (37.5°) limited SSc patient who developed malaise, and cough persisting despite antibiotics (ampicillin/minocycline). Chest CT revealed 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 treatment 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 adjunctive 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<sup>6</sup> 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<sup>6</sup> recommend one intravenous TCZ infusion (4–8 mg/kg), which can be repeated after 12 hours if needed (dose not exceeding 800 mg). Publications of new data need to be closely monitored and might change this advice. The presence of mycotic and/or bacterial superinfection 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 patients experiencing mild signs of infection, in addition to other ongoing treatments.<sup>6</sup> Despite lack of evidence, antimalarials can be administered as chloroquine 500 mg two times per day for 20 days or HCQ at 200 mg two times per day, from 5 to 20 days.<sup>6,22</sup> Outside clinical trials, WHO does not suggest the routinely use of corticosteroids for treatment of viral pneumonia<sup>6,25–27</sup> and corticosteroids should be carefully employed in SSc (increased risk of scleroderma renal crisis).<sup>28</sup> In infected hospitalised SSc patients, preventive anticoagulation is advised.<sup>29</sup>

## CONCLUSIONS

The SARS-CoV-2 infection is a global challenge and large initiatives (<https://rheum-covid.org>, [https://www.eular.org/eular\\_covid19\\_database.cfm](https://www.eular.org/eular_covid19_database.cfm)) will be of great help. The WSF and European Scleroderma 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.<sup>30</sup>

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

## Author affiliations

<sup>1</sup>Department of Experimental and Clinical Medicine, Division of Rheumatology, Università degli Studi di Firenze, Firenze, Toscana, Italy

<sup>2</sup>Rheumatology Department, Cochin Hospital, APHP, Paris Descartes University, Paris, France

<sup>3</sup>Unit of Microbiology and Virology, San Raffaele Hospital, Milano, Lombardia, Italy

<sup>4</sup>Unit of Microbiology and Virology, Università Vita Salute San Raffaele, Milano, Lombardia, Italy

<sup>5</sup>Vita-Salute San Raffaele University, Milan, Italy

<sup>6</sup>Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), IRCCS San Raffaele Scientific Institute, Milan, Italy

<sup>7</sup>Rheumatology department, University of Belgrade School of Medicine, Belgrade, Serbia

<sup>8</sup>Department of Translational Medical Sciences and Center for Basic and Clinical Immunology Research (CISI), University of Naples Federico II, Naples, Italy

<sup>9</sup>Department of Rheumatology, Royal Free Hospital, University College London, London, UK

<sup>10</sup>Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland

<sup>11</sup>Rheumatology department, University of Michigan, Ann Arbor, Michigan, USA

<sup>12</sup>Department of Medicine, Division of Rheumatology, University of California at Los Angeles, Los Angeles, California, USA

<sup>13</sup>University of Washington, Seattle, Washington DC, USA

<sup>14</sup>Translational Matrix Biology, Medical Faculty, Cologne, Germany

<sup>15</sup>Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan

<sup>16</sup>Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea

<sup>17</sup>Rheumatology & Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

<sup>18</sup>Ragon Institute, Massachusetts General Hospital, Cambridge, Massachusetts, USA

<sup>19</sup>Rheumatology department, Shantou Central Hospital, Shantou, Guangdong, China

<sup>20</sup>Department of Rheumatology, Peking Union Medical College Hospital, Peking Union Medical College & Chinese Academy of Medical Sciences, Key Laboratory of Rheumatology and Clinical Immunology, Ministry of Education, Beijing, China

<sup>21</sup>Infectious Diseases Unit, Department of Translational and Precision Medicine, Sapienza University of Rome, Roma, Lazio, Italy

**Correction notice** This article has been corrected since it published Online First. The author affiliations have been corrected.

**Contributors** All authors contributed to manuscript preparation and approved the submitted version.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** MMC reports grant and personal fees from Actelion, Biogen, Bayer, Boehringer Ingelheim, CSL Behring, Eli-Lilly, outside the submitted work. CB reports consultancy fee from Actelion, Eli Lilly. YA reports personal fees from Actelion, Bayer, BMS, Boehringer and Curzion, and grants and personal fees from Inventiva, Roche and Sanofi. MC; NSD: none. LD received consultation honoraria from Abbvie, Amgen, Biogen, Bristol-Myers Squibb, Celltrion, Novartis, Pfizer, Roche, Sanofi-Genzyme, and SOBI. CPD has received consultancy fees and/or research grant funding from Actelion, GlaxoSmithKline, Bayer, Sanofi-Aventis, Inventiva, Boehringer Ingelheim, Roche, CSL Behring, UCB Pharma, Leadiant Biosciences, Corbus, Acceleron. OD had consultancy relationship and/or has received research funding from Abbvie, Actelion, Acceleron Pharma, Amgen, AnaMar, Baecon Discovery, Blade Therapeutics, Bayer, Boehringer Ingelheim, Catenion, Competitive Drug Development International Ltd, CSL Behring, Curzion Pharmaceuticals, Ergonex, Galapagos NV, Glenmark Pharmaceuticals GSK, Inventiva, Italfarmaco, iQvia, Lilly, medac, Medscape, Mitsubishi Tanabe Pharma, MSD, Novartis, Pfizer, Roche, Target Bio Science and UCB in the area of potential treatments of scleroderma and its complications. In addition, OD has a patent mir-29 for the treatment of systemic sclerosis issued (US8247389, EP2331143). Grants (2 Jahre) from Actelion, Bayer, Boehringer Ingelheim, Mitsubishi Tanabe Pharma Patent issued: mir-29 for the treatment of systemic sclerosis (US8247389, EP2331143). Comment: To investigate potential treatments of scleroderma and its complications. DF has received consulting fees, speaking fees and/or honoraria from Pfizer and research support from Regeneron, Gilead and Seattle Genetics. DEF: Grant/Research Support Corbus, Galapagos GSK, Pfizer, Talaris, CSL Behring, Mitsubishi; Consultant Actelion, Amgen, Corbus, Galapagos, Novartis, Pfizer, Roche/Genentech, Talaris, CSL Behring, Boehringer Ingelheim; DK reports personal fees from Actelion, Abbvie, Bayer, Boehringer-Ingelheim, Chemomab, Corbus, CSL Behring, Genentech/Roche, Gilead, GSK, Mitsubishi Tanabi, Sanofi-Aventis, UCB Pharma. He reports grants from Bayer, Boehringer-Ingelheim, Genentech/Roche, Pfizer, Sanofi-Aventis and has stock options in Eicos Sciences. MK has received consultancy fees and/or research grant funding from Abbvie, Actelion Pharmaceuticals, Astellas, Bayer, Boehringer Ingelheim, Chugai, Corbus, CSL Behring, Eisai, Mochida, Nippon Shinyaku, Novartis, Ono, Pfizer, Reata and Tanabe-Mitsubishi. SP reports SAB from Abpro. TK received consultancy fee and grant funding from Actelion.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

#### ORCID iDs

Cosimo Bruni <http://orcid.org/0000-0003-2813-2083>

Christopher P Denton <http://orcid.org/0000-0003-3975-8938>

Oliver Distler <http://orcid.org/0000-0002-0546-8310>

Dinesh Khanna <http://orcid.org/0000-0003-1412-4453>

Masataka Kuwana <http://orcid.org/0000-0001-8352-6136>

Eun Bong Lee <http://orcid.org/0000-0003-0703-1208>

Mengtao Li <http://orcid.org/0000-0003-4252-2889>

Yukai Wang <http://orcid.org/0000-0003-2468-3208>

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