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*Case Report*

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# COVID-19 in a patient with SISTEMIC sclerosis: The role of ruxolitinib

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## Abstract

We describe the case of a 78-year-old Italian woman with COVID-19 affected by Systemic Sclerosis with pulmonary fibrosis treated with Ruxolitinib (Ruxolitinib was provided free of charge by Novartis International AG). We chose Ruxolitinib, as a second-line treatment, after administering a standard therapy with hydroxychloroquine and lopinavir/ritonavir, due to a rapid deterioration in the patient's lung function. Ruxolitinib is a janus kinase inibithor with selectivity for subtypes JAK1 and JAK2. A rapid improvement in the patient's respiratory function, objectified with an increase in $PO_2/FiO_2$ value, has been observed in the 10 days after the introduction of Ruxolitinib. Surprisingly we noticed a reduction in pulmonary fibrosis by comparing the chest- CT made before and after the COVID-19 diagnosis. JAK/STAT signalling is involved both in pathogenesis of the second part of COVID-19 and in the modulation of fibrosis in patients with SSc. The use of ruxolitinib should be a new therapeutic option in patients with COVID-19 and lung fibrosis.

## Keywords

SARS-Cov-2, Sistemic sclerosis, ruxolitinib, anti-JAK

## Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a recently discovered coronavirus, is responsible for COVID-19, a disease that in a few months has become pandemic. The symptoms and signs of SARS-CoV-2 infection are not specific ranging from fever, dry cough, fatigue, headache, dysgeusia, anosmia, acute lung injury with shortness of breath up to the Acute Respiratory Distress Syndrome (ARDS) that can lead to death of the patient.[1,2]

If the very early stage of the pathology is characterized by direct damage mediated by the virus itself, many of the later complications appear to be linked to a cytochinic cascade. Cytokines and chemokines have long been thought to play an important role in immunity and immunopathology during virus infections. A rapid and well-coordinated innate immune response is the first line of defense against viral infections, but dysregulated and excessive immune responses may cause immunopathology.[3,4]

Severe and critically affected patients develop bilateral viral pneumonia, which is categorized as hypersensitivity pneumonitis.[5] Autopsy lung tissue shows diffuse infiltration of hyperactivated T-cells, as does T-cell typing in the peripheral blood.[6]

Different therapeutic strategies have been adopted in order to moderate the cytokine storm such as interleukin 1 (IL-1) and interleukin 6 (IL-6) inhibitors.[7] An interesting strategy is using a Janus Kinase Inhibitor (JAK inhibitor), Ruxolitinib, that is a potent and selective JAK inhibitor with

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**Table 1.** The laboratory values before and after 10 days from the administration of ruxolitinib.

| Variable | Before ruxolitinib | 10 days after ruxolitinib |
|---|---|---|
| Red blood cells (cells × $10^6$/mmc) | 4.55 | 5.21 |
| White blood cells(cells × $10^3$/μL) | 6.43 | 8.16 |
| Neutrophils (cells × $10^3$/μL) | 5.95 | 5.96 |
| Lymphocytes (cells × $10^3$/μL) | 0.14 | 1.72 |
| Platelets (cells × $10^3$/mmc) | 305 | 196 |
| Hb (g/dL) | 8.9 | 10.1 |
| VES (mm/h-range 2–15) | 54 | 32 |
| PCR (mg/L-range 0–5) | 43 | 0.96 |
| Ferritin (ng/mL) | 320.5 | 260 |
| Procalcitonin (ng/mL) | 0.09 | 0.02 |
| CREATININE (mg) | 0.73 | 0.51 |
| GOT/AST (UI/L) | 18 | 20 |
| GPT/ALT (UI/L) | 17 | 38 |
| γGT (UI/L) | 15 | 15 |
| Creatinkinase(U/L) | 33 | 31 |
| LDH (U/L) | 468 | 250 |
| Total bilirubuin (mg/dL) | 2.73 | 1.7 |
| Direct Bilirubin (mg/dL) | 1.32 | 0.6 |
| D-dimer (mg/L) | 1.41 | 1.21 |

selectivity for subtypes JAK1 and JAK2. JAK1 and JAK2 recruit signal transducers and activators of transcription (STATs) to cytokine receptors leading to modulation of gene expression. It is used for the treatment of intermediate or high-risk myelofibrosis and for polycythemia vera and it has also been shown to improve cases of chronic graft versus host disease in patients following a bone marrow transplant.

## Case Report

A seventy-eight-year-old white woman with diagnosis of SSc posed on first days of March 2020, with hepatic steatosis and a previous ischemic cerebellar stroke, presented to the hospital emergency room for acute pulmonary insufficiency with acute shortness of breath, dry cough and fever.

The patient, few months before admission to hospital for respiratory failure, had a diagnosis of systemic sclerosis characterized by thickening and hardening of the skin, three episodes of Raynaud phenomenon, pain and rigidity of joints and positivity of Antinuclear Antibodies (ANA) and Slc-70 antibodies.

The diagnosis of intermediate variant SS was recent, therefore no specific treatment had yet been started, and no capillaroscopy or biopsy have been performed yet.

The diagnosis of COVID-19 pneumonia was made by real-time PCR on oropharyngeal and nasopharyngeal swabs and a standard treatment with hydroxychloroquine 200 mg bid and protease inhibitors (lopinavir/ritonavir) 250 mg bid was started.

The chest radiograph (CXR) of the 24th of March 2020 showed a bilateral pneumonia confirmed by a second CXR (07/04//2020) that demonstrated the increase of bilateral opacifications. Due to the rapid worsening of respiratory function, a chest computed tomography (chest-CT) scan was performed showing bilateral pneumonia with peripheral groundglass opacities with predominant distribution at the lower lobes and presence of pleural effusion. The chest CT scan confirmed the presence of a paraseptal and centrolobulaire emphysema associated to a bilateral lung fibrosis (reticular interstitial thickening) attributable to systemic sclerosis, already highlighted in a chest CT carried out in March. Even if the standard therapy with hydroxychloroquine was completed, we noticed a rapid worsening of the pulmonary function needing a C-PAP ventilation with a hemogasanalysis showing a pH of 7.48, $pCO_2$ 46.8 mmHg, $pO_2$ 70.8 mmHg and a $SpO_2$ of 94% during C-PAP supplementation with a PEEP value of 15 $cmH_2O$ and a $FiO_2$ of 50% obtaining a P/F value of 141.6.

On the 11th of April the therapy with Ruxolitinib 5 mg/bid for 2 weeks was started. Some of the laboratory values we collected before the administration of Ruxolitinib are shown in Table 1.

In the first 3 days of administration of Ruxolitinib we observed a slighty improvement of the lung function but 7 days after starting the therapy with Ruxolitinib the hemogasanalysis showed the following parameters: pH 7.41, $pCO_2$ 41.7 mmHg, $pO_2$ 75.7 mmHg and a $SpO_2$ of 94.2% during supplementation with Venturi mask at 40% of $FiO_2$ with a P/F value of 189.

Ten days after starting the therapy with Ruxolitinib the hemogasanalysis showed a pH of 7.44, $pCO_2$ of 35.4 mmHg, $pO_2$ 63.4 mmHg and a $SpO_2$ of 92.9% in

ambient air ($FiO_2$ 21%) with a P/F value of 301.9. The chest-CT of the 18th of April 2020 showed the signs of paraseptal and centrolobulaire emphysema with a reduction of the bilateral groundglass opacities and a reduction of the signs associated to the pulmonary fibrosis described by the previous chest-CT. The laboratory values we collected 10 days after the administration of Ruxolitinib are shown in Table 1. The patient well tolerated the treatment Ruxolitinib, as demonstrated by the absence of thrombocytopenia, anemia, neutropenia and by the absence of opportunistic infections that are the major side effect of this drug.

These findings demonstrate that Ruxolitinib not only improved the lung function depressed by SARS-Cov-2 infection but it is involved in reduction in the pulmonary fibrosis improving the thickness and the stiffness of tissue making less difficult for lungs to work properly.

## Discussion

The second phase of the SARS-CoV-2 infection is characterized by a cytokines storm involving the activation of JAK-STAT pathways. The cytokine storm, also called cytokine release syndrome (CRS), is the major cause of morbidity for several critical patients of COVID-19.[7] It causes death of several SARS-CoV and MERS-CoV infected patients.[8] SARS-CoV-2 causes activation of different immune cells like macrophages, monocytes and dendritic cells that help the secretion of pro-inflammatory cytokine IL-6 and other inflammatory cytokines. It also activates the IL-6–sIL-6R–JAK-STAT signalling.[9]

Systemic sclerosis is a multisystem idiopathic disease characterized by vascular abnormalities, connective tissue disorders and fibrosis. One of the central histopathologic hallmarks of SSc is the uncontrolled and persistent activation of fibroblasts, which release excessive amounts of extracellular matrix.[10]. Type I cytokines implicated in the pathogenesis of systemic sclerosis are translocated to the nuclear receptor of the target tissue via the JAK-STAT (Janus kinase-signal transducer and activator of transcription) pathway. Currently there are no drugs aimed exclusively at the treatment of pulmonary fibrosis in SSc and the most used aids, acting on the immune system cells, reduce inflammatory changes and the production of molecules that support and amplify the mechanism of fibrosis. Although there is not a single suggested dosage, Ruxolitinib has been used to treat numerous cases of SARS-CoV2 pneumonia as demonstrated in several studies of the scientific literature in which it has been used showing manageability and efficacy. Gozzetti et al. demonstrated a reduction of the COVID-19 Inflammation Score in 14 patients treated up to 14 days with Ruxolitinib at 7.5 mg per day. Other authors, such as D'Alessio et al., used Ruxolitinib at a dosage of 5 mg bid for 7 days and then tapered to 5 mg daily to complete a 10-days course of treatment association with methyl-prednisolone 1 mg/kg intravenously for 3 days followed by 0.5 mg/kg for 5 days. Several clinical trials are underway to test Ruxolitinib in COVID-19 infection, demonstrating that Ruxolitinib in COVID-19 patients with hyperinflammation, can prevent multiorgan failure related to the cytokines storm.[11—13] Other Italian authors such as Mortara et al. used Ruxolitinib at the dosage of 5 mg twice a day, the same dosage used for the patient described in this clinical case, for 15 days showing a reduction of C-reactive protein and an increase of $PaO_2/FiO_2$ ratio in a few days. Caradec et al. successfully used Ruxolitinib to treat a patient with idiopatic pulmonary fibrosis with a COVID-19 diagnosis, using switching hydroxychloroquine for Ruxolitinib 10 mg twice a day. Other authors such as Sammartano et al. they used Ruxolitinib to treat a 59-year-old man with a diagnosis of Blastic Plasmocitoid Dendritic Cell Neoplasm who developed COVID-19 related pneumonia. Kaplansky et al. used Ruxolitinib at the dosage of 5 mg twice a day up to 28 days, in association with Anakinra, to treat adult older than 18 years with a COVID-19 pneumonia needing Intensive Care Unit. We describe the case of a female patient with acute SARS-CoV-2 infection with a recent diagnosis of untreated SSc. As the diagnosis of COVID-19 was made a standard therapy with hydroxychloroquine 200 mg bid and protease inhibitors (lopinavir/ritonavir) 250 mg bid was started. After the end of the standard therapy we noticed the persistent worsening of the patient's respiratory function we evaluated the possibility of introducing the therapy with Ruxolitinib, that is a drug used for the treatment of intermediate or hight-risk myelofibrosis, a type of myeloproliferative disorder that affects the bone marrow and in for selected cases of polycythemia vera. We chose this therapy because it is a janus kinase inhibitor with selectivity for subtypes JAK1 and JAK2. A rapid improvement in the patient's respiratory function, objectified with an increase in $PO_2/FiO_2$ value, has been observed in the 10 days after the introduction of Ruxolitinib. Surprisingly we also observed a reduction in pulmonary fibrosis on post-treatment chest CT scan, compared to chest CT scan performed before the COVID-19 diagnosis. In our case the fast improvement of the lungs function and the reduction of lungs fibrosis is explainable with several investigative studies that have shown the importance of STAT3 as an important cellular mediator of TGF-β-induced differentiation of resting fibroblasts into myofibroblasts which in turn increases type I collagen release.[14] Inhibition of STAT-3 phosphorylation reduces the pro-fibrotic effect of TGF β. In addition, type I cytokines (especially IL-6) play a key role in SSc where gene signature scores were correlational with disease activity. Cytokine activation involves phosphorylation and transcription via JAK-STAT, TYK2 (tyrosine kinase) pathway. Moreover, it has been reported that SARS-CoV-2 uses angiotensin-2-converting enzyme (ACE2) as a cell receptor in humans,[15] can cause

interstitial lung damage at first and then parenchymal lesions. Pulmonary fibrosis is a pathological consequence of acute and chronic interstitial lung disease. In COVID-19 the inflammatory status, the improper removal of ROS or an excessive supply of a high percentage of oxygen, could be associated with damage and fibrosis in COVI- 19 patients.[16]

## Conclusions

JAK/STAT signalling is involved both in pathogenesis of the second part of COVID-19 and in the modulation of fibrosis in patients with SSc. The use of a molecule capable of blocking this signalling pathway may play a pivotal role in halting the inflammatory in these two conditions as demonstrated in the clinical case described. In this work it is not possible to describe a certain correlation between the use of Ruxolitinib to treat SARS_CoV-2 pneumonia and the reduction of lung fibrosis due to SSc because PFT and HRCT before the treatment are not available but it should be a new and useful therapeutic option in patients with COVID-19 and lung fibrosis.

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