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Letter to the Editor

COVID-19 in a patient with idiopathic pulmonary fibrosis successfully treated with Ruxolitinib

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The severe acute respiratory syndrome related to SARS-Cov-2 may be due to a huge cytokines storm, with high levels of serum mediators such as tumor necrosis factor α (TNF-α), CXCL10, Interleukin (IL)-6 (IL-6) and IL-8 [1].

The Janus kinases-signal transducer and activator of transcription proteins (JAK-STAT) is a signaling pathway that plays a major role in regulation of the cytokine release. JAK inhibitors, used in inflammatory diseases and myeloproliferative syndrome, could be a therapeutic approach in Covid 19.

We report the case of a patient with essential thrombocythemia (ET) and idiopathic pulmonary fibrosis (IPF) hospitalized for severe Covid 19 who had a dramatic improvement under Ruxolitinib.

A 69-year-old male with a 25 pack-year smoking history presented to the emergency room on March the 27th with cough, fever and increasing dyspnea over the last 8 days.

The patient had a medical history of arterial hypertension, atrial fibrillation, chronic urticaria, and idiopathic pulmonary fibrosis (IPF) diagnosed in 2018. After diagnosis of IPF made on multidisciplinary team discussion, the patient received pirfenidone from September 2018 to April 2019, interrupted for hepatic and skin toxicity. Pulmonary function tests in September 2019 showed forced vital capacity of 3.99 liters (103% of predicted value), forced expiration volume in 1 second of 2.98 L (100% of predicted value), diffusing lung capacity of 39% of predicted value. Fig. 1A illustrates his chest computed tomography (CT) in September 2019, with reticulations, honeycombing, traction bronchectasis with sub-pleural distribution and ground glass opacities in areas of fibrosis. In December 2019, the occurrence of an ischemic stroke revealed an essential thrombocytemia (ET) with positive JAK2 V617F mutation detected in the blood (platelets 1.421 G/L). Hydroxycarbamide was subsequently initiated at a 1500 mg daily-dose.

At admission, patient's medication included apixaban, aspirin, atenolol, omeprazole, levocetirizine and hydroxycarbamide. The patient had a 5-day course of symptoms with fever and cough. On examination, blood pressure was 146/89 mmHg, heart rate was 77 beats/min, temperature was 39.1 °C; and oxygen saturation was 90% on room air, with a respiratory rate of 30 per minute.

Pulmonary auscultation found bibasal crackles. The results of initial blood workup were as follows:

- white blood cells count 5.7 G/L, lymphocytes 2.1 G/L, hemoglobin 13.3 g/dL, platelets 369 G/L;
- C reactive protein (CRP) 62 mg/L (normal < 5 mg/L), procalcitonine 0.16 ng/l (normal < 0.5 ng/L);
- fibrinogen 6.59 g/l (normal < 4 g/L), D-dimer 2008 ng/ml (normal < 500 ng/mL);
- and normal liver enzymes and renal function.

SARS-Cov-2 real time polymerase chain reaction test on oropharyngeal swab was positive. The CT scan showed bilateral ground-glass opacities and crazy paving compatible with COVID-19 with severe extension. IPF related lesions were considered stable (Fig. 1B).

At admission in our pulmonology unit, the patient required 4 L/min of oxygen (saturation 95%). Antibiotherapy with ceftriaxone, azithromycin in addition with hydroxychloroquine were started according to the local standard of care guidelines at he time of diagnosis.

On day 2 of hospitalization, needs for oxygen increased until 6 L/min to reach 95% oxygen saturation. Blood inflammatory markers worsened, with CRP 133 mg/L, ferritinemia 950 μg/L (normal range 30–400 μg/L), LDH 612 UI/L (normal range 135–225 UI/L). Based on his ET with JAK2 mutation, and in accordance with his haematologist, we decided to switch hydroxycarbamide for ruxolitinib 10 mg twice daily and we stopped all the antibiotics and hydroxychoroquine. He experienced a dramatic improvement with apyrexia on day 2 of this management and rapid decrease of oxygen flow on day 4 (sat 98% with 3 L/min). Inflammatory syndrome rapidly decreased and CRP normalized at day 8. No adverse outcome was observed. The patient was discharged on April the 14th without oxygen treatment. Fig. 1C illustrates his CT scan 10 days after discharged with healing of Covid-19 lesions.

1. Discussion/Conclusion

Ruxolitinib is a tyrosine kinase inhibitor which inhibits JAK1 and JAK2. It is approved for use in primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis, and in polycythemia vera patients who are resistant or intolerant to hydroxycarbamide. Ruxolitinib has also demonstrated efficacy as an anti-inflammatory drug in acute graft versus host disease [2].

JAK inhibition could affect both cellular viral entry of Covid 19 and inflammation [3].

SARS-Cov-2 binds on ACE2 receptor, which is a cell-surface protein widely distributed in the heart, kidney, blood vessels, and especially alveolar epithelial cells. The virus may invade and enter cells through endocytosis. One of the known regulators of

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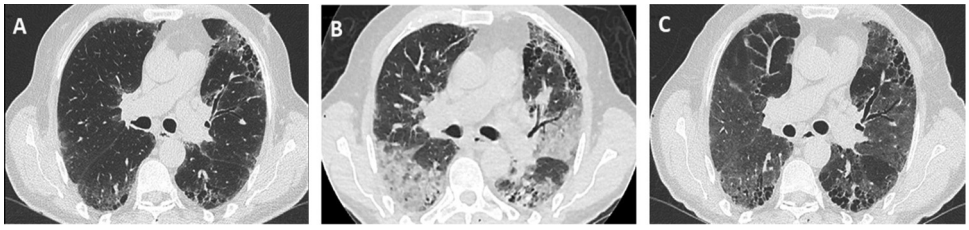

Fig. 1. Chest computed tomography. A. September 2019; B. March 2020; C. April 2020.

endocytosis is the AP2-associated protein kinase 1 (AAK1). AAK1 inhibitors can interrupt the passage of the virus into cells and may be helpful in preventing virus infection [4]. Therefore, Ruxolitinib may inhibit viral infection of cells through the inhibition of AAK1. Furthermore, JAK inhibitors act by inhibiting the activity of one or more of the JAK family of enzymes, including JAK1, JAK2, JAK3 and TYK3. The JAK-STAT pathway is central to cellular response to exogenous signals in the immune system. The JAK family of enzymes are responsible for signal transduction and JAK inhibitors play a major role in inhibiting and blocking cytokine release (including proinflammatory IL-6) that can contribute to Covid-19's related cytokine storm. Ruxolitinib is an inhibitor of JAK 1/2 and also works as an immunomodulator decreasing the cytotoxic T lymphocytes and increasing the Treg cells. Thus, Ruxolitinib may attenuate the dysregulated immune response caused by Covid-19 that generates the pneumonia and subsequent severe acute respiratory syndrome [5].

Moreover, few studies have suggested an increased activation of the JAK-STAT pathway in IPF that may participate in lung fibrosis but no clinical data is available regarding JAK-inhibitors efficacy or tolerance in this setting [6]. We report the first case of successful Ruxolitinib treatment in an IPF patient suffering from Covid-19. Our experience with IPF patients and the natural evolution of IPF foreshadowed a pejorative issue. This case report has several limitations. First, the patient had an ET with JAK2 mutation and IPF, two rare diseases, and it is not generalizable to the general population. Second, the patient was treated in accordance with local guidelines at the time of diagnosis including azithromycin and hydroxychloroquine. These two drugs are currently evaluated in phase 3 trials for COVID-19. Third, no causal relationship between ruxolitinib use and clinical improvement could be drawn. Indeed, spontaneous favorable outcome of COVID-19 without specific treatment is possible; therefore we cannot exclude in our case a spontaneous improvement regardless to ruxolitinib use.

Our data suggests a safe profile and possible efficacy of JAK-inhibitors in COVID-19 patients, but further well-conducted studies are needed. More than 10 clinical trials evaluating the efficacy of ruxolitinib are currently ongoing (clinicaltrials.gov). Ruxolitinib has no routine clinical indication in COVID-19 outside of clinical studies.

Disclosure of interest

YU reports personal fees, non-financial support and grants from Oxyvie, Boehringer Ingelheim and Roche outside the submitted work. The other authors declare that they have no competing interest.

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