Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the editor

Side effects of ruxolitinib in patients with SARS-CoV-2 infection: Two case reports

Sir,

Finding an effective anti-inflammatory therapy based on novel biological drugs may be the key to reducing morbidity and mortality in patients with novel coronavirus disease 2019 (COVID-19).

Tocilizumab has been used to control the high levels of cytokines, particularly interleukin-6, produced in certain COVID-19 patients to decrease the immune system response and thus reduce potential lung damage [1].

We achieved some satisfactory results using tocilizumab, but the drug became temporarily unavailable because of sudden supply issues. We then evaluated the appropriateness of influencing the systemic immune-inflammatory state with compassionate use of ruxolitinib in two patients. This led to unexpected results.

Case 1 was a 74-year-old male. He presented to the emergency room (ER) after 10 days of cough and fever with rapid onset of confusional state and severe dyspnoea. Reverse transcriptase-polymerase chain reaction (RT-PCR) of a nasal swab confirmed SARS-coronavirus-2 (SARS-CoV-2) infection at hospital admission. The patient was started on non-invasive ventilation, enoxaparin 6000 IU and lopinavir 200 mg/ritonavir 50 mg two tablets two times per day, and dexamethasone 20 mg and hydroxychloroquine 400 mg per day.

The patient had persistent deterioration; therefore, after 5 weeks of hospitalization, he received 2 subcutaneous injections per 2 cycles a week of tocilizumab 162 mg and showed subsequent clinical and radiological improvement.

A week later, levels of C-reactive protein (CRP), interleukin-6, lactate dehydrogenase (LDH) and haptoglobin increased again, despite clinical stability.

To prevent a relapse, on the sixth week, ruxolitinib 5 mg was administered 2 tablets per day for 2 days, and 4 tablets per day for 3 days, then precociously tapered. Treatment with ruxolitinib was suspended because of the appearance of purpuric lesions on the skin of the dorsal and upper limbs, with concomitant reduction in platelet levels (from 141.000 to 61.000) in 5 days and a deep tissue infection of the left arm. Treatment with steroids and antibiotics was initiated.

Case 2 was a 63-year-old Caucasian woman with a history of hypothyroidism treated with levothyroxine. She reported fever and mild dyspnoea. On the tenth day, she had a positive SARS-CoV-2 nasal swab and was admitted to hospital. Therapy was initiated with enoxaparin 6000 IU, hydroxychloroquine 200 mg and lopinavir 200 mg/ritonavir 50 mg two tablets two times per day.

Haemodynamic and laboratory values (including interleukin-6) remained acceptable. The patient required prolonged low-volume oxygen therapy and compassionate use of ruxolitinib was needed. On the twelfth day after admission, the patient was started on ruxolitinib 5 mg two times per day for 3 days, and then the dose was doubled. On the day ruxolitinib was doubled the SARS-CoV-2 swab was negative; however, due to the onset of a troublesome herpes labialis, ruxolitinib was then reduced to 5 mg/day and acyclovir therapy was initiated. Four days later, haematocrits showed a progressive reduction of haemoglobin values to 8.7 g/dL and the patient developed an erythrodermic rash on her whole body surface [Fig. 1]. Ruxolitinib was promptly stopped and steroid therapy was administered for 5 days.

Ruxolitinib is used for the treatment of intermediate- or high-risk myelofibrosis and polycythaemia vera. This drug inhibits janus kinase (JAK) enzymes, with selectivity for subtypes JAK1 and JAK2, which are often dysregulated in myelopathies [2].

In addition, ruxolitinib may reduce expression of related genes, and thus the inflammatory response, by altering signal transducers and activators of transcription (STATs) linked to cytokine receptors [3]. This may be effective in certain COVID-19 patients in whom the host response is causing a cytokine storm [1,3]. Moreover, the anti-inflammatory and pro-apoptotic effect of ruxolitinib on senescent cells, which are thought to be used by the virus to escape and alter the immune system, may be a key factor in the treatment of COVID-19 in patients with a poor prognosis, e.g. elderly patients [4].

The expected immunomodulating effect of ruxolitinib needs to be assessed; this drug may increase the risk of opportunistic infections. Impairing the JAK signal transduction pathway in patients in an inflammatory state may exacerbate the incidence of known side effects, such as thrombocytopenia and anaemia [2].

Severe drug reactions were observed after administering ruxolitinib at two different stages of COVID-19 in the two cases reported here. In the first case, the patient had high levels of inflammatory markers and poor respiratory function, which are indications for the use of tocilizumab [1], and was treated with ruxolitinib 7 weeks after first symptoms (the patient had received tocilizumab up until the week before). In the second case, ruxolitinib was given 13 days after onset of symptoms to a moderately stable patient to prevent worsening of symptoms. The timing of initiation of treatment with ruxolitinib and the severity of illness differed in these two patients; however, both patients were required to stop ruxolitinib treatment earlier than expected. This was because the first patient developed a soft-tissue infection and both patients developed cutaneous reactions with purpuras and a rapid drop in haematocrit values. Such side effects were probably worsened by the association with ritonavir, an inhibitor of CYP3A4, which may have increased ruxolitinib serum concentration [5].

In our opinion, the role of ruxolitinib as an immunomodulating drug in SARS-CoV-2 infection needs to be better defined in terms of safety and management of its potentially severe side effects, particularly in multidrug regimens with antiretroviral therapies.

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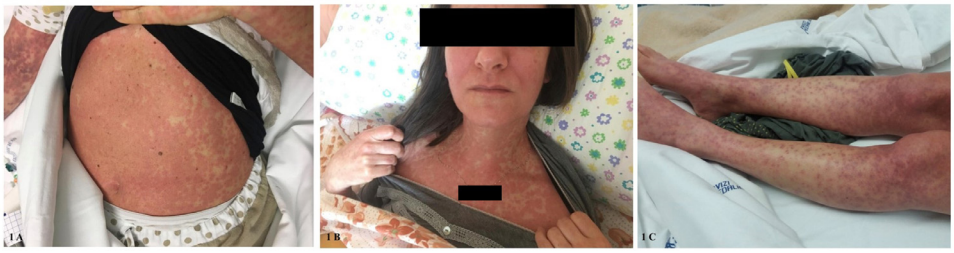

Fig. 1. (**A-B-C**) diffuse, erythematous, non-bleaching, eruptive reaction, probably of vasculitic origin, on the second day of ruxolitinib administration.

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