Combined IL-6 and JAK/STAT inhibition therapy in COVID-19-related sHLH, potential game changer

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Coronavirus disease 2019 (COVID-19), caused by the novel SARS-CoV-2, leads to significant mortality and morbidity with increasing evidence for inflammatory pathways being implicated in the lung damage it causes.1,2 Severe COVID-19 patients present with increased inflammatory markers, akin to secondary haemophagocytic lymphohistiocytosis (sHLH), that have been shown to predict mortality.3,4 There is emerging evidence for the use of an interleukin 6 (IL-6) inhibitor, tocilizumab (TCZ), for suppression of the inflammatory cytokine storm in this context.5–7 Ruxolitinib (RXB), a Janus kinase/signal transducers and activators of transcription (JAK-STAT) inhibitor, has also been shown to have proven efficacy in the treatment of sHLH.8 Both agents appear to be promising in the fight against SARS-CoV-2 infection,9,10 leading to an increasing number of trials being registered with their use.11,12 Until this point, no single agent has shown a survival benefit against SARS-CoV-2 and it is possible that monotherapy may not suppress inflammation enough to overcome the COVID-19-related cytokine storm and hyper-inflammation.

We have obtained compassionate use access for ruxolitinib in severe COVID-19-related sHLH and used it successfully in combination with TCZ, for patients who were deteriorating despite maximal medical support. We present two cases where the combined use of these agents in immunocompromised patients with HLH secondary to COVID-19 led to clinical improvement.

A 74-year-old female presented with fevers. She had recovered from an autograft for high-grade B-cell lymphoma two months prior. Initial investigations showed pancytopenia with elevated C-reactive protein (CRP), patchy left-sided opacification on her chest X-ray (CXR), normal oxygen saturations and a positive SARS-CoV-2 swab. She was treated for neutropenic sepsis and was discharged after 11 days (Fig 1).

She re-presented three days later (day 0) with confusion, breathlessness and fever. CXR showed changes consistent with COVID infection, as shown in Fig 2. She commenced broad-spectrum antibiotics but became increasingly hypoxic requiring continuous positive airway pressure (CPAP) ventilation. On day 3 her ferritin rose to 25 600 ng/l (from 11 800 ng/l on admission) and her oxygen requirement increased. At this point, RXB was commenced to treat COVID-19-related sHLH (HScore: 214). By day 8 there was no clinical improvement despite maximal medical management; her breathing became more laboured and she was tiring. The decision was made to give TCZ along with treatment-dose low-molecular-weight heparin (LMWH) as a final attempt to treat sHLH (HScore: 185). After 24 h, she had improved clinically. On day 15 she was weaned off CPAP and completed a weaning course of prednisolone following two weeks of RXB. She was discharged one month after readmission.

A 54-year-old male was admitted with fevers, cough and breathlessness (day 0). He had a history of non-Hodgkin lymphoma and had been in remission for the last nine months. Initial investigations showed elevated CRP, bilateral consolidation on his CXR and a positive SARS-CoV-2 swab. After 24 h, she had improved clinically. On day 15 she was weaned off CPAP and completed a weaning course of prednisolone following two weeks of RXB. She was discharged one month after readmission.

A 54-year-old male was admitted with fevers, cough and breathlessness (day 0). He had a history of non-Hodgkin lymphoma and had been in remission for the last nine months. Initial investigations demonstrated a raised CRP, bilateral consolidation on his CXR and a positive SARS-CoV-2 swab. Broad-spectrum antibiotic treatment was
Fig 1. (A) Trends of C-reactive protein (CRP), inspired oxygen concentration (FiO₂) whilst on continuous positive pressure ventilation (CPAP), ferritin and D-dimer during the patient’s illness. (B) Trends of C-reactive protein (CRP), body temperature, ferritin and D-dimer during the patient’s illness. The blue box denotes the three-day course of tocilizumab and the green box indicates the 14-day course of ruxolitinib. [Colour figure can be viewed at wileyonlinelibrary.com]

Fig 2. X-ray (XR) and computed tomography (CT) imaging for both patients demonstrating the typical changes consistent with acute respiratory distress syndrome (ARDS). (A) Chest XR and (B) chest CT of patient 1 and (C) chest XR and (D) chest CT of patient 2.
commenced, and he was enrolled on the RECOVERY trial and randomised to lopinavir and ritonavir.

On day 8, he desaturated and was started on CPAP. A computed tomography (CT) scan showed COVID-19-related lung changes. Following the initial CXR findings, subsequent worsening is shown on CT in Fig 2. Due to further respiratory deterioration, he was intubated on day 16. On day 17 his ferritin level was 80 000 ng/l. He was started on TCZ to treat COVID-19-related sHLH (HScore: 180). He received three doses and his inflammatory parameters improved. He then deteriorated until he was on maximal inotropic and ventilator support. Given his extremely poor prognosis, he was commenced on RXB in a final attempt to treat the sHLH (HScore: 230), as well as on a treatment-dose LMWH. Within 48 h, he was apyrexial and had improved biochemically. After two weeks of RXB, a weaning course of prednisolone (10 mg) was completed. He was successfully extubated on day 53 and stepped down from the intensive treatment unit on day 56. He was discharged nine weeks after his admission.

Distinct differences between typical sHLH and that associated with COVID-19 have been noted; the latter is lung-centric, with an emergent acute respiratory distress syndrome (ARDS) and absence of organomegaly. There is therefore a diagnostic challenge to distinguish between COVID-19 ARDS and patients with additional sHLH. The magnitude of the raised cytokine levels may not be reliable in differentiating from other causes of elevated cytokines and dependable cut-off values do not exist. In order to recognise sHLH in COVID-19, monitoring inflammatory markers along with calculation of the HScore may be useful. This is a clinical score which was developed to predict the likelihood of sHLH, encompassing one cytologic, three clinical and five biologic variables. We utilise a modified version through exclusion of the non-mandatory bone marrow haemophagocytosis criteria; an adjusted score of >130 was considered to accurately classify the presence, or otherwise, of sHLH in 90% of patients.

Both patients presented here, each receiving dual anti-cytokine treatments, were immunocompromised. They received treatment for sHLH and in both cases the use of a single agent did not lead to sustained clinical improvement. TCZ and RXB were given in differing sequences, but the addition of the second agent served to reverse a life-threatening situation. Both patients had a dramatic clinical improvement and normalisation of inflammatory markers, and were ultimately discharged. Haematological experience with these agents, together with the data presented here, suggests IL-6 inhibition induces rapid cytokine suppression, whilst JAK/STAT inhibition administered over a longer period may help to sustain this response.

These cases highlight that there is a need for recognition of sHLH in severe COVID-19 and indicate that there may be a role for the use of combination anti-cytokine treatment in the context of severe disease in high-risk patients. There are increasing numbers of anti-cytokine agents being used in clinical trials and our experience highlights the potential combination of RXB and TCZ in severe COVID-19 infection, which appears to have been well tolerated by both patients. In both our patients, a rapid reduction in the inflammatory markers needed a further sustained response and this was possible with the use of JAK/STAT inhibitor, alongside the TCZ. Pacritinib and baricitinib are JAK inhibitors entering clinical trials to target the inflammatory state secondary to COVID-19, but may also have anti-viral properties. The JAK inhibitors may be late in coming to the COVID-19 party but are certainly beginning to look like one of the game changers in the fight against severe hyper-inflammation. We do not have levels of IL-6 to account for in vivo activity of TCZ, but the monitoring of the inflammatory parameters certainly provides indirect evidence for the role of immunomodulators in the management of severe COVID infection.

There is a need to understand the implications of significant immunosuppression, possibly leading to secondary infections; information on toxicity and efficacy can be obtained by well-conducted larger studies, which is the need of the hour.

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Conflicts of interest

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