Leukemia (2020) 34:2815–2816
https://doi.org/10.1038/s41375-020-01038-8

CORRESPONDENCE

Early phase studies

The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19

Alessandro Gozzetti[1] · Enrico Capochiani[2] · Monica Bocchia[1]

Received: 3 July 2020 / Revised: 23 July 2020 / Accepted: 21 August 2020 / Published online: 2 September 2020

With great interest, we had the opportunity to read the paper by La Rosée F et al. [1] in which between March 30th and April 15th, 2020, using a newly developed COVID-19 Inflammation Score (CIS), patients were prospectively stratified for targeted inhibition of cytokine signaling by the Janus Kinase (JAK) 1/2 inhibitor ruxolitinib (Rux). Fourteen patients were treated up to 14 days with Rux at 7.5 mg per day (at an intermediate dose between GvHD, 5 mg bid, and hemophagocytic lymphohistiocytosis, 15 mg bid) with a CIS ≥ 10 out of 16 points. The authors reported that 12/14 patients achieved significant reduction of CIS by ≥25% on day 7 with a sustained clinical improvement in 11/14 patients. We would like to report our results in COVID-19 patients with acute respiratory distress syndrome (ARDS) while employing a different Rux schedule at higher doses than those reported by La Rosée. The Ruxolitinib for the treatment of ARDS (RESPIRE, NCT04361903) study was approved by the National Ethics Committee. For each patient treated with Rux, parameters of inflammation and organ function were measured before treatment and again every 12, 24, or 48 h. Between March 10th and April 7th we treated 18 hospitalized patients (12 males/6 females; median age 62.5 years, range 28–86) with Rux 20 mg bid for the first 48 h and subsequent two-step de-escalation at 10 mg bids and 5 mg bids for a maximum of 14 days of treatment. Major endpoint of the treatment was to avoid respiratory worsening and progression to mechanical ventilation. Main inflammatory laboratory findings at baseline were: Fibrinogen (g/L) 4.4 (2.1–21.6) Ferritin (ng/mL) 841 (321–3348) CRP (mg/L) 17.8 (4–82) PCT (ng/ml) 0.6 (0.1–3.3) LDH (IU/L) 301 (189–506) ALT (U/L) 55 (34–213) D-Dimer (ng/mL) 747 (202–1724) TNF-alpha (pg/ml) 2.2 (1–10.6) MCP-1 (pg/ml) 524 (152–1471) IL-6 (pg/ml) 24.5 (4.5–111). The median time from the onset of COVID-19-related symptoms and to the beginning of Rux therapy was 9 days (range 4–15). Fourteen out of 18 patients had parameters evaluable for CIS, 12/14 had CIS > 10. All 18 patients started Rux treatment on progressive ARDS, showing a median PaO2/FiO2 ratio of 159 (range 106–208) on noninvasive ventilation (NIV) and they were in imminent need to proceed to mechanical ventilation in accordance with the guidelines of our ICUs. Overall, after the introduction of Rux no evolution from NIV to mechanical ventilation was seen in 16/18 patients and no response in two patients. Interestingly, the CIS in these two patients was 14 and 8. Sixteen out of 18 patients showed a significant improvement in respiratory response already in the first 48 h. After 7 days of Rux treatment, 11/18 patients showed fully recovered respiratory function (pO2 > 98% in spontaneous breathing), 4/18 patients had minimal oxygen requirement (2–4 L/min) 1/18 patients showed stable disease, and 2/18 patients showed progressive disease. At day 14 of Rux treatment, 16/18 patients showed complete respiratory function. No patient died. Our results confirm the efficacy of Rux in reducing severe respiratory distress. Rux is a potent and selective inhibitor of JAK 1 and 2, with selectivity against tyrosine kinase (TYK)2 and JAK3, resulting in a powerful anti-inflammatory activity. We decided to delay mechanical ventilation in favor of Rux treatment with the assumption that in unselected COVID-19 patients with acute hypoxemic respiratory failure this drug could reduce the hyperinflammatory status causing ARDS, thus potentially lower intubation rates and ultimately improve patient outcome. Differently from the study of La Rosée et al., we used higher doses of Rux, with the intent to achieve a rapid and clinically evident response, given the severity of the patients treated.

Larger studies are warranted in order to assess the best dosage and timing while using this powerful drug. As shown by our efforts, the use of Rux has proven to be quite promising with this short-term high

✉ Alessandro Gozzetti
gozzetti@unisi.it

[1] Division of Hematology, University of Siena, Siena, Italy

[2] Hematology Unit, Center for Translational Medicine, Azienda USL Toscana NordOvest, Livorno, Italy

dose schedule, in rapidly improving COVID-19-related severe ARDS.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Reference

1. La Rosée F, Bremer HC, Gehrke I, Kehr A, Hochhaus A, Birndt S, et al. The Janus kinase 1/2 inhibitor ruxolitinib in COVID-19 with severe systemic hyperinflammation. Leukemia. 2020;34:1805–15. https://doi.org/10.1038/s41375-020-0891-0.