



## Could ruxolitinib be effective in patients with COVID-19 infection at risk of acute respiratory distress syndrome (ARDS)?

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Dear Editor,

As of March 29, the COVID-19 pandemic has infected around 670,000 people worldwide, causing over 30,000 deaths. Italy was among the countries in the world severely affected by the pandemic with around 80,000 infected people and over 10,000 deaths [1]. The lethality from COVID-19 infection varies from 2 to 9% and is particularly high, up to 15%, in elderly patients over 65 years of age. The current therapeutic strategies to deal with infection are exclusively supportive and acute respiratory distress syndrome (ARDS) represents the major cause of mortality [2, 3]. A group of COVID-19 patient may have a cytokine storm syndrome, resulting in a rapid failure respiratory function [4]. Multiple guidelines on therapeutic management and support for patients with COVID-19 infection have been developed by several scientific companies [5].

Secondary hemophagocytic lymphohistiocytosis (sHLH) is a hyperinflammatory syndrome secondary to several triggers including sepsis, characterized by a marked increase of cytokines with multi-organ failure and very high mortality rate [6]. sHLH shares with COVID-19 infection an increase in ferritin plasma level and several interleukins (IL): IL-2, IL-6, IL-7, G-CSF, interferon (IFN) gamma, TNF-alpha. Recently, high ferritin and IL-6 plasma values have been associated with lethality rate in COVID-19 infection [3]. Tocilizumab, an IL-6 inhibitor, has been proposed in the treatment of COVID-19 infection.

Ruxolitinib reduces the spleen volume and the circulating values of pro-inflammatory interleukins, in particular IL-6 and TNF-alpha [7]. Recently, preliminary data obtained on 7 sHLH patients treated with ruxolitinib 15 mg bis in die

(BID) have shown encouraging results on overall survival, observing an improvement of inflammatory markers such as ferritin and the soluble IL-2 receptor [8]. In oncohematological patients, with a variable scenery of immune-depression related to the disease, ruxolitinib has been associated with an increased risk of viral and bacterial infection [9], probably secondary to a cytotoxic T lymphocyte (CTL)-dependent mechanism and a non-cytolytic cytokine-dependent mechanism mediated by inflammatory cytokines [10]. Nevertheless, in a patient without oncohematological disease, a short exposition to ruxolitinib will most likely not be sufficient to induce an immune-depleted condition. Since ruxolitinib has proven to be a well-tolerated and relatively manageable drug even in the elderly population with myelofibrosis, it is suggested here to be used in elderly patients with high risk of ARDS secondary to COVID-19 infection.

Eligibility criteria should include patients with age  $\geq$  65 years requiring oxygen treatment with one or more criteria of respiratory function worsening [5]:

- (i) Patients has dyspnea or *staccato speech* (the patient is unable to count rapidly up to 20 after a deep breath) at rest or during minimal activity (sitting up in bed, standing, talking, swallowing, coughing);
- (ii) Breathing rate  $> 22$ ;
- (iii)  $\text{PaO}_2 < 65$  mmHg or  $\text{SpO}_2 < 90\%$ ;
- (iv) Significant worsening of chest X-ray.

We suggest the following ruxolitinib schedule:

- Dexamethasone 20 mg/die for 5 day, thereafter 10 mg/die for 10 days
- Ruxolitinib 15 mg BID for 21 days; in case of clinical worsening and platelets value  $> 150 \cdot 10^9/l$ , increase ruxolitinib until 20 mg BID; after 21 gg, whether patient have an improvement, debulk ruxolitinib 10 mg BID for 1 week and 5 mg BID for a further week, before stopping it.

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At baseline and after 5, 10, 20, and 30 days from the beginning of ruxolitinib, all patients should be evaluated for ferritin and serum should be stored for further analysis of IL-2, IL6, TNF-alpha, IL-10, and IFN gamma values. Primary endpoints should be considered overall survival at 30 and 60 days, and secondary endpoint should include the cumulative incidence or ARDS onset.

This is a time of a dramatic effort by the scientific community in search of direct anti-viral drugs and supportive therapies aimed to reduce fatal complications of COVID-19 infection.

### Compliance with ethical standards

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

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