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Feasibility of tocilizumab in ICU patients with COVID-19

To the Editor,

The optimal treatment strategy of COVID-19 in the intensive care unit (ICU) is still unclear. Symptoms similar to cytokine release syndrome (CRS) have been described in the literature and have been associated with severe and fatal issues in patients with COVID-19. Many authors suggest that all patients with severe COVID-19 should be screened for hyperinflammation using laboratory trends to identify the subgroup from which specific anti-inflammatory drugs such as IL-6 receptor inhibitor could decrease acute respiratory distress syndrome and mortality.[1,2] We read with interest several case series published in *Journal of Medical Virology* about tocilizumab and COVID-19 and present our results to describe the outcome of severe patients treated with tocilizumab and its safety in a real-life practice.[3-7] In this retrospective case series, all patients diagnosed with COVID-19 by semiquantitative real-time polymerase chain reaction on nasopharyngeal swabs admitted in an ICU between 15 March and 30 April 2020 and treated with tocilizumab were included. Infusion of tocilizumab (8 mg/kg) was decided in case of increase of inflammatory parameters (at least two among fibrinogen >8 g/L, ferritin >1000 ng/mL, D-dimers >3000 ng/mL, and CRP > 150 mg/L), persistent fever (tympanic temperature ≥38.1°C during 24 hours) and/or pulmonary involvement (ratio of the partial pressure of oxygen to the fraction of inspired oxygen [PaO_2/FiO_2] <300 mm Hg) in the first 5 days. When the corrected QT was below 460 ms, patients received hydroxychloroquine, ceftriaxone and respiratory support adapted with the clinical state. Ten men with a median age of 66 years were included: 7/10 had, at least, one cardiovascular comorbidity (six had hypertension and three had diabetes). The median SAPS II was 29. The median time between the first symptoms of COVID-19 and ICU admission was 7 days (2 to 10). All patients were febrile and seven patients required invasive ventilation included one before tocilizumab. In eight patients, chest computed tomography scan showed bilateral ground-glass opacities. Median PaO_2/FiO_2 was 156 mm Hg at admission, 94 mm Hg before tocilizumab, and 230 mm Hg 3 days later. The median time between ICU admission and tocilizumab administration was 3 days. All patients received concomitant treatment by hydroxychloroquine and three of them got hydrocortisone in addition to restore hemodynamic stability. Median values of inflammatory parameters before tocilizumab were CRP = 246 mg/L, fibrinogen = 10 g/L, D-dimers = 1354 ng/mL, and ferritin = 2751 ng/mL. Apyrexia was obtained 3 hours after tocilizumab infusion in the median. At day 3, CRP and fibrinogen decreased of 83% (43 mg/L) and 40% (6 g/L), respectively (Table 1). The median length of stay in ICU was 11 days. One patient still needed invasive ventilation on day 14 and one patient died on day 4 (pulmonary embolism). Two patients who received hydrocortisone had infectious complications: one aspergillosis and one bacterial ventilator-associated pneumonia due to *Serratia*. No adverse drug reaction attributed to tocilizumab was reported. This case series of 10 patients confirms the safety of the use of tocilizumab for the treatment of COVID-19 CRS in the context of ICU. CRP and fibrinogen can be used to guide tocilizumab prescription early in patient admitted to ICU for acute respiratory symptoms or CRS. The use of tocilizumab was associated with rapid apyrexia, improvement of respiratory and biological parameters, and could reduce the length of hospitalization.[8] Tocilizumab is an interleukin 6 receptor inhibitor used for a long time for rheumatic diseases and more recently in CRS due to CAR T-cell associated toxicities. The use of tocilizumab was based on literature data suggesting that hospitalized patients with COVID-19 can develop a syndrome of dysregulated and systemic immune overactivation described as a cytokine storm or hyperinflammatory syndrome that worsens acute respiratory distress. Elevated IL-6 levels have been described in patients with severe COVID-19 and several case series have illustrated good outcomes with this treatment intravenously or subcutaneously.[3-7,9] Moreover, recommendations from Italian intensivists (SIAARTI) already include IL-6 inhibitor for patients

TABLE 1 Laboratory tests before and after tocilizumab

	Normal range	Before tocilizumab	D+3 after tocilizumab
PaO_2/FiO_2, mm Hg	> 400	94 (75;130)	230 (171;278)
CRP, mg/L	0-5	246 (216;274)	43 (21;52)
D-Dimers, ng/mL	0-500	1354 (749;3992)	1931 (1515;5000)
Fibrinogen, g/L	2-5	10 (9;10)	6 (5;6)
Procalcitonin, µg/mL	0-0.5	0.47 (0.33;1.22)	0.30 (0.22;0.75)
Ferritin, ng/mL	5-200	2751 (2300;3815)	2265 (1633;2730)

Note: Data are medians (interquartile 1; interquartile 3).
Abbreviations: CRP, C-reactive protein; D, day after tocilizumab infusion day.

with severe COVID-19.[10] Tocilizumab is most often well tolerated but may expose to adverse drug reactions such as elevation of hepatic transaminases, transient neutropenia, hypersensitivity reactions, and intestinal perforation. So, patients should be carefully monitored. In practice, it is difficult to select the best candidates to benefit from tocilizumab therapy and good timing. Conversely to IL-6 plasmatic level, CRP and fibrinogen are two easily accessible markers that could be useful in critical patients. Our results need to be confirmed by controlled trials because of the limited number of patients. In severe and critical COVID-19 patients, cytokine storm is associated with acute respiratory distress, and tocilizumab seems to be an effective and safe treatment in selective patients.

Nahéma Issa[1]
Margot Dumery[1]
Olivier Guisset[1]
Gaelle Mourissoux[1]
Fabrice Bonnet[2]
Fabrice Camou[1]

[1]*Medical Intensive Care and Infectious Diseases Unit, Saint-Andre Hospital, Bordeaux, France*
[2]*Internal medicine and Infectious Diseases Unit, Saint-Andre Hospital, Bordeaux, France*

Correspondence
Nahéma Issa, Medical Intensive Care and Infectious Diseases Unit, Hôpital Saint-André, CHU BORDEAUX, 1 rue Jean Burguet, 33075 BORDEAUX CEDEX, France.
Email: nahema.issa@chu-bordeaux.fr

ORCID

Nahéma Issa http://orcid.org/0000-0002-3443-6115

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