Early tocilizumab treatment could improve survival among COVID-19 patients

Sirs,

We read with great interest the recent paper by Sciascia *et al*. (1) in which they observed an improvement in respiratory and laboratory parameters after tocilizumab administration in COVID-19 patients. Here we report a prospective case series involving 58 patients diagnosed of severe acute respiratory syndrome (SARS-CoV-2) infection and treated with tocilizumab plus corticosteroids in Mataró, Spain. Our results are consistent with those found by our colleagues. However, choosing the appropriate time to start toiclizumab and perhaps adding corticosteroid pulses could improve patient survival.

Pathogenesis of severe acute respiratory syndrome (SARS-CoV-2) infection is still under study. It appears that infection passes through multiple phases (2). An initial phase involving incubation and viral replication period, a second where patients develop a viral pneumonia and possibly hypoxia and finally, some patients may transit to a third phase which manifests as an extra-pulmonary systemic hyperinflammation syndrome. In this stage markers of systemic inflammation appear to be elevated and a cytokine storm mediated by overproduction of proinflammatory cytokines have been observed (3). Clinical experiences in China suggest that interleukin-6 is one of the most important cytokines involved in COVID-19-induced cytokine storms. Tocilizumab, a monoclonal antibody against iL-6 receptor, has been successfully used in small series of severe cases (4, 5). Corticosteroids are widely used to decrease the host inflammatory response. However, evidence of the benefit of treatment in patients infected by SARS-CoV-2 is very limited and not conclusive (6).

Over a 5-week period, from March 21 to April 27 2020, a total of 58 patients received at least one dose of tocilizumab. The mean age was 60.6 years and 42 (72.4%) were males. Of these patients, 19 (32.4%) where admitted to intensive care unit and 8 (13.8%) died. Laboratory values before tocilizumab administration are summarised on Table I. The patients who died presented statistically significantly higher inflammatory markers such as lactate dehydrogenase (LDH) and D-dimer. Although no other significant differences were found, those who died had worse parameters before tocilizumab treatment.

Table I. Median (Standard deviation) of biomarkers in COVID-19 patients before tocilizumab administration.

	Exitus (n=8)	Alive (n=50)	*p*
D-dimer (μg/l)	2,055 (15294.2)	730 (5094.5)	***< 0.01***
C-reactive protein (mg/dl)	13.0 (8.7)	13.8 (9.8)	*0.65*
Ferritin (ng/ml)	1,457.0 (1732.2)	1,580.0 (1337.9)	*0.79*
LDH (UI/l)	520.5 (134.5)	375.0 (107.8)	***< 0.01***
IL-6 (pg/ml)	67.2 (81.9)	19.8 (48.6)	*0.32*
Absolut lymphocits count (/μl)	480.0 (239.4)	600.0 (342.1)	*0.21*
pO2/FiO2 ratio (mmHg)	106.8 (60.8)	120.6 (55.2)	*0.44*

On the other hand, 57 (98.3%) patients received intravenous pulse steroid therapy during 3–5 days. Administration of corticosteroid was before tocilizumab use on 22 (38.6%) patients, at the same day (± 1) on 31 (54.4%) and 4 (7.0%) after tocilizumab administration. We observed a mortality trend depending on the time of corticosteroid administration according to tocilizumab prescription. The mortality rate was 9.1% (2), 16.1% (5) and 25.0% (1), depending on whether the corticosteroid administration was before, during or after tocilizumab, respectively.

A better understanding of the right time to start immunomodulatory drugs to reduce the cytokine storm is urgently needed to guide clinicians to fight SARS-CoV-2 infection. Our results suggest that early administration of tocilizumab to prevent cytokine storm, results in a lower mortality. Although the use of corticosteroids is highly controversial, according to our experience its prescription at the beginning of the inflammatory phase and before tocilizumab presents better outcomes

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