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Letter to the Editor

Use of the interleukin 6 inhibitor tocilizumab in Japanese patients with cytokine release syndrome caused by COVID-19-related acute respiratory distress syndrome: A case series

Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), can induce acute respiratory distress syndrome and multiorgan failure [1]. Excessive production of proinflammatory cytokines has been observed in patients with COVID-19, and interleukin 6 (IL-6)-driven cytokine release syndrome (CRS) is considered to play a vital role in the development of COVID-19 [1]. Blocking the IL-6 signaling pathway has recently drawn attention as a potential method to reduce COVID-19-related CRS [2]. However, it is controversial whether corticosteroids, administered as anti-inflammatory treatment, can ameliorate COVID-19-related CRS [3]. Here, we have described the clinical course of seven patients with laboratory-confirmed COVID-19 who were treated with tocilizumab (TCZ), a humanized anti-human IL-6 receptor antibody. Although the study data are preliminary, they suggest the efficacy of TCZ in the treatment of COVID-19-related CRS in Japanese patients with COVID-19.

We conducted a case series of all adult patients with confirmed severe COVID-19 treated with TCZ (off-label use) at University of Ryukyus Hospital between March and May 2020. The inclusion criteria were generated based on protocols from previous studies [4,5]. Patients were administered a single dose of intravenous TCZ (8 mg/kg), up to two additional doses were allowed. The primary endpoint was improvement in the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) and the values of the following biomarkers: C-reactive protein (CRP), IL-6, lymphocytes, and tumor necrosis factor-α (TNF-α). Adverse events and survival measures were the secondary endpoints. Clinical data were collected at baseline (day 0) and on days 3, 7, and 14. The Mann–Whitney test was used for comparison of variables. Statistical analyses were preformed using Prism (GraphPad Software, CA, USA); $p < 0.05$ was considered significant. The study was approved by the ethics committee of University of Ryukyus for Medical and Health Research Involving Human Subjects (approval number: 1616, June 11, 2020). Written informed consent was obtained from all patients to publish this case series.

The patients were predominantly male (6/7), and the median patient age was 70 years (interquartile range [IQR] 63–77 years). The median time from symptom onset to diagnosis was 9 days (IQR 4–9 days). Although all patients received favipiravir, nafamostat, and azithromycin before TCZ, no clinical improvement was seen.

Fever was observed in all patients. Only four (57.1%) patients with hypoxia presented with dyspnea; the median time to progress to dyspnea from the onset of COVID-19 was 5 days (IQR 2–8 days). All patients required oxygen therapy, including nasal cannula in two (28.6%), mask oxygen in two (28.6%), and high-flow oxygen therapy in three (42.8%). The three patients who received high-flow oxygen therapy eventually required invasive ventilation owing to severe acute respiratory failure; two patients received TCZ after intubation, whereas one patient received TCZ 2 days before intubation.

All patients showed lymphopenia (median 14.7%; IQR 6.4%–21.4%) and elevated CRP (median 15.26 mg/dL; IQR 11.77–20.68 mg/dL), ferritin (1005 ng/mL, IQR 562.1–1877 ng/mL), and IL-6 (median 108 pg/mL; IQR 33.1–160 pg/mL) levels. Four (57.1%) patients presented abnormal D-dimer levels (median 1.6 μg/mL; IQR 0.3–23.7 μg/mL).

Fever resolved within 24 h in six (85.7%) patients after TCZ administration. As one patient had received a systemic corticosteroid (methylprednisolone, 1 mg/kg/day), fever was not observed at TCZ initiation.

Six (85.7%) patients had significant improvement in PaO_2/FiO_2 after TCZ administration ($p = 0.03$; Fig. 1). The oxygen levels improved in four (57.1%) patients within 3 days of TCZ therapy. These patients did not require oxygen support at day 14. Despite TCZ administration, the condition of two patients deteriorated, resulting in invasive ventilation. Extracorporeal membrane oxygenation (ECMO) was introduced for a 45-year-old patient in addition to mechanical ventilation. After three doses of TCZ and a 3-day course of a systemic corticosteroid (methylprednisolone, 1000 mg/day), the patient recuperated, and ECMO was safely withdrawn at day 14 of initial TCZ administration. Improvement in oxygen levels were seen in

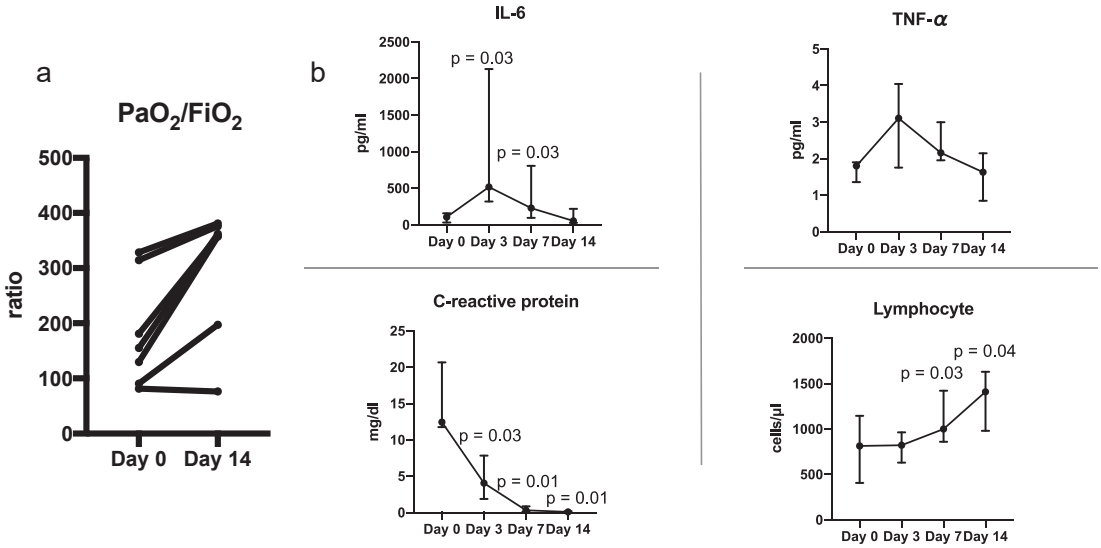

Fig. 1 – Changes in oxygen levels and biomarker values after tocilizumab administration (n = 7) (results are presented as median and interquartile). a) Changes in oxygen levels. Abbreviations: PaO_2/FiO_2: Ratio of arterial oxygen partial pressure to fractional inspired oxygen. b) Clinical trends of biomarkers. Abbreviations: COPD: chronic obstructive pulmonary disease, COVID-19: coronavirus disease, CRP: C-reactive protein, PaO_2/FiO_2: ratio of arterial oxygen partial pressure to fractional inspired oxygen, SpO_2: oxygen saturation, TCZ: tocilizumab.

an 83-year-old patient at day 14 under mechanical ventilation after two consecutive TCZ doses. Nevertheless, the patient's condition was complicated with multiple subcortical hemorrhagic infarctions. Death was reported in a 74-year-old male patient who had diabetes, chronic arterial fibrillation, and a history of smoking (one pack per day for 40 years). The patient was diagnosed with COVID-19 pneumonia on day 7 after the onset of symptoms and had already been under invasive ventilation before TCZ administration. However, the patient developed catheter-related sepsis shortly after timely improvement of oxygen levels and died on day 33 due to a sudden onset of severe bradycardia.

After TCZ administration, lymphocyte counts, which stayed at similar levels through day 3, showed a steady increase from days 7–14 (Fig. 1). CRP levels had decreased sharply at day 3, but by day 7, CRP levels returned to normal in all patients and remained normal at day 14. IL-6 levels in six patients significantly increased on day 3, followed by a consistent decline. Similarly, TNF-α levels showed a downward trend after a sharp increase on day 3.

Consolidation of the fibrotic change with ground-glass opacity was observed on computed tomography (CT) scan around day 7 in four severe cases. The three patients who underwent invasive ventilation showed bilateral diffuse lung infiltration on chest radiography, but the abnormal findings gradually resolved once gas exchange improved, except in the patient who died. Among the survivors, the median hospitalization duration in five patients was 27 days. The remaining patient was hospitalized for >8 weeks for poststroke care. Infusion-related reactions (n = 1), hypertriglyceridemia (n = 1), and bacteremia (n = 1) were adverse events of TCZ administration.

This case series evaluated the clinical efficacy and safety of TCZ in seven patients with severe COVID-19. Rapid improvement of clinical symptoms, recuperation from hypoxia, and marked changes in proinflammatory markers were observed. An increase in IL-6 levels after TCZ administration reflected the inhibition of IL-6 binding to the IL-6 receptor [4]. Although randomized control trials are warranted to validate the efficacy of TCZ, our data support previous preliminary studies on TCZ treatment for COVID-19 [4–6]. Nevertheless, the benefit of TCZ might be small for critically ill patients.

In this study, marked improvement in hypoxia after treatment with TCZ was not observed in three patients. These patients had lower PaO_2/FiO_2 (median 90.7; IQR 81.4–155.4) than the other four patients (median 247.6; IQR 142.6–325). Further, they had higher IL-6 levels (median 63.8 pg/mL; IQR 30.63–202.9 pg/mL) than the other four patients (median 109 pg/mL; IQR 108–160 pg/mL). IL-6 signals through two main inflammatory pathways referred to as cis-signaling or trans-signaling [7]. While cis-signaling activates acquired and innate immunity, trans-signaling can result in the dysfunction of endothelial cells, leading to vascular permeability and coagulation disorders [7]. Once these inflammatory pathways have been amplified by excessive IL-6, terminating the cytokine cascade may be challenging. Indeed, IL-6 levels correlate with mortality [6]. Therefore, TCZ should be administrated of at an early stage.

This study has several limitations. Because the number of cases was small, it was difficult to measure and account for confounding variables. In addition, the data may not be generalizable to a larger population.

In conclusion, TCZ administration may ameliorate COVID-19-induced CRS. Well-designed controlled trials are required to investigate the efficacy of TCZ and determine the parameters that physicians should monitor during treatment in view of safety.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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