Case Report

Tocilizumab in COVID-19: enthusiasm vs. evidence

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ABSTRACT

Based on the pathophysiological characterization of COVID-19, initial studies suggested the use of tocilizumab (TCZ), a recombinant humanized monoclonal antibody of the immunoglobulin G1 class, for management of the cytokine storm witnessed in severe cases. Thus, we decided to present a case series of 18 patients with severe COVID-19 treated with TCZ at our hospital. Our results coincide with the fact that the routine use of TCZ in severe COVID-19 is not robustly supported. We believe that the efficacy and safety of this drug and other related molecules should be validated in large randomized clinical trials.

KEY WORDS: COVID-19, tocilizumab, treatment

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INTRODUCTION

Months after the national lockdown imposed by various countries in response to the COVID-19 pandemic, the need for an effective treatment persists. Despite implementing supportive therapy and glucocorticoids (GCs) as the standard of care, hospitalization wards and intensive care units (ICUs) remain overwhelmed while the death toll continues to rise. Based on the pathophysiological characterization of COVID-19, initial studies suggested the use of tocilizumab (TCZ), a recombinant humanized monoclonal antibody of the immunoglobulin G1 class, for management of the cytokine storm witnessed in severe cases.[1] It was believed that a course of GC, followed by TCZ, would accelerate the recovery of respiratory function, decrease mortality, and reduce the likelihood of invasive mechanical ventilation.[2] In low-to-middle-income countries, because of limited resources and lack of appropriate infrastructure, treatment options that may delay or prevent the admission of COVID-19 patients to the ICU are often greeted with enthusiasm and promoted. In this light, we decided to report the outcomes of severe COVID-19 patients treated with TCZ at our hospital.

CASE REPORT

The medical ward of our hospital admitted 450 patients from April to June 2020, out of which 391 presented moderate-to-severe COVID-19. TCZ was used in 18 out of the 391 patients. This group of patients comprised adults (above 18 years of age) and excluded pregnant women. The mean age (standard deviation) of patients was 58.8 (12.4) and 67.7% were male. Table 1 shows the patients' clinical characteristics. The decision to treat certain patients with moderate-to-severe COVID-19 with TCZ was based on clinical worsening, with none of the already established contraindications for administering the drug[2] and with C-reactive protein > 24 mg/L. Laboratory studies of interleukin 6 (IL-6), D-dimer, and ferritin were not available in our hospital. Patients received a single dose (8 mg/kg, minimum of 400 mg) of TCZ in the form

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Table 1: Characteristics of severe COVID-19 patients treated with tocilizumab

Characteristics	Patients (*n*=18)
Age, mean (SD)o	58.8 (12.4)
Male sex, *n* (%)	12 (67.7)
Onset of symptoms to hospital admission, median (IQR)⁺	8 (7-14)
Comorbidities*, *n*/total *n* (%)	
Overweight/obesity	12/18 (66.7)
Exposure to biomass	5/17 (29.4)
Arterial hypertension	2/17 (11.8)
Laboratory findings	
PaO_2:FiO_2 (mm Hg on admission), median (IQR)†	73.5 (61-99)
Reactive C protein, median (IQR)‡	48 (17.5-144)
Neutrophilia (≥7000/mm³), *n*/total *n* (%)	13/17 (76.5)
Lymphocytopenia (≤1500/mm³), *n*/total *n* (%)	9/17 (52.9)
Low platelet count (≤150,000/µl), *n*/total *n* (%)	2/17 (11.8)
Computed tomography findings, *n* (%)	
Ground-glass opacities	17 (94.4)
Interstitial compromise	12 (66.7)
Consolidations	9 (50)
Cystic changes	1 (5.6)
Complications, *n*/total *n* (%)	
Elevation of transaminases	4/17 (23.5)
Pulmonary embolism	2/17 (11.8)
Other**	5/17 (29.4)
Outcome, *n* (%)	
Hospital length of stay (days), median (IQR)	11 (7-24)
Mortality	8 (44.4)

*No patients with diabetes mellitus reported, **Pericardial effusion, pneumopericardium, NSTEMI, respiratory acidosis, and interstitial lung disease, Available data in †14 patients, ‡16 patients, and ⁺17 patients. SD: Standard deviation, IQR: Interquartile range, NSTEMI = Non-ST-Elevation Myocardial Infarction

of an intravenous infusion over 60 min. No secondary infections or adverse effects were reported. The mortality for the 391 patients was 53%, and complications such as pulmonary thromboembolism and pneumopericardium were reported. In patients who received TCZ, there was a 44.4% (8/18) mortality. Limitations to our findings include not establishing uniform criteria for administering the drug and thus being susceptible to selection bias. It is important to highlight that, at the time of the TCZ administration, there were not enough beds, ventilators, and high-flow devices available in the ICU. Therefore, TCZ was indicated for patients with an unstable and life-threatening condition based on the results of previous observational clinical studies and pathophysiological plausibility.[3]

DISCUSSION

Studies have suggested the cytokine storm as the main pathophysiological mechanism for severe cases of COVID-19.[4] Therefore, if TCZ could successfully inhibit the soluble and membrane-bound IL-6 receptors,[5] it would mitigate the hyperinflammatory state of these patients and contribute to their recovery. However, this proposed mechanism of action may not translate to a successful outcome in the clinical practice. Although observational studies may support the use of TCZ,[6,7] without data from clinical trials, these could increase uncertainty regarding management of patients with severe COVID-19.[8]

For instance, encouraging the use of TCZ, a recent meta-analysis reported that when compared to a control group of 512 subjects, the TCZ group of 294 subjects was found to have a significantly less all-cause mortality (prevalence ratio [RR]: 0.38; 95% confidence interval [CI]: 0.16–0.93).[6] In addition, another meta-analysis showed that the administration of immunomodulatory agents, namely TCZ and anakinra (IL-1 inhibitor), significantly decreased the mortality rate and ameliorated clinical symptoms in COVID-19 patients (RR: 0.22, 95% CI: 0.09–0.53).[7] Nevertheless, preliminary data from COVACTA (the first global, randomized double-blind, placebo-controlled Phase III trial) indicated that neither the primary objective of improving clinical status in patients with severe COVID-19 nor the secondary objective of reducing mortality in this group was achieved.[9,10] Therefore, we emphasize the need to generate more data on the potential efficacy of this drug and remain expectant toward the results of the other 21 ongoing TCZ clinical trials.[11] Finally, other IL-6 inhibitors' clinical trials, such as the ones being performed for sarilumab and siltuximab, are currently in development.[12]

Concisely, according to the evidence available, the routine use of TCZ in severe COVID-19 is not robustly supported. We believe that the efficacy and safety of this drug and other related molecules should be validated in large randomized clinical trials. Therefore, initial enthusiasm for trying to extrapolate disease pathophysiology to patient outcomes with no evidence provided by clinical trials explains heterogeneous and discouraging findings like the ones presented in this letter.

Declaration of the patient consent

The authors certify that they have obtained all appropriate patient consent forms. In these, the patients have given their consent for clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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