Case Report

Tocilizumab in COVID-19: enthusiasm vs. evidence

Paola Zeña-Huancas¹, Franco León-Jiménez¹,², Mayte Bryce-Alberti², Arianna Portmann-Baracco³

¹Internal Medicine, Hospital de la Amistad Perú-Corea Santa Rosa, Piura, Peru, ²Facultad de Medicina, Universidad Señor de Sipán, Piura, Peru, ³Facultad de Medicina, Universidad Peruana Cayetano Heredia, Lima, Peru

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

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. 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. 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 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

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: WKHLRPMedknow_reprints@wolterskluwer.com

How to cite this article: Zeña-Huancas P, León-Jiménez F, Bryce-Alberti M, Portmann-Baracco A. Tocilizumab in COVID-19: Enthusiasm vs. Evidence. Lung India 2021;38:574-6.
DISCUSSION

Studies have suggested the cytokine storm as the main pathophysiological mechanism for severe cases of COVID-19. However, if TCZ could successfully inhibit the soluble and membrane-bound IL-6 receptors, 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, without data from clinical trials, these could increase uncertainty regarding management of patients with severe COVID-19.

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]. 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). 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. 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. Finally, other IL-6 inhibitors’ clinical trials, such as the ones being performed for sarilumab and siltuximab, are currently in development.

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.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Le RQ, Li L, Yuan W, Shord SS, Nie L, Habtemariam BA, et al. FDA approval summary: tocilizumab for treatment of chimeric antigen receptor t cell-induced Severe or life-threatening cytokine release syndrome. Oncologist 2018;23:943-7.
2. Ramiro S, Mostard R, Mastard-Checa C, Dongen CM, Dormans T, et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: Results of the CHIC study. Ann Rheum Dis 2020;79:1-9.
3. Guaraldi G, Meschiati M, Cozzi-Leprini A, Millic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID-19: a retrospective
cohort study. Lancet Rheumatol. 2020 Aug;2(8):e474-e484. doi: 10.1016/S2665-9913(20)30173-9. Epub 2020 Jun 24. Erratum in: Lancet Rheumatol. 2020 Oct;2(10)e391. PMID: 32835257; PMCID: PMC7314456.
4. Calabrese LH. Cytokine storm and the prospects for immunotherapy with COVID-19. Cleve Clin J Med 2020;87:389-93.
5. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: Interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents 2020;55:105954.
6. Misra S, Nath M, Hadda V, Vibha D. Efficacy of various treatment modalities for nCOV-2019: A systematic review and meta-analysis. Eur J Clin Invest. 2020;50:e13383.
7. Talaie H, Hosseini SM, Nazari M, Fakhri Y, Mousavizadeh A, Vatanpour H, et al. Is there any potential management against COVID-19? A systematic review and meta-analysis. Daru 2020;28:765-77.
8. Sinha P, Matthay MA, Calfee CS. Is a “Cytokine Storm” Relevant to COVID-19? JAMA Intern Med 2020;180:1152-4.
9. Roche provides an update on the phase III COVACTA trial of actemra/roactemra in hospitalised patients with severe COVID-19 associated pneumonia; 2020. Available from: https://www.roche.com/investors/updates/inv-update-2020-07-29.htm. [Last accessed 2020 Aug 19].
10. A Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia (COVACTA). Identifier NCT04320615. Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety and Efficacy of Tocilizumab in Patients With Severe COVID-19 Pneumonia; 2020 July 31. Available from: https://clinicaltrials.gov/ct2/show/NCT04320615. [Last accessed on 2020 Aug 04].
11. National Institutes of Health. 2020. ClinicalTrials.Gov; 2020. Available from: https://clinicaltrials.gov/ct2/home. [Last accessed 2020 Aug 19].
12. Shubham A, Zeenat F. IL-6 inhibitors in the treatment of serious COVID-19: A promising therapy? Pharmaceut Med 2020;34:223-31.