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High Mortality Rate in Severe COVID-19 Despite Tocilizumab Administration: A Case Series

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ABSTRACT

Introduction: Tocilizumab is a potential therapeutic agent for modulating cytokine storms, a known cause of multiorgan failure and mortality in severe COVID-19. However, recent studies present conflicting results regarding its outcome and effectiveness. This study aims to assess the outcomes of severe COVID-19 patients treated with tocilizumab.

Objective: We report the mortality rate of patients with severe COVID-19 after tocilizumab administration.

Methods: A case series study involving 11 patients was conducted in the intensive care unit. Data on demographics, medical history, length of hospital stay, vital signs, laboratory and radiology examination, and drugs administered were collected. Statistical analysis used IBM SPSS version 17.

Results: The patient mortality rate reached 72.7%, with a median of two and 4.5 days of tocilizumab administration in patients who recovered and died, respectively. Comorbidities included hypertension (27.3%), type 2 diabetes mellitus (45.5%), and obesity (63.6%). Other therapies co-administered with tocilizumab include antibiotics, vasopressors, convalescent plasma, and remdesivir. Despite promising changes in laboratory parameters in almost every patient, radiological improvement was found in only 28.58% of patients.

Conclusion: This study highlights that tocilizumab administration in severe COVID-19 has a good safety profile, with no serious adverse effect observed, although a high mortality rate was observed even after tocilizumab administration in patients with severe COVID-19.

INTRODUCTION

The novel coronavirus disease 2019 (COVID-19) case in the middle of 2020 has overwhelmed clinicians at the COVID-19 center with the increasing number of patients admitted to the intensive care unit (ICU), along with the growing phenomenon of the "cytokine storm," which was sufficient to cause multiorgan failure. It is responsible for clinical deterioration and increasing mortality rates in COVID-19 patients (Campochiaro et al., 2022; McKenzie et al., 2022).

One of the pro-inflammatory cytokines found to play a vital role in this cytokine storm is interleukin 6 (IL-6). Large amounts of IL-6 are released and bind to its receptors, thereby

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activating multiple inflammatory cascades. Correlation studies supported the crucial role of IL-6 and C-reactive protein (CRP) in the COVID-19 cytokine storm, which was shown by the positive correlation between IL-6 and CRP to patient severity and poor clinical outcome (Campochiaro et al., 2022; Ruan et al., 2020). Since then, research has focused on finding drugs that target the blockade of the IL-6 receptor. Tocilizumab, an IL-6 receptor antagonist, is the most frequently evaluated drug. Tocilizumab has been thoroughly studied for the treatment of hyperinflammatory syndrome or cytokine storms in patients with severe COVID-19. Various observational studies have demonstrated the efficacy of tocilizumab in improving patients' symptoms, radiological features, and laboratory parameters,(Alattar et al., 2020; AlBahrani et al., 2021; Albertini et al., 2021; Keske et al., 2020; Xu et al., 2020) suggesting tocilizumab as a promising therapy for severe COVID-19. A meta-analysis involving all studies testing the effectiveness of tocilizumab confirms the positive results of the drug (Domingo et al., 2021). However, recent case series and randomised controlled trials reported the opposite (McKenzie et al., 2022; Salvarani et al., 2021; Veiga et al., 2021)

Apart from the pros and cons of tocilizumab's efficacy for severe COVID-19, until recently, there has been no conclusion about the right time for tocilizumab administration to obtain its maximum benefits. In its living guidelines, the World Health Organization (WHO) does not specify the appropriate timing. At the same time, in several clinical trials, the administration of tocilizumab is recommended as early as possible at the beginning of hospital admission (World Health Organization, 2022). Therefore, this study aimed to report on the outcomes of severe COVID-19 patients after administering tocilizumab for severe COVID-19 patients.

METHODS & MATERIALS

This retrospective case series involved 11 severe COVID-19 patients in the intensive care unit (ICU) who received at least one dose of tocilizumab in 2020-2021. Data were retrieved from inpatients' medical records. No exclusion criteria were applied. Demographic data, medical history, length of hospital stay, vital signs, laboratory and radiology examination results, and drugs administered during concurrent treatment with tocilizumab were retrospectively obtained from medical records. The Ethical Review Board approved this study with an ethical clearance letter number 1010/UN14.2.2.VII.14/LT/2020.

Tocilizumab administration refers to the COVID-19 management guidelines by the Ministry of Health of the Republic of Indonesia with the criteria as follows: sequential organ failure assessment (SOFA) score <3, CURB-65 score >2, or <93% oxygen saturation which can be corrected with oxygen fraction (FiO2) <50% (equivalent to oxygen supplementation ≤6 L/minute by nasal cannula or simple face mask), or respiratory rate >30 times/minute, or chest radiograph showing bilateral multilobed infiltrates, with one of the following biologic markers: D-dimer 0.7 g/L; IL-6 40 pg/mL; lymphocyte count <800 × 109/L; ferritin 700 g/L; fibrinogen >700 mg/dL; and CRP >25 mg/L. The dose of tocilizumab was eight mg/kg body weight given intravenously.(Burhan et al., 2020)

The oxygen saturation reported in this study resulted from peripheral measurements using an oximeter. Changes in radiological appearance were observed by comparing the interpretation of the chest radiograph before and after tocilizumab administration. Changes in laboratory and radiological parameters were observed 24 hours before and after tocilizumab administration. Radiological changes were defined as the changes in the size of lesions on chest radiographs before and after Tocilizumab administration. The outcomes reported in this study were

improvements in laboratory, radiological, and patient mortality rates post-tocilizumab administration.

Variables with categorical scales were reported in the distribution of frequency and percentage. In contrast, numerical variables were reported as mean (and standard deviation) if the data were normally distributed, or as median (and interquartile range) if the data were not normally distributed. The numerical data normality of the distribution test was performed using the Shapiro-Wilk test. Statistical analysis was performed using IBM Statistical Package and Service Solution software version 17.

RESULT

The demographic data and clinical characteristics of the patients are shown in Table 1. Tocilizumab was administered in a mean of four days (± 1.78) after ICU admission, with a median of two days in recovered patients and 4.5 days (IQR = 3) in those who died. All the patients received steroids as part of the protocol for the management of severe COVID-19. In addition, some patients received levofloxacin (81.8%), ceftriaxone (36.4%), vasopressors (81.8%), convalescent plasma (18.2%), and remdesivir (18.2%).

Table 1. Baseline patient characteristics.

Patient characteristics at ICU admission	Recovered (n = 3)	Dead (n = 8)
Age** - years	66#	56 (12)
Sex – n (%)		
Male	4 (44.4)	5 (55.6)
Female	1 (50)	1 (50)
Comorbidities – n (%)		
Type 2 Diabetes Mellitus	1 (20)	4 (80)
Hypertension	1 (33.3)	2 (66.7)
Obesity	1 (14.3)	6 (85.7)
Other therapies received – n (%)		
Levofloxacin	2 (22.2)	7 (77.8)
Ceftriaxone	1 (25)	3 (75)
Steroids	3 (27.3)	8 (72.7)
Vasopressor	1 (11.1)	8 (88.9)
Convalescent plasma	1 (50)	1 (50)
Remdesivir	1 (50)	1 (50)
Vital signs at ICU admission		
Temperature** - °C	37.3#	36.55 (1.8)
Systole* – mmHg	142.33 ± 5.68	122.88 ± 11.93
Diastole* – mmHg	82.00#	76.50 (10)
Pulse rate** – times/minute	93#	98.50 (10)
Respiratory rate* – times/minute	31.67 ± 7.63	26.38 ± 5.47
Oxygen saturation* - %	89.67 ± 4.51	92.88 ± 5.66

*Mean (± SD), **Median (IQR), #IQR could not be determined because the sample size is small

The overall average length of patient care was 12.36 days (± 5.60), with the final result that only three people recovered (27.3%) and the rest died (72.7%). Patients who recovered received tocilizumab within two to four days after admission to the ICU, with an average length of stay of 14.33 days (± 7.63) compared to patients who died, with two to seven days period of tocilizumab

administration and an average length of stay 11.63 days (± 5.09). The median time to receive tocilizumab in patients who recovered was two days from admission to the ICU; on the other hand, it was 4.5 days in patients who died. Patients who experience recovery have an age range of 30-66 years, while those who die are 47-70.

Table 2. Pre and post-tocilizumab changes

Parameters	Pre-Tocilizumab		Post-Tocilizumab	
	Recovered	Dead	Recovered	Dead
Laboratory parameters				
WBC** – x10³/µL	8.07#	13.20 (14.11)	21.29#	21.85 (16.27)
CRP** – mg/L	148.8#	93.55 (81.59)	34.3#	62.16 (238.14)
LDH* – U/L	660.33 ± 49.69	711.12 ± 285.97	572.66 ± 303.12	687.50 ± 219.41
PT** – seconds	10.30#	11.05 (1.63)	9.90#	11.95 (2.25)
Procalcitonin* – ng/mL	0.49 ± 0.46	1.36 ± 1.37	0.04 (± 0.01)	2.26 ± 1.53
Ferritin* – ng/mL	1638.66 ± 1228.36	2012.25 ± 1412.93	1485 ± 1223.22	2024.75 ± 1507.97
Radiologic changes – n (%)				
Decreased lesions			1 (50)	1 (50)
Persistent lesions			1 (100)	0 (0)
Increased lesions			0 (0)	4 (100)

WBC, white blood cell count; CRP, c-reactive protein; LDH, lactate dehydrogenase; PT, prothrombin time
*Mean (± SD), **Median (IQR), #IQR could not be determined because the sample size is small

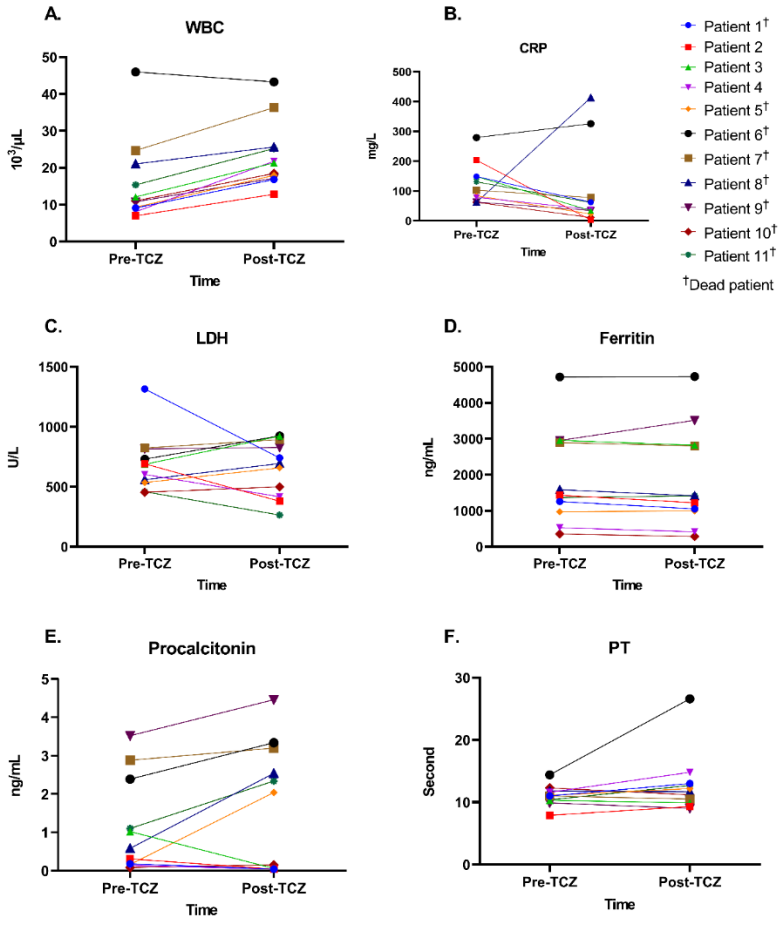

Figure 1. Pre and post-tocilizumab changes in laboratory values

A comparison of changes in laboratory and radiological parameters 24 hours before and after tocilizumab administration is shown in Table 2. Table 2 shows that based on its mean or median, post-tocilizumab CRP and LDH levels decreased, even in patients who died. PT, procalcitonin, and ferritin tended to decrease post-tocilizumab in patients who recovered and vice versa in patients who died. The post-tocilizumab median PT and mean procalcitonin levels reached the normal range in recovered patients. An increase in WBC count was observed in all patients. This difference is further visualized in Figure 1. One patient died despite radiological improvement of the pulmonary lesion. Generally, five patients did not experience radiological improvement of the lesions after tocilizumab administration (71.42%). No serious adverse effects were observed during treatment.

DISCUSSION

Nearly three-quarters (72.7%) of the patients in this study died. This mortality rate is much higher than that reported in a similar, recently published case series (44 %). In that case series, patients received tocilizumab with a mean of seven days post-hospitalisation and often at the peak of their critical condition (McKenzie et al., 2022).

In this study, patients who recovered received tocilizumab within a median of two days from admission to the ICU, in contrast to 4.5 days in patients who died. Although tocilizumab was administered earlier in this study, other factors that we have not yet identified may have influenced the high mortality rate. A recent case series suggested that age >60 years was a risk factor and predictor of poor clinical outcomes.(McKenzie et al., 2022) However, this study found the opposite result. The median age of the patients who recovered was 66 years, while that of those who died was 56. One of the factors that may have increased the risk of death in this study is that more than half of the patients who died (66.7%) had comorbidities (hypertension, type 2 diabetes mellitus, and obesity). Previous studies seem to found that increasing age and comorbidities are consistently associated with poor severe COVID-19 clinical outcomes (CDC COVID-19 Response Team, 2020; Onder et al., 2020).

This case series had several limitations. Besides the nature of a retrospective descriptive study design, frontline physicians were the ones making decisions during treatment; therefore, many variables could not be controlled. Moreover, observations were made within a short period, focusing on 24 hours before and after tocilizumab administration. It is difficult to determine whether the resulting recovery was the effect of tocilizumab independently, bearing in mind that all patients received steroids as the standard management of severe COVID-19 in Indonesia, and no control group was used for comparison. Because of the limitations in assessing IL-6 levels, this study relied on CRP, LDH, and ferritin levels as markers of cytokine storm. Despite that, using CRP in this study is appropriate because previous studies have shown a positive correlation between IL-6 and CRP with the severity and clinical outcome of COVID-19. Reflecting on this case series, this study showed that not every patient with severe COVID-19 benefited from tocilizumab administration. Patient selection criteria and the timing of tocilizumab administration are the most critical foundations for achieving maximum benefits, which remains a difficult challenge for most physicians.

CONCLUSION

This study found a high mortality rate in severe COVID-19 despite tocilizumab administration. Although the administration of tocilizumab was found to be safe in this study, further research is needed to determine the appropriate patient selection criteria and best timing of its administration.

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