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RESEARCH ARTICLE

Tocilizumab therapy in COVID-19 patients

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Abstract

A severe pneumonia-associated respiratory syndrome caused by the new coronavirus 2 (SARS-CoV-2) was identified in December 2019 as Coronavirus Disease 2019 (COVID-19). It has spread rapidly and has become a worldwide health challenge. Some patients experienced severe complications, including acute respiratory distress syndrome (ARDS), and have even progressed to an intensive care unit (ICU) admission and death. Research has reported that pathogenic T cells and inflammatory monocytes prompt an inflammatory storm with large amounts of interleukin 6. Consequently, IL-6 receptor inhibitors have been repurposed to treat COVID-19, but their exact role in treatment remains unclear. Tocilizumab (TCZ), a monoclonal antibody against IL-6, emerged as an alternative treatment in COVID-19 patients with ARDS syndrome. Therefore, the authors hypothesise that tocilizumab might be effective in decreasing the inflammatory storm and reducing mortality in COVID-19 severe cases. This observational retrospective study explored the use of a single dose of tocilizumab 400 mg intravenous infusion for an hour in COVID-19 patients. The results showed that tocilizumab could not improve the parameters related to mortality rates, such as IL-6 levels, leukocytes, C-reactive protein (CRP), Neutrophil-to-lymphocyte ratio (NLR), and ferritin. IL-6 levels increased after tocilizumab administration.

Introduction

COVID-19 characterised by pneumonia-like symptoms was first discovered in Wuhan City, Hubei Province, China, in mid-December 2019. The infection caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) activates the immune system to produce cytokines (pro-inflammatory and anti-inflammatory) and chemokines. In some severe and critical cases, cytokine hyperproduction (termed cytokine storm) occurs, causing an aggressive immune response that will lead to attacks on the surrounding healthy alveolar cells (Bhaskar *et al.,* 2020). In this condition, immune cell regulation is often damaged, resulting in increased inflammatory cytokines production that can trigger acute respiratory distress syndrome (ARDS), leading to multiorgan damage and increased risk of death (Mortaz *et al.,* 2020). Several cytokines and chemokines are involved in the cytokine storm, but IL-6 has the most prominent role in cytokine release syndrome (CRS). Indeed, higher IL-6 levels were found in deceased patients, indicating IL-6 association with disease severity and higher mortality rates (Kim *et al.,* 2020; Fajgenbaum and June, 2020). Hence, the use of IL-6 receptor inhibitors, such as tocilizumab (TCZ), a recombinant human monoclonal antibody, is expected to be effective in COVID-19 patients with ARDS complications (Tanaka *et al.,* 2013).

Aim

This study aimed to explore the use of tocilizumab in COVID-19 patients, associated laboratory data (IL-6 levels, leucocytes, Neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), and ferritin), and therapeutic outcomes (mortality rate and clinical outcomes).

Methods

This observational retrospective study was conducted between June 2020-February 2021 among a sample of 30 COVID-19 inpatients (with or without comorbidities) who received 400 mg single-dose TCZ by intravenous infusion and had complete IL-6 data. Clinical laboratory

parameters, including IL-6 levels, leukocytes, NLR, CRP, procalcitonin, and ferritin, were collected and analysed descriptively. This study was approved by the Research Ethics Commission of Airlangga University Teaching Hospital and was declared "*Ethically Eligible*".

Results

Most patients were males and belonged to the elderly age category (more than 65 years). The three most common comorbidities were diabetes mellitus, hypertension, and acute kidney injury (AKI). Of the total sample, 50% were in critical condition and admitted to the ICU with a ventilator. Furthermore, 11 (36.67%) patients had severe disease, and only four (13.0%) patients had a moderate condition. Patients admitted to the ICU with ventilators had the shortest average length of stay (12.0 ± 4.40 days, ranging from 5-23 days) due to death before finally therapy.

Table I shows parameter values before and after TCZ administration. Regarding IL-6, it varied between 155 pg/ml and 275 pg/ml on average. The leukocyte value was already high (leukocytosis) before TCZ administration, indicating a severe infectious condition supported by increased procalcitonin, up to 20-fold upper limit normal (ULN). In non-ventilated and non-ICU patients, the average leukocyte value increased slightly but was still in the normal range. Among non-ICU patients, one showed an increase in NLR of 4.5 times; this patient had a worsening condition and was transferred to the ICU. Based on the data, patients had a mean baseline CRP value making them eligible for TCZ administration. In this study, the CRP value did not consistently increase or decrease after TCZ administration, likely due to considerable data variations. In general, this parameter is only used for inflammatory or infectious conditions and is not specific for COVID-19.

Table I: Laboratory profile of COVID-19 patients receiving Tocilizumab

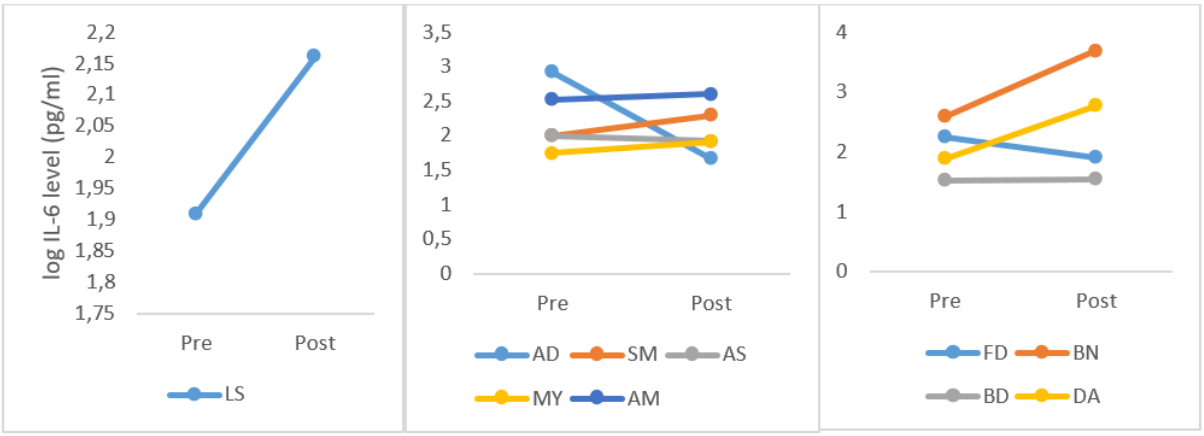
Parameters	Non ICU		ICU non-ventilator		ICU ventilator	
	Pre	Post	Pre	Post	Pre	Post
Interleukin-6 (≤7 pg/ml)	155.74 ± 151.88 (n=3)	207.85 ± 166.89 (n=3)	275.54 ± 368.11 (n=4)	228.12 ± 248.90 (n=4)	198.51 ± 176.91 (n=3)	1705.54 ± 2853.17 (n=3)
Leucocyte (5-10 x 10^3/µL)	3.44 (n=1)	6.75 (n=1)	8.16 ± 4.37 (n=11)	8.72 ± 1.61 (n=11)	13.48 ± 9.82 (n=14)	21.81 ± 13.22 (n=14)
NLR	1.42 (n=1)	6.53 (n=1)	10.82 ± 11.29 (n=9)	5.63 ± 5.08 (n=9)	10.35 ± 7.82 (n=13)	23.29 ± 23.89 (n=13)
CRP (<10 mg/L)	58.95 ± 42.94 (n=2)	77.21 ± 88.41 (n=2)	63.51 ± 45.47 (n=9)	43.85 ± 53.28 (n=9)	69.69 ± 47.17 (n=8)	43.17 ± 47.43 (n=8)
Procalcitonin (<0,5 µg/mL)	0.105 ± 0.08 (n=2)	0.05 ± 0.0 (n=2)	0.54 ± 0.81 (n=10)	0.22 ± 0.44 (n=10)	1.73 ± 4.30 (n=10)	26.90 ± 62.66 (n=10)
Ferritin (10-300 ng/mL)	NA	NA	1020.96 ± 535.21 (n=5)	1675.04 ± 1295 (n=5)	1203.83 ± 648.38 (n=7)	1156.36 ± 669.48 (n=7)

The initial ferritin level before TCZ administration was about 4-fold Upper Limit of Normal (ULN) and increased by 1.6-fold ULN in non-ventilated ICU patients, indicating the presence of a viral infection and replication in patients (Figure 1). Based on the results of radiological data, 30 patients (100.0%) showed COVID-19 pneumonia. As many as five patients had bacterial cultures after TCZ administration, with the following results: 80% were *Acinetobacter baumannii,* and 20% were *Pseudomonas aeruginosa* cultures. Additionally, 10% of patients had no bacterial growth.

Table II displays the effect of corticosteroid therapy and convalescent plasma (CP) as a supportive therapy along with TCZ on changes in IL-6 values. This combination showed better outcomes in non-ventilated ICU patients with decreased IL-6 levels and improved outcome therapy.

Discussion

The nonlinear dose-dependent pharmacokinetic profile and the long elimination half-life (±13 days) of TCZ were the basis for administering it once every four weeks (Oldfield *et al*., 2009). According to Nishimoto and colleagues (2009), the administration of TCZ will increase IL-6 levels in the serum to reach the peak within 14 days, then a steady state until day 42. Therefore, the right time for sampling and determining IL-6 levels required caution. Table I shows that IL-6 values tended to increase until patient discharge. At the end of treatment, 80% of patients had abnormal IL-6 levels. The length of treatment for patients ranged from 12-16 days, showing that IL-6 levels reached a steady state. This result aligns with that of Nishimoto and colleagues (2008), stating that IL-6 levels would return to normal (<35 pg/mL) within 24 weeks (168 days) (Nishimoto *et al*., 2008).



(A) moderate grade (Non-ICU) (B) severe grade (ICU no ventilator) (C) critical grade (ICU with ventilator)

Figure 1: Profile of IL-6 levels in COVID-19 patients receiving tocilizumab

Table II: Effects of corticosteroids and convalescent plasma

Classification	Therapy	n	IL-6		Clinical outcomes
Non ICU (n=3)	Corticosteroid + CP	2	330.57 80.37	397 145.2	↑, survived
	Corticosteroid	1	56.29	81.35	↑, survived
ICU non ventilator (n=4)	Corticosteroid + CP	2	827.5 99.92	44.9 83.99	↓, survived
	Corticosteroid	2	77.34 97.41	589.2 194.4	↑, 1 died and 1 survived
ICU with ventilator (n=3)	Corticosteroid + CP	2	176.5 33.63	81.1 35.33	↓, died ↑, died
	Corticosteroid	1	385.4	>5000	↑, died

According to the Indonesian Pulmonary Doctors Association Guidelines (PDPI, 2020), TCZ should be given when the patient is in the early stage of inflammation, characterised by the following: oxygen saturation <93% or respiratory rate >30 per minute or chest X-ray with bilateral multilobar infiltrates, one of the biologic markers, i.e., D-dimer level 0.7 g/L, IL-6 40 pg/mL, lymphocytes < 800 × 10^9/L, ferritin ≥ 700 g/L, fibrinogen > 700 mg/dL, CRP > 25 mg/L (PDPI, 2020), and patients requiring mechanical ventilation support (Cortegiani *et al*., 2021). In this study, all patients met the above criteria. Our results showed that IL-6 levels tended to increase after TCZ use. Patients with baseline IL-6 levels higher than the normal value tended to have a poor prognosis (Stone *et al*., 2020). As many as 10% of patients admitted to the ICU with ventilation experienced increased IL-6 levels of ± 12.5 times the initial value. Although IL-6 values tended to increase, the average IL-6 levels in ICU non-ventilated patients showed a decrease. However, these data could not be used as a reference because one ICU non-ventilated patient experienced a drastic decrease of up to 18 times the initial value of 827.5 pg/ml and then decreased to 44.9 pg/ml within ten days after TCZ use. IL-6 levels were specific to each patient according to their immune system. In patients thought to have a very good immune system, the progression of the disease was very slow. The pharmacokinetics and pharmacodynamics of TCZ varied widely; thus, its effects on patients differed individually (Kukar *et al*., 2009). Therefore, several findings related to the use of TCZ in COVID-19 patients are still controversial.

A study reported an increase in serum IL-6 levels after TCZ use due to the inhibition of the IL-6R receptor by TCZ (Xu *et al*., 2020). This blockade due to TCZ and IL-6R binding impedes IL-6 clearance (Nishimoto *et al*., 2008) and leads to its accumulation in the serum, thus explaining increased IL-6 levels in COVID-19 patients treated with TCZ (Luo *et al*., 2020). Also, IL-6 levels in ICU patients with ventilation were high.

In this study, 57% of patients showed insufficient clinical improvement, and TCZ did not reduce the need for mechanical ventilation. Several factors can explain this result, including the inappropriate timing of TCZ use that would determine the success of therapy.

Therefore, TCZ should be given at the early onset of systemic pulmonary inflammation (PDPI, 2020). The improvement of therapeutic outcomes and hospital discharge after TCZ use were 100% in non-ICU patients and 75% in ICU non-ventilated patients. This result can be considered as the right time for TCZ therapy. The total number of patients who had clinical improvement was 60% (in non-ICU and ICU non-ventilated patients). The mortality rate of patients in ICU with ventilation reached 100.0%, indicating that TCZ use has not been able to reduce the IL-6 storm.

Other inflammatory parameters such as leukocytes, NLR, CRP, and ferritin showed high values after TCZ use, indicating that the hyperinflammatory process still occurred in COVID-19 patients. Corticosteroids and convalescent plasma may produce better outcomes if given to ICU non-ventilated patients, as shown in Table II.

Conclusions

This study showed that tocilizumab could not improve the parameters related to mortality rates, such as IL-6 levels, leukocytes, CRP, NLR, and ferritin. IL-6 levels increased after tocilizumab administration. This parameter is associated with high mortality rates.

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