The Importance of the Timing of Tocilizumab Administration in Moderate to Severely Ill COVID-19: Single Centered Experience Case series

Eric Daniel Tenda[1], Setiabakti Andrian[2], Sedjahtera Albert[2], Moses M. Asaf[1], Ceva W. Pitoyo[1], Siti Setiati[3], Imam Subekti[4]

[1] Division of Respirology and Critical Illness, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[2] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[3] Division of Geriatric Medicine, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - CEEBM Cipto Mangunkusumo Hospital, Jakarta, Indonesia.
[4] Division of Endocrine Metabolic and Diabetes, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - COVID-19 Board Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Corresponding Author:
Eric Daniel Tenda, MD., PhD. Division of Respirology and Critical Care, Department of Internal Medicine, Faculty of Medicine Universitas Indonesia - Cipto Mangunkusumo Hospital. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. Email: eric.tenda@ui.ac.id.

ABSTRAK

Salah satu penyebab utama kematian pada COVID-19 adalah disregulasi sistem kekebalan tubuh yang menyebabkan badai sitokin, sindrom inflamasi sistemik yang berpotensi fatal. Interleukin 6 (IL-6) adalah sitokin pro-inflamasi yang diproduksi sebagai respons terhadap infeksi dan cedera jaringan dan diyakini memainkan peran penting dalam peristiwa badai sitokin, yang ditandai oleh peningkatannya dalam proses tersebut. Dengan pertimbangan peran IL-6 sebagai sitokin pro-inflamasi dalam proses badai sitokin pada COVID-19, melihat IL-6 sebagai target terapeutik sangat mungkin. Tocilizumab adalah antibodi monoklonal yang secara kompetitif menghambat pengikatan IL-6 ke reseptornya (IL-6R). Penggunaan IL-6R blocker direkomendasikan untuk pasien COVID-19 derajat berat dalam pedoman terapi terbaru yang diterbitkan oleh Organisasi Kesehatan Dunia (WHO), tetapi waktu pemberiannya belum ditentukan. Sementara, beberapa penelitian sebelumnya tentang penggunaan tocilizumab pada pasien COVID-19 menunjukkan hasil yang beragam serta belum merujuk pada kadar IL-6 plasma tertentu untuk memutuskan waktu pemberian tocilizumab. Dalam rangkaian kasus ini, kami menyajikan tiga pasien dengan infeksi COVID-19 sedang hingga berat yang menerima tocilizumab sebagai tambahan untuk terapi perawatan standar. Seri kasus ini memperkenalkan gagasan baru bahwa penggunaan tocilizumab tepat waktu sebagaimana ditandai oleh kadar IL-6 plasma pada pasien COVID-19 sedang hingga berat berpotensi meningkatkan kondisi klinis secara keseluruhan dan meningkatkan tingkat kelangsungan hidup.

Kata kunci: *case series, COVID-19, interleukin-6, timely, tocilizumab.*

ABSTRACT

One of the main causes of death in COVID-19 is the dysregulation of the host's immune system which leads to cytokine storm, a potentially fatal systemic inflammatory syndrome. Interleukin 6 (IL-6) is a pro-inflammatory

cytokine that is produced in response to infections and tissue injuries and is believed to play a pivotal role in the event of a cytokine storm, as signified by its increase in the process. Considering the role of IL-6 as a pro-inflammatory cytokine in the process of cytokine storm in COVID-19, perceiving IL-6 as a therapeutic target could prove to be promising. Tocilizumab is a monoclonal antibody that competitively inhibits the binding of IL-6 to its receptor (IL-6R). The use of IL-6R blocker is recommended for severe COVID-19 patients in the latest therapeutic guideline published by the World Health Organization (WHO), but the timing of the administration has not been specified. While previous studies about the use of tocilizumab in COVID-19 patients have shown various results, these studies do not emphasize on plasma IL-6 levels when deciding the time of tocilizumab administration. In this case series, we present three patients with moderate to severe COVID-19 infections that receive tocilizumab as an adjunct to the standard of care therapy. This case series introduces the novel idea that the timely use of tocilizumab as signified by plasma IL-6 levels in moderate to severe COVID-19 patients could potentially improve overall clinical condition and increase survival rate.

Keywords: *case series, COVID-19, interleukin-6, timely, tocilizumab.*

INTRODUCTION

COVID-19 infected patients exhibit initial phase of viral replication followed by host driven immune response which sometimes leads to acute respiratory distress syndrome (ARDS) due to the dysregulation of immune system. Dysregulation of immune system during the infection may lead to a cytokine storm, as signified by increased levels of pro-inflammatory cytokines, such as IL-6.[1] IL-6 is a pro-inflammatory cytokine that is produced in response to acute environmental stress, such as infections and tissue injuries.[2] IL-6 also induces haemostasis and coagulation, increases vascular permeability, which could lead to pulmonary damage and ARDS.[3] A publication by Coapescu et al. has suggested that an increase in IL-6 in SARS-CoV-2 infection is synonymous with increased disease severity that translates into sepsis, ARDS/mechanical ventilation, and mortality. Hence, seeing IL-6 as a therapeutic target for SARS-CoV-2 infection is highly plausible and a possibility worth studying.[4] Tocilizumab is an IL-6 antagonist, primarily applied in autoimmune diseases such as rheumatoid arthritis. Cytokine-directed therapy has recently been proposed especially in critically ill COVID-19 patients in order to preserve organ functions amidst the inflammation storm. One recent open-label random clinical trial on IL-6 receptor (IL-6R) antagonist shows promising results in severe cases of COVID-19 in adjunction with the standard care of therapy.[5] Studies from China reported that the use of IL-6 antagonists in COVID-19 patients resulted in the resolution of fever and hypoxemia, and subsequent improvements in serum CRP levels and CT findings.[6] The widely used COVID-19 management guideline in Indonesia that was published in December 2020 included the usage of tocilizumab in COVID-19 once the standard regimen therapy does not show clinical improvement.[7] It is recommended to use IL-6R blockers at the earliest signs of clinical deterioration or at the earliest indication of clinical transition into severe COVID-19, which usually happens around after the first week of infection.[8] Moreover, in World Health Organization's (WHO) latest COVID-19 therapeutic guideline, the use of tocilizumab and sarilumab as IL-6 receptor blockers are strongly recommended in severe and critical COVID.[9] However, the WHO guideline did not specify the recommended timing for the administration of IL-6R blockers. This absence of information is what prompted the authors to write this manuscript and is the main point of discussion of this case series. The concept that the use of IL-6R blockers in a specific period of time (as signified by plasma IL-6 levels) could potentially increase its efficacy in treating moderate to severe COVID-19 patients is the main novelty of this case series. The inclusion criteria in this case series include: patients positive for COVID-19 infection as diagnosed by SARS-CoV-2 RT-PCR, moderate to severe COVID-19 patients as classified by the COVID-19 management guideline in Indonesia, and patients that have consensually agreed to be featured in this research. In this case series, we

present the successful timely use of tocilizumab in the management of moderate to severe COVID-19 patients.

CASE ILLUSTRATIONS

Case 1

A 61-year-old male patient was admitted to hospital with an initial complaint of fever that started four days prior to hospital admission. Additional complaints included unproductive cough, shortness of breath and fatigue. The patient also had a comorbidity of controlled hypertension. COVID-19 diagnosis was confirmed based on the positive SARS-CoV-2 RT-PCR done on January 6th, 2020. Physical examination on admission showed a body temperature of 38.3^{0}C, a heart rate of 111x/min, a respiration rate of 20x/min with bilateral rhales more prominent at the base of the lungs, a peripheral oxygen saturation measurement of 94% on room air. Favipiravir was given on admission as part of the initial treatment along with the standard of care therapy. Breathing difficulty worsened on the 3rd day of hospitalization (7th day of symptoms' onset) with peripheral saturation of 88% in room air, which increased to 97% with supplemental oxygen delivered through non-rebreathing mask at 11 lpm. On the 4th day of hospitalization (8th day of symptoms' onset), remdesivir was given as a replacement for favipiravir as there was no observable clinical improvement and an intravenous antiviral was deemed necessary by the primary physician, along with the addition of intravenous dexamethasone. After 10 days of intravenous remdesivir and dexamethasone administration, the patient's condition plateaued and there was still no observable clinical improvement. Blood gas analysis on the 14th day (18th day of symptoms' onset) of hospitalization showed acute respiratory distress syndrome and blood test showed elevated inflammatory markers. Empirical antibiotics of cefepime 1 g tid and levofloxacin 750 mg qd were started on 14th day of hospitalization while waiting for sputum culture. Thorax CT-scan on the 14th day of hospitalization showed multifocal ground glass opacity with crazy paving and thickening of the interlobular septae. IL-6 was found to be elevated to 118.70 pg/mL on the 16th day of hospitalization (20th day of symptoms' onset) and the sputum culture was found to be sterile. The patient was then admitted into intensive care unit on the 16th day of hospitalization and supplemental oxygenation was changed to high-flow nasal cannula with an FiO2 of 80% and a flow of 50 lpm. The patient received plasma convalescent therapy of 200 mL per day on the 15th and 16th day of hospital care, and tocilizumab 400 mg qd single dose was given on the 18th day of hospitalization (22nd day of symptoms' onset). The patient was weaned for oxygen and supplemental oxygen delivery was changed back to non-rebreathing mask on the 20th day of hospitalization (24th day of symptoms' onset) and the patient was subsequently discharged from the ICU. On the 23rd day of hospitalization (27th day of symptoms' onset), SARS-CoV-2 RT-PCR was found to be negative and the patient was admitted into the general ward. A follow-up thorax CT-scan was done, and the result showed decreased ground glass opacities and the development of fibrosis of the lungs. After five days of hospitalization in the general ward, the patient was then discharged and scheduled for outpatient control.

Case 2

A 69-year-old male patient complained shortness of breath six days prior to hospital admission. Additional complaints included unproductive cough and fatigue. The patient had a medical history of valvular heart disease and a comorbidity of controlled hypertension. Physical examination on admission showed an oxygen saturation of 93% on room air with a respiration rate of 22x/min, a heart rate of 114x/min, and a temperature of 37.1^{0}C. Chest X-ray performed on admission showed inhomogeneous opacity in the right lung. Initially, the patient was treated with remdesevir 200 mg qd, subsequently adjusted to 100 mg qd for 10 days, ceftriaxone 2 g qd, levofloxacin 750 mg qd along with the standard of care therapy. On the 3rd day of hospitalization (9th day of symptoms' onset), the patient's breathing difficulty worsened and the patient subsequently experienced septic shock,

with blood pressure dropping to 69/46 mmHg, procalcitonin was also found to be elevated to 0.86 ng/mL. Antibiotic was escalated to meropenem 2 g tid IV while norepinephrine was initiated. IL-6 value was found to be elevated to 134.4 pg/mL on the 8th of hospitalization (14th day of symptoms' onset), and tocilizumab 400 mg qd single dose was given subsequently. The patient's condition improved clinically (MAP >65 mmHg, RR 22x/min, SpO2 99% with supplemental oxygen delivered through nasal cannula at 3 lpm) and norepinephrine was stopped on the 10th day of hospitalization (16th day of symptoms' onset). Blood test showed that IL-6 level had decreased to 31.28 pg/mL on the 4th day after tocilizumab administration. After the administration of tocilizumab, the patient's clinical condition improved progressively. Patient was then discharged from the hospital after 30 days of hospitalization.

Case 3

A 35-year-old male patient complained shortness of breath followed by cough, high fever, and fatigue three days prior to hospital admission. Based on the SARS-CoV-2 RT-PCR result, the patient was confirmed positive for COVID-19 one day before admission, and chest radiograph showed heterogeneous opacity on the basal region of the right lung. Upon admission, the physical examination showed the patient had a breathing rate of 20x/min with peripheral oxygen saturation of 98% on room air, a heart rate of 89x/min, and a temperature of 41.0^{0}C. The patient was given the standard of care until day five of hospitalization. On the 5th day of hospitalization (8th day of symptoms' onset), the patient's oxygen saturation decreased to 93% on room air with a respiratory rate of 24-26x/min. Laboratory examination showed that IL-6 serum level was significantly elevated to 141.9 pg/mL. The patient was then given tocilizumab 400 mg qd single dose and dexamethasone 4 mg tid. On day six of hospitalization (9th day

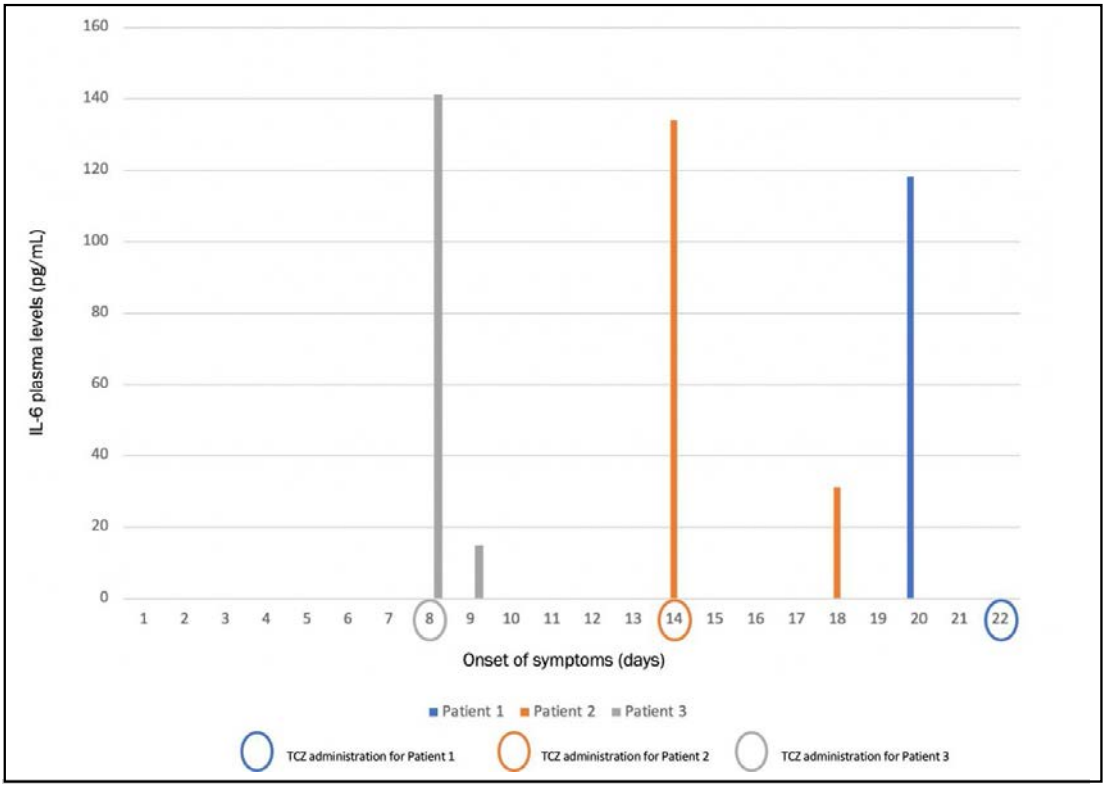

Figure 1. Bar graph showing the timeline of each patient's respective IL-6 levels and the timing of tocilizumab administration.

of symptoms' onset) and a day post tocilizumab administration, blood tests showed that IL-6 level was significantly lower at 14.97 pg/mL, with a simultaneous decrease in CRP. On day eight of hospitalization, evaluation of chest radiograph showed multiple heterogeneous opacities in both lungs. On day 11 of hospitalization, repeated SARS-CoV-2 RT-PCR came out negative, and the patient was subsequently discharged on the same day.

DISCUSSION

In this case report, we'd like to present the timely and selected use of tocilizumab in three patients with moderate-to-severely ill cases of COVID-19. All patients in this case report were given a standard therapy of remdesivir, prophylactic anticoagulant, azithromycin, dexamethasone, vitamin C, vitamin D and supportive oxygen supplementation. All patients consensually agreed to be subjects in this case report. Studies have shown that COVID-19 patients that were admitted to ICU showed higher plasma levels of inflammatory cytokines such as IL-6.[10, 11] Recent clinical trial data, however, resulted in mixed conclusions on the efficacy of tocilizumab in COVID-19 patients. Study done by Xu et al. in China suggested that tocilizumab administration to severely ill patients with elevated IL-6 resulted in better clinical symptoms such as reduced oxygen supplementation exigency and fever, as well as reduction in inflammatory markers such as procalcitonin and C-reactive protein (CRP).[12] Interestingly, the level of IL-6 did not decrease even after clinical symptoms improved.[12] Other studies, such as one done by Stone et al., concluded that tocilizumab failed in preventing intubation or death in COVID-19 patient when compared to placebo, although the level of IL-6 in the patient recruited in their study did not show high level of IL-6, unlike the levels of IL-6 found in our cases.[13] Some studies suggested that a cut-off value of 80 pg/mL was a good predictor for poorer prognosis in the patient,[14-16] Tocilizumab monoclonal antibody that competitively inhibits the binding between IL-6 and its receptor (IL-6R). Inhibiting the entire receptor complex will inhibit the subsequent inflammatory cascade due to IL-6 signal transduction. Measurement of IL-6 level before and after administration of tocilizumab is a prognostic factor of disease progression as it represents the level of inflammation in patients and the subsequent outcomes of the patients.[17] The timely introduction of tocilizumab as indicated by high IL-6 serum levels is crucial, as one observational study by Galván-Román et al. found that only those with high IL-6 levels (IL-6 cut-off of 30 pg/mL) with early introduction of tocilizumab showed clinical benefits in terms of PaO2/FiO2 ratio increase and survival rate, while patients with low IL-6 did not show improvement in their PaO2/FiO2 ratio nor increased survival rate after treatment with tocilizumab.[18] Another possible biomarker analogue of IL-6 that could potentially be used to validate the use of tocilizumab in COVID-19 patients is CRP, as the liver-produced CRP is induced primarily by plasma IL-6.[19] The preliminary results of the RECOVERY trial - a multicentre, randomised, controlled, open-label, platform trial which recruited more than 27,000 hospitalized adult patients with clinically suspected or confirmed COVID-19 - has shown that the efficacy of tocilizumab in severely ill COVID-19 patients (as shown by CRP levels of ≥75 mg/L) is significant and worth using.[20] Instead of overall condition improvement, the premature use of IL-6 antagonist could prove to be harmful as the extensive obstruction of IL-6 receptor simultaneously impedes α1-antitrypsin (AAT), which in turn could cause airway inflammation and lung tissue damage.[19] In our case series, all three patients' IL-6 serum levels exceeded both proposed cut-off of 30 pg/mL and 80 pg/mL by some studies, as it was also the hospital's therapeutic policy to administer tocilizumab using an IL-6 cut-off of 40 pg/mL in patients who are unresponsive to systemic corticosteroid therapy as signified by their oxygen demand and need for oxygen support. All three patients improved clinically post tocilizumab administration. However, it should be kept in mind that for the first patient, plasma convalescent was administered three days prior to tocilizumab administration and could act as a confounding factor to the patient's overall clinical improvement. COVID-19

infection might trigger inflammatory cytokines dysregulation and cause worsening clinical symptoms. IL-6 is one such pro-inflammatory cytokines that is responsible for the cytokine dysregulation. Tocilizumab as an IL-6 receptor blocker shows promising result, as shown in this case series when given at the correct time in patients with high serum levels of IL-6. Moreover, data from RECOVERY and REMAP-CAP trials have shown that the introduction of tocilizumab was beneficial, especially when given in adjunction with corticosteroid administration in patients with deterioration of clinical symptoms, usually accompanied by the increase in IL-6 and CRP levels.[5,20] The use of tocilizumab as recommended in this manuscript is also supported by WHO's latest therapeutic guideline (6 July 2021) which strongly recommends the use of IL-6R blockers (tocilizumab and sarilumab) in severe and critical COVID-19 patients in conjunction with systemic corticosteroids.[9] This recommendation was made based on the evidence that the use of IL-6R blockers in such patients reduces mortality (OR=0.86, 95% CI 0.79-0.95) and the need for invasive mechanical ventilation (OR=0.72, 95% CI 0.57-0.90) significantly.[21,22] Although the timing of administration has not been specified by the WHO, using plasma levels of IL-6 and CRP as reference for administration should be contemplated based on prior findings.

CONCLUSION

Based on our case series we see that the timely use of tocilizumab could prove useful in moderate to severe COVID-19 patients. The definition of timely in our case series refers to the plasma biomarker levels, specifically IL-6 plasma levels, as the administration of tocilizumab in all three of our cases differ in days of symptom's onset, yet all three patients showed clinical improvements. We suggest that further studies should emphasize on the IL-6 reference levels and CRP levels for tocilizumab administration.

STATEMENT OF ETHICS

All patients in this case series have given their written informed consent for this article to be published.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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AUTHOR CONTRIBUTIONS

Writers contribute equally in the preparation of the manuscript.

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