Tocilizumab as a Treatment for 'Cytokine Storm Syndrome' in COVID-19: A Case Report

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ABSTRAK

Coronavirus disease 19 (COVID-19) yang disebabkan oleh Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), saat ini tengah menjadi permasalahan di dunia, terutama karena tingginya kecepatan transmisi dan manifestasi klinis yang beragam. Acute respiratory distress syndrome (ARDS) dan kegagalan multiorgan merupakan kejadian tersering yang ditemukan pada kasus berat COVID-19. Laporan kasus ini mendeskripsikan seorang pasien berusia 53 tahun yang didiagnosis dengan COVID-19. Evaluasi lebih lanjut dari pasien ini menunjukkan adanya peningkatan bermakna kadar IL-6 dalam darah disertai dengan hiperferitinemia, yang sesuai dengan karakteristik sindrom badai sitokin. Pasien diterapi dengan tocilizumah, sebuah antibodi monoklonal dan antagonis reseptor IL-6. Ikatan antara tocilizumab dan IL-6 secara efektif menghambat dan menangani sindrom badai sitokin. Meskipun laporan kasus ini melaporkan efektivitas tocilizumab dalam tata laksana sindrom badai sitokin, tocilizumab juga diketahui memiliki berbagai efek samping yang perlu dipantau secara ketat selama

pengobatan. Diperlukan uji klinis terkendali untuk mengevaluasi efektivitas dan keamanan pemberian tocilizumab pada subjek dengan karakteristik klinis yang bervariasi dan dengan jumlah subjek yang lebih banyak.

Kata kunci: *COVID-19, SARS-CoV-2, acute respiratory distress syndrome (ARDS), Tocilizumab.*

ABSTRACT

Coronavirus disease 19 (COVID-19) which is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has been a problem worldwide, particularly due to the high rate of transmission and wide range of clinical manifestations. Acute respiratory distress syndrome (ARDS) and multiorgan failure are the most common events observed in severe cases and can be fatal. Cytokine storm syndrome emerges as one of the possibilities for the development of ARDS and multiorgan failure in severe cases of COVID-19. This case report describes a case of a 53-year-old male patient who has been diagnosed with COVID-19. Further evaluation in this patient showed that there was a marked increase in IL-6 level in blood accompanied with hyperferritinemia, which was in accordance with the characteristic of cytokine storm syndrome. Patient was treated with tocilizumab, a monoclonal antibody and is an antagonist to IL-6 receptor. The binding between tocilizumab and IL-6 receptors effectively inhibit and manage cytokine storm syndrome. Although this case report reported the efficacy of tocilizumab in managing cytokine storm syndrome, tocilizumab has several adverse effects requiring close monitoring. Further clinical randomized control trial is required to evaluate the efficacy and safety of tocilizumab administration in participants with various clinical characteristics and greater number of subjects.

Keywords: *COVID-19, SARS-CoV-2, acute respiratory distress syndrome (ARDS), Tocilizumab.*

INTRODUCTION

Coronavirus disease 19 (COVID-19) which is caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), until now has been a problem worldwide. The high rate of transmission in COVID-19 causes the disease difficult to control. COVID-19 was first found in December 2019 and by 15th December 2020 this disease has caused 1,618,374 mortality worldwide.[1] Although most cases cause mild clinical manifestation, some cases may cause severe clinical manifestation and death. Acute respiratory distress syndrome (ARDS) and multiorgan failure are the most common events found in severe cases and become the cause of death in most cases.

Until recently, cytokine storm syndrome emerges as one of the possibilities for the development of ARDS and multiorgan failure in patients with COVID-19.[2] Cytokine storm syndrome is a systemic inflammatory response that can be instigated by many factors, including infection and medications. Cytokine storm syndrome can be found in disease with disruption of immune system or immune related therapy, such as chimeric antigen receptor (CAR) T cell therapy, and viral infection.[3] A study which was performed by Huang et al found that in critically ill COVID-19 patients, there was an increase in proinflammatory cytokine concentration, such as IL-6, IL-10, IL-7, IL-2 and IFN-γ.[4] IL-6 itself has an important role in inflammatory reaction and immune response. Based on the previous study, it is known that IL-6 is the most important cytokine in the occurrence of cytokine storm syndrome in COVID-19. Therefore, tocilizumab (TCZ) which is a humanize antibody to IL-6 receptor was considered as a treatment in severe cases of COVID-19 to decrease mortality rate.[5] In this article, we reported a COVID-19 case who experienced cytokine storm syndrome, prompting tocilizumab as a therapeutic option.

CASE ILLUSTRATION

A male patient, 53-year-old, was admitted with the chief complaint of fever in the past 1 week prior to hospital admission. Fever was felt intermittently. The patient also complained of muscle and joint pain. He also complained of pain in the lower right and left abdomen, accompanied with diarrhea 1 time/day. There was sore throat and mild dry cough which occurred

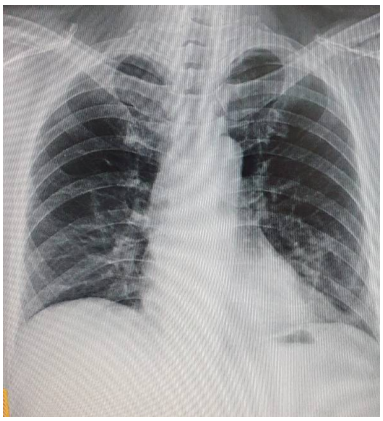

Figure 1. Chest X-ray, one day before admission. Result showing signs of pneumonia.

after 3 days. Complain of breathing difficulty was denied. On the third day of fever, patient underwent blood examination in the laboratory for dengue serology examination and obtained a negative result. Due to the persistent fever although without diarrhea, the patient underwent another blood test and chest x-ray. The results of chest x-ray examination showed signs of pneumonia (**Figure 1**). Chest CT revealed ground glass appearance (GGO), multifocal subpleural and fibro-parenchymal opacity in both lungs. He was further hospitalized.

Upon admission to the hospital, the patient was diagnosed as patient under surveillance of COVID-19. History of hypertension, diabetes, or cardiac disease was denied. History of allergy and other chronic disease was also denied. There was no other family member complaining similar symptoms. Physical and vital signs examination revealed that the patient was stable and there was no abnormality in general examination. Patient

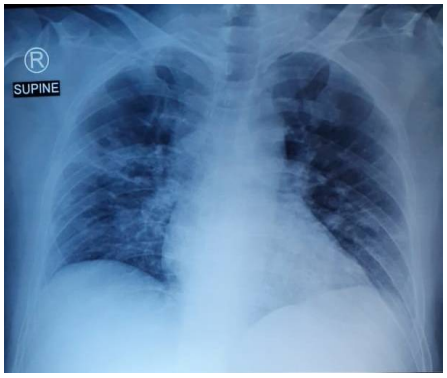

Figure 2. Chest X-ray, Day 4 admission. Result showing worsening signs of pneumonia.

was then hospitalized in isolation room.

During hospitalization, patient complained of intermittent fever. In the first three days of hospitalization, patient was afebrile. On day 4 of hospitalization, he felt intermittent fever for 4 days, with the highest recorded temperature was 38.9 ^{0}C. The patient also started to suffer from dry cough and occasional breathing difficulty particularly after physical activity, supported by the worsening of patient chest x-ray (**Figure 2**). Cough was usually felt after position changes, sometimes cough was accompanied with or without sputum. On hospitalization day-8, week-3 after the onset of fever, patient continuously had fever, body ache, and sleeping difficulty. During hospitalization, the patient did not have any gastrointestinal symptoms. Until hospitalization day-12, the fever condition was still intermittent, accompanied by cough and shortness of breath, but oxygen saturation was adequate with oxygen supplementation through nasal cannula 4-5 liter. Without oxygen supplementation, his oxygen saturation was 90-91%. However, based on observation every 6 hours, overall patient's hemodynamic condition is quite stable.

Several laboratory tests were performed to the patient. Complete blood count and differential count were still within normal range, although there was an increase in hematocrit to 38.8%, relative neutrophilia, and relative monocytosis. The relative increase in neutrophil and monocyte were in accordance with the increase of procalcitonin, quantitative CRP, and ferritin in infection or inflammation condition. Neutrophil-lymphocyte ratio (NLR) was initially increased from 6.35 and then it dropped to 4.94, before becoming back to normal normal 2.47. Ferritin serum examination revealed an increase in ferritin concentration 2277.08 ng/mL. The results of troponin and kidney function test were within normal limits. Liver function test showed an increase in AST to 41 U/L. CRP examination revealed a concentration of 7.1 mg/L in day 1 and continue to increase with highest CRP level was 95.5 mg/L. Additionally, patient also underwent plasma IL-6 level test and an increase in IL-6 with a value of 84.0 pg/mL was found. Serum ferritin examination showed an increase in ferritin level 2277.08 ng/mL. Patient also

underwent RT-PCR examination for SARS-CoV-2 and SARS-CoV-2 antibody examination, which revealed positive SARS-CoV-2 results and non-reactive SARS-CoV-2 antibody. Based on these clinical condition and laboratory findings, the patient was diagnosed with COVID-19 with cytokine storm syndrome.

Upon admission, the patient received azithromycin 500 mg o.d, hydroxychloroquine 400 mg p.o. b.i.d. continued with 400 mg p.o. o.d. dose, and oseltamivir 75 mg p.o. o.d. Oseltamivir was given for 3 days, but further continued with favipiravir as per protocol dose 800 mg b.i.d., continued with 400 mg b.i.d. dose for 2 weeks. Intravenous paracetamol drip was administered if his temperature was above 38.5 degree Celsius. Patient was also given Vitamin C 1000mg i.v. b.i.d., other multivitamin tablet p.o. o.d., vitamin D 1000 IU o.d, and Zinc 30 mg o.d. Before being hospitalized, patient experienced electrolyte disturbance, decreased potassium and sodium and received KCl drip. Patient also experienced hypocalcemia and was given calcium gluconate injection. During administration of hydroxychloroquine therapy, patient underwent EKG examination to monitor cardiac abnormalities, and during cardiology evaluation, no cardiac abnormality was found.

On hospitalization day-8, patient underwent blood coagulation system test. The patient had increased D-dimer and fibrinogen level with the result of 1080 mcg/mL and 700 mg/dL, respectively. (**Figure 3**). Based on these results, the patient was given enoxaparin as anticoagulant.

On day 10 of hospitalization, chest CT-scan without contrast was performed and showed worsening condition with further consolidation. This was in accordance with the typical appearance of pneumonia with fibrotic appearance in lower lobe and thickening of the right pleura.

On hospitalization day-10, patient was given anti-IL6, Tocilizumab or Actemra, and after administration of the 600 mg single dose tocilizumab, patient's condition ameliorated, fever subsides, cough and breathing difficulty gradually improves, until finally on day-18 the patient did not require supplemental oxygen. The patient was discharged on day-22 with good condition and normal laboratory parameters. Although RT-PCR from nasopharynx and oropharynx still showed positive results, the Ct (cycle threshold) value continue to increase, showing that the number of virus continue to decrease. Until week-6 after first complaint, RT-PCR from nasopharyngeal swab was still positive, but patient's clinical condition was good and improved, and the patient continued to do self-isolation. The chest x-ray taken before the patient was discharged also shown improvement (**Figure 4**). The patient's condition continued to

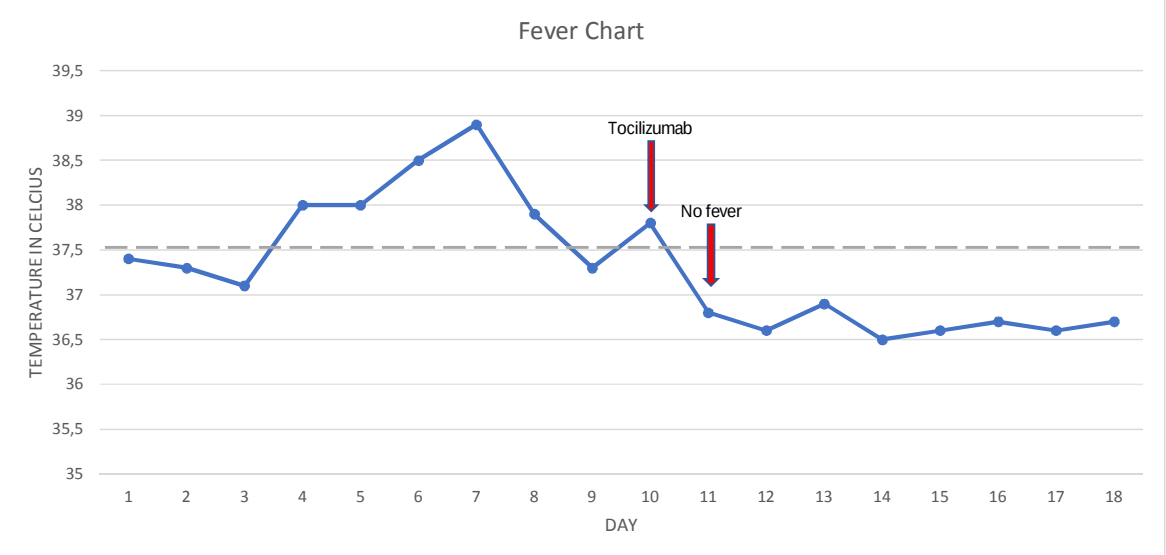

Figure 3. Fever patterns before and after treatment with Tocilizumab.

Table 1. Results of oxygen saturation and laboratory series

Tocilizumab ↓

Days of admission	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18
T(^{0}C)	37.4	37.3	37.1	38	38	38.5	38.9	37.9	37.3	37.8	36.8	36.6	36.9	36.5	36.6	36.7	36.6	36.7
RR (times/ min)	17	17	16	24	17	28	30	18	24	40	30	24	28	21	24	22	20	20
Peripheral oxygen saturation (%)	99	98	98	97	97	94	95	95	93	93	90	93	94	95	94	95	96	96
Neutrophil (x10^9/L)						80.8				74.3					65.7			
Lymphocyte (x10^9/L)						12.7				15					26.5			
ALT (U/L)	41									69					54			
AST (U/L)	28									93					94			
LDH (U/L)											319							
Natrium (meq/L)				133	128	134	133	130	132		**136**	136			135			
Total Calcium (mg/dL)				7.7			7.7		7.5		7.9				7.8			
Procalcitonin (nG/mL)	0.06						0.12				0.12							
CRP (mg/L)	7.1			10.3			75.4		95.5						4.3			
NLR							6.35			4.94					2.47			
PT (s)									13.4									
INR									1.02									
Fibrinogen									700									371
d-Dimer (ug/mL)									1080			1137			680			264
Ferritin (ng/ mL)			688.2						2277.08						865			
IL-6										84.0								
SARS-CoV-2 RT-PCR		Positive						Positive				Positive						
Antibody SARS-CoV-2		Non-reactive													Reactive IgM IgG			

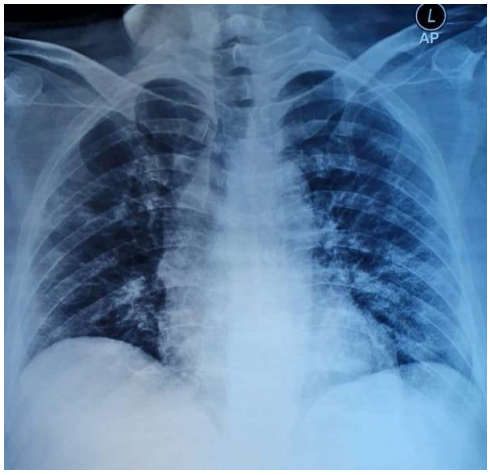

Figure 4. Chest X-Ray, Day 22. Result Showing Improving Signs of Pneumonia

improve and was able to carry on with normal activity 1 month after hospitalization with negative swab result.

DISCUSSION

COVID-19 is a highly transmitted infectious disease with various clinical manifestations, ranging from asymptomatic, mild pneumonia, severe pneumonia until critical clinical manifestation which causes death. Several studies reported that COVID-19 with severe manifestation showed an increase in proinflammatory cytokines causing cytokine storm syndrome.[2] Cytokine storm syndrome itself is marked by an increase in IL-6 level accompanied with hyperferritinemia[5].

In this case report, we presented a moderate COVID-19 case with cytokine storm syndrome which was marked by the increase in IL-6 level in the blood, hyperferritinemia with coagulation disorder, hypocalcemia and electrolyte disturbance. The patient was treated with tocilizumab. In this case, the patient showed clinical and laboratory parameters improvement after administration of tocilizumab. The most relieving lessons of this experience was that not only the fever subsided, but also the saturation improvement prevented this patient from being intubated and the need of mechanical ventilation. This finding was in accordance with previous study involving 21 severe and critically ill COVID-19 patients in China. In this retrospective study, it was found that administration of tocilizumab may improve clinical condition, which was supported with improvement of laboratory parameter such as decreased CRP and IL-6 level. Additionally, chest CT-scan also showed significant improvement after tocilizumab administration in almost all patients.[6] In this case, NLR may increase in early infection suggestive of systemic inflammatory response[7]. NLR examination has a sensitivity of 88% and specificity of 63.6% in determining the severity of COVID-19 [8]. Ferritin and CRP are acute phase proteins, which levels increase in infection or inflammatory condition.

Other study in China involving COVID-19 patients with more various clinical appearance, which were COVID-19 with moderate pneumonia, severe pneumonia, and critically ill patients. This study was performed in 15 patients and showed that after administration of tocilizumab, 80% of patients showed clinical improvement, decreased CRP and IL-6 levels. Administration of tocilizumab was considered to decrease or manage COVID-19 with cytokine storm syndrome.[9] In addition, another study was conducted in Italy involving 85 COVID-19 patients comparing 62 COVID-19 patients who were given tocilizumab and 23 patients receiving standard therapy of hydroxychloroquine, lopinavir, and ritonavir. Based on this study, it was found that the low dose tocilizumab administration might result in clinical improvement and decreased mortality in COVID-19 patients compared to patient who did not receive tocilizumab.[10]

Until now, the mechanism of cytokine storm syndrome in SARS-CoV-2 infection remains unknown. However, the incidence of cytokine storm syndrome is frequently associated with the increase in IL-6 level. IL-6 itself can be produced by almost all stromal and immune cells, such as B lymphocyte, T lymphocyte, macrophage, monocyte, dendritic cell, mast cell, and other non-lymphocyte cells, including fibroblast, endothelial cell, keratinocyte, glomerular mesangial cell, and tumor cell.[11-12] In SARS-CoV-2 infection, after the virus binds to the ACE-2 receptor in type II pneumocyte in the lungs, it will invade the cell and replicate resulting

in cellular apoptosis and necrosis. It will also trigger the inflammatory response, including the production of inflammatory response in the form of proinflammatory cytokine, macrophage and Th1 cell activation, followed by the production of IFN-γ, IL-17A, IL21, and IL-22 by neutrophil, Th17 cell, and $CD8^+$ cell. In normal condition, the production of proinflammatory cytokine is followed by the production of anti-inflammatory cytokine, so cytokine storm did not occur. Based on the study, the increase in IL-6 level in COVID-19 occurs because SARS-CoV-2 infects macrophage and cause the upregulation of IL-6 production and the decrease of interferon expressions. The increase in IL-6 will cause the rise in monocyte differentiation, B cell antigen-dependent differentiation modulation, IgG production by B cell, and Th2 response promotion by inhibiting Th1 polarization. Due to the SARS-CoV-2 invasion on pneumocytes and lung macrophages, local cytokine storm in COVID-19 patients is potentially higher than the systemic storm. Other studies reported that there was a strong correlation between IL-6 serum and the incidence of respiratory failure. This correlation is potentially stronger than the correlation of plasma IL-6 with the incidence of respiratory failure in ARDS (acute respiratory distress syndrome) due to other systemic sepsis, where plasma IL-6 is much higher than plasma IL-6 in COVID-19, but the lung lesion appearance and the respiratory failure can be less severe.[12] This explains that the respiratory failure in COVID-19 is more prominent than the fever, and this also explain the reason COVID-19 is more deadly. In this patient, the plasma IL-6 was 84 pg/ml, which was highly significant because the normal plasma IL-6 was 0 – 5 pg/ml or not more than 15 pg/ml. It can be imagined that the lung tissue IL-6 level was potentially much higher than 84 pg/mL in the plasma, and the lung damage is potentially severe. Based on a study, it was known that the increase of IL-6 level more than 80 pg/mL was correlated with higher risk to develop respiratory failure. The administration of anti-IL-6 may manage the cytokine storm syndrome which happen in COVID-19, either systemic or in the lungs.[13]

Tocilizumab is a monoclonal antibody and is an antagonist to IL-6 receptor. IL-6 will bind to the IL-6R receptor and form a complex, which will further bind to glycoprotein 130 (gp-130) signal transducer and stimulate the gene expression. IL-6R itself can be found not only in the transmembrane (mIL-6R) form, but also in the soluble (sIL-6R) form. These two forms of IL-6R will cause the signal transduction through different pathways, which are classic transduction and trans transduction pathway. In the classic transduction pathway, many cells did not respond to IL-6 signal due to the low expression of mIL-6R. Classic signal transduction is only limited to several cells, including macrophage, neutrophil, T lymphocyte, and other cells which express mIL-6R. In the cytokine storm syndrome due to COVID-19, there is an increase in IL-6 exceeding normal limits. This causes the high expression of mIL-6R and sIL-6R. In trans transduction pathway, sIL-6R itself can activate almost all cells in the body to regulate the pro-inflammatory reaction. Inhibition to trans transduction pathway has previously been known to be effective in managing several autoimmune diseases.[11,14-17] Tocilizumab itself is an anti-IL6 which can bind to both forms of IL-6R. The binding between tocilizumab and mIL-6R dan sIL-6R may inhibit the classic and trans transduction pathway, which effectively may inhibit and manage cytokine storm syndrome.[11,14,17]

Until now, tocilizumab has not received the approval to be used in the management of cytokine storm syndrome in COVID-19 in China. The recommendation of management of COVID-19 by WHO also stated that the use of tocilizumab in the management of COVID-19 is still limited to clinical trials. Nonetheless, "Diagnosis and treatment Plan of Novel Coronavirus Pneumonia (seventh trial edition)" in China recommends the use of tocilizumab in patient with wide lung lesion, in severe COVID-19 pneumonia, and in patients with high level of IL-6. Based on this recommendation, the recommended dose is 400 mg which is diluted in 100 mL NaCl 0.9% and given intravenously in 1 hour.[17]

Although the use of tocilizumab showed quite good efficacy in managing cytokine storm syndrome, there were several adverse effects which may happen due to the use of tocilizumab.

Based on United Stated FDA (Food and Drug Administration) there were several adverse effects which may appear: (1) serious infection: the most common infection is pneumonia, urinary tract infection, cellulitis, herpes zoster, gastroenteritis, diverticulitis, sepsis, and bacterial arteritis; (2) Gastrointestinal perforation which is reported as a complication of diverticulitis. Most patients who experienced gastrointestinal perforation use tocilizumab in conjunction with nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid, or methotrexate in the same time; (3) Infusion reaction: the most common reported adverse effects during administration are hypertension, headache, and skin reaction; (4) Anaphylaxis; this reaction is usually reported in the second to fourth administration of tocilizumab; and (5) laboratory parameter abnormality: such as thrombocytopenia, increased liver enzyme, and increased lipid profiles.[17,18]

CONCLUSION

Tocilizumab could be used as a therapy for cytokine storm syndrome in COVID-19 patients. However, the success of the treatment may be depending on the degree of COVID-19 severity. Further clinical randomized control trial is required to evaluate the efficacy and safety of tocilizumab administration in participants with various clinical characteristics and a greater number of subjects.

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