


Tocilizumab and PMX-DHP have efficacy for severe COVID-19 pneumonia

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Abstract

In coronavirus disease 2019 pneumonia, a cytokine storm resulting from an excessive inflammatory response to the viral infection is thought to play a role in the exacerbation of the pneumonia and its prognosis. Favipiravir and ciclesonide are not effective in the inhibition of the cytokine storm. In this case report, we describe the experience of tocilizumab administration and polymyxin B immobilized fiber direct hemoperfusion in severe coronavirus disease 2019 pneumonia patient. A 52-year-old man presented with fever and dyspnea and was diagnosed with coronavirus disease 2019 pneumonia based on a polymerase chain reaction test. Mechanical ventilation and favipiravir administration were started for respiratory failure. However, favipiravir could not be continued due to hepatic dysfunction. Consequently, tocilizumab was administered, and continuous hemodiafiltration and endotoxin adsorption therapy (polymyxin B immobilized fiber direct hemoperfusion) were performed for acute renal failure. C-reactive protein decreased from 44 to 3.52 mg/dL, and the patient's respiratory status improved over time, enabling mechanical ventilation to be withdrawn. This case indicates that adding polymyxin B immobilized fiber direct hemoperfusion to tocilizumab administration may further increase efficacy in coronavirus disease 2019 treatment; however, more case–control studies are needed.

Keywords

COVID-19, tocilizumab, acute renal injury, ARDS, PMX-DHP

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Introduction

Although inhalation of favipiravir and ciclesonide is currently being used to treat coronavirus disease 2019 (COVID-19) infection, these treatments have not shown convincing efficacy in severe cases.^{1,2} In COVID-19 pneumonia, a cytokine storm resulting from an excessive inflammatory response to the viral infection is thought to play a pivotal role in the exacerbation of the pneumonia and its prognosis.³ Favipiravir and ciclesonide are not effective in the inhibition of the cytokine storm. Tocilizumab (Actemra, Chugai pharmaceutical, Japan), a humanized anti-human interleukin (IL) 6-receptor monoclonal antibody, is a drug that can be used in rheumatoid arthritis and cytokine release syndrome,⁴ and it is considered effective against cytokine storm resulting from COVID-19 pneumonia.⁵ Tocilizumab and endotoxin adsorption therapy (polymyxin B immobilized fiber direct hemoperfusion: PMX-DHP) were used in a patient with

acute respiratory distress syndrome (ARDS) caused by COVID-19, and mechanical ventilation could be withdrawn. The case is described in this report.

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Table 1. Laboratory results before treatment.

Hematology		Chemistry		Serology	
RBC	443 × 10 ⁴ /μL	TP	6.9 g/dL	KL-6	456 U/mL
Hb	14 g/dL	Alb	4.4 g/dL	Ferritin	2815 ng/mL
WBC	5420/μL	AST	17 U/L	IgG	863 mg/dL
Neu	83.8%	ALT	17 U/L	IgM	86 mg/dL
Lym	11.3%	ALP	155 U/L	PCT	0.38 ng/dL
PLTS	263 × 10 ³ /μL	LDH	702 U/L	IL-6	1830 pg/dL
		CK	714 U/L	Other	
		BUN	21 mg/dL	D-dimer	0.7 μg/mL
		Cr	1.25 mg/dL		
		Na	132 mEq/L		
		K	3.8 mEq/L		
		Ca	8.4 mEq/L		
		CRP	19.967 mg/dL		

RBC: red blood cells; Hb: hemoglobin; WBC: white blood cells; PLTS: platelets; TP: total protein; Alb: albumin; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; CK: creatine kinase; BUN: blood urea nitrogen; Cr: creatine; CRP: C-reactive protein; KL-6: sialylated carbohydrate antigen KL-6; IgG: immunoglobulin G; IgM: immunoglobulin M; PCT: procalcitonin; LDH: lactate dehydrogenase; IL-6: interleukin-6.

Case report

A 52-year-old man presented to our hospital with fever and a sore throat. Acute laryngitis was diagnosed, acetaminophen prescribed, and the patient's clinical course was observed. However, the fever persisted, and the patient was examined in our department. A nasopharyngeal specimen was collected, a polymerase chain reaction test was positive for COVID-19, and the patient was found to be hypoxemic. He was therefore admitted. On arrival to our hospital, body temperature was 38.3°C; blood pressure, 144/82 mmHg; pulse rate, 94/min; and percutaneous oxygen saturation, 89% (10 L by mask). Breath sounds were clean, with no difference between left and right; no adventitious sounds or cardiac murmurs were heard. There was no pedal edema. Laboratory findings at admission are shown in Table 1 and Figure 1: blood tests showed white blood cells in the normal range, but an elevated neutrophil fraction of 83% and a severely elevated C-reactive protein (CRP) level of 19.97 mg/dL. Simple thoracic computed tomography (CT) showed diffuse ground-glass opacities in both lungs, some of which had mixed infiltrative shadows.

Clinical course is shown in Figure 2. Because the respiratory failure was severe, management with mechanical ventilation was started immediately after admission. Favipiravir was administered by nasogastric tube at a dose of 1800 mg on the first day and 800 mg on subsequent days. Although the patient's respiratory status did not worsen, bilirubin and transaminase elevations were seen. The elevations were attributed to drug-induced liver injury caused by favipiravir, which was therefore discontinued on day 4. However, because the CRP level had worsened, tocilizumab administration (8 mg/kg) was started on day 5. Blood tests on the following day also showed CRP to be elevated, and tocilizumab was therefore administered a second time. CRP subsequently decreased over time. At the same time, deterioration of kidney function and

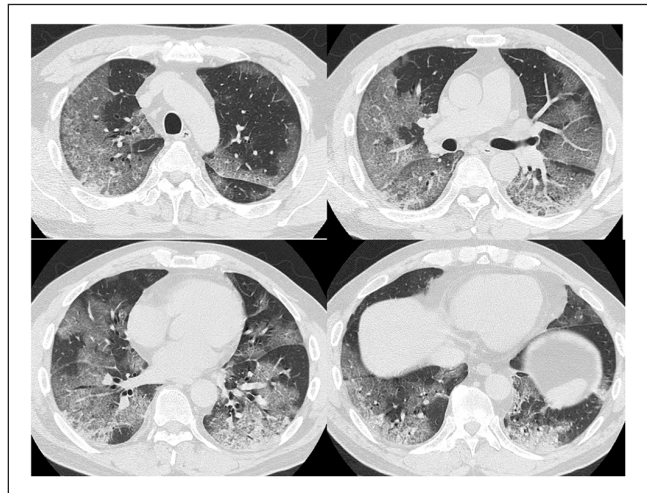


Figure 1. Lung CT on day 1 (before treatment). Ground-glass opacity was observed in both lungs, and some infiltrated shadows were also observed in lower lung.

decreased urine output were seen after admission. Continuous dialysis was therefore started on day 5, and PMX-DHP was performed on days 7 and 8. The creatine level decreased, and sufficient urine output was obtained after the start of continuous dialysis. Consequently, continuous dialysis was withdrawn on day 16. Although the respiratory failure improved little following tocilizumab administration, improved oxygenation was seen with the improvement in CRP, and the patient was extubated on day 27. Lung CT performed after extubation (Figure 3) and at the time of his discharge (Figure 4) showed extensive residual infiltrative shadows. However, the patient's condition stabilized with administration of 3 L of oxygen by nasal cannula, and he was discharged on day 54 after rehabilitation under home oxygen therapy.

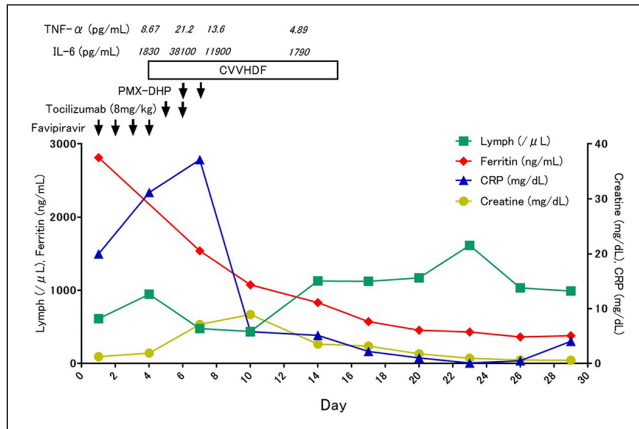


Figure 2. Clinical course.

CVVHDF: continuous venovenous hemodiafiltration; PMX-DHP: polymyxin B immobilized fiber direct hemoperfusion; IL-6: interleukin-6; TNF- α : tumor necrosis factor alpha; CRP: C-reactive protein

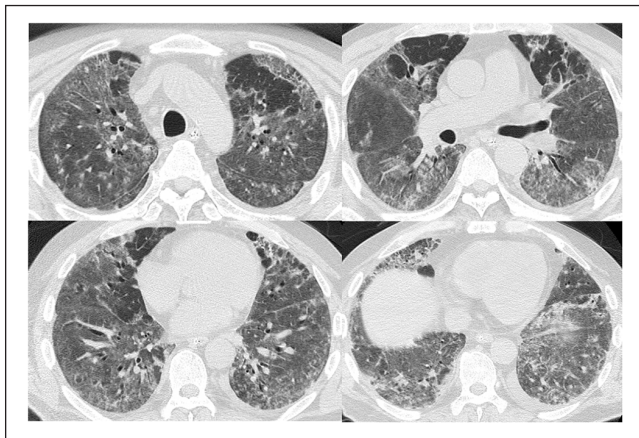


Figure 3. Lung CT on day 30 (after extubation).

Ground-glass opacity was observed in both lungs, although lung shadows were getting better than before treatment.

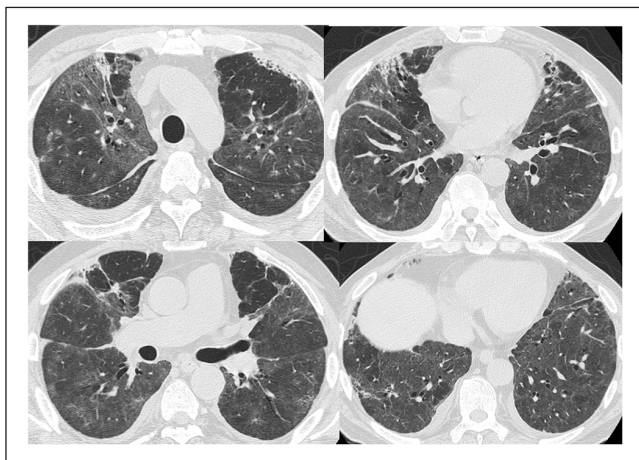


Figure 4. Lung CT on day 51 (before discharge).

Ground-glass opacity was still observed in both lungs. However, lung shadows were much better than lung CT of after extubation.

Discussion

Although a cytokine storm resulting from viral infection is thought to play a role in the exacerbation of COVID-19 pneumonia, there are few treatments that control a cytokine storm. Many reports have been published in other countries on the use of tocilizumab in COVID-19 pneumonia, but there have been few such reports in Japan.^{6,7} IL-6 is thought to play a critical role in pneumonia and airway inflammation resulting from viral infection, and there is evidence suggesting that it may be a prognostic factor in COVID-19 pneumonia.⁸ Consequently, controlling IL-6 may inhibit the worsening of viral infections. A study in patients with juvenile idiopathic arthritis who contracted influenza found that, in the patients given tocilizumab, fever and CRP were lower before treatment, whereas there was no difference in worsening of the influenza virus infection or in the risk of worsening.⁹ In the present case, CRP decreased and the fever subsided beginning from day 3 of tocilizumab administration. However, it was not until 1 week after the start of administration that the oxygen concentration used in mechanical ventilation could be reduced and approximately 28 days until mechanical ventilation was withdrawn. This may have been because the delay in tocilizumab administration prevented inhibition of cytokine storm development. Although there are data that corticosteroids prevent the aggravation of COVID-19 pneumonia, we did not consider steroid use due to lack of evidence when we experienced this case.¹⁰

Continuous hemodiafiltration was performed in the present case because of concomitant acute renal failure. In addition, PMX-DHP using a Toraymyxin (TORAY, Japan) and adsorption column was performed at the same time following the start of tocilizumab administration. Although the use of PMX-DHP to adsorb activated neutrophils and reduce hypercytokinemia, including inflammatory mediators, has been found effective in ARDS,¹¹ there have been no reports of the effectiveness of PMX-DHP in COVID-19 pneumonia, and its effectiveness is unknown. However, Kudo et al. reported that PMX-DHP was effective against ARDS caused by influenza virus¹² and PMX-DHP has been found to significantly reduce IL-6.¹³ Although the blood IL-6 level increased, to 38,000 pg/mL, following tocilizumab administration in the present case, it decreased to 11,900 pg/mL early after PMX-DHP was performed and decreased further, to 1790 pg/mL, after 5 days. Han et al. reported that IL-6 and IL-10 are disease severity predictors. We consider that cytokine storm mainly occurred by IL-6 is the cause of COVID-19 pneumonia, since the tocilizumab had efficacy in present case.¹⁴ It is clinically normal situation for serum IL-6 to elevate with the tocilizumab administration. The tocilizumab blocks the IL-6 receptor rather than IL-6 itself, so negative feedback is applied and serum IL-6 was elevated.^{15,16} These findings suggest that there is a strong possibility that PMX-DHP would also be effective against ARDS caused by COVID-19. Lin et al.¹⁷ performed continuous dialysis and plasma exchange to treat cytokine storm and reported that high-volume hemofiltration was effective in removing cytokines and stabilizing

hemodynamics. In the present case, continuous dialysis after PMX-DHP was performed using a sepXiris (Baxter, Japan) filter, which is a continuous dialysis cytokine adsorption filter consisting of an AN69ST membrane. This filter can not only regulate uremic substances and fluids, but it can also remove cytokines by adsorption. Matsuda et al.¹⁸ examined the effectiveness of a filter consisting of polymethylmethacrylate (PMMA) that was capable of cytokine adsorption and reported it to be effective in ARDS patients. Moreover, Kobashi et al.¹⁹ compared the 28-day survival rates in patients with sepsis after treatment using two types of hemofilters, one consisting of AN69ST and the other of PMMA, and they reported that the AN69ST filter, the type used in the present case, was more useful. However, a characteristic of COVID-19 is thrombus formation resulting from severe inflammation, hypoxemia, bed rest, and disseminated intravascular coagulation.²⁰ Although nafamostat has been used at high doses, dialysis circuits have been clogged by thrombi, often necessitating circuit replacement.

Even at 1 month after onset, thoracic CT performed after mechanical ventilation had been withdrawn showed residual diffuse ground-glass opacities, and the sialylated carbohydrate antigen (KL-6) level had increased to ≥ 2000 U/mL (normal: < 499 U/L), indicating fibrogenesis of lung tissues. With regard to the effect of fibrogenesis of lung tissues, although there is a report suggesting that it indicates a good prognosis in COVID-19 infection,²¹ there is another report indicating that lung fibrosis results in a poor clinical outcome.^{22,23}

Conclusion

It was possible to save a patient with ARDS resulting from COVID-19 by administering tocilizumab and performing PMX-DHP. Although tocilizumab appears to be useful against COVID-19 pneumonia, caution must be exercised with regard to secondary infection when using it. We believe adding PMX-DHP to tocilizumab administration may further increase efficacy in COVID-19 treatment; however, more case–control studies are needed.

Author contributions

S.S., K.N., A.F., Y.T., H.A., M.O., Y.I., H.Y., T.I., and S.M. contributed to the clinical patient care and management. S.S. and S.M. contributed to the manuscript preparation. All authors have read and approved the final manuscript.

Consent for publication

Written, informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article:

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

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Informed consent

Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

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References

- Kimura H, Kurusu H, Sada M, et al. Molecular pharmacology of ciclesonide against SARS-CoV. *J Allergy Clin Immunol* 2020; 146(2): 330–331.
- Joshi S, Parkar J, Ansari A, et al. Role of favipiravir in the treatment of COVID-19. *Int J Infect Dis* 2020; 102: 501–508.
- Domingo P, Mur I, Pomar V, et al. The four horsemen of a viral apocalypse: the pathogenesis of SARS-CoV-2 infection (COVID-19). *Ebiomedicine* 2020; 58: 102887.
- Le RQ, Li L, Yuan W, 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: 943–947.
- Corominas H, Castellví I, Pomar V, et al. Effectiveness and safety of intravenous tocilizumab to treat COVID-19-associated hyperinflammatory syndrome: covizumab-6 observational cohort. *Clin Immunol* 2020; 223: 108631.
- Zhang Y, Zhong Y, Pan L, et al. Treat 2019 novel coronavirus (COVID-19) with IL-6 inhibitor: are we already that far. *Drug Discov Ther* 2020; 14(2): 100–102.
- Toniati P, Piva S, Cattalini M, et al. Brescia International Research and Training HUB (BIRTH). Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmun Rev* 2020; 19(7): 102568.
- Chiaretti A, Pulitanò S, Barone G, et al. IL-1 β and IL-6 upregulation in children with H1N1 influenza virus infection. *Mediators Inflamm* 2013; 2013: 495848.
- Kawada J, Kitagawa Y, Iwata N, et al. Clinical characteristics of influenza virus infection in juvenile idiopathic arthritis patients treated with tocilizumab. *Mod Rheumatol* 2013; 23(5): 972–976.
- Sterne JAC, Murthy S, Diaz JV, et al. Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. *JAMA* 2020; 324: 1330–1341.
- Yatera K, Yamasaki K, Kawanami T, et al. A case of successful treatment with polymyxin B-immobilized fiber column direct hemoperfusion in acute respiratory distress syndrome after influenza A infection. *Intern Med* 2011; 50(6): 601–605.
- Kudo K, Binh NG, Manabe T, et al. Clinical preparedness for severe pneumonia with highly pathogenic avian influenza A

- (H5N1): experiences with cases in Vietnam. *Respir Investig* 2012; 50(4): 140–150.
13. Ikeda T, Ikeda K, Nagura M, et al. Clinical evaluation of PMX-DHP for hypercytokinemia caused by septic multiple organ failure. *Ther Apher Dial* 2004; 8(4): 293–298.
 14. Han H, Ma Q, Li C, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. *Emerg Microbes Infect* 2020; 9(1): 1123–1130.
 15. Kleveland O, Kunszt G, Bratlie M, et al. Effect of a single dose of the interleukin-6 receptor antagonist tocilizumab on inflammation and troponin T release in patients with non-ST-elevation myocardial infarction: a double-blind, randomized, placebo-controlled phase 2 trial. *Eur Heart J* 2016; 37(30): 2406–2413.
 16. Galván-Román JM, Roy-Vallejo E, Marcos-Jiménez A, et al. IL-6 serum levels predict severity and response to tocilizumab in COVID-19: an observational study. *J Allergy Clin Immunol* 2020; 147: 72–80.
 17. Lin JH, Chen YC, Lu CL, et al. Application of plasma exchange in association with higher dose CVVH in cytokine storm complicating COVID-19. *J Formos Med Assoc* 2020; 119: 1116–1118.
 18. Matsuda K, Moriguchi T, Oda S, et al. Efficacy of continuous hemodiafiltration with a cytokine-adsorbing hemofilter in the treatment of acute respiratory distress syndrome. *Contrib Nephrol* 2010; 166: 83–92.
 19. Kobashi S, Maruhashi T, Nakamura T, et al. The 28-day survival rates of two cytokine-adsorbing hemofilters for continuous renal replacement therapy: a single-center retrospective comparative study. *Acute Med Surg* 2018; 6: 60–67.
 20. Guan WJ, Ni ZY and Hu Y. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med* 2020; 30382: 1708–1720.
 21. Pan Y, Guan H, Zhou S, et al. Initial CT findings and temporal changes in patients with the novel coronavirus pneumonia (2019-nCoV): a study of 63 patients in Wuhan, China. *Eur Radiol* 2020; 30(6): 3306–3309.
 22. Pan F, Ye T, Sun P, et al. Time course of lung changes on chest CT during recovery from 2019 novel coronavirus (COVID-19) pneumonia. *Radiology* 2020; 13: 200370.
 23. d'Alessandro M, Cameli P, Refini RM, et al. Serum KL-6 concentrations as a novel biomarker of severe COVID-19. *J Med Virol* 2020; 92(10): 2216–2220.