Original Article

Effect of tocilizumab treatment in mildly-obese patients with coronavirus disease 2019: a case series

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Background: The coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is an increasingly widespread international medical problem. Several randomized trials and observational studies in patients with COVID-19 have been performed. However, the standard treatment strategy has not yet been established. The purpose of this study is to report effect of tocilizumab treatment combined with remdesivir, dexamethasone, and heparin on obese Japanese patients with COVID-19. Tocilizumab is a monoclonal antibody against the interleukin-6 (IL-6) receptor. Obesity, characterized by systemic enlarged adipocytes, promotes proinflammatory cytokine expression in adipose tissue. More specifically, obesity induces detrimental adipocytokine production including tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and IL-6. In addition, its production in the adipose tissue is associated with body mass index (BMI) and adipocyte size. IL-6 can promote inflammation not only in the adipose tissues but also in endothelial cells and triggers systemic inflammation.

Methods: A cross-sectional observational study was conducted. The study sample consisted of 96 patients between August 2020 and January 2021 at Showa University Fujigaoka Hospital.

Results: Overall, 56.3% (54 of 96) were administered with remdesivir, 54.2% (52 of 96) with dexamethasone, 19.8% (19 of 96) with anticoagulant therapy with heparin. Of the patients, nine were administered tocilizumab with remdesivir, dexamethasone, and heparin. The current study indicated that single-dose treatment of tocilizumab in combination with remdesivir, dexamethasone, and heparin is beneficial for obese Japanese patients with COVID-19.

Conclusions: We believe that the severity of obesity is related to the anti-IL-6 treatment sensitivity in patients with COVID-19.

Keywords: Coronavirus disease 2019 (COVID-19); interleukin-6 (IL-6); tocilizumab; obesity; case series

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Introduction

Novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) first appeared at the end of 2019 and subsequently spread worldwide. Nowadays, the coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 is an increasingly widespread international medical problem. COVID-19 may begin with high viral replication in the initial phase, but subsequent inflammation caused by host immune response may play an important role in COVID-19 (1).

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In addition, recent studies suggest that this condition is accompanied by thrombotic microangiopathy (2). Remdesivir, an antiviral medication; dexamethasone, a corticosteroid; and heparin, an anticoagulant, are recommended for the treatment of COVID-19 (3-5); however, the treatment strategy is not well established. The levels of inflammatory cytokines, including tumor necrosis factor-α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and interleukin-6 (IL-6), produced by visceral and subcutaneous adipose tissues, are elevated in patients with COVID-19 (6). Thus, a monoclonal antibody against the IL-6 receptor, tocilizumab, an agent originally used to treat Castleman disease and rheumatoid arthritis, is expected to be a promising treatment for COVID-19. Several prospective studies on tocilizumab treatment in patients with COVID-19 have been reported, but its efficacy remains controversial (7-13). Here, we report the effectiveness of tocilizumab, especially in Japanese patients with COVID-19. The degree of obesity varies depending on race, ethnicity, and region. Compared with foreign countries, the body mass index (BMI) tends to be lower in Japan (14). Obesity might be related to anti-IL-6 treatment sensitivity in patients with COVID-19. We present the following article in accordance with the AME Case Series reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-2022-49/rc).

Methods

Population and data collection

An observational study was conducted to investigate the efficacy of tocilizumab in patients with COVID-19 at Showa University Fujigaoka Hospital from August 2020 to January 2021. COVID-19 was diagnosed based on real-time reverse transcription polymerase chain reaction (rRT-PCR) to detect SARS-CoV-2 using samples derived from the nasopharynx. Inclusion criteria for tocilizumab treatment were presented as follows: briefly, a ratio of the partial pressure of oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2) (P/F ratio) of <100 Torr on admission or respiratory exacerbation during remdesivir and dexamethasone therapy. Exclusion criteria included a history of intestinal fistula, blood lymphocyte of <500/μL and liver dysfunction (defined as an aspartate aminotransferase or alanine aminotransferase level of >100 U/L), due to the risk for intestinal bleeding, infection due to cytopenia, and hepatic failure. Serum IL-6 level was measured immediately before tocilizumab administration. One-time tocilizumab was intravenously administered at a dose of 8 mg/kg of body weight. The onset was defined as the day the patient had ≥37.5 ℃ body temperature or the day of confirmation of positive rRT-PCR in an asymptomatic case. Chronic renal failure was defined as estimated glomerular filtration rate of <60 mL/min/1.73 m^2. Patients were followed up until hospital discharge or death. All clinical data were collected from patients' medical records. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Committee of Showa University (Approval No. FR20200004) and informed consent was taken from all individual participants. A copy of the written consent is available for review by the editorial office of this journal.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) for continuous variables or as percentages for categorical variables. Group mean values were compared using the Mann-Whitney rank-sum test. Pearson's chi-squared test was used for the univariate analysis of the association between two categorical variables. Statistical significance level was set at $P<0.05$. All statistical analyses were performed using JMP software version 16.0 (SAS Institute, Cary, NC, USA).

Results

As shown in *Table 1*, the study population consisted of 96 patients (62 men and 34 women) with a mean age of 70.2 (range, 24–101) years, all of whom were Japanese. No age and sex bias were observed between the tocilizumab and control groups, whereas BMI and the duration from onset on admission were significantly higher in patients receiving tocilizumab. Among them, 51 (53.1%) had hypertension; 32 (33.3%) had diabetes mellitus; 28 (29.2%) had heart failure; 17 (17.7%) had malignancies including pharyngeal cancer, laryngeal cancer, non-small-cell lung cancer, prostatic cancer, colorectal cancer, and breast cancer; and 7 (7.3%) had chronic renal failure. There was no significant difference in the underlying conditions between the tocilizumab and control groups. Overall, 56.3% (54 of 96) were administered with remdesivir, 54.2% (52 of 96) with dexamethasone, 19.8% (19 of 96) with anticoagulant therapy with heparin, due to respiratory failure or preclinical respiratory failure. The decisions were based on the COVID-19 Japanese guideline. Of

Table 1 Association of each variable with COVID-19 patients

Characteristics	Total (n=96)	Tocilizumab group (n=9)	Control group (n=87)	P value
Age (years), mean ± SD	70.2±15.1	68.6±13.9	70.4±15.2	0.7294
Sex, n (%)				
Female	34 (35.4)	1 (11.1)	32 (36.8)	0.3846
Male	62 (64.6)	8 (88.9)	55 (63.2)	
BMI (kg/m^2), mean ± SD	23.1±5	26.1±4.6	22.8±5	0.0369*
Days from symptom onset on admission, mean ± SD	4.7±4	9.9±4.1	4.4±3.9	0.0123*
P/F ratio, mean ± SD	300.1±106.8	99.4±39.8	321.3±88.3	<0.0001*
Comorbidities, n (%)				
Hypertension	51 (53.1)	6 (66.7)	45 (51.7)	0.4117
Diabetes	32 (33.3)	3 (33.3)	29 (33.3)	1
Heart failure	28 (29.2)	2 (22.2)	26 (29.9)	0.6302
Myocardial infarction	6 (6.3)	0 (0.0)	6 (6.9)	0.4158
Chronic obstructive pulmonary disease	3 (3.1)	0 (0.0)	3 (3.4)	0.5714
Asthma	5 (5.2)	1 (11.1)	4 (4.6)	0.4025
Chronic kidney disease	7 (7.3)	0 (0.0)	7 (8.0)	0.3768
Malignancy	17 (17.7)	2 (22.2)	15 (17.2)	0.7094
In-hospital drugs, n (%)				
Remdesivir	54 (56.3)	9 (100.0)	45 (51.7)	0.0054*
Dexamethasone	52 (54.2)	9 (100.0)	43 (49.4)	0.0037*
Heparin	19 (19.8)	8 (88.9)	11 (12.7)	<0.0001*

*, P<0.05 was considered significant. COVID-19, coronavirus disease 2019; SD, standard deviation; BMI, body mass index; P/F ratio, a ratio of the PaO_2 to the FiO_2; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen.

the patients, nine were administered tocilizumab with remdesivir, dexamethasone, and heparin. Characteristics and clinical status of tocilizumab-treated patients are shown in *Table 2*. Five indicated a P/F ratio of <100 Torr at the time of admission, and four revealed that a P/F ratio decreased to 200 Torr during hospitalization. Case 2 was an 80-year-old male who was on a ventilator in the ICU. The other 8 were admitted to the general ward and were given oxygen through face masks. Study patients consisted of eight males and one female with ages ranging from 49 to 85 years. Five patients had BMI of >25 kg/m^2 (defined as obesity in Japan). The duration between the presumed time of infection and tocilizumab treatment ranged from 7 to 17 days. Serum IL-6 levels were elevated (>100 pg/mL) in four patients. The levels of IL-6 were not associated with the tocilizumab treatment sensitivity. Seven patients recovered from respiratory failure, five of whom had a BMI of >25 kg/m^2. Meanwhile, two patients resulted in death from hypoxia based on respiratory insufficiency, both of whom had a low BMI. Therefore, obese patients effectively responded to tocilizumab treatment compared with patients who were not obese. No serious adverse events regarding tocilizumab were reported in this study, including bleeding events, bacterial infection, and liver dysfunction. There was no particular opinion from the patients regarding the administration of tocilizumab. During the last follow-up in June 2021, surviving patients had no sequela. In summary, the present study revealed that tocilizumab combined with remdesivir, dexamethasone, and heparin can be useful for obese Japanese patient with COVID-19.

Table 2 COVID-19 patients receiving tocilizumab

Case	Age	Gender	BMI (kg/m^2)	P/F ratio	IL-6 (pg/mL)	Days from onset to administration	Unit	Artificial respiration	Status
1	83	Female	28.5	68.8	27	17	General	–	Alive
2	80	Male	20.2	74.5	125	7	ICU	+	Dead
3	49	Male	30.1	76.4	109	8	General	–	Alive
4	60	Male	31.7	61.3	111	7	General	–	Alive
5	62	Male	23.9	124.4	8	17	General	–	Alive
6	51	Male	27.3	104.4	72	8	General	–	Alive
7	67	Male	31.0	105.3	8	10	General	–	Alive
8	80	Male	22.5	190.6	106	7	General	–	Alive
9	85	Male	20.1	88.9	60	8	General	–	Dead

BMI, body mass index; P/F ratio, a ratio of the PaO_2 to the FiO_2; IL-6, interleukin 6; ICU, intensive care unit; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen.

Discussion

Several randomized trials and observational studies in patients with COVID-19 have been performed (7-13); however, the efficacy of tocilizumab has not yet been established. The REMAP-CAP study reported that the mortality risk was decreased in patients treated with tocilizumab compared with those not treated with tocilizumab (13). Meanwhile, several randomized studies showed no improvement in survival following treatment with tocilizumab in patients with COVID-19 (7-12). Hence, studies on tocilizumab are inconsistent, and the role of tocilizumab in the treatment of COVID-19 remains conflicting. Moreover, some difficulties are encountered while interpreting the study results. First, administration rates of remdesivir and steroids were reported as 0–52.6% and 10–93% (7,9,11), respectively; however, in this study, tocilizumab was concurrently administered with remdesivir and steroids. Antiviral drugs are useful for the management of the initial phase of COVID-19, and an anti-inflammatory strategy should be implemented after an excessive inflammation induced by the host immune response. Additionally, early anticoagulant therapy is reportedly useful for patients with COVID-19 (5). Thromboembolic risk is elevated, and thrombotic events are strongly associated with mortality in patients with COVID-19 (15,16). Furthermore, heparin has been reported to block the SARS-CoV-2 viral spike protein from binding with endothelial cells (17). In the current study, heparin was initiated for 88.9% (8 out of 9) of patients treated with tocilizumab; however, anticoagulant usage varied in multicenter studies reported in literature (7,8). Data from the current study suggest that a single agent could not prevent the progression of the inflammatory response in COVID-19 and that combination therapy with antiviral, corticosteroid, anticoagulant, and tocilizumab creates an additive or synergistic effect in patients with COVID-19. In fact, recent reported trials revealed additive and synergistic interaction between IL-6 receptor antagonists and glucocorticoids (12,13). Second, the definition of obesity differed between those randomized studies and this study. The prevalence of obesity according to World Health Organization (WHO) criteria (defined by a BMI of ≥30 kg/m^2) in those studies reached up to 50%, and the median BMI was approximately 30 kg/m^2. In contrast, this study found that the mean BMI was 23.1±5 kg/m^2 and that only 33.3% (3 of 9) of patients had WHO-defined obesity in the tocilizumab-treated group. The Japanese criteria defined obesity as a BMI of ≥25 kg/m^2. Thus, the situation of obesity in Japan is significantly different from that in other countries. Especially in the United States, the prevalence of obesity exceeds 45% and the percentage of obese individuals with a BMI of ≥35 kg/m^2 reaches up to 18% (18). In contrast, the prevalence of obesity defined according to the WHO criteria accounts for 4% in Japan (14). Obesity, characterized by enlarged adipocytes, induces detrimental adipocytokine production, including TNF-α, MCP-1, and IL-6 (19). It has been reported that IL-6 promotes inflammation not only in the adipose tissue but also in endothelial cells and triggers systemic

inflammation (6). Its production in the adipose tissues is associated with BMI and adipocyte size (20). In studies demonstrating the effectiveness of tocilizumab in patients with COVID-19, tocilizumab was administered twice instead of a once (8,9,13). High doses of tocilizumab might be needed for the management of morbidly-obese patients with COVID-19. The current study suggests that severely ill patients with COVID-19 who are mildly obese may receive the clinical benefit from a single-dose of tocilizumab.

The current study had several limitations. First, the study was carried out at a single facility, which might have reduced the generalizability of the findings. Second, statistically analysis of the survival rate was not possible in this study because of the small number of investigations in patients with COVID-19 who were treated with tocilizumab in combination with remdesivir, dexamethasone, and heparin.

Obesity induces detrimental inflammatory cytokines, including IL-6, and serum IL-6 level has been reported to be increased in patients with COVID-19. Tocilizumab, a monoclonal antibody against the IL-6 receptor, should therefore be considered, particularly for obese patients with COVID-19. The severity of obesity might be related to anti-IL-6 treatment sensitivity in patients with COVID-19. In the future, large clinical studies should be designed with these issues in mind.

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Footnote

Reporting Checklist: The authors have completed the AME Case Series reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-2022-49/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-2022-49/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-2022-49/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Institutional Ethics Committee of Showa University (Approval No. FR20200004) and informed consent was taken from all individual participants. A copy of the written consent is available for review by the editorial office of this journal.

References

1. Cevik M, Tate M, Lloyd O, et al. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe 2021;2:e13-22.
2. Batlle D, Soler MJ, Sparks MA, et al. Acute kidney injury in COVID-19: emerging evidence of a distinct pathophysiology. J Am Soc Nephrol 2020;31:1380-3.
3. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 - final report. N Engl J Med 2020;383:1813-26.
4. WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group; Sterne JAC, Murthy S, et al. Association between administration of systemic corticosteroids and mortality among critically Ill patients with COVID-19: a meta-analysis. JAMA 2020;324:1330-41.
5. Rentsch CT, Beckman JA, Tomlinson L, et al. Early initiation of prophylactic anticoagulation for prevention of coronavirus disease 2019 mortality in patients admitted to hospital in the United States: cohort study. BMJ 2021;372:n311.
6. Di Renzo L, Gualtieri P, Pivari F, et al. COVID-19: Is there a role for immunonutrition in obese patient? J Transl Med 2020;18:415.
7. Veiga VC, Prats JAGG, Farias DLC, et al. Effect of

tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. BMJ 2021;372:n84.
8. Hermine O, Mariette X, Tharaux PL, et al. Effect of tocilizumab vs usual care in adults hospitalized with COVID-19 and moderate or severe pneumonia: a randomized clinical trial. JAMA Intern Med 2021;181:32-40.
9. Salama C, Han J, Yau L, et al. Tocilizumab in patients hospitalized with Covid-19 pneumonia. N Engl J Med 2021;384:20-30.
10. Stone JH, Frigault MJ, Serling-Boyd NJ, et al. Efficacy of tocilizumab in patients hospitalized with Covid-19. N Engl J Med 2020;383:2333-44.
11. Salvarani C, Dolci G, Massari M, et al. Effect of tocilizumab vs standard care on clinical worsening in patients hospitalized with COVID-19 Pneumonia: A Randomized Clinical Trial. JAMA Intern Med 2021;181:24-31.
12. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in hospitalized patients with severe Covid-19 pneumonia. N Engl J Med 2021;384:1503-16.
13. REMAP-CAP Investigators; Gordon AC, Mouncey PR, et al. Interleukin-6 receptor antagonists in critically Ill patients with Covid-19. N Engl J Med 2021;384:1491-502.
14. Ng M, Fleming T, Robinson M, et al. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013. Lancet 2014;384:766-81.
15. Zhang L, Feng X, Zhang D, et al. Deep vein thrombosis in hospitalized patients with COVID-19 in Wuhan, China: Prevalence, Risk Factors, and Outcome. Circulation 2020;142:114-28.
16. Bilaloglu S, Aphinyanaphongs Y, Jones S, et al. Thrombosis in hospitalized patients with COVID-19 in a New York City health system. JAMA 2020;324:799-801.
17. Clausen TM, Sandoval DR, Spliid CB, et al. SARS-CoV-2 infection depends on cellular heparan sulfate and ACE2. Cell 2020;183:1043-57.e15.
18. Ward ZJ, Bleich SN, Cradock AL, et al. Projected U.S. State-level prevalence of adult obesity and severe obesity. N Engl J Med 2019;381:2440-50.
19. Lumeng CN. Innate immune activation in obesity. Mol Aspects Med 2013;34:12-29.
20. Gustafson B. Adipose tissue, inflammation and atherosclerosis. J Atheroscler Thromb 2010;17:332-41.

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