Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Clinical Effect of Early administration of Tocilizumab Following the Initiation of Corticosteroid Therapy for Patients with COVID-19

Takaya Kawamata (, Yoshinori Tanino (, Takefumi Nikaido (, Hiroyuki Minemura (, Yuki Sato (, Ryuichi Togawa (, Natsumi Watanabe (, Ryuki Yamada (, Riko Sato (, Takumi Onuma (, Hikaru Tomita (, Mikako Saito (, Mami Rikimaru (, Yasuhiro Suzuki (, Yasuhiko Tsukada (, Kiwamu Nakamura (, Keiji Kanemitsu (, Ken Iseki (, Yoko Shibata (, PII: S1341-321X(22)00247-1 DOI: https://doi.org/10.1016/j.jiac.2022.08.021 Reference: JIC 1994 To appear in: Journal of Infection and Chemotherapy Received Date: 30 March 2022 Revised Date: 20 August 2022 Accepted Date: 24 August 2022

Please cite this article as: Kawamata ( T, Tanino ( Y, Nikaido ( T, Minemura ( H, Sato ( Y, Togawa ( R, Watanabe ( N, Yamada ( R, Sato ( R, Onuma ( T, Tomita ( H, Saito ( M, Rikimaru ( M, Suzuki ( Y, Tsukada ( Y, Nakamura ( K, Kanemitsu ( K, Iseki ( K, Shibata ( Y, Clinical Effect of Early administration of Tocilizumab Following the Initiation of Corticosteroid Therapy for Patients with COVID-19, Journal of Infection and Chemotherapy (2022), doi: https://doi.org/10.1016/j.jiac.2022.08.021.

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 Japanese Society of Chemotherapy and The Japanese Association for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.
Clinical Effect of Early administration of Tocilizumab Following the Initiation of Corticosteroid Therapy for Patients with COVID-19

Takaya Kawamata (kawamata@fmu.ac.jp)⁎, Yoshinori Tanino (ytanino@fmu.ac.jp)⁎⁎, Takefumi Nikaido (taken@fmu.ac.jp)⁎, Hiroyuki Minemura (hiromine@fmu.ac.jp)⁎, Yuki Sato (yukisato@fmu.ac.jp)⁎, Ryuichi Togawa (ryuichi@fmu.ac.jp)⁎, Natsumi Watanabe (natsumiw@fmu.ac.jp)⁎, Ryuki Yamada (aegis05@fmu.ac.jp)⁎, Riko Sato (riko-f@fmu.ac.jp)⁎, Takumi Onuma (takumi02@fmu.ac.jp)⁎, Hikaru Tomita (hikarut@fmu.ac.jp)⁎, Mikako Saito (saito-m@fmu.ac.jp)⁎, Mami Rikimaru (mamir@fmu.ac.jp)⁎, Yasuhiro Suzuki (yasuyasu@fmu.ac.jp)⁎, Yasuhiko Tsukada (ytsukada@fmu.ac.jp)⁎, Kiwamu Nakamura (kinakamu@fmu.ac.jp)⁎, Keiji Kanemitsu (kane2@fmu.ac.jp)⁎, Ken Iseki (ken@fmu.ac.jp)⁎, Yoko Shibata (shibatay@fmu.ac.jp)⁎.

Department of Pulmonary Medicine⁎, Department of Emergency and Critical Care Medicine⁎⁎, and Department of Infection Control⁎, Fukushima Medical University, Hikarigaoka 1, Fukushima 960-1295, JAPAN

* These authors contributed equally to this work.

Corresponding Author: Yoshinori Tanino, MD, PhD
Department of Pulmonary Medicine, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, JAPAN
Tel: (+81)24-547-1360; FAX: (+81)24-548-9366; E-mail: ytanino@fmu.ac.jp

All authors meet the ICMJE authorship criteria. KT and YT wrote the manuscript and contributed to the concept, study design, and data acquisition and interpretation. YoS provided supervision. All authors contributed to the data acquisition and critical revision of the manuscript. The final manuscript was read and approved by all authors.
Abstract

**Introduction:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first broke out in Wuhan in December 2019, and has since caused a global pandemic. The efficacy of several drugs has been evaluated, and it is now evident that tocilizumab has a beneficial effect, especially combined with corticosteroids, in patients with Coronavirus Disease 2019 (COVID-19). However, the optimal timing of tocilizumab administration has not yet been established. The goal of the present study was to determine the optimal timing of tocilizumab administration after starting corticosteroid therapy in patients with COVID-19.

**Methods:** We retrospectively analyzed the clinical characteristics of patients who were hospitalized for COVID-19 and treated with tocilizumab and corticosteroids in our hospital. The patients were divided into concurrent and sequential groups. The concurrent group received tocilizumab ≤ 24 hours after corticosteroids, and the sequential group received tocilizumab > 24 hours after corticosteroid administration.

**Results:** The baseline clinical characteristics of tocilizumab administration were similar between the two groups. White blood cell counts were significantly lower and C-reactive protein levels were significantly higher in the concurrent group than the sequential group. In the concurrent group, tocilizumab administration led to a
significant decrease in maximum body temperature. In addition, there were significantly more oxygen-free days in the concurrent group than in the sequential group. However, survival rate was not significantly different between the concurrent and the sequential groups.

**Conclusions:** In the combination therapy with tocilizumab and corticosteroids, early administration of tocilizumab after starting corticosteroid treatment is effective when treating COVID-19.

**Keywords:** Tocilizumab, Corticosteroids, COVID-19, SARS-CoV-2
Abbreviations

ARDS: Acute respiratory distress syndrome

CRP: C-reactive protein

COVID-19: Coronavirus Disease 2019

SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2

TCZ: Tocilizumab
Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) first broke out in Wuhan in December 2019, and has since caused a global pandemic. As of November 2021, the death toll of coronavirus disease 2019 (COVID-19) has exceeded five million people worldwide, and the world is facing a crisis.

SARS-CoV-2 infection causes cytokine release syndrome, leading to acute respiratory distress syndrome (ARDS) in patients with COVID-19\textsuperscript{1,2}. The RECOVERY trial group demonstrated that 10-day use of dexamethasone improved 28-day mortality in hospitalized patients with COVID-19\textsuperscript{3}. On the other hand, Interleukin-6 (IL-6) is considered to play important roles in the pathogenesis of COVID-19. A remarkable increase in IL-6 is suspected to disturb the innate immunity\textsuperscript{4}, and treatment with tocilizumab (TCZ), a humanized anti-IL-6R monoclonal antibody, was reported to improve mortality in patients with severe COVID-19\textsuperscript{5–7}. A meta-analysis showed that the efficacy of TCZ was more evident when used with corticosteroid therapy\textsuperscript{8}. However, the optimal timing of TCZ administration after starting corticosteroid therapy has not yet been established. The goal of the present study was to determine the optimal timing of TCZ administration in COVID-19 patients treated with corticosteroids.
Patients and Methods

Study design and setting

This single center retrospective observational study was performed at Fukushima Medical University Hospital. PCR-positive COVID-19 patients who were hospitalized between April 2020 and March 2021 were reviewed, and those who were treated with TCZ and corticosteroids were included. The research period of this study was prior to the spread of the Alpha variant in Fukushima Prefecture. Written informed consent for compassionate use of TCZ was obtained from all patients. The clinical characteristics were retrospectively analyzed, and the patients were divided into two groups according to the timing of TCZ administration after corticosteroid administration: a concurrent group, whose TCZ was administered up to 24 hours after corticosteroid administration; and a sequential group, whose TCZ was administered after 24 hours.

Assessment of COVID-19 severity was performed according to the definition issued by the Japanese Ministry of Health, Labor and Welfare: mild, patients without pneumonia or respiratory failure; moderate-1, patients with pneumonia but without respiratory failure; moderate-2, patients with pneumonia and respiratory failure (percutaneous oxygen saturation < 94% on room air) but do not require mechanical ventilation/extraorporeal membrane oxygenation (ECMO); or severe, patients with
pneumonia and respiratory failure who require mechanical ventilation/ECMO\textsuperscript{9}. The need for informed consent was waived because the study is retrospective. This study was approved by the Ethics Committee of Fukushima Medical University (approved number 2020-118).

**TCZ treatment**

Corticosteroids were started for moderate, severe or critical COVID-19 patients. Since there are no standard criteria for the combination of corticosteroids and TCZ, it was decided by each attending physician whether TCZ should be given to patients up to 24 hours after corticosteroids (the concurrent group) or not. Among the patients who started corticosteroid monotherapy, TCZ was added to those who had worsening symptoms or development of hypoxemia during the course (the sequential group). TCZ was administered at a dose of 400 mg or 800 mg intravenously. When clinical improvement was insufficient after the first dose, TCZ was re-administered after an interval of at least 8 hours. Standard treatments such as antibiotics, corticosteroids, heparin and oxygen therapy were continued at the physician's discretion.

**Data collection**

The main goal of the current study was to determine if early administration of TCZ after starting corticosteroid treatment is clinically effective. The efficacy was evaluated
by analyzing the duration of oxygen therapy, the duration of corticosteroid treatment and the survival rate. In addition, differences in laboratory data and adverse effects were compared between the concurrent and sequential groups. Regarding adverse effects, we analyzed blood specimens obtained within 28 days after TCZ administration, and compared the number of patients with severe neutropenia (neutrophils < 500/μL), severe thrombocytopenia (platelets < 25,000/μL), and/or bacteremia between the two groups.

Statistical analysis

The continuous variables are shown as mean and standard deviation and the categorical variables are shown as numbers and percentages. The Mann-Whitney U test was applied to the continuous variables, and the chi-square test or Fisher's exact test were used for the categorical variables. The Kaplan-Meier approach was used for survival analysis, and log-rank test was used to compare survival curves. P-values < 0.05 were considered statistically significant. SPSS for Windows version 25.0 (IBM Corp, Armonk, NY, USA) was used for the statistical analysis.

Results

Baseline characteristics of COVID-19 patients treated with TCZ.

One hundred and thirty COVID-19 patients were admitted to our hospital during the
study period, 50 of whom were treated with TCZ and corticosteroids: the concurrent group (n=32) and the sequential group (n=18). In the sequential group, TCZ was added at 5.39 ± 2.57 days after starting corticosteroids. The clinical characteristics of the patients in these two groups at admission are shown in Table 1. At the time of TCZ administration, despite no difference in P/F ratio or D-dimer levels, white blood cell counts and neutrophil fractions were significantly lower, and C-reactive protein (CRP) levels were significantly higher, in the concurrent group compared to the sequential group (Table 2). However, the severity of COVID-19 at the time of TCZ administration evaluated using the sequential organ failure assessment (SOFA\textsuperscript{10}) score, a simple scoring tool reported by Webb \textit{et al.}\textsuperscript{11}, DOAT\textsuperscript{12} score did not differ between the two groups. TCZ was administered significantly earlier from symptom onset in the concurrent group compared to the sequential group (7.53 ± 4.01 vs 9.83 ± 3.33 days, p = 0.034) (Table 1).

**Outcomes of COVID-19 patients**

The outcomes of the patients after TCZ administration are shown in Table 3. Regarding the concomitant medications during hospitalization, there was no difference between the two groups except for the proportion of dexamethasone use, which was higher in the sequential group (Table 1). In some patients, dexamethasone was
administered following methylprednisolone, or *vice versa*. TCZ administration led to a significant decrease in maximum body temperature and CRP levels in the concurrent group compared to the sequential group (Figure 2). In addition, the duration of oxygen therapy (13.9 ± 16.2 vs 22.8 ± 13.7 days, *p*=0.035) and corticosteroid treatment (14.8 ± 12.4 vs 24.3 ± 14.1 days, *p*=0.007) were significantly shorter in the concurrent group compared with the sequential group (Figure 1a, b). However, no significant difference was observed regarding mortality or intratracheal intubation period between the two groups (Figure 1c). Adverse effects such as hematological toxicity were similar between the groups during the observation period (Table 4 and Figure 2).

**Discussion**

In the present study, we showed that early administration of TCZ after starting corticosteroid treatment reduced the duration of both oxygen therapy and corticosteroid treatment. These results suggest that it is better to use TCZ as early as possible, probably concurrently with corticosteroid treatment in patients with severe COVID-19. To the best of our knowledge, this is the first report showing the efficacy of early TCZ administration after starting corticosteroid treatment.

The SARS-CoV-2 infection caused COVID-19 pandemic. The majority of COVID-
19 patients are mild; however, some patients develop acute respiratory failure leading to death. Wu et al. analyzed symptomatic patients with COVID-19, and reported that 5% of the patients became critically ill, with a mortality rate of 49%. Cytokine release syndrome is related to the development of acute respiratory failure such as ARDS. Although several inflammatory mediators are involved in cytokine release syndrome, IL-6 is considered to play various important roles in the pathogenesis of ARDS in COVID-19. These findings suggest that TCZ is clinically effective for the treatment of severe COVID-19. However, the results of randomized clinical trials conducted on TCZ during the early stages of the COVID-19 pandemic were inconsistent. The main causes of the inconsistency in the results of the trials are considered to be due to differences in timing of TCZ administration, disease severity and concomitant use of corticosteroids. Regarding optimal timing of TCZ administration, around the start of clinical deterioration may be best in order to obtain the maximum efficacy of TCZ. In the REMAP-CAP trial, which demonstrated that TCZ improved clinical outcomes of COVID-19, including survival, a 24-hour window after starting organ support such as invasive and non-invasive respiratory support in the intensive care unit was used for randomization as the clinical deterioration period. In another large randomized clinical trial, the RECOVERY trial in which improvement of survival due to TCZ treatment was
also demonstrated, randomization was performed around 10 days after onset of COVID-19 symptoms\textsuperscript{5}. In the RECOVERY study, patients with hypoxia and evidence of systemic inflammation indicated by increased levels of CRP were included. Although the timing of clinical deterioration did not depend on the timing of symptom onset, evaluation of the severity of hypoxia and levels of CRP might have contributed to the detection of clinical deterioration in the RECOVERY study. Another important cause of the inconsistency in the results of the previous trials is concomitant use of corticosteroids. Dexamethasone was reported to improve mortality in hospitalized COVID-19 patients who received either invasive mechanical ventilation or oxygen alone\textsuperscript{3}. In addition, a meta-analysis by the REACT Working Group showed that administration of systemic corticosteroids improved 28-day all-cause mortality in critically ill patients with COVID-19\textsuperscript{25}. Based on these results, corticosteroids are now regarded as one of the main therapies, and TCZ is usually used with corticosteroids in patients with COVID-19. However, the optimal timing of TCZ administration after starting corticosteroid therapy has not been determined, because corticosteroids were not used in around one-third of the reported COVID-19 patients in whom the effect of TCZ was analyzed\textsuperscript{26–28}. From the point of investigating the optimal timing of TCZ administration in severe COVID-19 patients, the results of the present study provide
valuable evidence, as corticosteroids were used in all patients.

This study has several limitations. First, this was a retrospective single center study with a relatively small sample size. Second, the inclusion criteria of the patients were not previously defined, and it is possible that the severity of COVID-19 was not uniform. Although clinical characteristics of the two groups were almost similar, some prognostic factors, such as P/F ratio and ferritin, were different. These differences between the groups may have affected the results. Third, because the timing of TCZ administration after corticosteroid therapy was not previously determined, disease severity when starting corticosteroid therapy varied between the groups. There is a possibility that more corticosteroid-resistant patients were included in the sequential group. The possibility cannot be ruled out completely, however, even though the clinical characteristics of the two groups were similar (Supplementary Table 1). Finally, the proportion of each type of corticosteroid used in the concurrent and sequential groups was different. Dexamethasone was used more frequently in the sequential group compared to the concurrent group. Because it has not been clarified whether the effect of methylprednisolone was similar to that of dexamethasone\textsuperscript{29–32}, the differences in the type of corticosteroids used in the two groups may have affected the results of the present study.
Conclusion

The present study demonstrated that TCZ may be more effective when administered concurrently with corticosteroids in clinically ill patients with COVID-19. However, further evidence is needed to draw a definitive conclusion.

Acknowledgement

None.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None.

References

[1] Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science
[2] Price CC, Altice FL, Shyr Y, Koff A, Pischel L, Goshua G, et al. Tocilizumab Treatment for Cytokine Release Syndrome in Hospitalized COVID-19 Patients: Survival and Clinical Outcomes. Chest 2020;158:1397-1408. https://doi.org/10.1016/j.chest.2020.06.006.

[3] The RECOVERY Collaborative Group. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med 2021;384:693-704. https://doi.org/10.1056/NEJMo2021436.

[4] Mazzoni A, Salvati L, Maggi L, Capone M, Vanni A, Spinicci M, et al. Impaired immune cell cytotoxicity in severe COVID-19 is IL-6 dependent. J Clin Invest 2020;130:4694-4703. https://doi.org/10.1172/JCI138554.

[5] The RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet 2021;397: 1637-1645. https://doi.org/10.1016/S0140-6736(21)00676-0.

[6] The REMAP-CAP Investigators. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med 2021;384:1491-1502. https://doi.org/10.1056/NEJMo2100433 (2021).
[7] Kewan T, Covut F, Al-Jagheer MJ, Rose L, Gopalakrishna KV, Akbik B. Tocilizumab for treatment of patients with severe COVID-19: A retrospective cohort study. eClinicalMedicine 2020;24:100418. https://doi.org/10.1016/j.eclinm.2020.100418.

[8] The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis. JAMA 2021;326:499-518. https://doi.org/10.1001/jama.2021.11330.

[9] Suzuki Y, Shibatay, Minemura H, Nikaido T, Tanino Y, Fukuhara A, et al. Real-world clinical outcomes of treatment with casirivimab-imdevimab among patients with mild-to-moderate coronavirus disease 2019 during the Delta variant pandemic. Int J Med Sci 2022;19:834-841. https://doi.org/10.7150/ijms.71132

[10] Vincent JL, Mendonca A, Cantraine F, Moreno R, Takala J, Suter P, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26:1793-1800. https://doi.org/10.1097/00003246-199811000-00016.
[11] Webb BJ, Levin NM, Grisel N, Brown SM, Peltan ID, Spivak ES, et al. Simple scoring tool to estimate risk of hospitalization and mortality in ambulatory and emergency department patients with COVID-19. PLoS One 2022;17:e0261508. https://doi.org/10.1371/journal.pone.0261508.

[12] Yoko S, Hiroyuki M, Yasuhito S, Takefumi N, Yoshinori T, Atsuro F, Ryuzo K et al. Development and external validation of the DOAT and DOATS scores: simple decision support tools to identify disease progression among nonelderly patients with mild/moderate COVID-19. https://www.medrxiv.org/content/10.1101/2021.12.13.21267698v1 [accessed 22 March 2022]

[13] Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA 2020;323:1239-1242. https://doi.org/10.1001/jama.2020.2648.

[14] Li P, Lu Z, Li Q, Wang Z, Guo Y, Cai C, et al. Administration Timing and Efficacy of Tocilizumab in Patients With COVID-19 and Elevated IL-6. Front Mol Biosci 2021;8:651662. https://doi.org/10.3389/fmolb.2021.651662.
[15] Guirao JJ, Cabrera CM, Jimenez N, Rincon L, Urra JM. High serum IL-6 values increase the risk of mortality and the severity of pneumonia in patients diagnosed with COVID-19. Mol Immunol 2020;128:64-68. https://doi.org/10.1016/j.molimm.2020.10.006.

[16] Zhu J, Pang J, Ji P, Zhong Z, Li H, Li B, et al. Elevated interleukin-6 is associated with severity of COVID-19: A meta-analysis. J Med Virol 2021;93:35-37. https://doi.org/10.1002/jmv.26085.

[17] Campochiaro C, Dagna L. The conundrum of interleukin-6 blockade in COVID-19. Lancet Rheumatol 2020;2:e579-e580. https://doi.org/10.1016/S2665-9913(20)30287-3.

[18] Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, 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. https://doi.org/10.1001/jamainternmed.2020.6820.

[19] Salvarani C, Dolci G. Massari M, Merlo DF, Cavuto S, Savoldi L, 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. https://doi.org/10.1001/jamainternmed.2020.6615.
[20] Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med 2020;383:2333-2344. https://doi.org/10.1056/NEJMo2028836.

[21] Veiga VC, Prats J, Farias DLC, Rosa RG, Dourado LK, Zampieri FG, 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. https://doi.org/10.1136/bmj.n84.

[22] Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021;384:20-30. https://doi.org/10.1056/NEJMo2030340.

[23] Rosas IO, Diaz G, Gottlieb RL, Lobo SM, Robinson P, Hunter BD, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. Intensive Care Med 2021;47:1258-1270. https://doi.org/10.1007/s00134-021-06507-x.

[24] Angriman F, Ferreyro BL, Burry L, Fan E, Ferguson ND, Husain S, et al. Interleukin-6 receptor blockade in patients with COVID-19: placing clinical trials into context. Lancet Respir Med 2021;9:655-664. https://doi.org/10.1016/S2213-2600(21)00139-9.
[25] The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA 2020;324:1330-1341. https://doi.org/10.1001/jama.2020.17023.

[26] Yang R, Xiong Y, Ke H, Chen T, Gao S. The role of methylprednisolone on preventing disease progression for hospitalized patients with severe COVID-19. Eur J Clin Invest 2020;50:e13412. https://doi.org/10.1111/eci.13412.

[27] Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020;180:934-943. https://doi.org/10.1001/jamainternmed.2020.0994.

[28] Fadel R, Morrison AR, Vahia A, Smith ZR, Chaudhry Z, Bhargava P, et al. Early Short-Course Corticosteroids in Hospitalized Patients With COVID-19. Clin Infect Dis 2020;71:2114-2120. https://doi.org/10.1093/cid/ciaa601.

[29] Fatima SA, Asif M, Khan K, Siddique N, Khan AZ. Comparison of Efficacy of Dexamethasone and Methylprednisolone in Moderate to Severe COVID 19 Disease. Ann Med Surg (Lond) 2020;60:413-416.
Figure legends

Figure 1. Clinical outcomes in the concurrent and sequential groups.

(a) Duration of oxygen therapy after corticosteroid treatment was significantly shorter in
the concurrent group compared to the sequential group (p = 0.035). (b) Duration of corticosteroid therapy was significantly shorter in the concurrent group compared to the sequential group (p = 0.007). (c) Survival rate was not significantly different between the concurrent and the sequential groups (p = 0.278).

**Figure 2. Time course of clinical parameters after starting TCZ treatment.**

(a) In the concurrent group, body temperature significantly decreased from baseline at 1 and 6 days after TCZ administration compared with the sequential group. (b, d) In the concurrent group, CRP levels were significantly higher and white blood cell counts were significantly lower on the day of TCZ administration compared with the sequential group. (c, e, f) There were no significant differences in ferritin levels, hemoglobin or platelets during the observation period between the two groups (* P < 0.05).
| Patients features                                      | Concurrent use (n=32) | Sequential use (n=18) | p-value |
|-------------------------------------------------------|-----------------------|-----------------------|---------|
| Age, years                                            | 65.8 ± 15.4           | 66.7 ± 11.9           | 0.430   |
| Sex, male                                             | 21 (65.6)             | 10 (55.6)             | 0.552   |
| Body mass index, kg/m²                                 | 25.6 ± 3.44           | 25.7 ± 3.16           | 0.936   |
| Severity, mild/moderate-1/moderate-2/severe           | 0/1/28/3              | 0/0/15/3              | 0.578   |
| SOFA                                                  | 2.47 ± 1.61           | 2.44 ± 1.04           | 0.700   |
| Simple scoring tool                                   | 8.52 ± 1.75           | 8.64 ± 1.63           | 0.633   |
| DOAT score                                            | 1.91 ± 0.73           | 1.83 ± 0.86           | 0.697   |
| Body temperature, °C                                   | 37.7 ± 0.97           | 37.3 ± 0.62           | 0.198   |
| Days between symptom onset and admission, days        | 5.06 ± 3.72           | 3.39 ± 2.45           | 0.128   |
| Days between symptom onset and TCZ administration, days| 7.53 ± 4.01           | 9.83 ± 3.33           | 0.034   |
| Comorbidities                                         |                       |                       |         |
| Smoking                                               | 15 (46.9)             | 8 (44.4)              | 1.000   |
| Arterial hypertension                                 | 21 (65.6)             | 8 (44.4)              | 0.232   |
| Type 2 diabetes mellitus                              | 11 (34.4)             | 8 (44.4)              | 0.552   |
| Chronic kidney disease                                | 12 (37.5)             | 5 (27.8)              | 0.548   |
| Concomitant medication                                 |                       |                       |         |
| Remdesivir                                            | 23 (71.9)             | 15 (83.3)             | 0.497   |
| Antibiotics                                           | 16 (57.1)             | 12 (66.7)             | 0.374   |
| Methylprednisolone                                    | 25 (78.1)             | 13 (72.2)             | 0.748   |
| Dexamethasone                                         | 9 (28.1)              | 12 (66.7)             | 0.016   |

Data are expressed as number (%) or mean ± standard deviation
| Laboratory data     | Concurrent use (n=32) | Sequential use (n=18) | p-value |
|---------------------|-----------------------|-----------------------|---------|
| White blood cells, /μL | 6730 ± 2410           | 10100 ± 3530          | 0.001   |
| Neutrophils, %      | 75.8 ± 10.5           | 89.6 ± 3.60           | <0.001  |
| Lymphocytes, %      | 16.8 ± 8.63           | 5.61 ± 2.20           | <0.001  |
| Monocytes, %        | 6.44 ± 2.71           | 4.50 ± 2.60           | 0.027   |
| Eosinocytes, %      | 0.56 ± 1.08           | 0.11 ± 0.47           | 0.085   |
| Basophils, %        | 0.31 ± 0.47           | 0.22 ± 0.43           | 0.499   |
| Hemoglobin, g/dl    | 13.0 ± 2.19           | 13.6 ± 1.57           | 0.337   |
| Platelets, ×10^4/μL | 22.3 ± 8.32           | 25.4 ± 9.15           | 0.284   |
| Albumin, g/dl       | 2.99 ± 0.53           | 2.86 ± 0.35           | 0.490   |
| AST, IU/ml          | 51.0 ± 41.6           | 49.6 ± 42.0           | 0.262   |
| LDH, IU/ml          | 364 ± 101             | 394 ± 135             | 0.724   |
| CRP, mg/dl          | 9.38 ± 5.15           | 6.14 ± 6.80           | 0.004   |
| BNP, pg/ml          | 47.4 ± 61.9           | 40.4 ± 60.5           | 0.746   |
| Ferritin, ng/ml     | 653 ± 541             | 872 ± 510             | 0.097   |
| D-dimer, μg/ml      | 3.58 ± 11.0           | 2.22 ± 1.86           | 0.324   |
| KL-6, U/ml          | 491 ± 740             | 535 ± 640             | 0.739   |
| P/F ratio, Torr     | 265 ± 65.2            | 222 ± 81.3            | 0.108   |

AST: aspartate aminotransferase, LDH: lactate dehydrogenase, CRP: C-reactive protein, BNP: brain natriuretic peptide, KL-6: Krebs von den lungen-6, P/F ratio: PO2/FiO2 ratio. Data are expressed as mean ± standard deviation.
Table 3. Outcomes after administration of tocilizumab

| Outcome                                      | Concurrent use (n=32) | Sequential use (n=18) | p-value |
|----------------------------------------------|-----------------------|-----------------------|---------|
| Duration of corticosteroid treatment, days   | 14.8 ± 12.4           | 24.3 ± 14.1           | 0.007   |
| Duration of oxygen therapy after TCZ administraion, days | 13.9 ± 16.2           | 22.8 ± 13.7           | 0.035   |
| Duration of intratracheal intubation, days   | 5.75 ± 16.7           | 5.44 ± 13.3           | 0.875   |
| All-cause Mortality                          | 2 (6.3)               | 3 (16.7)              | 0.278   |

Data are expressed as number (%) or mean ± standard deviation.
Table 4. Adverse effects after using tocilizumab

|                                      | Concurrent use (n=32) | Sequential use (n=18) | p-value |
|--------------------------------------|-----------------------|-----------------------|---------|
| Minimum white blood cells number, /μL| 3420 ± 1350           | 3450 ± 1490           | 0.944   |
| Minimum hemoglobin level, g/dl       | 11.4 ± 2.20           | 11.5 ± 1.58           | 0.895   |
| Minimum platelets number, 10⁴/μL    | 12.7 ± 5.92           | 22.6 ± 5.55           | 0.592   |
| Severe neutropenia                   | 0 (0)                 | 0 (0)                 | 1.000   |
| Severe thrombocytopenia              | 2 (6.3)               | 1 (5.3)               | 1.000   |
| Positive of blood bacterial culture  | 1 (3.1)               | 0 (0)                 | 1.000   |

Data are expressed as number (%) or mean ± standard deviation
