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.

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Original Article

Clinical effect of early administration of tocilizumab following the initiation of corticosteroid therapy for patients with COVID-19☆

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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 h after corticosteroids, and the sequential group received tocilizumab >24 h 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.

1. 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.

☆ 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.

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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

SARS-CoV-2 infection causes cytokine release syndrome, leading to acute respiratory distress syndrome (ARDS) in patients with COVID-19 [1,2]. The RECOVERY trial group demonstrated that 10-day use of dexamethasone improved 28-day mortality in hospitalized patients with COVID-19 [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 [4], and treatment with tocilizumab (TCZ), a humanized *anti*-IL-6R monoclonal antibody, was reported to improve mortality in patients with severe COVID-19 [5–7]. A meta-analysis showed that the efficacy of TCZ was more evident when used with corticosteroid therapy [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.

2. Patients and methods

2.1. 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 2021were 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 h after corticosteroid administration; and a sequential group, whose TCZ was administered after 24 h.

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/extracorporeal membrane oxygenation (ECMO); or severe, patients with pneumonia and respiratory failure who require mechanical ventilation/ECMO [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).

2.2. 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 h 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 h. Standard treatments such as antibiotics, corticosteroids, heparin and oxygen therapy were continued at the physician's discretion.

2.3. 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.

2.4. 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.

3. Results

3.1. 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

Table 1
Clinical characteriscs of COVID-19 patients at the time of starting tocilizumab treatment.

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/m^2	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.

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 [10]) score, a simple scoring tool reported by Webb et al. [11], DOAT [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).

4. 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 (Fig. 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 (Fig. 1a and b). However, no significant difference was observed regarding mortality or intratracheal intubation period between the two groups (Fig. 1c). Adverse effects such as hematological toxicity were similar between the groups during the observation period (Table 4 and Fig. 2).

5. 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 COIVD-19, and reported that 5% of the patients became critically ill, with a mortality rate of 49% [13]. Cytokine release syndrome is related to the development of acute respiratory failure such as ARDS [1,2]. 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 [14–16]. These findings suggest that TCZ is clinically effective for the treatment of severe COVID-19 [2,17]. However, the results of randomized clinical trials conducted on TCZ during the early stages of the COVID-19 pandemic were inconsistent [18–23]. 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 [24]. 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-h 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 [6]. 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 [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 [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 [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 [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,

Table 2
Laboratory data of COVID-19 patients at the time of starting tocilizumab treatment.

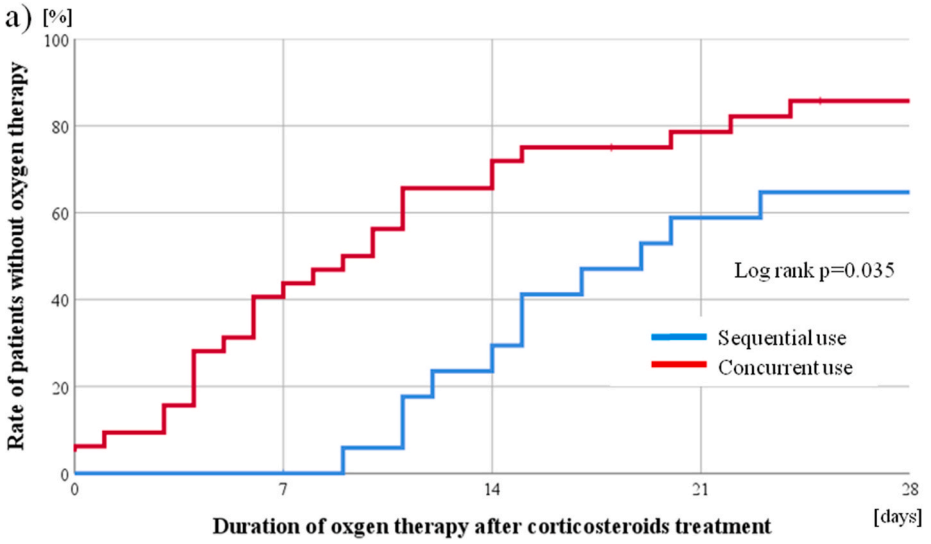
Laboratory data	Concurrent use (n = 32)	Sequential use (n = 18)	p-value
White blood cells,/μL	6730 ± 2410	10100 ± 3530	0.001
Neutrophils, %	75.8 ± 10.5	89.6 ± 3.60	<0.001
Lymphocytes, %	16.8 ± 8.63	5.61 ± 2.20	<0.001
Moonocytes, %	6.44 ± 2.71	4.50 ± 2.60	0.027
Eosinocytes, %	0.56 ± 1.08	0.11 ± 0.47	0.085
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

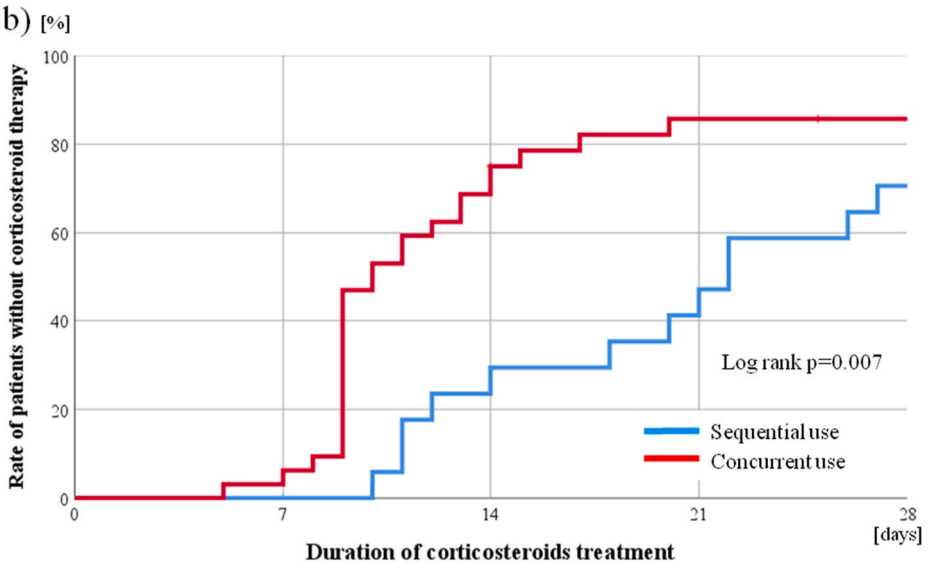
AST:aspartate aminotransferase, LDH: lactate dehydrogenase, CRP: C-reactive protein, BNP: brain natriuretic peptide, KL-6: Krebs von den lungen-6, P/F ratio: PaO_2/FiO_2 ratio. Data are expressed as mean ± standard deviation.

Table 3
Outcomes after administration of tocilizumab.

	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.





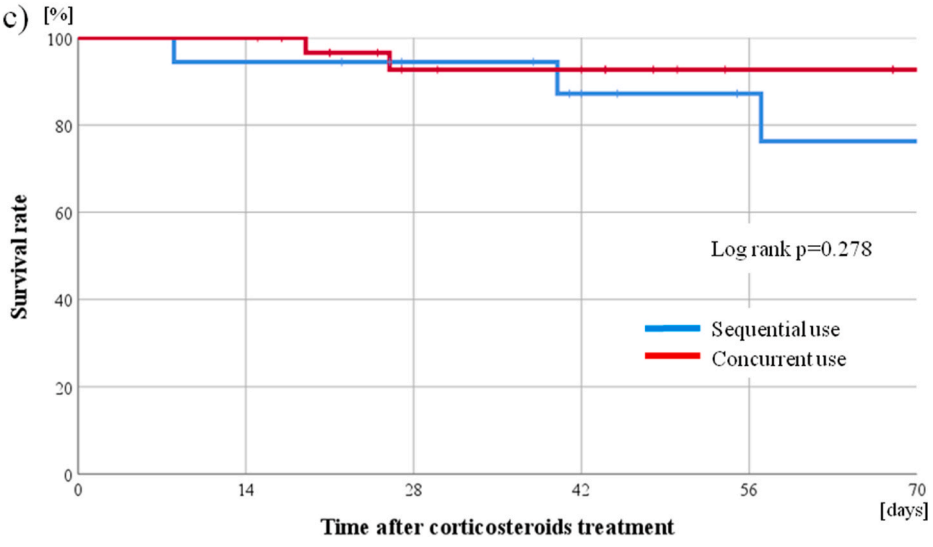


Fig. 1. Clinical outcomes in the concurrent and sequential groups.
(a) Duration of oxygen therapy after corticosteroid treatment was significantly shorter in the concurrent group compared to the sequential group ($p = 0.035$). (b) Duration of corticosteroid therapy was significantly shorter in the concurrent group compared to the sequential group ($p = 0.007$). (c) Survival rate was not significantly different between the concurrent and the sequential groups ($p = 0.278$).

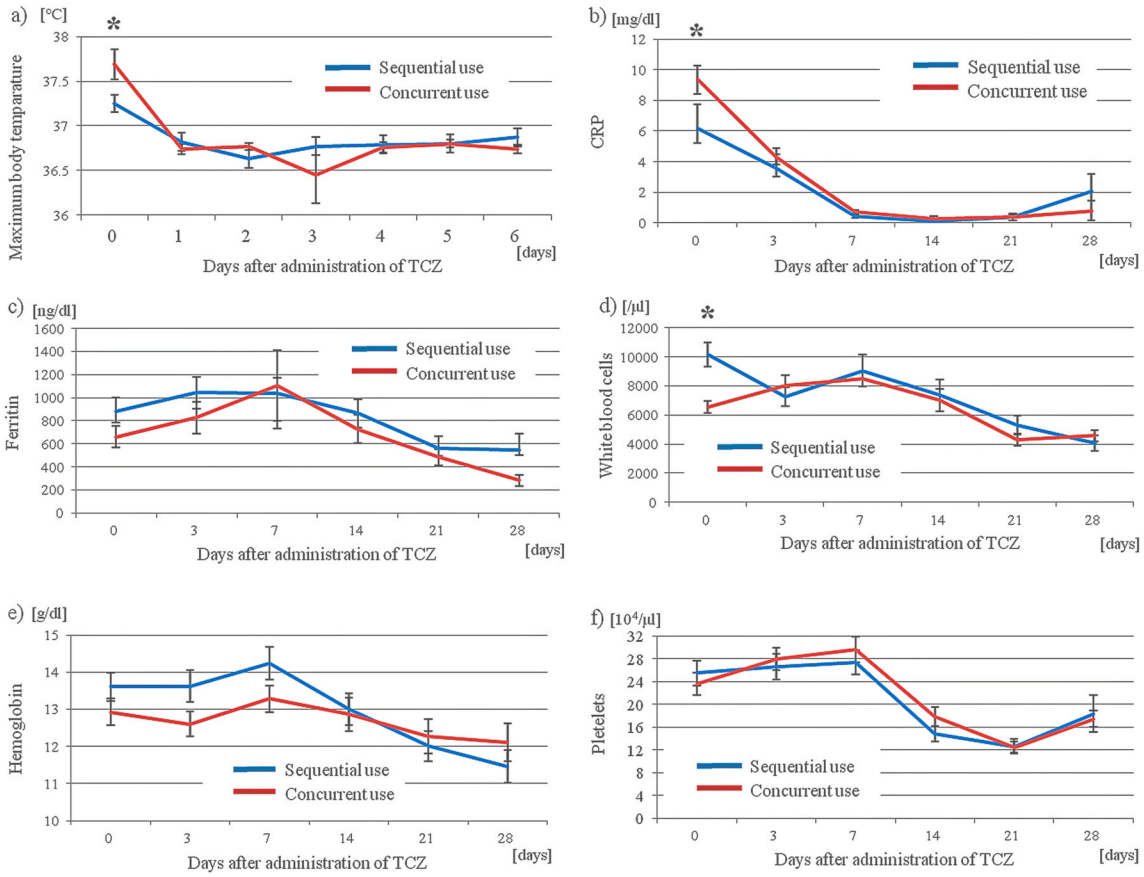


Fig. 2. Time course of clinical parameters after starting TCZ treatment.
(a) The concurrent group had a significantly higher maximum body temperature at baseline, but there was no significant change after tocilizumab administration. (b, d) In the concurrent group, CRP levels were significantly higher 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 (*$P < 0.05$).

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, 10^4/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.

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 [29–32], the differences in the type of corticosteroids used in the two groups may have affected the results of the present study.

6. 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.

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Declaration of competing interest

None.

Supplementary Table 1
Laboratory data of COVID-19 patients at the time of starting corticosteroid treatment

Laboratory data	Concurrent use (n = 14)	Sequential use (n = 6)	p-value
White blood cells,/μL	5760 ± 1238	6230 ± 2020	0.353
Neutrophils, %	73.1 ± 9.64	79.7 ± 10.2	0.109
Lymphocytes, %	19.4 ± 8.92	12.6 ± 6.47	0.131
Moonocytes, %	6.69 ± 2.51	6.83 ± 4.67	0.779
Eosinocytes, %	0.43 ± 0.94	0.01 ± 0.01	0.494

(*continued on next page*)

Supplementary Table 1 (*continued*)

Laboratory data	Concurrent use (n = 14)	Sequential use (n = 6)	p-value
Basophils, %	0.29 ± 0.47	0.83 ± 0.41	0.062
Hemoglobin, g/dl	12.5 ± 2.27	14.3 ± 2.64	0.153
Platelets, × 10^4/μL	20.1 ± 7.71	18.2 ± 5.60	0.779
Albumin, g/dl	2.91 ± 0.61	3.25 ± 0.39	0.274
AST, IU/ml	51.1 ± 42.6	68.3 ± 61.9	0.904
LDH, IU/ml	354 ± 102	374 ± 152	0.841
CRP, mg/dl	9.91 ± 5.53	9.21 ± 8.61	0.444
BNP, pg/ml	44.7 ± 54.4	57.6 ± 127	0.312
Ferritin, ng/ml	580 ± 329	1090 ± 1180	0.397
D-dimer, μg/ml	1.80 ± 2.08	1.57 ± 1.65	0.659
KL-6, U/ml	303 ± 124	263 ± 75.1	0.718
P/F ratio, Torr	263 ± 71.2	312 ± 96.7	0.239
SOFA score	2.78 ± 1.53	1.83 ± 0.983	0.179

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2022.08.021.

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