Journal of Acute Disease

Original Article

doi: 10.4103/2221-6189.326909 jadweb.org

Effect of pulsed corticosteroids and tocilizumab on hyperinflammation in COVID−19 patients with acute respiratory distress syndrome

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ABSTRACT

Objective: To compare the efficacy of pulsed-dose corticosteroids (≥250 mg methylprednisolone, 3 days) and tocilizumab in treating COVID-19-related hyperinflammation.

Methods: This prospective observational study included RT-PCR positive COVID-19 patients with acute respiratory distress syndrome, who were admitted to the COVID-19 Adult Intensive Care Unit of Prof Dr. Murat Dilmener Emergency Hospital (Istanbul, Turkey) between December 1, 2020 and February 28, 2021. Clinical, laboratory and radiological examinations were used to diagnose COVID-19 associated hyperinflammation. Three cohort groups were formed: the pulsed-dose corticosteroids group (250 mg methylprednisolone for 3 days), the tocilizumab group (8 mg/day single dose or 400 mg/day for 2 days), and the combined group (pulsed-dose corticosteroid+tocilizumab). The difference in mortality rates among the groups was compared primarily. The most common cause(s) of death was determined. Furthermore, adverse events (secondary infection, acute kidney injury, arrhythmia, gastrointestinal system bleeding) for 28 days were recorded.

Results: A total of 60 patients were included in this study, with 20 patients in each group. There was no statistically significant difference between the 3 groups in mortality rates (55% in the pulsed corticosteroid group, 60% in the tocilizumab group, 50% in the combined group, χ^2=0.404, P=0.817). Infectious causes were found to be the most common cause of mortality in all the three groups, and no difference was found between them (χ^2=0.404, P=0.817). There was also no difference in the development of adverse events such as secondary infection, acute kidney injury, arrhythmia, and gastrointestinal bleeding among the groups (P>0.05).

Conclusions: Corticosteroids can be used instead of tocilizumab to treat hyperinflammation in COVID-19 patients with acute respiratory distress syndrome .

KEYWORDS: COVID-19; Acute respiratory distress syndrome; Hyperinflammation; Pulse dose steroid; Tocilizumab

1. Introduction

In the year of 2019, the outbreak of coronavirus disease 2019 (COVID-19) swept over the whole world irresistibly. World Health Organization (WHO) proclaimed it a pandemic on March 11, 2020, after it spread to many parts of the world[1]. COVID-19 continues to threaten global public health since its inception. As of May 1, 2021,

Significance

There are large series of randomized controlled studies about tocilizumab treatment reducing mortality in hospitalized COVID-19 patients with hypoxemia and increased C-reactive protein level. However, there aren't enough randomized controlled studies on the use of pulsed-dose corticosteroids for this purpose. In this prospective observational study, no difference was found between pulsed-dose corticosteroid and tocilizumab treatments in terms of mortality rates and side effects in COVID-19 ARDS patients admitted to the intensive care unit.

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How to cite this article: Aslan M, Sabaz MS, Yilmaz R, Aşar S, Şeker YT, Hergünsel GO. Effect of pulsed corticosteroids and tocilizumab on hyperinflammation in COVID-19 patients with acute respiratory distress syndrome. J Acute Dis 2021; 10(5): 195-201.

Article history: Received 17 May 2021; Revision 13 July 2021; Accepted 20 July 2021; Available online 4 October 2021

there had been 150989419 confirmed COVID-19 cases and 3173576 deaths, according to WHO data[2].

SARS-CoV-2 uses the ACE-2 receptor to enter the cell in the human body[3]. SARS-CoV-2 infection can cause a wide range of clinical manifestations, ranging from asymptomatic to life-threatening diseases, in an average of 22 d (18-25 d) from disease onset to clinical recovery[4].

The first stage of COVID-19 disease is relatively mild, with nonspecific symptoms such as fatigue, fever, myalgia, dry cough, and diarrhea. The virus primarily affects the lower respiratory tract, intestines, and nasopharynx as it is proliferating in the host cell. Mild respiratory and systemic symptoms predominate all the presentations[5]. During the second stage of the infection [about the 7th day of the onset (4th-9th day)], when patients develop viral pneumonia that induces dyspnea or is accompanied by bilateral penetration and a ground-glass appearance, hospitalization is requested[5]. In the third stage of the disease, a small proportion of patients progress to the most serious type, which is defined by acute respiratory distress syndrome (ARDS) alone or in combination with the extrapulmonary systemic hyperinflammatory syndrome, often referred to as cytokine storm syndrome (CSS)[6]. This severe manifestation of COVID-19 occurs 7-14 d after disease onset[5]. At this stage, the viral load reduces, and the present pathology is the result of hyperinflammation rather than viral load[7-8]. As a result, immunomodulatory therapy may be more effective than antiviral therapy at this stage.

CSS is a term that refers to a group of hyperinflammatory clinical syndromes that include hemophagocytic lymphohistiocytosis, macrophage activation syndrome, macrophage activation-like syndrome in sepsis, and cytokine release syndrome[6,7,9,10]. Some patients with particularly severe disease present hyperinflammatory states characterized by extremely high C-reactive protein (CRP), ferritin, and D-dimer[4,5,7].

It is reported that corticosteroids and anti-cytokines may be effective in the treatment of hyperinflammation associated with COVID-19[11-17]. Although prospective randomized studies have shown that tocilizumab is beneficial to CSS treatment for a variety of reasons, a limited number of available studies on the use of pulsed corticosteroid (PDC) in COVID-19 disease are contradictory[12,13,18,19]. Treatment with tocilizumab (IL-6 receptor antagonist) is not always available due to the cost, distribution, and supply issues. In these cases, pulsed corticosteroid dosing (250 mg/d methylprednisolone or equivalent, for 3 d) may be an alternative. Tocilizumab can also be used if the acute phase reactan (CRP, ferritin) values are not improved after 3 d of PDC therapy, and clinical deterioration persists[14]. The risk of secondary infections, on the other hand, can increase as a result of the immunosuppression caused by these treatments.

This study aims to compare the efficacy of PDC and tocilizumab in the treatment of hyperinflammation in COVID-19 patients with mild, moderate, and severe ARDS in the intensive care unit (ICU).

2. Patients and methods

2.1. Study design

This prospective observational study was conducted at COVID-19 ICU in Prof Dr. Murat Dilmener Emergency Hospital (Istanbul, Turkey) between December 1 2020 and February 28 2021.

2.2. Study population

Inclusion criteria: (1) All 445 adult (≥18 years old) ICU patients with a positive COVID-19 reverse transcriptase-polymerase chain reaction (RT-PCR, Bio-Speedy COVID-19 RT-qPCR detection Kit-Bio-axis Turkey) test; (2) Patients with increased acute phase reactants due to hyperinflammation, increased respiratory support, or who experienced ARDS or multiple organ dysfunction syndrome during the first week after ICU admission.

Exclusion criteria: (1) Patients with co-infections (evidence of concurrent bacterial or fungal infection at ICU admission); (2) Patients who developed mortality within the first 2 d of ICU admission; (3) Patients with renal failure who required renal replacement therapy; (4) Patients with end-stage liver disease, malignant neoplastic disease, pregnant women; (4) Patients whose informed consent could not be obtained.

2.3. Ethical consideration

Informed consent was obtained in writing from all patients, either directly from themselves or by their legal guardians. Ethical approval of the study protocol was obtained from the Ethics Committee of Health Sciences University Bakırköy DR. Sadi Konuk Training and Research Hospital Clinical Practices Ethics Committee (Decision-number: 2020-25-21, Date: 21.12.2021).

2.4. Procedures

SARS-CoV-2 infection was detected by nasal+oropharyngeal swab or tracheal aspirate using RT-PCR test. Treatment of COVID-19 ARDS patients followed the WHO COVID-19 clinical management guidelines[20]. Favipiravir (2×1600 mg on the first day, then 2×600 mg) treatment for antiviral therapy was completed in 5 d as part of routine treatment. Low molecular weight heparin (20.1 mg/kg, per day) and prophylactic antibiotic therapy (piperacillin/tazobactam 44.5g, 3 d) were initiated. Additionally, the WHO's guideline on the use of corticosteroids in the COVID-19 pandemic recommends 6 mg/day dexamethasone or the equivalents (40 mg methylprednisolone, 200 mg hydrocortisone) for 7-10 d in COVID-19 patients who require respiratory support, and this dose was administered to patients as part of routine treatment[21].

Diagnosis of hyperinflammation in COVID-19 is at least as one of the follows: (1) CRP concentration 150 mg/L; (2) CRP doubled within 24 h with clinical worsening; (3) Increased need for

respiratory support within 24-48 h; (4) Ferritin concentration≥1500 μg/L or ferritin≥700 μg/L doubled within 24 h; (5) CRP concentration≥50 mg/dL and ferritin concentration≥700 μg/L. In addition, accompanying high fever (≥38 ℃), elevated neutrophil/lymphocyte ratio (≥10), D-dimer, thrombocyte, neutrophil, lymphocyte, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH) values were recorded. These cutoff values were determined through an examination of the authors' clinical observations and discussions in the literature[5,7,9-11,13,14,22].

A single principal physician who followed each patient determined the diagnosis and treatment of hyperinflammatory response to COVID-19. The responsible investigator followed, recorded, and assessed each patient's demographic, laboratory, and clinical data. These patients diagnosed with COVID-19 associated hyperinflammation were divided into three cohort groups: the PDC group received 3 d of PDC treatment, the tocilizumab group received tocilizumab (8 mg/d single dose or 400 mg/day for 2 d) treatment, and the combined group received tocilizumab (8 mg/d single dose or 400 mg/d for 2 d) after 3 d of PDC treatment.

Thorax CT scans of COVID-19 patients were regularly performed before ICU admission, and daily arterial blood gas measurements were taken at the beginning on the day of hospitalization. The diagnosis of ARDS was made using the 2012 Berlin criteria and was classified as mild ($<200 PaO_2/FIO_2 \leq 300$), moderate ($100<PaO_2/FIO_2 \leq 200$), or severe ($PaO_2/FIO_2 \leq 100$)[23].

Demographics of the patients on the day of ICU admission, previous medical treatment, COVID-19 time of onset of symptoms, Acute Physiology and Chronic Health Evaluation (APACHE) Ⅱ, and Sequential Organ Failure Assessment (SOFA) disease severity scores

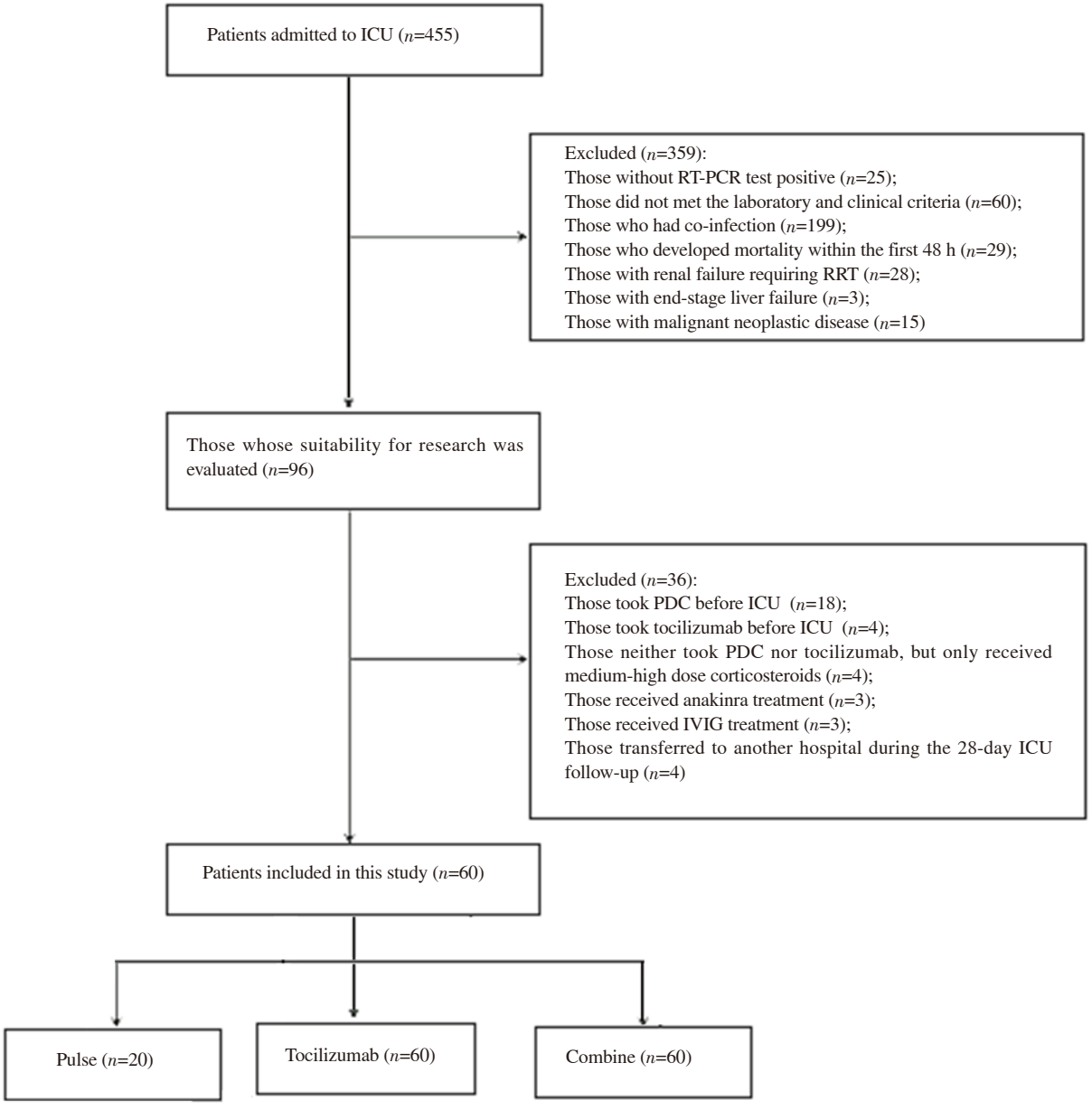

Figure 1. The study flowchart. ICU: Intensive care unit; RRT: Renal replacement treatment; PDC: Pulse dose of corticosteroid; IVIG: Intravenous immunolgobulin.

were recorded. The Charlson Comorbidity Index was calculated by recording the presence of comorbidities from medical records or the patients themselves.

From the day PDC or tocilizumab therapy was initiated until discharge, death, or 28-day follow-up, respiratory support and laboratory tests (hemogram, coagulation profile, creatinine, AST, ALT, LDH, CRP, ferritin, procalcitonin, D-dimer, troponin-Ⅰ, serum electrolyte concentrations daily), culture results, and clinical status for infection detection (received in case of fever or increased infection parameters) were recorded.

During the 28-day follow-up period, undesired adverse conditions [acute kidney injury (AKI), GIS bleeding, arrhythmia and others] were identified and recorded, regardless of whether they were related to the medicalcare used or not. The diagnosis of AKI was made according to the KDIGO criteria[24].

2.5. End points

The difference in 28-day ICU mortality rates among the three cohort groups was assessed as the primary outcomes. The most common cause(s) of death was determined by the following physicians. The causes of death were classified as respiratory (death due to any hypoxic condition), cardiac (arrhythmia, myocardial infarction, sudden cardiac arrest), infectious (bacterial sepsis, secondary infections), and other reasons.

The difference among the groups in terms of mean mechanical ventilation duration, the average length of stay in the ICU, and the development of adverse events (secondary infection, acute kidney injury, arrhythmia, gastrointestinal system bleeding) for 28 d was evaluated) for 28 d was evaluated as the secondary outcomes.

2.6. Statistical analysis

The SPSS 22.00 software was used to analyze the data obtained in the study. The Shapiro-Wilk test was used to determine if the data were normally distributed. Categorical variables are given as frequency (n) and percentage (%), numerical variables mean ± standard deviation or median and interquartile intervals (IQR). One Way Anova test was used for comparison of numerical data. When One Way Anova assumptions could not be achieved, Kruskal Wallis test was used. For categorical variables, the *Chi*-square test was used, and Fisher's exact test was used when the *Chi*-square test's

Table 1. Demographic and baseline information of the patients.

Parameter	Pulse–dose corticosteroid group	Tocilizumab group	Combined group	$H/\chi^2/F$	P
Age	62.5 (49.5-77.5)	54.0 (50.0-64.0)	63.0 (56.0-70.5)	5.928	0.052
Gender				0.616	0.735
Female	7 (35%)	7 (35%)	5 (25%)	-	-
Male	13 (65%)	13 (65%)	15 (75%)	-	-
BMI, kg/m^2	26.1 (25.4-27.7)	25.9 (24.6-27.6)	27.1 (25.7-28.5)	0.364	0.881
CCI	2 (0-4)	1 (1-2)	1 (0-3)	3.919	0.141
Pre–admission treatment					
Favipiravir use, n (%)	20 (100%)	20 (100%)	20 (100%)	0.000	>0.999
Favipiravir usage period, d	5.00±1.06	5.94±1.47	5.41±1.31	2.159	0.340
Steroid use, n (%)	13 (65%)	17 (85%)	12 (60%)	3.333	0.189
Steroid usage time, d	4 (3-5)	5 (4-7)	5 (2-5)	4.628	0.099
Admission clinical and laboratory data					
Symptom onset time, d	12 (9-15)	12 (11-14)	11 (10-15)	0.281	0.869
APACHE Ⅱ score	16 (10-23)	13 (10-18)	15 (11-18)	0.745	0.689
SOFA score	5 (4-7)	5 (4-6)	6 (4-7)	0.340	0.844
ARDS grade				0.763	0.943
Mild	9 (45%)	11 (55%)	9 (45%)	-	-
Moderate	6 (30%)	5 (25%)	7 (35%)	-	-
Severe	5 (25%)	4 (20%)	4 (20%)	-	-
High fever (>38 ℃)	4 (20%)	12 (60%)	7 (35%)	6.910	0.032
CRP, mg/L	127 (94-151)	141 (112-192)	158 (146-175)	2.466	0.219
Ferritin, ng/mL	1448 (823-2958)	1459(1183-2346)	1375 (840-1846)	1.960	0.375
D–dimer, mcg/mL	1.42 (0.76-3.58)	1.11 (0.65-2.05)	1.20 (0.75-1.40)	1.460	0.482
Lymphocyte, ×10^3 cells/μL	0.66 (0.42-0.84)	0.52 (0.25-0.76)	0.75 (0.62-1.08)	3.996	0.136
Neutrophil, ×10^3 cells/μL	8.80±3.90	9.14±4.42	11.05±1.14	2.575	0.242
Neutrophil/lymphocyte ratio>10, n (%)	19 (95%)	17 (85%)	14 (70%)	4.560	0.102
Platelet, ×10^9/L	88±19	62±14	97±21	2.079	0.388
AST, IU/L	68 (46-90)	49 (42-58)	40 (33-49)	0.019	0.990
ALT, IU/L	67 (42-84)	51 (34-121)	42 (22-69)	1.539	0.463
LDH, IU/L	533 (500-713)	552 (431-698)	529 (428-641)	0.760	0.684
Procalcitonin, ng/mL	0.23 (0.08-0.28)	0.14 (0.10-0.29)	0.24 (0.14-0.34)	3.887	0.143

BMI: Body mass index; CCI: Charlson comorbidity index; APACHE Ⅱ: Acute Physiology and Chronic Health Evaluation Ⅱ; SOFA: Sequential Organ Failure Assessment; ARDS: Acute respiratory distress syndrome; CRP: C-reactive protein; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; LDH: Lactate dehydrogenase.

conditions were not met. The significant level of this study was set at α=0.05.

3. Results

This study included 60 patients who met the study's inclusion criteria, and they were divided into three groups: the PDC group, the tocilizumab group, and the combined group, with 20 patients in each group (Figure 1). Table 1 shows the demographic and baseline information of the patients in the 3 cohort groups.

Rates of antiviral (favipiravir) and anti-inflammatory (corticosteroid) treatment use (medium to high dose) by patients before ICU admission were similar among the 3 groups (P>0.999 and P=0.189, respectively).

On the first day of the study, there was no difference in the APACHE Ⅱ and SOFA scores among the groups (P=0.689 and P=0.844, respectively). Similarly, there was no difference among the 3 groups in severity of ARDS (mild, moderate, severe) (P=0.943).

In the evaluation of the patients in terms of the presence of high fever (≥38 ℃) at ICU admission, significant difference were noted among the three groups (P=0.032).

On the day of initiation of pulse dose steroid or tocilizumab treatment, CRP, ferritin, procalcitonin, D-dimer, AST, ALT, LDH, neutrophil, and lymphocyte laboratory mean values were similar among the 3 groups. Additionally, there was no difference in the percentage of patients with neutrophils/lymphocytes>10 among the groups (P=0.102) (Table 1).

ICU mortality of the patients is shown in Table 2. The 28-day mortality rate was 55% (11 patients) in the pulse-dose corticosteroid group, 60% (12 patients) in the tocilizumab group, and 50% (10 patients) in the the combined group. There was no statistically significant difference was determined regarding the 28-day mean mortality rates among the 3 groups (P=0.817). In addition, infection was the most common cause of mortality in all groups, and no difference was found among the groups in causes of death (P>0.05). In terms of the mean duration of mechanical ventilation for 28 d, the average length of stay in the ICU, and the development of adverse events (secondary infection, AKI, arrhythmia, GIS bleeding), no statistically significant differences were observed between the groups.

4. Discussion

In the current study, no difference was determined in 28-day mortality rates, mechanical ventilation period, or length of stay in the intensive care unit between patients treated with pulse-dose corticosteroid, tocilizumab, or both of these treatments for hyperinflammation in COVID-19 ARDS patients. However, the RECOVERY working group demonstrated a 4% decrease in mortality and improved clinical outcomes with the combined use of tocilizumab in 2 022 patients with hypoxemia and systemic inflammation hospitalized due to COVID-19, compared to those receiving standard treatment only (2 094 patients)[17]. A relatively low dose of corticosteroids (6 mg dexamethasone, 40 mg prednisolone, or equivalent for up to 10 d) has been shown to decrease mortality in COVID-19 patients requiring respiratory support[16,21]. However, the benefit of treating COVID-19 associated hyperinflammation with higher doses of corticosteroids has remained unknown. In a recent study promoting the use of pulsed dose corticosteroids, it was discovered that mortality rates were significantly lower in the pulse dose methylprednisolone group than in the standard treatment group in 68 severe COVID-19 patients in the early pulmonary phase of the disease[18]. Rubio *et al*. performed a retrospective observational study to determine the efficacy of pulse-dose corticosteroid use in patients with COVID-19 related cytokine storm. They classified 92 patients into 3 groups: Those who received only pulse-dose corticosteroid, those who received only tocilizumab, and those who received both pulse-dose corticosteroid and tocilizumab. The combined group was found to have the lowest mortality rate [5 (8.3%)][13] compared to other 2 groups [1 (11.1%), 1 (4.4%), respectively, P=0.04]. Rodrguez-Bano *et al*. conducted an observational study, included 778 patients in 60 hospitals in Spain with laboratory- and clinically confirmed hyperinflammation. In terms of 21-day intubation and mortality development, patient groups receiving tocilizumab, intermittent-

Table 2. Primary and secondary outcome measurements by treatment groups.

Parameter	Pulse–dose corticosteroid group	Tocilizumab group	Combined group	H/χ^2	P
Mortality	11 (55%)	12 (60%)	10 (50%)	0.404	0.817
Causes of mortality					
Infection	9 (45%)	10 (50%)	8 (40%)	0.404	0.817
Hypoxemic	1 (5%)	1 (5%)	2 (10%)	0.536	0.765
Cardiac	1 (5%)	1 (5%)	0 (0%)	1.034	0.596
MV duration	9 (8-12)	11 (7-18)	11 (10-16)	1.982	0.371
ICU stay duration	9 (8-12)	14 (9-17)	12 (9-16)	5.655	0.059
Adverse events					
Secondary infection	11 (55%)	10 (50%)	11 (55%)	0.134	0.935
AKI	8 (40%)	6 (30%)	6 (30%)	0.600	0.741
Arrhythmia	2 (10%)	4 (20%)	3 (15%)	0.784	0.676
GIS bleeding	1 (5%)	1 (5%)	1 (5%)	0.000	1.000

MV: Mechanical ventilation, ICU: Intensive care unit; AKI: Acute kidney injury; GIS: Gastrointestinal system.

high dose steroids, pulse-dose corticosteroid, or combined therapy were compared to the control group of 344 patients who did not receive treatment. The mortality rate in the tocilizumab group was found to be the lowest (P<0.001), and the mortality rate in the pulsed corticosteroid group was found to be lower than the other groups (P=0.06)[14]. Unlike our study, both research evaluating the use of tocilizumab and pulsed corticosteroid involved patient groups (non-intubated) with an earlier stage of disease and less severe disease. Because this research was performed on a more severe patient group, no significant difference in the findings of the studies mentioned above.

One of the problems associated with the combined use of pulsed corticosteroid, tocilizumab, or both in the development of secondary infections and other adverse events. In this study, no statistically significant difference in secondary infection development was identified among the groups. At the same time, secondary infectious causes were the most common cause of mortality, accounting for 45% in the pulsed corticosteroid group, 50% in the tocilizumab group, and 40% in the combined group. But, are these high secondary infection rates due to COVID-19 disease-induced immunodeficiency or the immunosuppressive treatment used? Otherwise, it could not be differentiated whether it was related to primary healthcare or not. Kimmig *et al*. performed a retrospective study of the development of secondary infection in 111 critical COVID-19 patients (54 who received tocilizumab, 57 did not). In the study, it was found that the bacterial and fungal secondary infection rate was higher in the group that used tocilizumab than in the group that did not[25]. Rodrguez-Bano *et al*. conducted a study, in which no difference in secondary infection or gastrointestinal system bleeding was observed between the groups treated with pulsed corticosteroid and those treated with tocilizumab[14].

There were no differences in terms of ARDS severity levels (mild, moderate, severe) between the groups in this study. It was found that 22% of the patients included in the study had a combination of ARDS and hyperinflammatory responses. It is shown that 15%-40% of patients with COVID-19 associated pneumonia developed ARDS, which is the major cause of morbidity and mortality[9,26].

There was no difference in mean age, gender, BMI, Charlson SA values, disease severity scores, and laboratory biomarkers between the groups in the current study. However, high fever (38℃) was statistically lower in the pulsed corticosteroid (4 patients, 20%) than in the tocilizumab group (12 patients, 60%), but there was no statistical difference among the pulsed corticosteroid group, the combined group, and the tocilizumab combined group. There was no statistically significant difference between steroid and favipiravir usage rates before ICU admission, it may be highly related to steroid use (pulse-dose corticosteroid of 65%, actemra of 85%, and combined of 60%).

This study was conducted as a single-center study and had a relatively small sample size. The small sample size may have resulted in fewer clinical incidents. On this issue, prospective randomized controlled studies with a larger sample size should be conducted.

In conclusion, the use of pulsed corticosteroid alone could be a viable alternative to tocilizumab treatment in patients with ARDS associated with COVID-19 disease who experience hyperinflammation. Due to the low cost, ease of transportation, and availability of corticosteroids, they can allow for earlier treatment of the COVID-19 associated hyperinflammatory response. Although there is no statistically significant difference between the groups in terms of secondary infection or adverse events related to the combined treatment of tocilizumab and pulse-dose corticosteroid, the high rates of secondary infection and infectious causes cannot be ignored.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

Study design: M.A., Y.T.Ş., G.O.H.; Data collection and analysis: M.A., R.Y.; Manuscript writing: M.A, M.S.S, R.Y., Y.T.Ş., G.O.H.; Statistical expertise: M.S.S.; Critical revision for important intellectual content: M.A., M.S.S., Y.T.; Contributed to the final version of the manuscript: M. A., M.S.S, S.A.

References

[1] World Health Organization. Coronavirus disease (COVID-19) outbreak-About the virus. [Online] Available from: www.euro.who.int. [Accessed on July 11 2021].

[2] Wold Health Organization. WHO Coronavirus Disease (COVID-19) Dashboard. [Online] Available from: https://covid19.who.int/. [Accessed on May 1 2021].

[3] Lu RJ, Zhao X, Li J, Niu PH, Yang B, Wu HL, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet* 2020; **395**(10224): 565e574.

[4] Amigues I, Pearlman AH, Patel A, Reid P, Robinson PC, Sinha R, et al. Coronavirus disease 2019: investigational therapies in the prevention and treatment of hyperinflammation. *Expert Rev Clin Immunol* 2020; **16**(12): 1185-1204.

[5] Zhou F, Yu T, Du RH, Liu Y, Liu ZB, Xiang J, et al. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; **395**(10229): 1054-1062.

[6] Henderson LA, Canna SW, Schulert GS, Volpi S, Lee PY, Kernan KF, et al. On the alert for cytokine storm: immunopathology in COVID-19. *Arthritis Rheumatol* 2020; **72**(7): 1059-1063.

[7] Manson JJ, Crooks C, Naja M, Ledlie A, Goulden B, Liddle T, et al. COVID-19-associated hyperinflammation and escalation of patient care: a retrospective longitudinal cohort study. *Lancet Rheumatol* 2020; **2**(10):

e594-e602.

[8] Joynt GM, Wu WKK. Understanding COVID-19: What does viral RNA load really mean? *Lancet Infect Dis* 2020; **20**(6): 635-636.

[9] Gustine JN, Jones D. Immunopathology of hyperinflammation in COVID-19. *Am J Pathol* 2021; **191**(1): 4-17.

[10]Webb BJ, Peltan ID, Jensen P, Hoda D, Hunter B, Silver A, et. al. Clinical criteria for COVID-19 associated hyperinflammatory syndrome. *Lancet Rheumatol* 2020; **2**(12): e754-e763.

[11]Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* 2020; **395**(10229): 1033-1034.

[12]TC Sağlık Bakanlığı Halk Sağlığı Genel Müdürlüğü. COVİD-19 Antisitokin-Antiinflamatuar Tedaviler, Koagülopati Yönetimi, Bilimsel Danışma Kurulu Çalışması, 7 Kasım 2020. [Online] Available from: https://covid19.saglik.gov.tr/TR-66341/antisitokin-antiinflamatuar-tedaviler-koagulopati-yonetimi.html. [Accessed on July 11 2021].

[13]Rubio JLC, de Dios Luna del Castillo J, de la Hera Fernández J, Arrabal EG, Ruiz MC, Centeno NO. Effectiveness of corticoid pulses in patients with cytokine storm syndrome induced by SARS-CoV-2 infection. *Med Clin (Barc)* 2020; **155**(4): 159-161.

[14]Rodríguez-Bano J, Pachon J, Carratala J, Ryan P, Jarrín I, Yllescas M, et al. Treatment with tocilizumab or corticosteroids for COVID-19 patients with hyperinflammatory state. *Clin Microbiol Infect* 2021; **27**(2): 244-252.

[15]The REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM. Nichol AD. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. *N Eng J Med* 2021; **384**(16): 1491-1502.

[16]RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Malham M, Bell JL. Dexamethasone in hospitalized patients with COVID-19. *N Eng J Med* 2021; **384**(8): 693-704.

[17]RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (recovery): A randomised, control, open-label, platform trial. *Lancet* 2021; **397**(10285): 1637-1645.

[18]Edalatifard M, Akhtari M, Salehi M, Naderi Z, Jamshidi A, Mostafaei S, et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients. *Eur Respir J* 2020; **56**(6): 2002808.

[19]Sauñe PM, Bryce-Alberti M, Portmann-Baracco AS, Accinelli RA. Methylprednisolone pulse therapy: An alternative management of severe COVID-19. *Respir Med Case Rep* 2020; **31**: 101221.

[20]World Health Organization. COVID-19 clinical management, living guidance, 25 January 2021. [Online] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2021-1. [Accessed on July 11 2021].

[21]World Health Organization. Corticosteroids for COVID-19, WHO/2019-nCoV/Corticosteroids/2020.1, 2 september 2020. [Online] Available from: https://www.who.int/publications/i/item/WHO-2019-nCoV-Corticosteroids-2020.1. [Accessed on July 11 2021].

[22]Ramiro S, Mostard RLM, Magro-Checa C, van Dongen CMP, Dormans T, Buijs J, et al. Historically controlled comparison of glucocorticoids with or without tocilizumab versus supportive care only in patients with COVID-19-associated cytokine storm syndrome: results of the CHIC study. *Ann Rheum Dis* 2020; **79**(9): 1143-1151.

[23]The ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E. Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; **307**(23): 2526-2533.

[24]Arif Khwaja. KDIGO Clinical Practice Guideline for Acute Kidney injury. *Nephron Clin Pract* 2012; **120**(4): c179-c184.

[25]Kimmig LM, Wu D, Gold M, Pettit NN, Pitrak D, Mueller J, et al. IL-6 Inhibition in critically ill COVID-19 patients is associated with increased secondary infections. *Front Med* 2020; **7**: 583897.

[26]Huang CL, Wang YM, Li XW. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020; **395**(10223): 497-506.