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ORIGINAL RESEARCH

The role of IL-6 receptor inhibitor treatment in critical patient monitoring with COVID-19

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Abstract

Objectives: The COVID-19 disease can manifest itself with acute respiratory distress syndrome, renal failure, and septic shock in critically ill patients. There are opinions that there is a correlation between high IL-6 levels and disease severity. In our intensive care unit, we evaluated the changes in the laboratory data and radiological involvement severity of our patients who underwent tocilizumab treatment and examined the appropriate laboratory parameter in the treatment follow-up and its effect on survival.
Methods: In the critical patient follow-up of COVID-19, 17 of the 23 patients treated with tocilizumab had a mortal course (Group 1) and the remaining 6 (Group 2) were. The C-reactive protein, lactate dehydrogenase, IL-6, D-dimer, procalcitonin, albumin, and ferritin values, which were routinely screened in our clinic on the day of tocilizumab treatment and the 5th day after, were recorded. Both the change between the two groups and the change between days 1 and 5 were analyzed.
Results: A total of 23 patients (55.35 $\pm$ 13.31 years) were included in the study. The computed tomography severity score assessed at the intensive care unit admission was statistically significantly higher in Group 2. The procalcitonin and lactate dehydrogenase values measured on day 5 after tocilizumab were significantly lower in Group 2. On the 5th day after treatment, the levels of C-reactive protein, ferritin, chest X-rays, IL-6 and D-dimer statistically significantly changed compared to the first day of the treatment. In correlation with the decrease in PCT as of the 5th day after tocilizumab administration, an increasing tendency was observed in 28-day survival.
Conclusion: This study demonstrated that tocilizumab treatment may positively contribute to the treatment by decreasing cytokine levels. PCT and LDH follow-up before and after treatment in critically ill patients who are receiving tocilizumab treatment can give an idea about survival.

Keywords

Coronavirus; IL-6 receptor inhibitor; Intensive care units; Tocilizumab; LDH; PCT; CRP

1. Introduction

COVID-19 disease, which develops due to coronaviruses, was first identified as causing respiratory diseases in Wuhan, Hubei Province, China in December 2019; Acute respiratory distress syndrome (ARDS), acute renal failure, and multiple organ failure have been identified as possible clinical signs associated with coronaviruses [1]. The presence of an unregulated immune response and hyperinflation that may exacerbate this condition has been advocated [2]. Preliminary reports showed that severely ill COVID-19 patients with poor prognosis had elevated levels of interleukin-6 (IL-6) [3]. In Chinese reports, low lymphocyte count and high levels of ferritin, lactate dehydrogenase (LDH), transaminase, and D-dimer have been associated with poor prognosis and cytokine storm in COVID-19 [4]. IL-6 is one of the main cytokines involved in the cytokine storm caused by COVID-19 infection [5]. It has been stated that tocilizumab (TCZ) can resist inflammatory cytokine release syndrome in patients with severe COVID-19 disease and the importance of early diagnosis and treatment [3, 6].

The data of 2 international, multicenter, randomized controlled studies conducted with TCZ are as follows; In the COVACTA [7] study, although the time to discharge from the hospital was shortened, no significant difference could be shown between the placebo group on the 28th day in terms of clinical status or mortality. In the EMPACTA [8] study, it was shown that patients who received TCZ had lower intubation need or mortality on the 28th day compared to the placebo group.

The safety of TCZ for use in rheumatoid arthritis has been demonstrated in five phases III double-blind controlled studies [9]. However, it was approved for the treatment of cytokine

release syndrome during the pandemic and close follow-up was recommended in terms of risks such as severe infections, thrombocytopenia, neutropenia, liver damage, and development of secondary infection [5]. In the multicenter international study [10] in a large group of patients in the intensive care unit (ICU), nine serious adverse events, including one secondary bacterial infection, five bleeding events, two cardiac events, and one visual impairment, were reported in the TCZ treatment group. Eleven serious adverse events were reported in the control group, including four bleeding events and seven thromboses. In the COVECTA study, the side effect profile was similar to that of the placebo group.

In the present study, we aimed to retrospectively present the clinical outcomes and the effect of treatment on the radiological changes and laboratory parameters associated with cytokine storm in our patients who were diagnosed with COVID-19 and treated with the IL-6 receptor inhibitor TCZ in the ICU. Thus, we aimed to recommend more appropriate follow-up parameters in patients receiving TCZ treatment.

2. Materials and methods

Following the approval of the Ethics Committee (Protocol No: 2020/514/179/15 Date: 11-JUN-2020), the data of the patients who were followed up with the diagnosis of COVID-19 in the intensive care units designated to patients with coronavirus in our hospital between March 23 and June 15, 2020, were retrospectively analyzed. Patients' data including age, gender, date of ICU admission, and severity of involvement according to chest X-rays (CXR) obtained before and after treatment, whether they received immune plasma therapy or not, TCZ doses received and 28-day ICU mortality was accessed in the hospital information system and recorded.

Inclusion criteria:

(1) Patients older than 18 years old, whose SARS-CoV-2 infection was confirmed with a real-time Polymerase Chain Reaction (PCR) using nasopharyngeal swabs.

(2) Patients who underwent computed tomography (CT) before ICU admission.

(3) Patients who were administered TCZ due to COVID-19 infection during ICU stay.

Exclusion criteria:

(1) Patients whose data could not be accessed.

(2) Patients who were not diagnosed with COVID-19 by PCR test but were given TCZ due to potential COVID-19 diagnosis according to radiological and clinical findings.

In this study, C-reactive protein (CRP), LDH, IL-6, D-dimer, procalcitonin (PCT), and ferritin were considered as positive acute phase reactants that could indicate cytokine storm, and albumin was considered as a negative acute-phase reactant. The CRP, LDH, IL-6, D-dimer, PCT, albumin, and ferritin values, which were routinely screened in our clinic on the day of tocilizumab treatment and the 5th day after, were recorded.

TCZ was administered at a dosage of 8 mg/kg (maximum 800 mg) by two consecutive intravenous infusions 12 hours apart. All patients receiving intravenous TCZ were treated according to a standard pharmacological protocol, including antiviral drugs (favipiravir in a regimen of 1600 mg loading dose followed by 2 × 600 mg maintenance dose, for 5 days in total), antibiotic prophylaxis (azithromycin, ceftriaxone, or piperacillin/tazobactam), and 400 mg hydroxychloroquine. Additionally, patients who received convalescent immune plasma therapy were also noted.

Analyzes of the data obtained were interpreted by making the comparison between 17 patients with no survival at day 28 (Group 1) and 6 patients with survival (Group 2) in the light of the laboratory data of these 23 patients receiving treatment recorded on the day of tocilizumab treatment and 5 days after the treatment. Patients' respiratory support type (invasive mechanical ventilation (IMV)), and the used oxygen delivery system (face mask (FM) or high-flow nasal cannula (HFNC)) were recorded before the treatment.

TCZ treatment was applied to patients without active infection, acquired immunosuppressive disease, and active tuberculosis.

2.1 Scoring of chest radiography and thorax tomography involvement

All CT examinations for the screening of SARS-CoV-2 pneumonia were performed with three scanners (128 section Philips ingenuity and 16-section Toshiba Alexion) without the use of contrast material. The main scanning protocol was as follows: tube voltage, 120 kVp; tube current modulation,120 mA-380 mA; detector configuration, 64 × 0.625 mm or 16 × 0.625 mm; rotation time, 0.5–0.7 s; slice thickness, 5 mm; and pitch, 0.984. The reconstruction kernel was lung with a thickness and an interval of 0.625 mm. All images were viewed in both lungs (width, 1200 HU; level, –700 HU) and mediastinal (width, 350 HU; level, 40 HU) settings. One radiologist (O.A.) with 20 years of experience, was blinded to the other clinical information and reviewed the chest CT scans independently in random order.

The images were interpreted using the lung window setting. A standardized protocol was followed for assessing the CT images [11]. The subsegmental, segmental, and lobar anatomic distributions were recorded. The extent of the lesions was evaluated as focal, multifocal, and diffuse. The zonal predominance was evaluated as upper, middle, lower lung; central, middle, or peripheral location [12]. A mixed pattern was described as the presence of crazy paving and air bronchogram [13]. Each of the five lung lobes was assessed for the degree of involvement.

Scoring the percentages of each of the five lobes was performed using the Severity Score [14]:

(1) <5% involvement

(2) 5%–25% involvement

(3) 26%–49% involvement

(4) 50%–75% involvement

(5) >75% involvement

The total CT score is the sum of the individual lobar scores and can range from 0 (no involvement) to 25 (maximum involvement) when all the five lobes show more than 75% involvement.

The CXR scoring system includes two steps. First, the lungs were divided into six zones on frontal chest projection (two upper zones, two middle, and two lower). Second, each zone

was scored based on the following:

0: No lung abnormalities

1: Interstitial infiltrates

2: Interstitial predominance with interstitial and alveolar infiltrates

3: Alveolar predominance with interstitatial and alveolar infiltrates

The researchers added the scores of the six lung zones for an overall score between 0 and 18. A thoracic radiologist (O.A.) independently assessed each chest X-ray, evaluating the original score.

2.2 Statistics

Findings were analyzed using IBM SPSS Statistics 25. In the paired comparison of numerical data groups, the Independent Samples *T* test was used for those who fit the normal distribution, the Mann Whitney-U test for those who did not, and the Chi-square test for the examination of discrete variables. The results were evaluated at a 95% confidence interval, and the value of $P < 0.05$ was considered statistically significant [15].

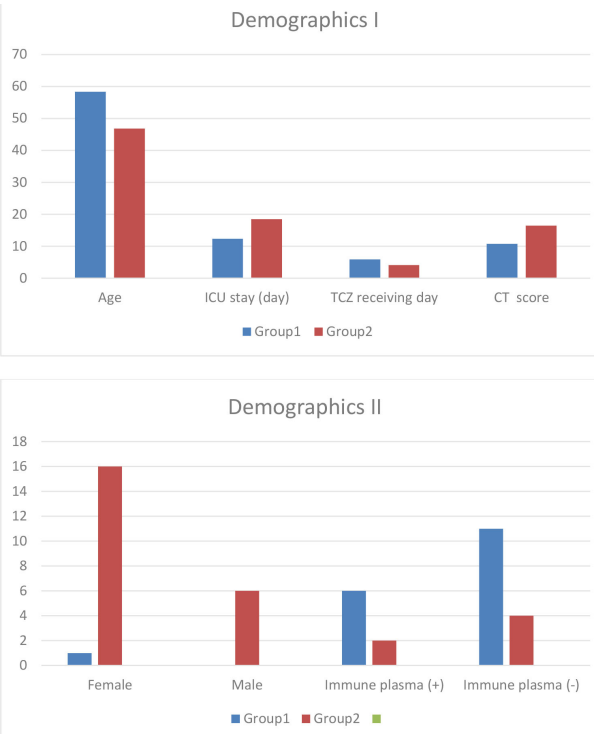

FIGURE 1. Demographic characteristics of theg roups. CT, Computed Tomography; ICU, Intensive Care Unit; TCZ, Tocilizumab.

3. Results

None of the patients enrolled in the study needed to be excluded from the study. A total of 23 patients aged from 22 to 81 years of age (55.35 ± 13.31 years) were included in the study. While immune plasma was administered to eight patients, 15 patients did not receive immune plasma. Seventeen patients (Group 1) who did not survive till day 28 and 6 patients who survived (Group 2) were evaluated.

Our patients who were divided into two groups according to their 28-day survival results in the ICU did not significantly differ in demographic characteristics, the duration of treatment in the ICU, the day of ICU follow-up when TCZ treatment was applied, and whether they received immune plasma therapy or not. The CT severity score assessed at the ICU admission was statistically significantly higher in Group 1 compared to Group 2 ($P < 0.05$, Table 1 and Fig. 1).

FIGURE 2. Comparison of laboratory data between groups on the first and on the fifth day of TCZ treatment. CRP, C Reactive Protein; CXR, Chest X-Ray; IL, Interleukin; LDH, Lactate Dehydrogenase; PCT, Procalcitonin; 1^{st}, The first day of TCZ treatment; 5^{th}, Fifth day of TCZ treatment.

It was found that the PCT and LDH values of our patients measured on day 5 after TCZ were significantly lower in Group 2 than in Group 1 ($P < 0.05$, Table 2 and Fig. 2).

According to the data obtained on the 5th day after treatment, the levels of CRP, ferritin, IL-6, CXR, and D-dimer of 23 patients who were treated with TCZ statistically significantly changed compared to the first day of the treatment. While there was a significant decrease in CRP and ferritin values ($P < 0.05$), D-dimer, IL-6 and radiological involvement severity score significantly elevated ($P < 0.05$, Table 3).

No significant difference was detected between Group 1 and Group 2 regarding the respiratory support and O2 delivery system provided to the patients from day 1 to day 5 of the treatment (Table 4).

A statistically significant association was indicated between the increase of the CT score assessed at ICU admission and the decrease of PCT level on the 5^{th} day after treatment and survival on day 28 ($P = 0.006$ and 0.049, Table 5).

The treatment was not stopped due to the development of side effects in any of the patients who received TCZ.

TABLE 1. Demographic characteristics of the groups.

	Group 1 (n = 17)	Group 2 (n = 6)	*P*
Age	58.35 ± 11.92	46.83 ± 14.39	0.067^{s}
ICU stay (day)	12.35 ± 7.36 (11)	18.50 ± 11.96 (19)	0.505^{m}
CT score	10.75 ± 4.28	16.50 ± 2.26	0.006*^{s}
TCZ receivingday	5.94 ± 4.55 (5)	4.17 ± 3.06 (2.5)	0.396^{m}
Gender			
Female	1 (5.9%)	0 (0.0%)	0.544^{k}
Male	16 (94.1%)	6 (100.0%)	
Immuneplasma			
No	11 (64.7%)	4 (66.7%)	0.931^{k}
Yes	6 (35.3%)	2 (33.3%)	

CT, Computed Tomography; ICU, Intensive Care Unit; TCZ, Tocilizumab.
^{s} İndependent Samples T test: values are given as mean ± Standard deviation.
^{m} Mann Whitney U test: values are given as mean ± Standard deviation (median).
^{k} Chi-square test: values are given as frequency (percentage).
**P < 0.05: statistically significant difference.*

TABLE 2. Comparison of laboratory data between groups on the first and on the fifth day of TCZ treatment.

	Group 1 (n = 17)	Group 2 (n = 6)	*P*
CRP 1^{st}	183.84 ± 95.85	150.27 ± 120.09	0.603^{s}
CRP 5^{th}	70.21 ± 72.48	17.92 ± 15.37	0.143^{s}
IL-6 1^{st}	1059.4 ± 2737.8 (291.4)	588.8 ± 816.9 (294.7)	0.726^{m}
IL-6 5^{th}	1411.2 ± 1578.2 (922.9)	1576.2 ± 1891.4 (810.25)	0.877^{m}
LDH 1^{st}	691.18 ± 226.72	556.83 ± 142.09	0.192^{s}
LDH 5^{th}	1107.5 ± 924.0 (887.5)	510.75 ± 92.8 (527.5)	0.029*^{m}
D dimer 1^{st}	6534.7 ± 7861.3 (2370)	2006.0 ± 1302.95 (1580)	0.108^{m}
D dimer 5^{th}	13805.0 ± 12096.6 (7900)	10015.0 ± 13441.4 (4470)	0.268^{m}
PCT 1^{st}	4.80 ± 7.66 (1.13)	0.57 ± 0.42 (0.49)	0.090^{m}
PCT 5^{th}	1.51 ± 1.15 (1.375)	0.19 ± 0.13 (0.136)	0.011*^{m}
Albumin 1^{st}	26.24 ± 4.02 (25)	27.50 ± 3.45 (27.5)	0.418^{m}
Albumin 5^{th}	26.55 ± 5.50	30.0 ± 7.30	0.310^{s}
CXR score 1^{st}	10.76 ± 4.09	12.67 ± 2.94	0.309^{s}
CXR score 5^{th}	14.59 ± 2.89	13.50 ± 3.51	0.461^{s}
Ferritin 1^{st}	1107.9 ± 424.8 (1210)	796.9 ± 490.6 (621)	0.196^{m}
Ferritin 5^{th}	676.4 ± 438.7 (436.5)	339.0 ± 160.7 (316)	0.126^{m}

CRP, C Reactive Protein; CXR, Chest X-Ray; IL, Interleukin; LDH, Lactate Dehydrogenase; PCT, Procalcitonin; 1^{st}, The first day of TCZ treatment; 5^{th}, Fifth day of TCZ treatment.
^{s} Independent Samples T test: values are given as mean ± Standard deviation.
^{m} Mann Whitney U test: values are given as mean ± Standard deviation (median).
**P < 0.05: statistically significant difference.*

4. Discussion

This study evaluated the effect of TCZ therapy on the outcome of patients with COVID-19. Our results support the effectiveness of TCZ in the prevention or treatment of cytokine storms caused by COVID-19. In many patients, acute phase reactant levels such as CRP, PCT and ferritin decreased, whereas LDH, IL-6 and D-dimer levels increased. In correlation with the decrease in PCT as of the 5th day after TCZ administration, an increasing tendency was observed in 28-day survival.

In a comprehensive review on TCZ, CRP and IL-6 were preferred primarily as follow-up markers [16]. In our study,

TABLE 3. Changings on radiological involvement and laboratory data the first and 5th days of TCZ treatment.

	The first day (n = 23)	The fifth day (n = 23)	*P*
CRP	168.21 ± 102.88 (166.5)	55.26 ± 64.06 (33.2)	**0.003***
IL-6	936.64 ± 2376.5 (291.4)	1461.95 ± 1600.3 (922.9)	**0.050***
LDH	656.13 ± 213.56 (637)	958.31 ± 836.13 (792.5)	0.162
D-dimer	5505.5 ± 7154.2 (2335)	12857.5 ± 12096.1 (7075)	**0.009***
PCT	3.65 ± 6.76 (0.685)	1.07 ± 1.13 (0.415)	0.160
Albumin	26.57 ± 3.85	27.63 ± 6.1	0.544[s]
CXR scoring	11.26 ± 3.85	14.64 ± 2.63	**0.001***[s]
Ferritin	1056.64 ± 455.28 (1174.5)	587.08 ± 388.6 (420.0)	**0.005***[m]

CRP, C Reactive Protein; CXR, Chest X-Ray; IL, Interleukin; LDH, Lactate Dehydrogenase; PCT, Procalcitonin; TCZ, Tocilizumab.

[s] *IndependentSamples T test: valuesaregiven as mean ± Standard deviation.*

[m] *Mann Whitney U test: values are given as mean ± Standard deviation (median).*

[k] *Chi-square test: values are given as frequency (percentage).*

**P < 0.05: statistically significant difference.*

TABLE 4. Respiratory supports of the first and 5th days of TCZ treatment.

	Group 1 (n = 17)	Group 2 (n = 6)	*P*
1^{st} day respiratory supports			
Face mask	1 (5.9%)	1 (16.7%)	
HFNC	6 (35.3%)	3 (50.0%)	0.499[k]
Intubated	10 (58.8%)	2 (33.3%)	
5^{th} day respiratory supports			
HFNC	2 (11.8%)	3 (50.0%)	
Intubated	9 (52.9%)	2 (33.3%)	0.146[k]
Mortality	6 (35.3%)	1 (16.7%)	

HFNC, High-Flow Nasal Cannula; TCZ, Tocilizumab.

[k] *Chi-square test: values are given as frequency (percentage).*

TABLE 5. Relationshipbetween CT scoreand PCT changeswith ICU survival.

		CT score before TCZ	PCT on the 5th day after TCZ
Survival on the 28th day of hospitalization	Pearson correlation	0.570	0.578
	P value	0.006**	0.049*
	N	23	12

Correlation is significant at the 0.01 level (2-tailed).**

Correlation is significant at the 0.05 level (2-tailed).*

CT, Computed Tomography; ICU, Intensive Care Unit; PCT, Procalcitonin; TCZ, Tocilizumab.

emphasizing the importance of PCT follow-up may be remarkable in the follow-up of these patients. In a recent multi-center study [10] conducted on critically ill patients in the ICU, in which 353 patients were tocilizumab, 48 were sarilumab, and 402 were the control group, treatment with the interleukin-6 receptor antagonists tocilizumab and sarilumab was reported to improve outcomes. In this study, subgroup analysis was made according to CRP. In our study, it has been shown that tocilizumab treatment can positively contribute to the treatment by lowering cytokine levels.

Regarding the mean age and gender distribution of the patients, our results correspond to similar studies [17]. It has been reported that IL-6 can be used to assess the severity of the infection and predict prognosis in COVID-19 patients [18]. Similarly, some studies have defined hyperferritinemia and IL-6 as predictors of poor outcome and based on this, shown a hyperinflammatory process as the main cause of death [3]. In a case series of 15 patients with COVID-19, PanLuo *et al.* [19] shared their experiences with TCZ and reported that after TCZ treatment, blood plasma levels of IL-6 initially increased but then decreased, and CRP levels decreased. IL-6 is eliminated mainly by IL-6R mediated clearance [20], and binding of TCZ to IL-6 inhibits receptor-mediated clearance of IL-6, leading to its accumulation in serum. This is interpreted as the main

reason for elevated IL-6 levels in the first phase after TCZ treatment. When all our patients were considered regardless of survival, there was significant elevation in IL-6 and D-dimer levels from pre-treatment to post-treatment, while there was a significant fall in CRP levels. However, neither CRP nor D-dimer has been shown is to be effective in predicting survival.

In the study conducted by Toniative *et al*. [21], 10 days after TCZ administration, the levels of CRP, fibrinogen, and ferritin levels dropped off towards the normal range, while D-dimer and IL-6 levels were reported to increase in both improved and worsened cases. LDH and ferritin levels were determined as parameters that showed a significant decrease with treatment on day 5.

Analysis of the peripheral blood of 69 severely ill COVID-19 patients indicated elevated ferritin levels compared to patients with non-severe disease, and serum ferritin levels were concluded to be closely related to the severity of COVID-19 [22]. Consistent with this, another study reported that ferritin levels in patients who died of COVID-19 were elevated at admission to the hospital and during hospitalization. After the 16th day of hospitalization, the median values of serum ferritin levels exceeded the upper limit in these patients, and it was thought that ferritin levels increased steadily [4]. Although there was no significant difference between the patient groups in terms of serum ferritin levels in ourstudy, considering the association between elevated ferritin levels and poor prognosis, it was thought that a significant fall in ferritin levels after TCZ treatment support the effectiveness of the treatment.

In the series of 77 patients who received TCZ treatment, Moreno-Pérez *et al*. [23] stated that LDH was a marker of mortality and that according to all TCZ responses evaluated, no difference was found regarding the effect on the length of stay in the ICU. In our study, similar basal LDH levels were observed between the mortal group and the well-survived group, but the LDH level measured on the 5th day after treatment was found to be significantly higher in the mortal group.

Even though the TCZ response was shown with pre-treatment and post-treatment laboratory parameters in our study, no significant difference was found between the groups in the days of ICU stay. However, a statistically significant association was detected between the elevation of the thoracic CT score assessed at admission to the intensive care unit and survival at ICU on day 28.

In the autopsy results of the patients who died of COVID-19, macroscopic features that have been reported include pleurisy, pericarditis, pulmonary consolidation, pulmonary edema, and microscopic findings include inflammatory infiltrates mainly composed of monocytes and macrophages, and diffuse alveolar damage, minimal lymphocyte infiltration, and large atypical pneumocytes and multinucleated giant cells [24, 25]. Autopsy results are similar to macrophage activation syndrome (MAS) characterized by cytokine storm, yet in severe COVID-19 cases, there have been several abnormal laboratory parameters observed similar to those in MAS. The absence of other features such as classical organomegaly led to the assumption that hyperactivation of the immune system is mainly limited to the lung parenchyma [26].

The uncontrolled proliferation of immune cells, the production of proinflammatory mediators, and the development of cytokine storm syndrome are thought to be the main cause of lung involvement [27]. When we analyzed our results, we concluded that the patients that experienced the cytokine storm most intensively were the patients who benefited most from anti-cytokine treatment.

In a prospective series of 100 consecutive patients admitted to the hospital with ARDS on the 10th day of TCZ in Italy, 77 patients experienced a significant decrease in CXR and improvement in respiratory conditions, while 23 patients reported worsening breathing and 20 died [21]. In contrast with these results, our study consisting of 23 patients demonstrated a significant decrease in the CXR involvement score rated at the evaluation of the treatment on day 5, and there was no significant difference between the groups in terms of the type of respiratory support and the need for O2.

Another prominent treatment option in the management of critically ill COVID-19 patients has been the application of convalescent immune plasma. However, despite less comprehensive studies [28] recommending the procedure; there are studies with a higher number of patients that argue the procedure to be non-efficient [29]. In this study, 8 patients were administered immune plasma therapy and the rate of plasma therapy was similar between the groups. Therefore, we think that immune plasma treatment did not affect the results of TCZ treatment in this study group.

It is recommended to monitor the acute phase reactants such as CRP, PCT, ferritin, D-dimer for following the effectiveness of TCZ, which is applied as an alternative treatment method in COVID-19 patients [23]. In the data we evaluated retrospectively, the most effective change was detected in PCT values, and thus, it was thought to have an important value in reflecting survival. We found an increase in survival associated with a decrease in PCT, especially on day 5. We attribute this to the role of PCT as a secondary infection marker. The absence of secondary infection can be directly related to survival. These results made us think that PCT and LDH follow-up is more effective in predicting prognosis than radiological improvement in patientswith TCZ treatment.

The limitation of this study is retrospective design and low sample size.

5. Conclusions

All kinds of clinical data are valuable in COVID-19 infection, for which there is no definitive treatment yet and many therapies are presented in the guidelines as non-precise recommendations. This study demonstrated that TCZ treatment may positively contribute to the treatment by decreasing cytokine levels. PCT and LDH follow-up before and after treatment in ICU patients who are receiving TCZ treatment can give an idea about survival.

AUTHOR CONTRIBUTIONS

FÇ: Conceptualization, Methodology, Software. AS: Data curation, Writing—Original draft preparation. YB: Visualization, Investigation. EAD: Supervision. EB: Software, Validation. KTS: Writing—Reviewing and Editing.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The ethical committee of Kartal Dr. Lütfi Kırdar City Hospital declared ethical approval for the current study (Protocol No: 2020/514/179/15 Date: 11-JUN-2020).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, *et al*. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020; 395: 507–513.

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

[3] Aziz M, Fatima R, Assaly R. Elevated interleukin-6 and severe COVID-19: a meta-analysis. Journal of Medical Virology. 2020; 92: 2283–2285.

[4] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult in patients with COVID-19 in Wuhan, China: a retrospective cohort study. The Lancet. 2020; 395: 1054–1062.

[5] Zhang S, Li L, Shen A, Chen Y, Qi Z. Rational use of tocilizumab in the treatment of novel coronavirus pneumonia. Clinical Drug Investigation. 2020; 40: 511–518.

[6] Gupta S, Wang W, Hayek SS, Chan L, Mathews KS, Melamed ML, *et al*. Association between early treatment with tocilizumaband mortality among critically ill patients with COVID-19. JAMA Internal Medicine. 2021;181: 41–51.

[7] Rosas IO, Bräu N, Waters M, Go RC, Hunter BD, Bhagani S, *et al*. Tocilizumab in hospitalizedpatientswith severe COVID-19 pneumonia. The New England Journal of Medicine. 2021. (in press)

[8] Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, *et al*. Tocilizumab in patients hospitalized with COVID-19 pneumonia. New England Journal of Medicine. 2021; 384: 20–30.

[9] Genentech. Prescribing information. ACTEMRA® (tocilizumab) injection, for intravenous or subcutaneous use. 2019. Available at: https://www.gene.com/download/pdf/actemra_prescribing.pdf (Accessed: 11 March 2020).

[10] Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, *et al*. Interleukin-6 receptor antagonists in critically ill patients with COVID-19. The New England Journal of Medicine. 2021. (in press)

[11] Tung-Chen Y, Martí de Gracia M, Díez-Tascón A, Alonso-González R, Agudo-Fernández S, Parra-Gordo ML, *et al*. Correlation between chest computed tomography and lung ultrasonography in patients with coronavirus disease 2019 (COVID-19). Ultrasound in Medicine & Biology. 2020; 46: 2918–2926.

[12] Zhang R, Ouyang H, Fu L, Wang S, Han J, Huang K, *et al*. CT features of SARS-CoV-2 Pneumonia according to clinical presentation: a retrospective analysis of 120 consecutive patients from Wuhan city. European Radiology. 2020; 30: 4417–4426.

[13] De Wever W, Meersschaert J, Coolen J, Verbeken E, Verschakelen JA. The crazy-paving pattern: a radiological-pathological correlation. Insights into Imaging. 2011; 2: 117–132.

[14] Pan F, Ye T, Sun P, Gui S, Liang B, Li L, *et al*. Time course of lung changes at chest ct during recovery from coronavirus disease 2019 (COVID-19). Radiology. 2020; 295: 715–721.

[15] Geaorge D, Marrey P. IBM SPSS statistics 25 step by step: a simple guide and reference. 15th edition. NY: Routledge. 2018.

[16] Lan S, Lai C, Huang H, Chang S, Lu L, Hsueh P. Tocilizumab for severe COVID-19: a systematic review and meta-analysis. International Journal of Antimicrobial Agents. 2020; 56: 106103.

[17] Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, *et al*. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. JAMA Internal Medicine. 2020; 180: 1345.

[18] Chiaretti A, Pulitanò S, Barone G, Ferrara P, Romano V, Capozzi D, *et al*. IL-1 β and IL-6 upregulation in children with H1N1 influenza virus infection. Mediators of Inflammation. 2013; 2013: 495848.

[19] Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: a single center experience. Journal of Medical Virology. 2020; 92: 814–818.

[20] Nishimoto N, Terao K, Mima T, Nakahara H, Takagi N, Kakehi T. Mechanisms and pathologic significances in increase in serum interleukin-6 (IL-6) and soluble IL-6 receptor after administration of an anti-IL-6 receptor antibody, tocilizumab, in patients with rheumatoid arthritis and Castleman disease. Blood. 2008; 112: 3959–3964.

[21] Toniatia P, Pivab S, Cattalinid M, Garrafaf E, Regolaa F, CastellieF, *et al*. Tocilizumab for the treatment of severe COVID-19 Pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. Autoimmunity Reviews. 2020; 19: 102568.

[22] Liu T, Zhang J, Yang Y, Ma H, Li Z, Zhang J, *et al*. The potential role of IL-6 in monitoring severe case of coronavirus disease 2019. medRxiv. 2020. (in press)

[23] Moreno-Pérez O, Andres M, Leon-Ramirez J, Sánchez-Payá J, Rodríguez JC, Sánchez R, *et al*. Experience with tocilizumab in severe COVID-19 Pneumonia after 80 days of follow-up: a retrospective cohort study. Journal of Autoimmunity. 2020; 114: 102523.

[24] Hanley B, Lucas SB, Youd E, Swift B, Osborn M. Autopsy in suspected COVID-19 cases. Journal of Clinical Pathology. 2020; 73: 239–242.

[25] Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. The Lancet Respiratory Medicine. 2020; 8: 420–422.

[26] McGonagle D, Sharif K, O'Regan A, Bridgewood C. The role of cytokines including Interleukin-6 in COVID-19 induced pneumonia and macrophage activation syndrome-like disease. Autoimmunity Reviews. 2020; 19: 102537.

[27] Ruscitti P, Berardicurti O, Di Benedetto P, Cipriani P, Iagnocco A, Shoenfeld Y, *et al*. Severe COVID-19, another piece in the puzzle of the hyperferritinemic syndrome. An immunomodulatory perspective to alleviate the storm. Frontiers in Immunology. 2020; 11: 1130.

[28] Duan K, Liu B, Li C, Zhang H, Yu T, QuJ, *et al*. The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study. medRxiv. 2020. (in press)

[29] Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, *et al*. Effect of convalescent plasmatherapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. The Journal of the American Medical Association. 2020; 324: 460–470.

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