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Cornonavirus Pandemic

A retrospective evaluation of COVID-19 patients treated with Tocilizumab: who should be treated?

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Abstract

Introduction: Tocilizumab, can be used in the treatment of COVID-19 in patients developing cytokine storms. This study retrospectively evaluated patients treated with Tocilizumab.

Methodology: This study included 23 patients (17 men) admitted to the hospital and received Tocilizumab due to cytokine storms. The patients were categorized into three groups: "moderate, severe, and critical". Clinical outcomes after 7 days of hospitalization were classified as "death, disease aggravation, clinical stabilization, and clinical improvement".

Results: The mean age of the patients was 58±10.1 years. 52.2% of the patients were severely ill, and 47.8% were critically ill. After tocilizumab treatment, the mean lymphocyte count increased in all patients; the C-reactive protein levels dropped rapidly, except for one patient. After the first dose, the patients' fever dropped dramatically, and their oxygen support needs decreased. During the treatment, 82.6% of the patients were in the intensive care unit. At the end of the treatment, 56.5% had clinical improvement, 13% had clinical stabilization, and 4.3% had aggravation. Mortality occurred in 26.1%; 60.9% were discharged within a mean time of 19.14 ± 13.57 days after their treatment, and 18.2% of the critically ill and 91.7% of the severely ill patients recovered.

Conclusions: Despite high rates of recovery and discharge after the tocilizumab treatment in the severely ill patients, more than half of the critically ill patients died. Early tocilizumab treatment resulted in a high survival rate and reduced the rates of progression to more critical states and mortality. Tocilizumab treatment should be given early in patients developing cytokine storms.

Key words: tocilizumab; SARS-CoV-2; cytokine storms; interleukin-6; COVID-19.

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Introduction

In late 2019, a new coronavirus, Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) was reported [1]. Coronavirus Disease 2019 (COVID-19) is caused by this virus, and its major symptoms are fever, cough and dyspnea, while its minor symptoms are alteration of smell and taste, gastrointestinal symptoms, fatigue, asthenia, headache, and cutaneous manifestations [2-7]. The vast majority of patients infected with SARS-CoV-2 have mild to moderate respiratory illness. These people usually recover without any special treatment and without hospitalization. The elderly and those with underlying diseases such as cardiovascular diseases, diabetes, chronic respiratory disease and cancer are at a higher risk of developing severe illness [8]. In conditions such as various treatments, pathogens, cancers and autoimmune conditions, cytokine levels in the bloodstream may increase, and immune cell hyperactivation may develop. These life-threatening systemic inflammatory syndromes are called "a cytokine storm" and "cytokine release syndrome" [9]. Cytokine storms can also occur with the production of pro-inflammatory cytokines, particularly including IL-6, IL-1β, IL-2, IL-7, IL-8, IL-10, IL-17 and IFNγ [10,11].

At the beginning of the COVID-19 pandemic, there was an urgent need for the discovery of drugs and treatments that could be used, and existing therapeutic molecules were tested as the discovery of new drugs would take a long time. Lopinavir as a protease-inhibiting antiviral and favipiravir as an agent that inhibits viral RNA-dependent RNA polymerase were planned to be used in the treatment of COVID-19 [12]. A randomized controlled open-label study in which severe COVID-19 patients were treated with lopinavir/ritonavir was conducted. In the study, the mortality rate was lower, and the length of stay in the intensive care unit was shorter in the patients given this treatment than those in the control group. It was found

that the group who started lopinavir/ritonavir treatment early was more likely to have a shorter stay in the intensive care unit and faster clinical recovery [13]. Studies have shown that favipiravir, structurally modified lopinavir and similar compounds inhibit COVID-19 major protease (Mpro) and RNA-dependent RNA polymerase. In a study by Rafi *et al.*, the authors analyzed the physicochemical properties of potential drugs against COVID-19 and obtained the lopinavir analog, CID44271905, as an effective drug planned for the future [12].

Vitamin D increases cell-mediated reactions. It increases the activity of innate immunity by affecting monocytes and macrophages. It also partially enhances cellular innate immunity by stimulating the delivery of antimicrobial peptides, including human cathelicidins, LL-37 and defensins. The relationship between low-dose vitamin D administration and the development of SARS-CoV-2 infection has been investigated in many studies. While some studies have concluded that vitamin D deficiency is a risk factor for COVID-19, some studies have reported that vitamin D supplementation in healthy volunteers does not reduce the risk of developing respiratory tract infections [14]. In some studies, vitamin D has been considered a SARS-CoV-2 mitigation agent because it can impair the activities of 70% of SARS-CoV-2 proteins by changing the expression of 25% of the human genes encoding the protein targets of SARS-CoV-2. On the other hand, other studies have stated that vitamin D worsens SARS-CoV-2 infection by blocking chemotaxis, and vitamin D deficiency also increases thrombotic complications [14]. For these reasons, vitamin D supplementation has not yet entered the guidelines for the treatment of SARS-CoV-2.

In addition to antiparasitic drugs plus antiviral drugs, such as favipiravir and remdesivir, humanized monoclonal antibody inhibitors can be used in the treatment of COVID-19 [10,15,16]. Tocilizumab (TCZ), a monoclonal antibody inhibitor, binds to the IL-6 receptor with high affinity, preventing IL-6 from binding to its own receptor [17].

Our patients, who were diagnosed in the first two months of the pandemic, were depressed and fearful before TCZ treatment because they did not know the prognosis of COVID-19 and had a risk of being severely ill. Shmuel Tiosano *et al.* showed that TCZ treatment had a positive effect on the parameters reflecting the severity of depression and anxiety in patients with rheumatoid arthritis [18]. This information encouraged us to provide TCZ treatment for our patients.

TCZ treatment is included in algorithms for diagnosis and treatment in the National COVID-19 Guideline published by the Turkish Ministry of Health and being updated regularly [19]. TCZ treatment is initiated for patients whose clinical presentation is consistent with these algorithms. According to this guideline, in addition to treatment for COVID-19, TCZ can be used in the presence of persistent fever, elevated or elevating CRP and ferritin levels, increased D-dimer levels, cytopenia cases such as lymphopenia and thrombocytopenia, and impaired liver function.

Some drugs that are used increase the risk of contracting SARS-CoV-2. For example, angiotensin receptor blockers (ARBs) increase the risk of contracting SARS-CoV-2. Biologics, on the other hand, do not affect the risk of intensive care unit hospitalization and death, but they increase both the risk of infection and the risk of hospitalization [20]. In a cohort study of 3988 critically ill patients by Graselli *et al.*, characteristics affecting survival in intensive care units (ICU) were examined. Having a pre-existing comorbidity requiring mechanical ventilator support, being elderly and male were determined as the most significant characteristics that reduced survival rates. It has been reported that the survival rate of hypertension patients is low. Some other studies have determined that the diagnosis of hypertension was not an independent factor associated with mortality, but a history of chronic obstructive pulmonary disease, hypercholesterolemia and diabetes were independent risk factors for mortality. The effects of long-term drug usage by patients were investigated, and it was stated that angiotensin converting enzyme (ACE) inhibitors, ARBs, statins, corticosteroids and hypoglycemic agents up-regulate ACE2 receptors in the long term and may support an increase in viral replication. It was thought that this situation may increase the susceptibility of individuals to SARS-CoV-2 infection. However, the association of long-term treatment with ACE inhibitors or ARBs with mortality has not been proven [21].

This study investigated the response rates of patients who were hospitalized due to COVID-19 and received intravenous TCZ treatment at our hospital, which is a tertiary research and training hospital, as well as factors affecting these response rates.

Methodology

Study design and patients

This study was planned as a retrospective, observational study at our hospital, which is a tertiary research and training hospital and a reference center during the COVID-19 pandemic. The study included

patients who were admitted between 15 March 2020 and 15 May 2020 to the intensive care units and in-patient wards and were thought to have developed cytokine storms as defined by their clinical signs and laboratory findings. At the time of our study, IL-6 levels could not be measured in our hospital. For this reason, other criteria were used for the definition of a cytokine storm. Patients aged younger than 18 years old and those who were not receiving TCZ treatment were excluded from the study. This study was approved by the Ethics Committee of Hamidiye Scientific Research, Health Sciences University (21.05.2020, no 2020/6).

Data collection

Data were retrospectively obtained from the electronic medical records of our hospital and recorded in Excel data sheets. The collected data included information on age, sex, medical history (diabetes, hypertension, cardiovascular disease, chronic pulmonary disease, chronic liver disease and other comorbidities), clinical classification (fever, oxygen saturation, supplemental oxygen) and clinical outcomes. The laboratory data of the patients included white blood cell (WBC) count, neutrophil percentage, lymphocyte count, lymphocyte percentage, platelet count, lactate dehydrogenase (LDH), alanine aminotransferase (ALT) and aspartate aminotransferase (AST), procalcitonin, C-reactive protein (CRP), D-dimer and ferritin.

Clinical and laboratory data were recorded on the day before the treatment of TCZ, and on the first, third, fifth and seventh days of treatment. Therapies for the treatment of COVID-19 were also recorded. The clinical outcomes were evaluated as "death, disease aggravation, clinical stabilization, and clinical improvement" on the basis of changes in clinical and laboratory findings after a follow-up of 7 days.

Table 1. The characteristics of Covid-19 patients treated with TCZ.

Case no	Age	Gender	Comorbidity	Clinical classification	Therapy								Clinical outcomes
					Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	
1	63	M	DM. HT. COPD	Critically ill	TCZ:400mg+ AZT+FAV+HQ	TCZ:200mg+ AZT+FAV+HQ	AZT+FAV+HQ	AZT+FAV+HQ	HQ	HQ	HQ	HQ	D (the 7th day)
2	66	M	DM. HT. CHD	Severely ill	TCZ:400mg								CI
3	53	M	DM	Critically ill	TCZ:400mg	TCZ:200mg+ *AZT+*FAV+*HQ	AZT+FAV+HQ	AZT+FAV+HQ	AZT+FAV+HQ	AZT+FAV+HQ	HQ	HQ	CS
4	72	M	DM. HT. COPD	Critically ill	TCZ:400mg		TCZ:200mg						CS
5	62	M	None	Critically ill	TCZ:400mg	TCZ:200mg							D (the 6th day)
6	46	M	HT	Severely ill	TCZ:400mg+ FAV+HQ	TCZ:200mg+ FAV+HQ	HQ	HQ	HQ	HQ			CI
7	43	F	None	Critically ill	TCZ:400mg		TCZ:200mg						CI
8	55	M	None	Severely ill	TCZ:400mg+ FAV+HQ	TCZ:200mg+ FAV+HQ	FAV+HQ	FAV+HQ	HQ	HQ	HQ	HQ	CI
9	45	M	None	Severely ill	TCZ:400mg								CI
10	43	F	None	Severely ill	TCZ:600mg+ AZT+HQ	TCZ:400mg+ FAV+AZT+HQ	AZT+FAV+HQ	AZT+FAV+HQ	AZT+FAV+HQ	AZT+FAV	AZT+ FAV	AZT+FAV	CS
11	58	M	HT	Critically ill	TCZ:600mg+ AZT+FAV+HQ	AZT+FAV+HQ	FAV						CI
12	54	M	None	Critically ill	TCZ:400mg								D (the 6th day)
13	60	M	None	Severely ill	TCZ:800mg+ *FAV+HQ	FAV+HQ	FAV+HQ	FAV+HQ	FAV+HQ				CI
14	72	M	COPD	Critically ill	TCZ:400mg								DA
15	79	F	None	Severely ill	TCZ:400mg+ FAV+HQ	FAV+HQ	FAV+HQ	FAV					CI
16	55	M	Asthma	Critically ill	TCZ:400mg+ FAV+HQ	TCZ:400mg+ FAV+HQ	FAV+HQ	FAV+HQ	HQ				D (the 4th day)
17	54	M	HT	Critically ill	TCZ:400mg	TCZ:400mg							D (the 3th day)
18	72	F	DM. HT	Severely ill	TCZ:400mg+ FAV+HQ	TCZ:400mg+ FAV+HQ	FAV+HQ	FAV+HQ					CI
19	54	M	None	Critically ill	TCZ:800mg+FAV								D (1st day)
20	53	M	None	Severely ill	TCZ:400mg+ FAV+HQ	FAV+HQ							CI
21	50	M	None	Severely ill	TCZ:400mg+ AZT+FAV+HQ	FAV+HQ							CI
22	60	F	DM. HT	Severely ill	TCZ:400mg+ *FAV+HQ	FAV+HQ	FAV+HQ	FAV+HQ	FAV+HQ	HQ			CI
23	70	F	HT	Severely ill	TCZ:400mg+ *FAV+HQ	TCZ:200mg+ FAV+HQ	FAV+HQ	FAV+HQ	FAV+HQ				CI

TCZ: tocilizumab; *AZT: azithromycin 500mg; *FAV: favipiravir 3200mg; *HQ: hydroxychloroquine 800mg; AZT: azithromycin 250mg; FAV: favipiravir 1200mg; HQ: hydroxychloroquine 400mg; DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; CHD: chronic heart disease; CI: clinical improvement; CS: clinical stabilization; DA: disease aggravation; D: death.

Definitions

The patients were clinically classified on the basis of body temperature, oxygen saturation and supplemental oxygen, and other clinical signs. The type of pneumonia on the day of TCZ administration was determined according to the 5th edition of the Guideline for the Diagnosis and Treatment of Novel Coronavirus Pneumonia by the National Health Commission of the People's Republic of China [22]. Accordingly, the patients were classified as having mild illness, with mild clinical symptoms, but no findings of fever, respiratory symptoms and the radiologic absence of pneumonia; severe illness with respiratory distress [a respiratory rate of > 30/minute or an oxygen saturation of < 93% at rest or a PaO_2/FiO_2 value of < 300 mmHg (1 mmHg = 0.33 kPa)], and critically severe illness type with respiratory failure requiring mechanical ventilation, shock, or respiratory failure accompanied by the failure of other organs in the intensive care unit.

Statistical analysis

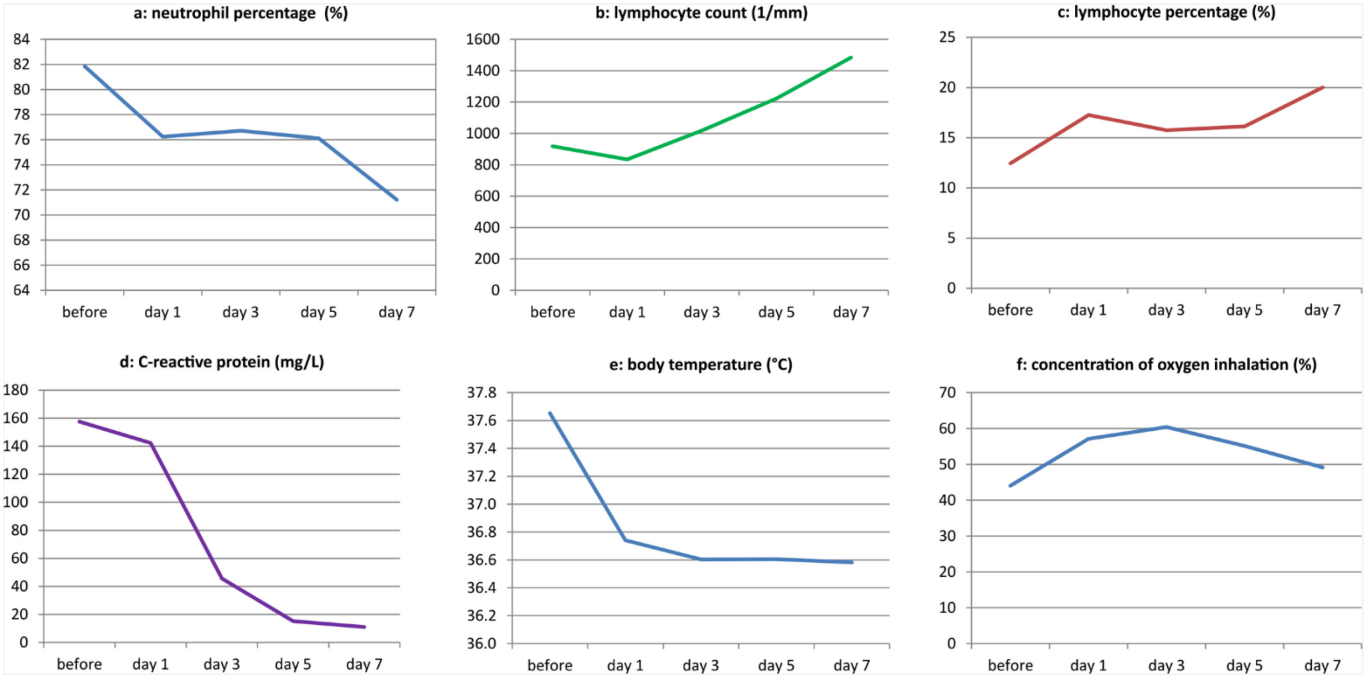
The continuous variables are expressed as mean, standard deviation, minimum and maximum values. Clinical and laboratory changes were analyzed using the Friedman test. p-value ≤ 0.05 was considered statistically significant.

Results

The sample of this study included 23 patients, and 17 (73.9%) of these patients were men. The mean age of the patients was 58 ± 10.1 (min: 43, max: 79) years. Twelve patients (52.2%) were severely ill, and 11 patients (47.8%) were critically ill. Nineteen patients (82.6%) had at least one comorbid chronic disease such as diabetes mellitus, hypertension, chronic obstructive pulmonary disease, chronic heart disease or asthma. At the time of starting intravenous TCZ treatment, the mean time of symptom onset was 11.04 ± 4.18 days (min: 3, max: 20), and the mean duration of hospitalization was 7.08 ± 3.20 days (min: 1, max: 13). The doses of TCZ ranged from 200 mg to 800 mg. Twelve patients (52.2%) received two doses. The clinical characteristics of the COVID-19 patients are summarized in Table 1.

Twenty-one patients (91.3%) had increased neutrophil percentages, and 95.7% of the patients had lymphopenia before the TCZ treatment. One week after the administration of TCZ, the neutrophil percentages of the patients decreased significantly (p= 0.002; Figure 1a), and their lymphocyte counts and percentages showed significant increases (p=0.033 and p= 0.005, respectively; Figure 1b, Figure 1c). CRP levels were substantially higher than the normal limits in 23 patients prior to the TCZ treatment (mean: 157.6 ± 73.01 mg/L;

Figure 1. The clinical and laboratory findings of COVID-19 patients at, before and after TCZ therapy.



Neutrophil percentage (a), lymphocyte count (b), lymphocyte percentage (c), C-reactive protein (d), body temperature (e), inhaled oxygen concentration (f). (Mean values before treatment, on the first, third, fifth and seventh days of treatment).

min: 28.1 mg/L, max: 326.2 mg/L; normal range: 0-8 mg/L). All but one patient had rapid significant decreases in CRP levels, ($p< 0.0001$; Figure 1d). One patient (4.3%) whose CRP level remained approximately ten times higher than the normal level did not need intensive care on the seventh day and was discharged on the 14th day. The laboratory findings and cut-off values of the COVID-19 patients before and after the TCZ treatment are summarized in Table 2.

While ten (43.5%) of the 23 patients had a body temperature of higher than 38 °C, six (60%) among these ten patients were severely ill, and four (40%) were critically ill. One died on the first day of the TCZ treatment. The body temperatures of the other nine patients decreased dramatically and significantly after the first dose of TCZ ($p= 0.041$ - Figure 1e). During the one-week course of these patients, overall, three (30%) patients, all of whom were critically ill, died. Seven patients with fever before the treatment showed clinical improvement. The change in oxygen supplementation requirements was found to be statistically significant ($p= 0.0008$ - Figure 1g). Table 3 shows the clinical signs of the COVID-19 patients before and after the TCZ treatment.

All but four patients (82.6%) were monitored in the intensive care unit during the TCZ treatment. At one week after the TCZ treatment, 13 (56.5%), among whom two were critically ill, improved clinically; three (13%), among whom two were critically ill, remained clinically stable; one (4.3%) showed progression of the disease, and six patients (26.1%) died.

One patient who had been clinically stable at one week of the treatment died on the 23rd day, making the number of deaths seven (30.4%). Thirteen patients whose clinical condition improved were discharged in good health, whereas one patient whose clinical condition worsened in the first week of the treatment was discharged on the 14th day of the treatment. Overall, 14 patients (60.9%) were discharged at an average of 19.14 ± 13.57 days after the TCZ treatment.

In the pre-treatment clinical evaluation, 11 patients were critically ill (47.8%), and 12 patients (52.2%) severely ill. Of the 11 critically ill patients before the treatment, six died (54.5%) during the first week of the course of the treatment, the condition of one patient worsened (9.1%), and two patients remained stable (18.2%). In this patient group, only two patients (18.2%) showed clinical improvement. Six critically ill patients also received supplemental oxygen with invasive ventilation, three of these patients died, the condition of one patient worsened, one patient remained stable, and one patient showed clinical improvement.

Table 2. The laboratory findings of Covid-19 patients at before and after TCZ therapy.

Test name	Normal range	Before TCZ therapy	Day 1	Day 3	Day 5	Day 7	*p*-value
White blood cell (1/mm³)	3600-11000	9086.9 ± 4705.8 6/23 (26.1%)	6670.0 ± 4115.7 6/21 (28.6%)	8133.6 ± 7985.2 7/22 (31.8%)	10475.3 ± 8579.3 5/19 (26.3%)	8730.0 ± 7051.6 4/17 (23.5%)	0.001
Neutrophils (%)	37-73	81.9 ±11.4 21/23 (91.3%)	76.3 ± 14.8 13/21 (61.9%)	76.7 ± 10.5 13/22 (59.1%)	76.1 ± 12.6 11/19 (57.9%)	71.2 ± 11.7 6/17 (35.3%)	0.002
Lymphocyte (/mm³)	1500-3500	918.3 ±519.3 22/23 (95.7%)	833.8 ±443.2 19/21 (90.5%)	1017.7 ±633.9 18/22 (81.8%)	1222.1 ±575.3 13/19 (68.4%)	1483.5 ±788.2 9/17 (52.9%)	0.033
Lymphocyte (%)	20.5-51.5	12.5 ±10.8 22/23 (95.7%)	17.3 ±13.0 14/21 (66.6%)	15.7 ±7.8 15/22 (68.2%)	16.1 ±9.3 11/19 (57.9%)	20.0 ±9.5 6/17 (35.3%)	0.005
Platelet (10³/mm³)	150-450	257.4 ± 114.6 4/23 (17.4%)	259.1 ± 93.8 3/21 (14.3%)	321.7 ± 148.5 4/22 (18.2%)	298.4 ± 137.4 5/19 (26.3%)	296.5 ± 134.6 6/17 (35.3%)	0.022
Lactate dehydrogenase (U/L)	200-450	925.2 ± 386.3 19/21 (90.5%)	807.5 ± 286.6 18/20 (90.0%)	816.6 ± 323.9 20/21 (35.2%)	958.4 ± 378.9 18/18 (100.0%)	766.4 ± 302.8 13/13 (100.0%)	0.300
Alanine aminotransferase (U/L)	5.0-40	75.7 ± 57.0 15/23 (65.2%)	69.1 ± 57.6 13/21 (61.9%)	86.8 ± 97.5 15/22 (68.2%)	127.7 ± 97.2 18/19 (94.7%)	121.0 ± 8 3.3 16/17 (94.1%)	0.074
Aspartate aminotransferase (U/L)	5.0-40	61.9 ± 36.1 14/23 (60.9%)	62.4 ± 49.1 11/21 (52.4%)	66.9 ± 56.8 13/22 (59.1%)	89.5 ± 70.6 16/19 (84.2%)	66.4 ± 47.8 11/17 (64.7%)	0.224
Procalcitonin (ng/mL)	0-0.5	0.16 ± 0.2 1/10 (10.0%)	3.6 ± 11.2 4/14 (25.6%)	2.4 ± 6.3 4/17 (23.5%)	2.3 ± 7.1 3/12 (25.0%)	0.3 ± 0.4 1/7 (14.3%)	0.238
CRP (mg/L)	0-8	157.6 ± 73.0 21/21 (100.0%)	142.4 ± 61.8 20/20 (100.0%)	45.6 ± 27.8 20/20 (100.0%)	15.2 ± 16.2 11/19 (57.9%)	11.1 ± 19.9 6/17 (35.3%)	< 0.0001
D-dimer (µg/L)	0-500	3842.6 ± 6611.5 11/19 (57.9%)	3509.3 ± 5819.5 11/13 (84.6%)	4987.6 ± 7988.3 15/16 (93.7%)	3612.8 ± 4549.5 9/11 (81.8%)	2144.6 ± 2503.2 8/9 (88.9%)	0.355
Ferritin (ng/mL)	5-204	1645.5 ± 1102.2 14/15 (93.3%)	3685.4 ± 6996.3 12/13 (92.3%)	1526.9 ± 2106.7 14/14 (100.0%)	524.0 ± 202.7 4/4 (100.0%)	614.9 ± 297.7 6/6 (100.0%)	0.809

Data is shown as means: ± standard deviation. (abnormal no/total no.%).

Table 3. The clinical findings of Covid-19 patients at before and after TCZ therapy.

Test name	Normal range	Before TCZ therapy	Day 1	Day 3	Day 5	Day 7	*p*-value
Temperature (ºC)	36.5-37.9	37.7 ± 1.1 14/23 (60.9%)	36.7 ± 0.6 7/22 (31.8%)	36.6 ± 0.4 7/22 (31.8%)	36.6 ± 0.4 6/19 (31.6%)	36.6 ± 0.6 8/17 (47.1%)	0.041
SpO2 (%)	90-100	89.5 ± 10.0 8/23 (34.8%)	92.6 ± 3.7 4/22 (18.2%)	90.6 ± 9.7 4/22 (18.2%)	92.2 ± 4.3 5/19 (26.3%)	90.5 ± 12.2 2/17 (11.8%)	0.826
Concentration of oxygen inhalation (%)	≥ 21	44.0 ± 15.9 18/23 (78.3%)	57.1 ± 20.2 21/22 (95.5%)	60.4 ± 22.5 21/22 (95.5%)	55.2 ± 24.9 16/19 (84.2%)	49.1 ± 21.8 14/17 (82.4%)	0.008

Data is shown as means: ± standard deviation. (abnormal no/total no.%).

Twelve severely ill patients received low-dose supplemental oxygen with only a mask or nasal cannula. At one week follow-up, 11 patients (91.7%) had clinical improvement, while one patient (8.3%) remained unchanged.

Discussion

TCZ is a monoclonal anti-IL-6 receptor antibody that is used in the treatment of many autoimmune diseases. Treatment with TCZ is promising in cytokine storms in COVID-19. However, the stage at which clinical TCZ therapy is more beneficial remains unclear [23].

Lymphocyte count is an important indicator for determining both the diagnosis and severity of the disease in COVID-19 patients [17]. Studies have reported low lymphocyte levels, increased D-dimer concentrations, elevated ALT levels and increased CRP levels in severely ill and critically ill patients [24]. Studies conducted in China and Italy reported decreased oxygen demand, decreased CRP levels and increased lymphocyte counts within 24-48 hours after TCZ treatment. Patients with elevated levels of CRP, ferritin and LDH and those who were not intubated had a better response to TCZ treatment [25]. Shengyu Zhang *et al.* administered TCZ to severely and critically ill COVID-19 patients, resulting in decreased body temperatures and oxygen requirement. In their study, 85% of the patients had lymphopenia before the treatment and on biochemical examination at the fifth day of the TCZ treatment, 52.6% had lymphocyte counts approaching normal limits, with 84.2% who had reduced CRP levels, which were elevated before the TCZ treatment [26].

In the National COVID-19 guideline published by the Turkish Ministry of Health, the treatment dose is not clearly specified [19]. Since guidelines for drug use have not been fully formed, we had to administer a high-dose or a low-dose according to the clinical condition of the patient. The TCZ treatment option was left to the decision of the physician, and no additional dose was given in the patients who showed a clinical response after the first dose, due to the problems in the supply of TCZ in Turkey.

Among the patients included in our study, 11 were critically ill, and 12 were severely ill. Of these 23 patients, the laboratory findings before the TCZ treatment showed that 95.7% had decreased lymphocyte counts, 57.9% had increased D-dimer levels, 65.2% had an increase in ALT, and all had elevated CRP levels. The patients' fever decreased dramatically immediately after the first dose of the TCZ treatment. Their oxygen need decreased, lymphocyte counts increased, and CRP levels rapidly decreased. However, 54.5% of the critically ill patients who received TCZ died within the first week, as reported in the literature.

Ruggero *et al.* administered TCZ to 62 patients to investigate the effect of low-dose TCZ treatment on mortality rates in patients with COVID-19-associated pneumonia. Critically ill patients and patients requiring mechanical ventilator support were not included in their study. Clinical improvement was observed in 92% of their patients given TCZ, and their patients were discharged after a mean duration of 12.5 days [27]. All patients included in our study were severely or critically ill patients, 60.9% of whom were discharged at their follow-up visit, with a mean hospital stay of 19.14 ± 13.57 days. The reason why our patients had longer hospital stay durations than the patients in the study by Ruggero *et al.* may have been primarily related to patient selection.

TCZ is an effective treatment for reducing the risk of progression of the disease in severely ill COVID-19 patients, as well as providing rapid and significant clinical improvements [17]. In an ongoing clinical trial, the efficacy and safety of TCZ are being assessed in the treatment of patients with mild clinical disease, who are at a high risk of developing severe and critical disease [24]. Multicenter studies with TCZ therapy in China are also still going on [28].

We observed a rapid clinical improvement with TCZ treatment in the severely ill COVID-19 patients, as opposed to the case in the critically ill patients. The severely ill patients in our study had high rates of recovery and discharge, but more than half of the critically ill patients died.

Limitations of the study

Since this study was conducted in the first two months of the pandemic period, and it was aimed to try TCZ for the first time in the world and in Turkey, the number of cases in whom TCZ was administered was low. Accordingly, in evaluating the findings of this study, which provides important information for the aforementioned period, the small number of cases should also be taken into consideration.

In our study, we provided TCZ treatment to every patient that we thought had cytokine storms, and we found that more than half of the critically ill patients died. Due to the small number of cases, we did not have a control group. Therefore, another limitation of the study was that we could not compare this rate to the mortality rates in the intensive care unit among COVID-19 patients who did not receive TCZ treatment.

Conclusions

TCZ treatment can be initiated to prevent cytokine storms in COVID-19 patients presenting with increased CRP, LDH and ferritin levels, lymphopenia and increased body temperature. Rapid recovery was observed with the TCZ therapy in the severely ill patients in our study, but no significant benefit of the TCZ treatment was found in the critically ill patients. The early initiation of TCZ treatment can improve survival and prevent the progression of the disease to a more critical stage. Early TCZ treatment in the presence of cytokine storms may be warranted before intubation and other intensive care needs are required or shock and organ failure develop in COVID-19 patients.

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