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Efficacy of Tocilizumab in Critically Ill COVID-19 Patients Followed in the Intensive Care Unit

Yoğun Bakım Ünitesinde Takip Edilen Kritik COVID-19 Hastalarında Tocilizumab Tedavisinin Etkinliği

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ABSTRACT *Objective:* In this retrospective and cross-sectional study, it was aimed to evaluate the efficacy of tocilizumab (TCZ) treatment in critical COVID-19 patients who were hospitalized in the intensive care unit (ICU) and developed cytokine storm.
Materials and Methods: The study included 219 critically ill COVID-19 patients followed in the ICU and treated with TCZ. All patients received 2 doses of 400 mg/day TCZ treatment during their stay in the ICU. Clinical conditions, laboratory data, inotrope requirement and chest radiographs before and after TCZ treatment were compared. Mortality rates at the 7th day, 28th day and total mortality rates of the patients were recorded.
Results: It was observed that there was a significant decrease in CRP values over time after TCZ treatment. There was a significant increase in leukocyte, lymphocyte, lactate, urea, creatinine, AST, D-dimer, LDH and PCT values. The 7-day mortality of the patients was 21%, the 28-day mortality was 64.8%, and the total mortality rate was 65.3%.
Conclusion: It was determined that after TCZ treatment, only CRP levels, which are among the inflammatory parameters, decreased significantly in patients, and the mortality rates were still high with the increase in the values of kidney and liver function tests of the patients.
Keywords: Coronavirus disease, intensive care unit, mortality rate, tocilizumab

ÖZ *Amaç:* Retrospektif ve kesitsel olarak planlanan bu çalışmada yoğun bakım ünitesinde (YBÜ) yatan ve sitokin fırtınası gelişen kritik COVID-19 hastalarında uygulanan tocilizumab (TCZ) tedavisinin etkinliğini değerlendirmeye çalıştık.
Gereç ve Yöntem: Çalışmaya, YBÜ'de takip edilen ve TCZ tedavisi uygulanmış olan 219 kritik COVID-19 hastası dâhil edildi. Tüm hastalara, YBÜ'de yattığı süre içinde 400 mg/gün 2 doz TCZ tedavisi verildi. TCZ tedavisinden önceki ve sonraki klinik durumları, laboratuvar verileri, inotrop ihtiyacı ve akciğer grafileri karşılaştırıldı. Hastalarda ait 7. gün, 28. gün ve total mortalite oranları kaydedildi.
Bulgular: TCZ tedavisinden sonra zamanla CRP değerlerinde anlamlı azalma olduğu görüldü. Lökosit, lenfosit, laktat, üre, kreatin, AST, D-dimer, LDH ve PCT değerlerinde ise anlamlı artış olduğu saptandı. Hastalara ait 7. günlük mortalite %21, 28 günlük mortalite %64,8 ve total mortalite oranı %65,3 olarak saptandı.
Sonuç: TCZ tedavisi sonrası hastalarda inflamatuar parametrelerden sadece CRP düzeylerinde anlamlı azalma olduğu, hastaların böbrek ve karaciğer fonksiyon testlerinde artış ile birlikte mortalite oranlarının hala yüksek seyrettiği saptanmıştır.
Anahtar Kelimeler: Koronavirüs hastalığı 2019, yoğun bakım ünitesi, tocilizumab

Introduction

COVID-19 which began in Wuhan, China in December 2019 as a 2019 global pandemic and has since spread rapidly around the world (1). It was named coronavirus disease 2019 (COVID-19) on February 11, 2020 (2). COVID-19, which spread rapidly through person-to-person transmission and became a worldwide public health problem, affected 603,711,760 people and caused the death of 6,484,136 individuals as of September 7, 2022 (3-5). Pneumonia, which rapidly worsens and causes respiratory failure, developed in most of the patients (6). Especially elderly and immunocompromised individuals have higher mortality and morbidity rates (7).

The fact that there is still no effective treatment for COVID-19, the need for effective treatments, especially for critically ill patients treated in intensive care units, is of great importance and studies on these treatments are continuing rapidly by scientists all over the world.

As the clinical course of COVID-19 progresses, patients begin a hyperinflammatory phase with dysregulation of adaptive immune responses. A cytokine storm then develops, accompanied by elevated plasma proinflammatory cytokine levels, including interleukin (IL) 2, 6, 7, 10 and granulocytes. Cytokine storm results in a prothrombotic environment, cardiomyopathy and ultimately multi-organ failure (8, 9).

In the treatment of cytokine storm, immunomodulatory treatments such as IL-1 inhibitors (anakinra), IL-6 inhibitors (tocilizumab-TCZ), corticosteroids (methylprednisolone) and intravenous immunoglobulin (IVIG) are applied (10). TCZ, a monoclonal antibody against the membrane-bound IL-6 receptor that inhibits the binding of soluble IL-6 and subsequent signal transduction, has been proposed as a therapeutic candidate to inhibit cytokine storm (11). In an observational study involving 544 patients with COVID-19, TCZ treatment was associated with a reduced need for subsequent invasive mechanical ventilation or a reduced risk of death (12). In another observational study, it was determined that TCZ treatment was thought to have association with a decrease in mortality among intubated COVID-19 patients (13).

In line with this information and recommendations, TCZ treatment, which is one of the immunomodulatory treatment methods, was used at the onset of clinical worsening in critically ill COVID-19 patients hospitalized in the intensive care unit (ICU) in our clinic. In this study, it was aimed to evaluate the effectiveness of TCZ treatment in critical COVID-19 patients by evaluating the effects of treatment on clinical, laboratory, lungs and mortality in critical COVID-19 patients who were treated with TCZ.

Materials and Methods

This study was carried out in ……. Hospital between 01.04.2020-30.11.2021. Ministry of Health Scientific Research Platform permission (20.10.2021), hospital management permission (25.10.2021), and University of Health Sciences Turkey, Diyarbakır Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee approval (dated 26.11.2021 and numbered 936) were obtained. The study was designed as a retrospective cross-sectional and was conducted in accordance with the 2013 criteria of the Declaration of Helsinki.

Patients who were diagnosed with COVID-19, whose nasopharyngeal samples were positive for at least one polymerase chain reaction (PCR) test, were followed up and treated in the ICU, were older than 18 years old, and received 2 doses of 400 mg/day TCZ during their stay in the ICU were included in the study. COVID-19 patients who were younger than 18 years of age, followed in the wards and did not receive TCZ treatment or were not given two doses, were excluded from the study. In addition, patients whose data could not be reached in the hospital system and patient file records, and patients who died while undergoing TCZ treatment were also excluded from the study. In line with these criteria, 235 patients who started TCZ treatment within the specified date range were included in the study. However, three patients died before the completion of TCZ treatment, and 13 patients were excluded from the study since sufficient data could not be reached in their file records. During the ICU follow-up process, the non-mortal patients were included in Group 1, while the mortal patients were included in Group 2 and evaluated.

After the patients were admitted to the ICU, their clinical status was evaluated with Acute Physiology and Chronic Health Evaluation II (APACHE II) and Glasgow Coma Score (GCS). According to the clinical condition of the patients, appropriate medical treatment, respiratory and oxygen support were provided by infectious diseases, chest diseases and anesthesiology and reanimation specialists. The data of the patients were collected by examining the hospital information system and patient file records. Demographic data of patients such as age and gender, comorbidity history, APACHE II and GCS scores at admission to ICU, vital signs,

arterial blood gases (pH, pCO_2, pO_2, lactate), hemogram parameters (leukocyte, neutrophil, lymphocyte, platelet count), biochemical parameters (urea/creatine, aspartate transaminase (AST), sodium, potassium, D-dimer, C-reactive protein (CRP), creatine kinase (CK), lactate dehydrogenase (LDH)), procalcitonin (PCT) and ferritin levels, the changes in the chest X-ray, and the necessity of inotropic support were recorded.

The clinical conditions, laboratory data, inotrope requirement and chest X-rays were compared during the 1-week period, the day before tocilizumab treatment (day 1), the day after two-day TCZ treatment (day 4), and the fourth day after treatment (day 7). While evaluating the clinical situation, the patient's need for oxygen support, the change in respiratory distress compared to the previous evaluation, and regression in existing complaints or observation of new findings were considered. The change in the chest X-ray was evaluated by an experienced specialist doctor who has been working in the ICU since the pandemic process began. It was recorded whether the patients developed death during the follow-up period in the ICU.

SPSS 20.0 for Windows software was used for statistical analysis. Numerical data were expressed as minimum-maximum and mean ± STD, while categorical data were expressed as numbers and percentages. Shapiro Wilk test was used to determine whether the numerical data fit the normality distribution. In the comparison of more than two groups, the data matching the normality distribution were evaluated with the ANOVA test in repetitive samples, while the Friedman test was used to compare the data that did not fit the normality distribution. In paired analyses, the data matching the normality distribution were evaluated with the t-test in dependent samples, and the data not complying with the normality distribution were evaluated with the Wilcoxon test. In all comparisons, $P<0.05$ was considered as significant.

Results

219 patients who were treated with TCZ and hospitalized in the COVID-19 ICU were included in this study. The mean age of the patients was 60.70±14.13, and 34.2% were female and 65.8% were male. While the mean APACHE II score of the patients was 16.47±8.52, the mean GCS was 14.46±1.34. The demographic, comorbidity status, GCS and APACHE II score data of the patients and the comparison of the data of the deceased-living patients are shown in Table 1. When Group I and Group II patients were compared in

Table 1. Comparison of demographic and clinical data of mortal and non-mortal patients receiving tocilizumab treatment

Characteristics	All patients (n=219) Mean±SD	Survivors (n=76) Mean±SD	Non-survivors (n=143) Mean±SD	p value
Age	60,70±14,13	57,9±15,1	62,15±13,36	0,092
APACHE II*	16,47±8,52	15,34±7,12	17,07±9,15	0,221
Glasgow Coma Score	14,46±1,34	14,61±1,19	14,38±1,14	0,077
	n (%)	**n (%)**	**n (%)**	
Gender Female	75 (34,2)	27 (35,5)	49 (64,5)	0,771
Male	144 (65,8)	48 (33,6)	95 (66,4)	
Comorbidity Yes	143 (65,3)	34 (44,7)	109 (76,2)	<0,001
No	76 (34,7)	42 (55,3)	34 (23,8)	
Diabetes Yes	83 (37,9)	17 (22,4)	66 (46,2)	0,001
No	136 (62,1)	59 (77,6)	77 (53,8)	
Hypertension Yes	93 (42,5)	22 (28,9)	71 (49,7)	0,003
No	126 (57,5)	54 (71,1)	72 (50,3)	

Table 1. Continued				
Characteristics	**All patients (n=219) Mean±SD**	**Survivors (n=76) Mean±SD**	**Non-survivors (n=143) Mean±SD**	**p value**
Coronary artery disease Yes	37 (16,9)	9 (11,8)	28 (19,6)	0,146
No	182 (83,1)	67 (88,2)	115 (80,4)	
Chronic kidney disease Yes	7 (3,2)	0 (0)	7 (4,9)	0,099
No	212 (96,8)	76 (100)	136 (95,1)	
COPD** Yes	18 (8,2)	7 (9,2)	11 (7,7)	0,697
No	201 (91,8)	69 (90,8)	132 (91,8)	

*APACHE II: Acute Physiology and Chronic Health Evaluation II
**COPD: Chronic obstructive pulmonary disease

terms of comorbidity, it was observed that patients with a mortal course had more comorbidities, DM and HT than non-mortal patients (p values: <0.001; 0.001; 0.003). There was no statistically significant difference between the two groups in terms of other clinical features and comorbidities (p>0.05).

The changes in vital signs and laboratory values over time in patients treated with tocilizumab are given in Table 2.

The change of vital signs over time in patients treated with TCZ is given in Figure 1. The variation of the values of infection markers over time in patients treated with tocilizumab is given in Figure 2. Considering this change, it was observed that mean arterial pressure (MAP) and CRP values decreased significantly over time (p values: <0.001; <0.001, respectively). Leukocytes, lymphocytes, lactate,

Table 2. The effect of tocilizumab treatment on vital signs and laboratory values				
Characteristics	**Day 1 (Mean±SD)**	**Day 4 (Mean±SD)**	**Day 7 (Mean±SD)**	**p value**
MAP*(mmHg)	93,59±13,63	92,78±13,97	86,06±15,51	**<0,001**
Heart rate	95,52±18,04	95,36±18,50	99,75±21,21	**0,015**
SpO_2	85,58±7,29	87,38±8,06	85,76±11,18	**<0,001**
Leukocytes (x103/uL)	11,17±4,90	11,31±6,22	13,29±7,19	**0,005**
Neutrophil (x103/uL)	9,89±4,73	9,97±5,86	11,51±6,79	0,124
Lymphocyte (x103/uL)	0,82±0,54	0,85±0,80	1,15±1,00	**<0,001**
Platelet (x103/uL)	255,57±105,22	281,55±124,40	266,97±145,92	**<0,001**
Lactate (mmol/L)	2,34±1,49	2,35±1,58	3,25±4,08	**0,037**
Urea (mg/dL)	49,64±31,84	62,02±45,30	83,60±61,61	**<0,001**
Creatine (mg/dL)	0,98±0,58	1,07±0,84	1,44±1,36	**<0,001**
AST (U/L)**	60,71±115,36	130,20±485,30	287,03±826,97	**0,034**
D-dimer (Ug/ml)	2,42±3,33	4,12±3,71	4,44±3,74	**<0,001**
C-Reactvie Protein (mg/L)	136,02±70,78	76,25±66,60	35,22±55,81	**<0,001**
Creatine kinase (IU/L)	242,29±417,58	231,98±505,17	298,33±609,24	**0,017**
Lactate dehydrogenase (U/L)	615,30±258,01	819,27±748,17	1080,71±1724,66	**<0,001**
Procalcitonin (ng/mL)	1,04±6,87	1,48±9,13	1,50±7,31	**<0,001**
Ferritin (µg/L)	1096,55±627,35	1146,68±622,91	1124,03±643,50	**<0,001**

*MAP: Mean Arterial Pressure
**AST: Aspartate Transaminase

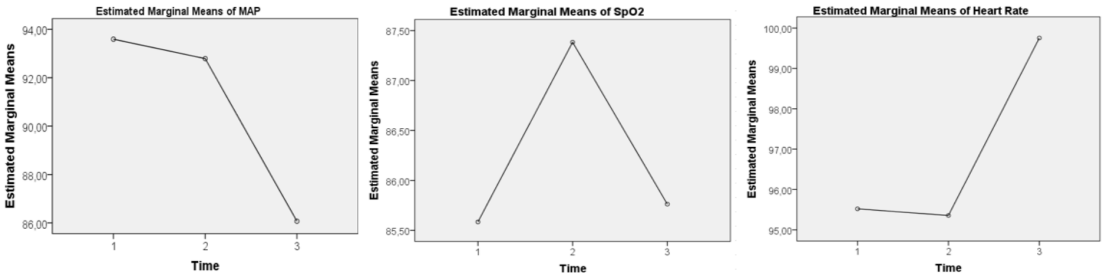

Figure 1. The effect of tocilizumab treatment on vital signs

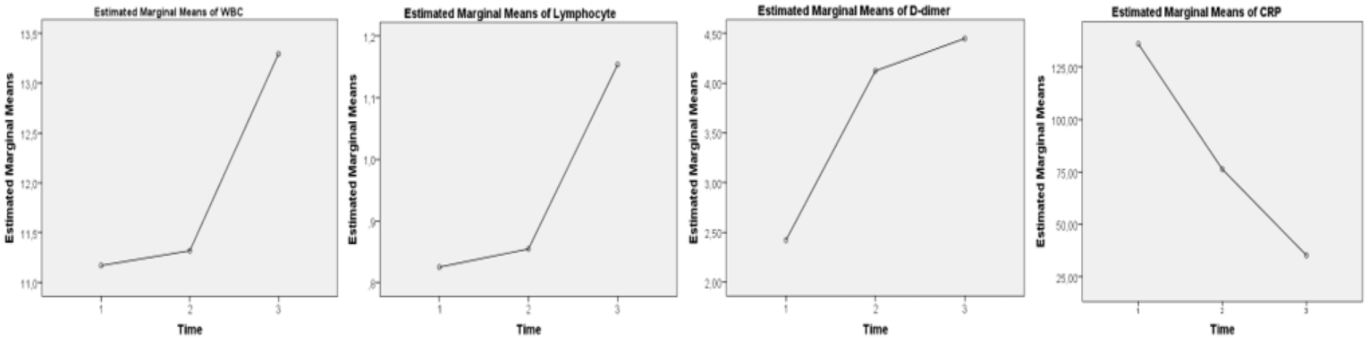

Figure 2. The effect of tocilizumab treatment on infection markers

urea, creatinine, AST, D-dimer, LDH and PCT values increased significantly over time (p<0.005). However, although there was a significant decrease in heart rate and CK values immediately after the treatment, an increase was observed in the later period (p values: 0.015; 0.017, respectively). However, while a significant increase was observed in peripheral oxygen saturation (SpO_2), platelet and ferritin values after treatment, a decrease was observed with time (p values: <0.001; <0.001; <0.001). Although there was an increase in neutrophil values over time, this difference was not statistically significant (p>0.05).

Information about the pre-treatment data of patients who received tocilizumab treatment, with and without mortality are given in Table 3. When these data were examined, laboratory values such as leukocytes, neutrophils, urea, D-dimer, LDH, lactate and PCT were higher in patients with a mortal course, while lymphocyte and AST values were found to be significantly lower (p<0.005). However, there was no statistically significant difference in terms of MAP, heart rate, PLT, creatine, CRP, CK, ferritin and inotrope requirements between patients who were and did not die before TCZ treatment (p>0.05).

Information on the post-TCZ treatment data of mortal and non-mortal patients is given in Table 4. After TCZ treatment, MAP was found to be significantly lower (p<0.001), while heart rate was higher (p<0.001) in mortal patients, and

Table 3. Comparison of pre-treatment data of mortal and non-mortal patients receiving tocilizumab treatment

Characteristics	All patients (n=219) Mean±SD	Survivors (n=76) Mean±SD	Non-survivors (n=143) Mean±SD	p value
MAP*(mmHg)	93,59±13,63	91,27±9,48	94,82±15,28	0,071
Heart rate	96,14±17,53	93,05±13,95	97,78±19,08	0,062
Leukocytes (x103/uL)	11,17±4,90	10,08±4,58	11,74±4,97	0,015
Neutrophil (x103/uL)	9,89±4,73	8,70±4,37	10,53±4,80	0,006
Lymphocyte (x103/uL)	0,82±0,54	0,92±0,49	0,77±0,57	0,007
Platelet (x103/uL)	255,57±105,22	256,50±103,25	255,08±106,61	0,892
Lactate (mmol/L)	2,34±1,49	2,26±1,99	2,39±1,16	0,044
Urea (mg/dL)	48,64±31,84	41,34±31,30	54,05±31,35	<0,001
Creatine (mg/dL)	0,98±0,58	0,92±0,42	1,02±0,64	0,567
AST** (U/L)	60,71±115,36	61,13±41,48	60,48±139,72	0,01

Table 3. Continued				
Characteristics	**All patients (n=219) Mean±SD**	**Survivors (n=76) Mean±SD**	**Non-survivors (n=143) Mean±SD**	**p value**
D-dimer (Ug/ml)	2,42±3,33	1,36±2,56	2,98±3,56	<0,001
C-Reactvie Protein (mg/L)	136,02±70,78	137,30±61,35	135,34±75,51	0,504
Creatine kinase (IU/L)	242,29±417,58	290,85±577,23	216,49±299,64	0,357
Lactate dehydrogenase (U/L)	615,30±258,01	527,49±189,70	661,97±277,26	<0,001
Procalcitonin (ng/mL)	1,04±6,87	0,43±0,91	1,36±8,48	0,003
Ferritin (µg/L)	1096,55±627,35	1049,51±617,17	1121,55±633,42	0,375
	n (%)	**n (%)**	**n (%)**	
Inotrope Yes	11 (5)	1 (1,3)	10 (7)	0,102
No	208 (95)	75 (98,7)	133 (93)	

*MAP: Mean Arterial Pressure
**AST: Aspartate Transaminase

Table 4. Comparison of post-treatment data of mortal and non-mortal patients receiving tocilizumab treatment				
Characteristics	**All patients (n=219) Mean±SD**	**Survivors (n=76) Mean±SD**	**Non-survivors (n=143) Mean±SD**	**p value**
MAP*(mmHg)	86,06±15,51	92,70±11,19	82,54±16,34	**< 0,001**
Heart rate	99,75±21,21	87,57±14,36	106,23±21,45	**< 0,001**
Leukocytes (x103/uL)	13,29±7,19	10,62±6,61	14,71±7,11	**< 0,001**
Neutrophil (x103/uL)	11,51±6,79	8,54±6,30	13,09±6,52	**< 0,001**
Lymphocyte (x103/uL)	1,15±1,00	1,37±0,74	1,03±1,10	**< 0,001**
Platelet (x103/uL)	266,97±145,92	367,87±130,70	213,34±123,79	**< 0,001**
Lactate (mmol/L)	3,25±4,08	2,15±0,87	3,84±4,91	**< 0,001**
Urea (mg/dL)	83,60±61,61	46,59±33,81	103,27±64,04	**< 0,001**
Creatine (mg/dL)	1,44±1,36	0,78±0,31	1,80±1,56	**< 0,001**
AST (U/L)**	287,03±826,97	54,79±42,15	410,45±1002,37	0,06
D-dimer (Ug/ml)	4,44±3,74	1,90±2,37	5,79±3,64	**< 0,001**
C-Reactvie Protein (mg/L)	35,22±55,81	12,59±17,14	47,25±64,86	**< 0,001**
Creatine kinase (IU/L)	298,33±609,24	96,28±133,88	405,72±725,88	**< 0,001**
Lactate dehydrogenase (U/L)	1080,72±1724,66	531,47±268,87	1372,63±2069,04	**< 0,001**
Procalcitonin (ng/mL)	1,50±7,31	0,10±0,24	2,25±8,97	**< 0,001**
Ferritin (µg/L)	1124,03±643,50	818,05±486,98	1286,65±658,58	**< 0,001**
	n (%)	**n (%)**	**n (%)**	
Chest X-RAY No Change	44 (20,1)	20 (26,3)	24 (16,8)	**< 0,001**
Progress	101 (46,1)	5 (6,6)	96 (67,1)	
Regress	74 (33,8)	51 (67,1)	23 (16,1)	
Inotrope Yes	57 (26)	2 (2,6)	55 (38,5)	**< 0,001**
No	162 (74)	74 (97,4)	88 (61,5)	

*MAP: Mean Arterial Pressure
**AST: Aspartate Transaminase

accordingly, the need for inotropes was significantly higher (p<0.001). When the laboratory values after treatment were examined, it was determined that leukocyte, neutrophil, lactate, urea, creatine, D-dimer, CRP, CK, LDH, PCT and ferritin values were significantly higher in mortal patients (p<0.05). Lymphocyte and platelet values were significantly higher in non-mortal patients (p values: <0.001; <0.001, respectively). Again, when compared with pre-treatment radiological imaging, it was observed that progression (67.1%) in mortal patients and regression (67.1%) in non-mortal patients were prominent in chest radiographs (p values: <0.001; <0.001, respectively).

When the effects of tocilizumab treatment on mortality were examined, it was found that 7-day mortality was 21%, 28-day mortality was 64.8%, and total mortality was 65.3%. Total mortality was significantly higher in patients with comorbidities (p<0.001). Especially in patients with DM (p=0.001) and HT (p=0.003), mortality was found to be significantly higher. There was no significant difference in terms of COPD (p>0.05). Considering the 7-day mortality, PCT values were found to be statistically significantly higher in patients with a mortal course than in non-mortal patients (p=0.016). In the evaluation of 28-day mortality, comorbidity rates were significantly higher in patients with a mortal course compared to non-mortal patients (p<0.001), while a significantly lower lymphocyte count was found (p=0.006). Leukocyte, PCT and D-dimer values were significantly higher in mortal patients (p values: 0.019; 0.003; <0.001, respectively).

Discussion

Cytokine storm seen during COVID-19 disease has been associated with mortality (14). It has been stated that the IL-6 receptor antibody TCZ, approved by the Food and Drug Administration, could provide clinical benefit for eligible COVID-19 patients with high inflammatory biomarkers (15). In this study, we found that after TCZ treatment, MAP and CRP values decreased and there was an increase in leukocyte, lymphocyte, lactate, urea, creatine, AST, D-dimer, LDH and PCT values. In addition, although there was a decrease in heart rate and CK values immediately after the treatment, there was an increase in the later period, and an increase was observed in SpO_2, platelet and ferritin values after the treatment, while a decrease was observed over time.

In our study, when mortal and non-mortal patients followed in the ICU and receiving TCZ treatment were compared, it was found that patients who developed mortality had more comorbidities, and that DM and HT were more common in patients with a mortal course. Considering the studies examining the relationship between comorbidity and COVID-19, de Cáceres et al. reported that HT is an important risk factor in the development of mortality in their study in which they evaluated 75 patients who developed cytokine storm and were given TCZ (16). Zhou et al., on the other hand, evaluated 191 patients and reported that the presence of comorbidity was higher in mortal patients, and additional diseases such as DM, HT and coronary artery disease were observed more frequently in mortal patients (17). In their study evaluating the effectiveness of TCZ, Kaya et al. emphasized the relationship between DM and HT history and mortality (18). Unlike these results, Keske et al. In their study with 43 patients, they found no difference in the presence of DM and HT in mortal and non-mortal patients (19). We think that the different results between studies are due to the difference in the patient populations included in the studies. Some studies included only ward patients, while others included ICU patients.

Klopfenstein et al. reported in a study in which they compared two patient groups given standard treatment and standard treatment + TCZ treatment in the service, that there was no significant difference between the two groups in terms of mortality, but higher mortality rates were observed in the standard treatment group compared to the TCZ group (20). de Cáceres et al. evaluated 75 patients who received TCZ treatment and reported that patients who received two or more doses of TCZ had higher mortality rates than those who received a single dose (13.5% vs 47.4%). In the same study, they observed that the only comorbidity significantly associated with ICU admission was obesity, 85% of obese patients needed mechanical ventilation and 62% died (16). Morena et al. found a 30-day mortality rate of 27% in their study with 45 COVID-19 patients followed in the service (21). Biran et al found the mortality rate to be 49% in patients hospitalized in the ICU and treated with TCZ in their multicenter and retrospective study (22). In their study with 52 patients hospitalized in the ICU, Yang et al observed that the 28-day mortality rate for critical cases increased up to 60.5%, like our study (23). Tiryaki et al found the mortality rate to be 78.1% in their study of 114 critical ICU patients

who were treated with IVIG (24). We think that the lower mortality rates in some different studies compared to our study may be since the patient group in our study was critically ill in the ICU, and the emergence of more mortal COVID-19 variants considering the periods in which the studies were conducted.

In our study, it was observed that MAP and CRP values decreased and leukocyte, lymphocyte, lactate, urea, creatine, AST, D-dimer, LDH and PCT values increased over time in patients treated with TCZ. In their study with 75 patients who were given TCZ treatment, de Cáceres et al. observed a significant decrease in CRP values and a significant increase in lymphocyte count on the 5th day after TCZ treatment, similar to our study. However, they did not report a significant change in D-dimer and ferritin values (16). Biran et al., in their study with 630 patients, found a decrease in CRP levels 3, 7 and 14 days after TCZ application, similar to our study. They found that there was no significant change in D-dimer, ferritin, or LDH values on the 3rd and 7th days after treatment in patients receiving TCZ. In addition, they reported a non-significant decrease in the oxygen percentage (FiO_2) of inspired air on the 1st day after treatment (22). Different reports have defined a correlation between ferritin, D-dimer, and LDH concentrations and the severity of COVID-19 (25, 26).

Keske et al., in their study with 43 patients who underwent TCZ treatment, found a significant decrease in CRP values after TCZ application, similar to our study. However, unlike our study, they reported that D-dimer and PCT values were significantly lower. They also reported an increase in lymphocyte percentage, a sharp decrease in CRP values, and a decrease in ferritin and D-dimer values after TCZ administration (19). Similar to our study, Kaya et al. found a significant decrease in CRP values and an increase in lymphocyte counts after TCZ treatment in both non-mortal and mortal patients. They reported a significant decrease in serum ferritin levels in non-mortal patients and a significant increase in mortal patients (18). Hirao et al., on the other hand, found that the median concentrations of CRP, PCT and fibrinogen decreased significantly in their study with 28 patients treated with TCZ. They also reported that the median lymphocyte and platelet counts increased significantly after treatment with TCZ (27). In their study with 21 patients who underwent TCZ, Xu et al. found a significant improvement in SpO_2 values and a decrease in oxygen uptake within 5 days after TCZ treatment. They observed that the lymphocyte percentage returned to normal in 10 patients (52.6%), and CRP values decreased significantly in 84.2% of the patients on the 5th day after treatment. They reported an increase in SpO_2 and lymphocyte counts, a decrease in leukocyte and CRP values, and a decrease in PCT over time after TCZ treatment (28). Wang et al., in their study with 138 COVID-19 patients, considered the decrease in lymphocyte percentage to be an important indicator for the diagnosis and assessment of severity in COVID-19 patients (6).

de Cáceres et al. found a decrease in lymphocyte count in most of the patients (91.8%) in the analysis before TCZ application. They found an increase in CRP, D-dimer and ferritin. They reported that there is a significant correlation between mortality and ICU admission in patients with D-dimer baseline values > 1.5 µg/ml (16). In their study with 544 patients with severe pneumonia, Guaraldi et al. reported that patients with high CRP and IL-6 concentrations had higher LDH and worse inflammatory profiles (12). In the study by Keske et al., IL-6, ferritin, CRP and D-dimer values in mortal cases were not statistically significant compared to non-mortal cases (19). Kaya et al., in their study with 308 patients who were given TCZ treatment, found that D-dimer values were significantly higher in mortal patients than in non-mortal patients both before and after TCZ treatment (18). Therefore, a decrease in ferritin and CRP levels and an increase in lymphocyte count can be considered as indicators of response to TCZ. In our study, we found that lymphocyte counts were significantly lower in patients who were mortal before TCZ treatment compared to non-mortal patients. We observed that laboratory values such as leukocytes, neutrophils, urea, D-dimer, LDH, lactate and PCT were significantly higher. These findings, which we determined, were found to be compatible with the data in many studies in the literature.

In the study performed by Xu et al., all patients had abnormal thorax CT findings at presentation in radiological imaging, and CT scans found that the lesions were completely resolved in 19 (90.5%) patients and partial improvement in the others after TCZ treatment (28). In the study by Hirao et al., they found a significant improvement in the changes in the lungs in repetitive chest X-ray or CT examinations after TCZ treatment (27). When we examined the repeated chest radiographs in our study, it was observed that there was no regression in 74 patients (33.8%), progression in 101 patients (46.1%), and no change in 44 patients (20.1%) after TCZ treatment.

Conclusion

It is thought that TCZ may have effective results in the treatment of COVID-19 disease, which still has no approved effective treatment, especially with the initiation of cytokine storm in the early period due to the high mortality risk. Decrease in ferritin and CRP levels and increase in lymphocyte count can be considered as indicators of response to TCZ. Critically ill patients treated in the ICU still have high mortality rates despite receiving two or more doses. Our study is single-center and retrospective, and there is a need for larger and multicenter studies on the subject.

Ethics

Ethics Committee Approval: Ministry of Health Scientific Research Platform permission (20.10.2021), hospital management permission (25.10.2021), and University of Health Sciences Turkey, Diyarbakır Gazi Yaşargil Training and Research Hospital Clinical Research Ethics Committee approval (dated 26.11.2021 and numbered 936) were obtained.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: R.S., O. U., Concept: R.S., O.U., Design: R.S., O.U., Data Collection and Process: R.S., Analysis or Interpretation: O.U., Literature Search: R.S., Writing: R.S., O.U.

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