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Tocilizumab treatment in COVID-19 patients: therapy's side effects and effect on mortality

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Abstract. – OBJECTIVE: This study aimed to determine the effect of tocilizumab use on mortality and the potential side effects in COVID-19 patients.

PATIENTS AND METHODS: The intensive care patients were divided into the tocilizumab group and the control group. Hemogram, biochemistry, acute phase reactant values, age, gender, comorbidity, and culture results were recorded on the 0th, 3rd, 7th, and 14th days. Factors affecting mortality between and within the groups and side effects were examined.

RESULTS: 32.14% of the patients were female, and 67.85% were male. The tocilizumab group had high alanine aminotransferase and potassium on day 3. On day 7, low levels of platelet, glucose, international normalized ratio, prothrombin time, and active partial thromboplastin time levels were observed. Procalcitonin, C-reactive protein, and fibrinogen levels were low on days 3 and 7. The relationship between the tocilizumab treatment and mortality was statistically not significant, although the APACHE score was low. In the tocilizumab group, the presence of additional disease and reproduction in culture significantly increased mortality.

CONCLUSIONS: Despite the risks of side effects, tocilizumab was used in COVID-19 treatment since it is an interleukin-6 blocker. Although the first publications stated that the treatment could decrease the mortality rate, later meta-analyses did not support these results. Our study also found that using tocilizumab did not make a difference in long-term mortality. We also observed that the known side effects were seen in short-term use.

Key Words:
Tocilizumab, CRITICAL care, COVID-19.

Introduction

COVID-19 is a disease caused by the new coronavirus called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which damages the lungs and other organs[1]. The new coronavirus infected millions of people, and the outbreak had devastating effects. Unfortunately, tens of thousands of patients were treated in intensive care units (ICU)[2]. A condition called prolonged COVID-19 began to be observed in patients who were subsequently discharged from intensive care. Persistent symptoms of this syndrome include fatigue, dyspnea, cognitive and mental impairments, chest and joint pains, palpitations, myalgia, smell and taste dysfunctions, cough, headache, and gastrointestinal and cardiac issues[3]. To protect against this virus, pharmaceutical companies and researchers tried to develop vaccines. However, some segments of society showed hesitancy towards the vaccines that were quickly introduced to the market[4]. It was also indicated that inconsistent risk messages from public health experts and elected officials may reduce vaccine uptake[5].

In the first days of the spread of the disease, while researchers were writhing in uncertainty, the physicians tried many drugs that could effectively treat the patients or reduce the transmission of the virus. Tocilizumab was one of these drugs. Tocilizumab is an interleukin-6 (IL-6) receptor-blocking drug. It can be used in rheumatoid arthritis, juvenile idiopathic arthritis, giant cell arteritis, treatment-resistant Takayasu's arteritis, systemic sclerosis, and adult Still's disease[6]. It was found that acute phase reactants (such as CRP and D-dimer, ferritin), and pro-inflammatory cytokines (such as IL-6 level) were significantly higher in COVID-19 patients. It was stated that it should be preferred in patients with a gradual increase in oxygen demand who were in the 2nd-3rd week of infection. Afterward, tocilizumab was used in many hospitals[7].

Side effects such as bacterial superinfection, high levels in liver function tests, neutropenia, and thrombocytopenia may develop in patients using tocilizumab. It is known that these side effects develop with the long-term use of tocili-

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zumab in treating rheumatic diseases. However, data on the side effects of short-term use of the drug were limited. Therefore, this study aims to determine the effect of tocilizumab use on mortality and the potential side effects in COVID-19 patients who followed up in our hospital's ICU.

Patients and Methods

This study was planned as a retrospective observational study. After obtaining the permission of the local ethics committee, patients hospitalized in the COVID-19 ICU between August 2021 and August 2022 were retrospectively screened. Our primary objective was to determine whether tocilizumab, used for the treatment of COVID-19, would show the same laboratory side effects.

Patient Selection

Local ethics committee permission was first obtained for this research. Then, patients who were hospitalized in intensive care between August 2021 and August 2022 were examined retrospectively. The patients who received tocilizumab constituted the tocilizumab group (n=70), while the patients who did not take it and were followed up in the same period formed the control group (n=70).

Inclusion criteria for the tocilizumab group were being over 18, hospitalized in the ICU with the diagnosis of COVID-19, receiving tocilizumab treatment, having an increase in acute phase reactants, an increase in pro-inflammatory cytokines, a progressive increase in oxygen demand, and being in the first week of the infection. Exclusion criteria were being under 18, being diagnosed with COVID-19 but not treated with tocilizumab, not being diagnosed with COVID-19, not being able to access patient data, and not needing oxygen therapy.

Inclusion criteria for the control group were being over 18, hospitalized in the ICU with the diagnosis of COVID-19, not receiving tocilizumab treatment, increased acute phase reactants, and increased pro-inflammatory cytokines, a progressive increase in oxygen demand, and being in the first week of the infection.

The tocilizumab group's laboratory tests were recorded on the 0^{th}, 3^{rd}, 7^{th}, and 14^{th} days and were reviewed retrospectively. Leukocyte (WBC), lymphocyte (LYM), neutrophil (NEU), platelet (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), blood urea nitrogen (BUN), creatinine, glucose, sodium, potassium, chloride, international normalized ratio (INR), prothrombin time (PT), and active partial thromboplastin time (aPTT) values were recorded.

Procalcitonin (PCT), lactate dehydrogenase (LDH), D-dimer, CRP, ferritin, fibrinogen, and pro-B-type natriuretic peptide (Pro-BNP) values are acute phase reactants and used to monitor the severity of the disease. They were recorded on the 0^{th}, 3^{rd}, 7^{th}, and 14^{th} days. Acute Physiology and Chronic Health Evaluation (APACHE) and Glasgow scores, which were calculated using these values and showed the probability of mortality in the ICU, were also recorded. In addition, the culture results of patients' blood, urine, and tracheal aspiration fluid samples were recorded. Additional diseases (such as hypertension, diabetes mellitus, cancer, etc.) that existed before the current situation were questioned and recorded.

Statistical Analysis

All statistical analyses were performed using SPSS 25 (IBM Corp., Armonk, NY, USA). The suitability of the variables for normal distribution was examined by analytical methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). In the descriptive analysis, mean ± standard deviation was given for normally distributed variables, whereas median and min-max values were given for non-normally distributed variables. Descriptive statistics were made by giving demographic characteristics, frequency, and percentage values. In order to make comparisons, an independent *t*-test was used for normally distributed data (for parameters with a Kolmogorov-Smirnov result of $p>0.05$) and a Mann-Whitney U test for non-normally distributed data (for parameters with a Kolmogorov-Smirnov result of $p<0.05$). The Chi-square test was used to compare categorical variables (such as the relationship between drug use and mortality). Differences were considered significant when the *p*-value was lower than 0.05.

Results

A total of 140 patients were included in the study. 32.14% (45 patients) of the patients were female, and 67.85% were male (95 patients). The mean age of the patients was 55.66±7.3 years in women and 60.05±8.9 years in men. The mean hospitalization time in the tocilizumab group was 11 days, whereas it was 4 days in the control group.

WBC, LYM, NEU, PLT, ALT, AST, ALP, BUN, creatinine, glucose, sodium, potassium, chloride, INR, PT, aPTT parameters were measured at 0th (first admission), 3rd and 7th day for both groups and values were compared. The values on the 14th day could not be compared because there were no patients in the control group who lived for 14 days. In the control group, LYM and aPTT values were significantly higher on day 0. On the 3rd day, ALT and potassium values were different. On day 7, there was a significant difference between PLT, glucose, INR, PT, and aPTT values (Table I).

When acute phase reactants between the tocilizumab group and the control group were compared, there was a difference between PCT, D-dimer, fibrinogen, and pro-BNP values on day 0. In the tocilizumab group, PCT, D-dimer, and pro-BNP were low, and fibrinogen was high. PCT, LDH, CRP, D-dimer, and fibrinogen values were significantly lower in the tocilizumab group on day 3. On day 7, PCT, CRP, and fibrinogen values remained high in the control group (Table I).

When day 0 and day 3 were compared in the tocilizumab group, a significant increase in BUN and D-dimer and a decrease in CRP and fibrinogen values were found. When day 0 and day 7 were compared, ALT, BUN, and D-dimer values increased, and AST, CRP, and fibrinogen values decreased. When day 0 and day 14 were compared, an increase in the values of LYM and ALT and a decrease in the values of PLT, CRP, and fibrinogen were found (Table II).

The relationship between tocilizumab intake and mortality was statistically not significant. The drug did not make any difference according to gender. There was a significant difference in intensive care scores. While the Glasgow score was high in the tocilizumab group, the APACHE score was low. The relationship between comorbidity and mortality was examined, but no significant relationship was found (Table III).

When factors affecting mortality in the tocilizumab group were compared, the presence of additional disease and reproduction in culture significantly increased mortality (Table IV).

Discussion

In this study, COVID-19 patients who were followed up in the ICU were retrospectively examined. Although the day 14 mortality was higher in the control group, there was no difference in the long term. There was a significant difference between the groups in the APACHE and Glasgow coma scales. When the complications between the groups were examined, the culture results were examined in terms of secondary infection, and it was seen that there was no difference. When the groups were compared, the deterioration of the levels of PLT, glucose, INR, PT, and aPTT was observed even in the first 7 days in the tocilizumab group. When we focused on the tocilizumab group, although there was an improvement in CRP and fibrinogen on the 14th day, deterioration in PLT and ALT values occurred. Thrombocytopenia and liver dysfunction had occurred even in as few as 14 days.

While tocilizumab has long been used to treat rheumatic diseases, it has gained a different use with the COVID-19 pandemic. Laboratory evidence of serious SARS-CoV-2 infections indicates that cytokine release syndrome (CRS) has a crucial pathogenic role. Although many proinflammatory cytokines are involved in CRS, interleukin-6 (IL-6) is the most important. It was also proved to be a poor prognostic factor. Anti-IL-6 agents were proposed as a promising treatment regimen for COVID-19[8,9]. Tocilizumab is a monoclonal antibody that targets both membrane-bound and soluble forms of the IL-6 receptor. Toniati et al[10] conducted a study evaluating the effectiveness of tocilizumab in the treatment of severe COVID-19. In a series of 100 patients with severe COVID-19 pneumonia complicated by acute respiratory distress syndrome (ARDS) and hyperinflammatory syndrome, tocilizumab use demonstrated rapid and sustained response and was associated with significant clinical improvement[10]. In another study by Ramaswamy et al[11], although patients treated with tocilizumab had high CRP and IL-6 values indicative of cytokine storm at first, tocilizumab still provided a short-term survival benefit.

In a single-center retrospective study conducted by Capra et al[12] in Italy, the researchers administered tocilizumab to patients with respiratory rate ≥30/min, oxygen saturation (SpO_2) ≤93% in room air, or the ratio of partial pressure of oxygen in arterial blood to the fraction of inspiratory oxygen concentration (PaO_2/FiO_2) ≤300 mmHg. The study[12] stated that the early administration of tocilizumab significantly reduced the mortality rate and could help treat

Table I. Hemogram/biochemistry and acute phase reactant values on days of 0th, 3rd, and 7th, and comparisons between groups.

	Day zero			Day 3			Day 7		
	Tocilizumab group	Control group	*p*	Tocilizumab group	Control group	*p*	Tocilizumab group	Control group	*p*
WBC (10^3/mL)	8.78 (5.45)	9.31 (6.53)	0.28[1]	9.47 (4.64)	9.59 (7.1)	0.4[1]	10.6 (7.2)	11.3 (6.6)	0.6[1]
LYM (10^3/mL)	0.68 (0.54)	1.01 (1.02)	0.001[1]	0.7 (0.585)	0.71 (0.77)	0.3[1]	0.87 (0.9)	0.77 (0.8)	0.8[1]
NEU (10^3/mL)	7.67 (5.46)	7.09 (5.42)	0.79[1]	8.17 (5.15)	8.37 (5.98)	0.7[1]	8.9 (8.2)	9.5 (7.3)	0.8[1]
PLT (10^3/mL)	228 ± 107	227 ± 102	0.9[2]	252 ± 122	235 ± 108	0.2[2]	99	274 ± 139	0.01[2]
ALT (U/L)	37 (30)	27 (35)	0.06[1]	45 (39)	32 (33)	0.02[1]	47 (36)	52 (89)	0.8[1]
AST (U/L)	52 (30)	43.5 (42)	0.3[1]	42 (41)	39 (26)	0.2[1]	41.5 (33)	39.5 (35)	0.8[1]
BUN (mg/dL)	39 (30)	48 (35)	0.4[1]	62 (42)	63 (58)	0.6[1]	64.5 (45)	52 (67)	0.3[1]
Creatinine (mg/dL)	1 (0.53)	1.16 (0.73)	0.1[1]	0.99 (0.59)	1.04 (0.86)	0.3[1]	0.98 (0.53)	0.97 (0.98)	0.9[1]
Glucose (mg/dL)	163 (117)	176 (143)	0.4[1]	166.5 (263)	163 (91)	0.9[1]	143 (332)	174 (115)	0.04[1]
Sodium (mmol/L)	134.9 ± 5.0	135.7 ± 5.2	0.7[2]	138.6 ± 6.3	140.3 ± 5.6	0.2[2]	138.1 ± 6	140.2 ± 7.3	0.4[2]
Potassium (mmol/L)	3.95 (0.8)	4.1 (0.8)	0.24[1]	4.4 (0.9)	4.1 (0.9)	0.04[1]	4.4 (1)	4.2 (1.3)	0.4[1]
Chloride (mmol/L)	100.6 (8)	99.5 (7.1)	0.95[1]	101 (19.7)	102 (6.4)	0.3[1]	101.6 (6.9)	100.9 (38.8)	0.7[1]
INR (%)	12.85 (1.9)	13.35 (3)	0.21[1]	12.9 (2)	13.6 (2.6)	0.1[1]	12.8 (1.7)	13.8 (2.2)	0.005[1]
PT (sn)	1.15 (0.17)	1.18 (0.26)	0.25[1]	1.16 (1.37)	1.21 (0.23)	0.2[1]	1.1 (0.15)	1.2 (0.2)	0.01[1]
aPTT (sn)	27.3 (5.9)	28.4 (7.5)	0.09[1]	28.6 (6.9)	28.3 (6.2)	0.8[1]	27.4 (5.6)	30 (8.2)	0.08[1]
PCT (ng/mL)	0.19 (0.35)	0.59 (4.02)	0.01[1]	0.13 (0.4)	0.44 (2.3)	0.005[1]	0.15 (0.2)	0.49 (1.9)	0.02[1]
LDH (U/L)	1611 (2,303)	345 (189)	0.24[1]	521 (-)	225 (174)	0.02[1]	488.5 (378)	339 (492)	0.8[1]
CRP (mg/dL)	142.6 ± 79.7	131.9 ± 102	0.1[2]	24.3 ± 30.3	103.2 ± 75.9	0.001[2]	17 ± 33.5	91.3 ± 97.1	0.001[2]
D-dimer (ng/mL)	447 (595)	696 (1,161)	0.05[1]	1,800 (3,627)	528 (2046)	0.003[1]	769 (1396)	478.5 (2474)	0.3[1]
Ferritin (ml/ng)	510 (1,070)	654 (912)	0.92[1]	508 (609.6)	443 (662.1)	0.3[1]	456.4 (699.4)	556.7 (881.3)	0.5[1]
Fibrinogen (mg/dL)	645 (206)	561 (270)	0.01[1]	265 (763)	558 (773)	0.001[1]	215 (86)	425 (266)	0.001[1]
Pro-BNP (pg/ml)	741 (2,093)	4,780 (6,640)	0.03[1]						

[1]Mann-Whitney U test, [2]Independent *t*-test, $p<0.05$: statistically significant. Median (IQR=interquartile range) values were given when the Mann-Whitney U test was performed, and mean±SD values were given when the Independent *t*-test was performed. Leukocyte (WBC), lymphocyte (LYM), neutrophil (NEU), platelet (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), international normalized ratio (INR), prothrombin time (PT), active partial thromboplastin time (aPTT), Procalcitonin (PCT), lactate dehydrogenase (LDH), and pro-B-type natriuretic peptide (Pro-BNP).

Table II. Comparisons between 0th day and day of the 4th, 7th, and 14th in the tocilizumab group.

	Day 0 and day 3 comparison			Day 0 and day 7 comparison			Day 0 and day 14 comparison		
	Day 0 average	Day 3 average	*p*	Day 0 average	Day 7 average	*p*	Day 0 average	Day 14 average	*p*
WBC (10^3/mL)	8.7 (5.45)	9.47 (4.64)	0.11[1]	8.7 (5.45)	10.6 (7.2)	0.07[1]	8.7 (5.45)	8.7 (6.41)	0.79[1]
LYM (10^3/mL)	0.68 (0.54)	0.7 (0.585)	0.98[1]	0.68 (0.54)	0.87 (0.9)	0.1[1]	0.68 (0.54)	1.27 (0.9)	0.003[1]
NEU (10^3/mL)	7.67 (5.46)	8.17 (5.15)	0.14[1]	7.67 (5.46)	8.9 (8.2)	0.11[1]	7.67 (5.46)	6.62 (7.61)	0.58[1]
PLT (10^3/mL)	225 ± 100	241 ± 119	0.3[2]	225 ± 100	205 ± 103	0.3[2]	231 ± 109	174 ± 77	0.009[2]
ALT (U/L)	37 (30)	45 (39)	0.88[1]	37 (30)	47 (36)	0.05[1]	37 (30)	75 (57)	0.003[1]
AST (U/L)	52 (30)	42 (41)	0.26[1]	52 (30)	41.5 (33)	0.006[1]	52 (30)	40 (40)	0.17[1]
BUN (mg/dL)	39 (30)	62 (42)	0.0001[1]	39 (30)	64.5 (45)	0.001[1]	39 (30)	54 (25)	0.12[1]
Creatinine (mg/dL)	1 (0.53)	0.99 (0.59)	0.44[1]	1 (0.53)	0.98 (0.53)	0.51[1]	1 (0.53)	0.99 (0.59)	0.25[1]
Glucose (mg/dL)	163 (117)	166.5 (263)	0.20[1]	163 (117)	143 (332)	0.06[1]	163 (117)	134.5 (90)	0.06[1]
INR (%)	12.85 (1.9)	12.9 (2)	0.52[1]	12.85 (1.9)	12.8 (1.7)	0.17[1]	12.85 (1.9)	12.2 (2.1)	0.13[1]
PCT (ng/mL)	0.19 (0.35)	0.13 (0.4)	0.39[1]	0.19 (0.35)	0.15 (0.2)	0.97[1]	0.19 (0.35)	0.26 (0.35)	0.12[1]
CRP (mg/dL)	137.3 ± 78.8	24.6 ± 32.3	0.001[2]	138 ± 81.1	18.7 ± 3.6	0.001[2]	104.4 ± 84.2	13.6 ± 2.4	0.001[2]
D-dimer (ng/mL)	447 (595)	1,800 (3,627)	0.001[1]	447 (595)	769 (1,396)	0.02[1]	447 (595)	439 (364)	0.32[1]
Ferritin (ml/ng)	510 (1,070)	508 (609.6)	0.86[1]	510 (1,070)	456.4 (699.4)	0.38[1]	510 (1,070)	389.4 (737.4)	0.27[1]
Fibrinogen (mg/dL)	645 (206)	265 (763)	0.0001[1]	645 (206)	215 (86)	0.0001[1]	645 (206)	244 (157)	0.001[1]

[1]Wilcoxon test, [2]Paired-samples *t*-test; $p<0.05$: statistically significant. Median (IQR=interquartile range) values were given when the Mann-Whitney U test was performed, and mean±SD values were given when the Independent *t*-test was performed. Leukocyte (WBC), lymphocyte (LYM), neutrophil (NEU), platelet (PLT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), international normalized ratio (INR), and Procalcitonin (PCT).

Table III. The relationship between mortality, gender, secondary infection, comorbidity, Apache and Glasgow Score between the tocilizumab and the control group.

	Tocilizumab group (n)	Control group (n)	Total (n)	p
Number of surviving patients	38	34	72	0.3[1]
Number of patients who died	32	36	68	
Total	70	70	140	
Male	48	47	95	0.5[1]
Female	22	23	45	
Total	70	70	140	
The number of patients with no reproduction in culture	54	58	112	0.4[1]
The number of patients with reproduction in culture	16	12	28	
Total	70	70	140	
	Tocilizumab group	**Control group**		**p**
APACHE (mean ± SD)	13.5 ± 5.6	15.8 ± 10.3 (mean ± SD)		0.04[3]
Glasgow	15 (0) (median, IQR)	15 (0) (median, IQR)		0.03[2]
	Patients with additional disease (n)	**Patients without additional disease (n)**	**Total**	**p**
Number of surviving patients	41	31	72	0.1[1]
Number of patients who died	46	22	68	
Total	87	53	140	

[1]Chi-square test, [2]Independent *t*-test, [3]Mann-Whitney U test; $p<0.05$: statistically significant. Median (IQR=interquartile range) values were given when the Mann-Whitney U test was performed, and mean±SD values were given when the Independent *t*-test was performed. Additional diseases mean chronic diseases such as hypertension, diabetes mellitus, cancer, etc. Acute Physiology and Chronic Health Evaluation (APACHE).

pneumonia associated with COVID-19. While respiratory function improved in 64.8% of hospitalized tocilizumab patients, 100% of the control group required mechanical ventilation. Infection was not reported. In another study[13] from Italy, patients who received (n: 21) and did not receive (n: 91) tocilizumab were examined. There were not any adverse effects after tocilizumab administration. This study found that treatment with tocilizumab did not significantly affect COVID-19 patient admission to the ICU or 7-day mortality rate.

Table IV. Examination of factors that may affect mortality in the tocilizumab group.

Tocilizumab group	Patients with additional disease (n)	Patients without additional disease (n)	Total	p
Number of surviving patients	17	21	38	0.02[1]
Number of patients who died	23	9	32	
Total	40	30	70	
	The number of patients with no reproduction in culture	**The number of patients with reproduction in culture**		
Number of surviving patients	25	13	38	0.01[1]
Number of patients who died	29	3	32	
Total	54	16	70	

[1]Chi-square test, $p<0.05$: statistically significant. Additional diseases mean chronic diseases such as hypertension, diabetes mellitus, cancer, etc.

A study in France found that patients using tocilizumab had a higher Charlson comorbidity index, a more severe course of the disease, and critical laboratory findings (such as severe lymphopenia and high CRP). Despite the small sample size (20 drug group, 25 control group patients) and its retrospective nature, the findings of this research strongly suggested that tocilizumab could reduce the number of ICU admissions and/or mortality in patients with severe SARS-CoV-2 pneumonia[14].

In the study of Quartuccio et al[15], 42 patients hospitalized for COVID-19 pneumonia receiving anti-cytokine drug therapy were compared with 69 patients receiving standard COVID-19 treatment. Tocilizumab constituted the majority of anti-cytokine drugs. The study stated that all of the tocilizumab group also received antiviral therapy, and 40% received glucocorticoid therapy. In the tocilizumab group, higher baseline CRP, IL-6, NEU, and lower LYM levels were detected. In addition, it was observed that tocilizumab treatment started in the ward gave a better response and resulted in less infection compared to the group treated in the ICU[15].

In a study[11] examining the effect of tocilizumab treatment on short-term mortality, given to 21 of 86 COVID-19 pneumonia patients, a 75% reduction in the risk of mortality as a result of treatment with the "Cox model" was found. The researchers also confirmed this relationship with the "treatment effects models", in which they showed that the risk of mortality was reduced by 52.7% compared to those who were not treated. Both models observed a short-term survival advantage in patients with severe COVID-19 pneumonia. In a study[16] conducted on 30 COVID-19 pneumonia patients under the age of 80 with severe oxygen therapy, rapidly worsening, high CRP levels, it was emphasized that IL-6 blockade could prevent a "cytokine storm", prevent admission to the ICU, and the need for mechanical ventilation.

In a study[17] conducted in the USA, 44 patients using tocilizumab had statistically significantly higher IL-6, triglycerides, AST, and ferritin levels. The hospital stay was longer, and the survival rate was higher. However, since it was a retrospective study and mortality is affected by various factors, it was emphasized that the results should be interpreted with caution. The researchers emphasized that there should be ongoing randomized controlled trials to definitively answer whether tocilizumab improves survival in patients with COVID-19 ARDS.

Meta-analysis studies[18,19] conducted yielded conflicting results. Lan et al[18] emphasized that although the mortality rate of patients treated with tocilizumab was lower than the control group, the difference was not statistically significant. In the study of Lan et al[18], the mortality rate for COVID-19 patients treated with tocilizumab ranged from 3.2% to 38.6%. The meta-analysis found no difference in terms of mortality, risk of hospitalization in the ICU, and mechanical ventilator requirement in patients receiving tocilizumab. The authors did not find conclusive evidence that tocilizumab provides any additional benefit to severe COVID-19 patients[18].

In another meta-analysis by Tleyjeh et al[19], four randomized controlled trials (RCTs) involving 771 patients were examined to understand the effect of tocilizumab on the risk of mechanical ventilation. The analysis demonstrated that the use of tocilizumab reduced the need for mechanical ventilation. No increased risk of infection or adverse effects were observed with tocilizumab. RCTs have shown that tocilizumab did not reduce short-term mortality. Low-confidence evidence from cohort studies[19] showed an association between tocilizumab and lower mortality. In the study by Cortegiani et al[20], 3 preclinical studies and 28 clinical studies involving 5,776 patients were examined. There was insufficient evidence regarding the clinical efficacy and safety of tocilizumab in patients with COVID-19.

Snow et al[21] conducted a systematic review and meta-regression of randomized controlled trials to determine the benefit of IL-6 blockade with tocilizumab for COVID-19. The primary outcome was determined as 28-30 days of mortality, and the secondary outcome was progression to severe disease. Severe illness was defined as the need for mechanical ventilation, admission to the ICU, or their combination. It was stated that tocilizumab reduced the need for mechanical ventilation but did not reduce admission to the ICU. They found evidence that the use of tocilizumab could be associated with a short-term mortality benefit, and they stated that this benefit could be related to reducing the need for mechanical ventilation[21].

Many changes have been made to treatment protocols throughout the COVID-19 pandemic. Many drugs that were initially used with hope, such as tocilizumab, were later withdrawn from use. Sometimes, new drugs came into use during the process. Molnupiravir (MOV) is one of them. In a study[22] conducted in Vietnam, MOV caused

a reduction in the risk of hospitalization or death in mild COVID-19 patients, and MOV was also found to be well tolerated and safe without any major adverse events during the administration period.

Sometimes, combinations of antivirals were tried, and treatment protocols were updated. Dallocchio et al[23] suggest that lopinavir, ritonavir, darunavir, and atazanavir activated interactions with the key binding sites of SARS-CoV-2 proteas. Furthermore, they demonstrated the ability of remdesivir, tenofovir, emtricitabine, and lamivudine to be incorporated. The combination of a protease inhibitor and two nucleoside analogues, drugs widely used to treat HIV infection, could be evaluated in clinical trials for the treatment of COVID-19[23].

One of the reasons for the difference in responses to drugs may be the difference in COVID-19 variants. A study conducted by Kaya et al[24] aimed to examine the COVID-19 severity and treatment responsiveness of critically ill patients between the original virus and emergent variations. They showed that the state of patients with emergent variants (PEV) was more severe than the patients with the original variant (POV) at the time of ICU admission. However, the prone position and steroids were not efficient in improving the partial-pressure-of-oxygen/fraction-of-inspired-oxygen ratios (P/F ratios). P/F ratios of PEV were significantly lower in non-invasive ventilation. These results suggest that early intubation might be necessary for PEV[24].

In this study, we found that tocilizumab did not affect long-term mortality, which is consistent with meta-analyses[18-20]. While it improved the scores we used in patient follow-up in intensive care, it did not alter the final result regarding mortality. Although no patients survived on day 14 in the control group, this outcome did not impact the final result. Despite the high survival rate at day 14 among patients receiving tocilizumab, there was no discernible difference in long-term mortality between the groups.

Although the number of patients in our study was higher compared to others, it still was a limited number. In some studies[10], patients were followed starting from the ward service; in our study, on the other hand, we examined patients' data in the first 14 days after admission to the ICU. The fact that severe patients who were already eligible for admission to the ICU constituted the study group may explain the differences in mortality. Since the life expectancy was not equal between the groups, laboratory data that would show the side effects of the drug for longer periods could not be analyzed.

Another limitation of our study was the inaccessibility of clinical symptoms, although it was easy to access laboratory information in patients' clinic records. Typical clinical side effects such as cough, nasal congestion, runny nose, sore throat, and headache can also be seen. In addition, liver toxicity symptoms such as abdominal pain and jaundice or allergic reactions may also be seen. However, this information could not be accessed because our study was designed retrospectively. By scanning laboratory findings and culture results, we were able to examine side effects such as bacterial superinfection, high levels in liver function tests, neutropenia, and thrombocytopenia.

Conclusions

There was no difference in mortality between the tocilizumab and control groups. Although the scores used in patient follow-up were lower in the tocilizumab group and mortality risk seemed low, the result did not change. We observed the feared side effects of tocilizumab (such as elevation in liver function tests and a tendency to decrease in LYM and PLT values compared with the basal values) even in the short period of therapy.

Conflict of Interest

The authors of this study declare that they have no conflict of interest.

Ethics Approval

The ethical approval for this study was obtained by the Ethical Committee of Buca Seyfi Demirsoy Research and Training Hospital (Permission number: 2020/21-02).

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Authors' Contributions

Pınar Ayvat: study design, data collection and processing, analysis and interpretation, literature review, writing the manuscript. Seyda Kayhan Omeroglu: data collection and processing, supervision, critical review.

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Availability of Data and Materials
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Informed Consent
Informed consent was obtained from each patient.

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