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Effect of Tocilizumab Use on Mortality in COVID-19 Patients Admitted to Intensive Care Unit

Yoğun Bakım Ünitesine Kabul Edilen COVID-19 Hastalarında Tocilizumab Kullanımının Mortalite Üzerine Etkisi

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ABSTRACT

Aim: Coronavirus disease 2019 (COVID-19) mostly proceeds with mild respiratory symptoms, but sometimes severe pneumonia, cytokine storm, and acute respiratory distress syndrome can develop. Anti-cytokine treatments are being tried for cytokine storm. In this study, we aimed to examine the effect of tocilizumab on mortality associated with COVID-19.
Material and Methods: The study included 146 patients with moderate-to-severe acute respiratory distress syndrome diagnosed with COVID-19. The patients were divided into two groups, receiving only standard treatment (ST group, n=44), and tocilizumab treatment in addition to standard treatment (TCZ group, n=102). Groups were compared in terms of demographic, clinic, and laboratory data. Also, mortality rates were determined to detect the effect of tocilizumab on mortality.
Results: Overall, 36.3% (n=53) of the patients were female, 63.7% (n=93) were male, and the mean age was 69.5±14.2 years. The mortality rate was 29.4% (n=30) in the TCZ group and 52.3% (n=23) in the ST group (p=0.009). While C-reactive protein, fibrinogen, and lactate levels on admission to the intensive care unit (ICU) were similar across the groups, the TCZ group had higher ferritin levels (p=0.006). On discharge from ICU, the TCZ group had a significant decrease in C-reactive protein (p<0.001), while their ferritin levels decreased to levels in the ST group (p=0.134). The absence of tocilizumab in the treatment regimen was associated with a 2.63-fold increase in the mortality risk.
Conclusion: Tocilizumab reduces the mortality in COVID-19 patients in ICU. However, further studies are warranted to better elucidate the efficacy and side effects of tocilizumab.
Keywords: COVID-19; cytokine storm; tocilizumab; mortality; interleukin 6.

ÖZ

Amaç: Koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) çoğunlukla hafif solunum semptomları ile seyreder, ancak bazen şiddetli pnömoni, sitokin fırtınası ve akut solunum sıkıntısı sendromu gelişebilir. Sitokin fırtınası için anti-sitokin tedaviler denenmektedir. Bu çalışmada, tocilizumabın COVID-19 ile ilişkili mortalite üzerindeki etkisinin incelenmesi amaçlandı.
Gereç ve Yöntemler: Çalışmaya, COVID-19'a bağlı orta-şiddetli akut solunum sıkıntısı sendromu olan 146 hasta dahil edildi. Hastalar sadece standart tedavi alanlar (ST grubu, n=44) ve standart tedavi ile birlikte tocilizumab tedavisi alanlar (TCZ grubu, n=102) olmak üzere iki gruba ayrıldı. Gruplar demografik, klinik ve laboratuvar verileri açısından karşılaştırıldı. Tocilizumabın mortalite üzerindeki etkisini tespit etmek için mortalite oranları da belirlendi.
Bulgular: Genel olarak, hastaların %36,3'ü (n=53) kadın, %63,7'si (n=93) erkek ve yaş ortalaması 69,5±14,2 yıl idi. Mortalite oranı TCZ grubunda %29,4 (n=30) ve ST grubunda ise %52,3 (n=23) idi (p=0,009). Hastaların yoğun bakım ünitesine (YBÜ) kabuldeki C-reaktif protein, fibrinojen ve laktat seviyeleri gruplar arasında benzer iken, TCZ grubunda ferritin seviyeleri daha yüksekti (p=0,006). YBÜ'den taburcu olduklarında TCZ grubunda C-reaktif protein'de anlamlı bir düşüş olurken (p<0,001), ferritin seviyeleri ST grubundaki seviyelere geriledi (p=0,134). Tedavi rejiminde tocilizumabın olmaması, mortalite riskinde 2,63 katlık bir artış ile ilişkili bulundu.
Sonuç: Tocilizumab YBÜ'de takip edilen COVID-19 hastalarında mortaliteyi azaltmaktadır. Bununla birlikte, tocilizumabın etkinliğini ve yan etkilerini daha iyi aydınlatmak için daha fazla çalışmaya ihtiyaç vardır.
Anahtar kelimeler: COVID-19; sitokin fırtınası; tocilizumab; mortalite; interlökin 6.

INTRODUCTION

Following the detection of a cluster of pneumonia cases of unknown origin in December 2019 in Wuhan city of the Hubei province of China, a novel β-coronavirus strain was isolated as the responsible causative agent (1). This disease, named as coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO), rapidly spread to other countries, resulting in a global pandemic (1,2). Since COVID-19 may lead to severe respiratory failure, which is a major cause of morbidity and mortality, it was also termed as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (3,4).

The reported mortality rates in severe COVID-19 cases exhibit a wide range from 35% to 50-62% (5-7). As of April 2022, there have been more than 505 million confirmed cases of COVID-19, with the total deaths exceeding 6.2 million (8). Although most patients have mild symptoms, those with comorbid conditions show a particular inclination for more severe disease courses including severe pneumonia and acute respiratory distress syndrome (ARDS), as well as increased mortality (9,10). ARDS represents the most devastating complication of COVID-19 (11). Severe ARDS results from intracellular replication of viruses and inflammatory response of the host (12). The pathogenesis of ARDS is associated with a cytokine storm involving high serum pro-inflammatory cytokine and chemokine levels; interleukins (IL) 1, 6, 8, and 12, tumor necrosis factor-alpha (TNF-α), and interferon (IFN)-γ (4). Certain clinical features of these more severe COVID-19 cases have been found to be akin to those in hemophagocytic lymphohistiocytosis (HLH), a life-threatening condition associated with increased release of cytokines (13). Although HLH may be a familial condition, it can also be acquired following viral infections, and therefore may presumably be triggered by SARS-CoV-2 (14).

Uncontrolled excessive production of pro-inflammatory cytokines such as IL-6 results in epithelial and endothelial apoptosis, abnormal coagulation, pulmonary fibrinolysis, and diffuse alveolar injury (15). The aim of COVID-19 treatment is to strengthen anti-viral immunity and to prevent hyper-inflammatory injury (16). Treatment options generally fall into two categories. The frontline approach involves the prevention of viral replication via antiviral treatments, and second-line treatments should aim to control the cytokine storm caused by IL-1 and IL-6 in patients with more advanced diseases requiring intensive care unit (ICU) admission. The choice and timing of medications to be utilized, particularly in the latter scenario, are of importance (17).

Tocilizumab is a monoclonal human antibody developed against the IL-6 receptor. The central role of IL-6 in the pathogenesis of cytokine release syndrome (CRS) and ARDS in patients with COVID-19 has been firmly established (11). Although many cytokines are involved in CRS, IL-6 is the most important culprit and is associated with poor prognosis (18). In CRS associated with COVID-19, tocilizumab treatment has been shown to stabilize patients by reducing acute phase reactants and to offer an effective treatment option for cytokine storm (19). When the key role of IL-6 in CRS induced by COVID-19 is taken into consideration, it may be assumed that the suppression of the immune responses occurring via IL-6 by tocilizumab may prove to be useful against the hazardous effects of hyperinflammation (20).

In this study, patients with COVID-19 pneumonia admitted to ICU due to moderate to severe ARDS were administered standard treatment with or without tocilizumab and were compared in terms of the changes in clinical, radiological, and laboratory parameters, intubation duration, length of ICU stay, and mortality rates, in order to elucidate the effect of tocilizumab on these parameters. A particular emphasis was placed on the effect of tocilizumab treatment on mortality.

MATERIAL AND METHODS

All patients consecutively admitted to the ICU, Pulmonology Department, Medical Faculty of Erzincan Binali Yıldırım University between April 2020 and March 2021 due to COVID-19 pneumonia were retrospectively screened. Of 229 patients with SARS-CoV-2 detected in a polymerase chain reaction (PCR), 75 were excluded due to the presence of mild ARDS (according to the diagnostic criteria of ARDS Berlin (21), 200< partial pressure of arterial oxygen / fraction of inspired oxygen (PaO_2/FiO_2) ≤300, positive end-expiratory pressure (PEEP), or continuous positive airway pressure (CPAP) ≥5 cm H_2O), 5 due to reasons other than ARDS (3 myocardial infarction, 2 acute renal failure), and 3 due to inability to use tocilizumab (pregnancy, active hepatitis B, fungal infection). Thus, a total of 146 patients participated in the study, including 44 patients with moderate to severe ARDS (according to the diagnostic criteria of ARDS Berlin (21), PaO_2/FiO_2 ≤200 + PEEP ≥5 cm H_2O) who received standard treatment (ST group), and 102 patients with moderate to severe ARDS who received tocilizumab in addition to standard treatment (TCZ group, standard treatment + 4-8 mg/kg tocilizumab with 24h intervals). In the standard treatment, in accordance with the recommendations of the COVID-19 Treatment Guide of the Ministry of Health of the Republic of Turkey; Favipiravir 2×1600 mg loading, 2×600 mg maintenance, enoxaparin 1 mg/kg, 6 mg/day dexamethasone or equivalent glucocorticoids, for example, 0.5-1 mg/kg of prednisolone or 32 mg/day of methylprednisolone and antibiotics (if signs of bacterial infection are present and according to the factor) were given (22). TCZ group patients, of the Scientific Committee of the Ministry of Health of the Republic of Turkey in accordance with the recommendations in the field of high flow oxygen therapy (HFOT) or mechanical ventilation (MV) and abnormal serum level of at least two biomarkers of C-reactive protein (CRP), D-dimer, lactate dehydrogenase (LDH), or ferritin, were patients that received approval by reference tocilizumab treatment (23). Data on demographics, vital parameters on admission, Charlson comorbidity index (CCI) scores, acute physiology and chronic health evaluation II (APACHE II) scores, other treatments, duration of MV, complications, length of hospital and ICU stay, and mortality were retrieved from patient files.

Two groups defined on the basis of the treatments administered, i.e. the ST group, and the TCZ group, were compared to examine the effect of tocilizumab on the clinical course, length of ICU and hospital stay, acute

phase reactants, and most importantly on the mortality rate. The study was approved by the Erzincan Binali Yıldırım University Ethics Committee for Clinical Research (date: 22.02.2021, no: 04/02).

Statistical Analysis

Statistical analyses were performed using IBM SPSS v.22 software (IBM Corp., Armonk, NY). Categorical variables were expressed as number and percentage, and continuous variables as mean±standard deviation, median, 25^{th}-75^{th} percentile, and minimum-maximum values. Chi-square and Fisher's exact tests were used to compare categorical variables between the groups. The normality of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were compared with Student's t-test or Mann-Whitney U test between the two groups. When comparing study parameters between the groups on discharge from the ICU, a correction for baseline measurements was made using ANCOVA. For all tests, a p level of <0.05 was considered for statistical significance.

RESULTS

A total of 146 patients with moderate to severe ARDS due to COVID-19 pneumonia were included. The mean age was 69.5±14.2 years. Of the 146 patients, 36.3% (n=53) were female, and 63.7% (n=93) were male. Two groups were defined based on the treatments administered, the TCZ group (n=102), and the ST group (n=44). The two groups were comparable with respect to gender, cigarette smoking status, APACHE II scores, ARDS stages, and CCI. Patients in the TCZ group had significantly lower mean age than in the ST group (p=0.030, Table 1). Most common comorbid conditions in decreasing order included hypertension (HT, 33%), cardiovascular disease (CVD, 17%), chronic obstructive pulmonary disease (COPD, 16.5%), and diabetes mellitus (DM, 10.8%). A comparison of vital parameters between the study groups showed comparable heart rate and systolic blood pressure (SBP) on admission (p=0.580, and p=0.052, respectively), while patients in the ST group had lower diastolic blood pressure (DBP) and mean arterial pressure (MAP) on admission (p=0.026, and p=0.025, respectively). Regarding hypoxemia, the TCZ group had significantly lower SaO_2, and P/F ratio, and significantly higher respiratory rate (p<0.001, p=0.004, and p<0.001, respectively). The demographic data, clinical features, and vital parameters on admission in study groups were presented in Table 1.

While CRP, fibrinogen, and lactate levels were comparable between the two groups at the time of ICU admission, ferritin levels were higher in the TCZ group. On the other hand, CRP was significantly decreased on discharge in the TCZ group, while ferritin decreased to levels similar to those in the ST group (p<0.001, and p=0.153, respectively, Table 2, Figure 1). Furthermore, patients in the ST group had higher D-dimer levels on admission, while these levels were similar on discharge from the ICU (p=0.033, and p=0.146, respectively, Table 2). While procalcitonin (PCT) was higher on admission to ICU in the ST group, PCT on discharge was comparable in the two groups on discharge (p=0.001, and p=0.540, respectively). Triglycerides, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol were significantly higher among the patients in the TCZ group than patients in the ST group (Table 2).

While hematologic parameters including lymphocyte, neutrophil count and percentage were comparable on admission, patients in the TCZ group had a significant increase in lymphocyte count on discharge. Also, although neutrophil count showed a similar decrease in both groups, neutrophil percentage showed a significantly more pronounced decline as compared to the ST group (Table 2). On admission, the neutrophil-to-lymphocyte ratio (NLR) was comparable in the groups, while it was significantly lower in the TCZ group on discharge (p=0.532, and p=0.006, respectively, Table 2, Figure 2). LDH levels, which are expected to rise in patients with lung injury, were significantly higher in the TCZ group on admission to ICU, while they were comparable between the two groups on discharge (p=0.004, and p=0.351, respectively). A comparison of laboratory parameters examined in both groups was presented in Table 2.

Table 1. Comparison of disease severity scores, vital parameters, and length of treatment in study groups

	ST Group (n=44)		TCZ Group (n=102)		p
	Mean±SD	**Median (Q_1-Q_3) [Min-Max]**	**Mean±SD**	**Median (Q_1-Q_3) [Min-Max]**	
Age (year)	73.4±15.5	75 (68-84) [18-96]	67.9±13.4	70 (60-78) [26-96]	**0.030**
APACHE II	24.1±6.8	24 (18.5-29) [12-42]	24.4±5.5	24 (20-28) [14-37]	0.952*
CCI	4.2±1.5	4 (3-5) [0-7]	3.5±1.8	4 (2-5) [0-8]	0.260*
SBP (mmHg)	106±23	100 (90-120) [60-170]	115±21	110 (100-130) [65-170]	0.052
DBP (mmHg)	63±11	60 (55-70) [35-90]	67±9.5	70 (60-70) [40-90]	**0.026***
MAP (mmHg)	77.5±14	76.7 (69.2-87.5) [43-110]	83±13	83 (73.3-90) [48-113]	**0.025**
Pulse (bpm)	110±20.5	112 (100-126) [56-148]	109±13	108 (98-116) [88-168]	0.580
SaO_2 (%)	89±6.5	89 (82.5-93) [74-98]	83±6	84 (80-86) [55-90]	**<0.001***
RR (min)	26±6	26 (22.5-32.5) [14-36]	30±3.5	29 (28-32) [23-40]	**<0.001***
P/F ratio	140±37	150 (111-177.5) [70-185]	120±38	120 (90-145) [60-195]	**0.004**
Intubation (days)	8.7±13.1	2.5 (0-13) [0-54]	9.5±12.5	6.5 (0-15) [0-66]	0.658*
ICU (days)	11.3±11.6	8 (4-14) [2-58]	17.6±12.2	14.5 (9-21) [4-75]	**<0.001***
Hospitalization (days)	20±15.5	15 (9.5-22) [3-74]	27±13	24 (18-32) [12-77]	**<0.001***

ST Group: standard treatment group, TCZ Group: tocilizumab in addition to standard treatment group, SD: standard deviation, Q_1-Q_3: 25^{th}-75^{th} percentile, APACHE II: acute physiology and chronic health evaluation II, CCI: Charlson comorbidity index, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, RR: respiratory rate, ICU: intensive care unit, *: Mann-Whitney U test was performed; otherwise, independent samples t-test was used

Table 2. Comparison of laboratory parameters on admission and discharge from the ICU in study groups

	ST Group (n=44)		TCZ Group (n=102)		p
	Mean±SD	**Median (Q_1-Q_3) [Min-Max]**	**Mean±SD**	**Median (Q_1-Q_3) [Min-Max]**	
PCT (ng/m)[a]	3.8±5.9	0.8 (0.2-4.8) [0.1-24]	1.2±3.3	0.3 (0.1-0.5) [0.1-20]	**0.001**
PCT (ng/m)[d]	2.1±5.6	0.4 (0.1-1.8) [0.1-35]	1.1±3.3	0.1 (0.1-0.2) [0.1-19]	0.540*
CRP (mg/L)[a]	122±103.2	116 (34-177) [11-489]	110±66.4	104.5 (64-132) [6-444]	0.484
CRP (mg/L)[d]	82±79.3	57 (22-137) [3-327]	33.8±58.1	7 (4-28) [1-289]	**<0.001***
FER (ng/mL)[a]	586±546.8	379 (141-881) [10-1650]	803±532	669 (457-1213) [50-2000]	**0.006**
FER (ng/mL)[d]	669±567.2	426 (172-1050) [16-1650]	658±479	519 (297-924) [40-1800]	0.153*
FIB (mg/dL)[a]	323±91.8	349 (271-374) [103-509]	332±69	348 (292-377) [77-501]	0.546
FIB (mg/dL)[d]	309±70.2	317 (258-364) [156-438]	299.4±89	304.5 (239-354) [45-501]	0.317*
D-dimer (µg/L)[a]	6261±9788	2640 (1276-6064) [236-45000]	4479±8721	1503 (1046-3650) [165-71500]	**0.033**
D-dimer (µg/L)[d]	2839±3077	1874 (968-3706) [421-16250]	3287±5084	1535 (910-3094) [224-36900]	0.146*
bLac (mmol/L) [a]	2.4±1.1	2.6 (1.7-3.1) [0.9-5.3]	2.2±1	2 (1.7-2.5) [1-9.8]	0.090
bLac (mmol/L)[d]	2.6±2.1	1.9 (1.4-3.3) [0.2-11.8]	2±1.6	1.5 (1.1-2.3) [0.5-11.2]	0.204*
Urea (mg/dL) [a]	87±63.7	68 (39-119) [13-278]	70±42.3	56.5 (44-94) [16-250]	0.376
Cr (mg/dL) [a]	1.4±0.9	1 (0.9-2) [0.4-4.9]	1.2±1	1 (0.9-1.3) [0.5-8.5]	0.359
ALT (u/L) [a]	74.5±175	23.5 (15.5-47.5) [5-1047]	57.7±68	41.5 (25-65) [9-567]	**0.004**
AST (u/L) [a]	74.2±118	38 (23.5-66) [10-657]	55.7±52	37 (29-63) [11-345]	0.405
LDH (u/L) [a]	450±232	379 (289-575) [166-1075]	529±188	488 (407-605) [188-1339]	**0.004**
LDH (u/L) [d]	466±379	333 (261-429) [137-2079]	455±341	384 (302-497) [166-3049]	0.351*
TC (mg/dL) [a]	145±48.5	139 (110-165) [49-293]	175.5±55	168 (140-205) [59-351]	**0.003**
HDL (mg/dL) [a]	30.3±8.5	31 (25-36) [12-47]	35.6±15.3	33 (26-44) [11-98]	**0.038**
LDL (mg/dL) [a]	87±34.5	91 (74-110) [8-153]	108±39.7	104 (79-134) [14-232]	**0.016**
TG (mg/dL) [a]	164±117.4	141 (88-203) [36-668]	203±113	177 (126-252) [51-630]	**0.005**
WBC ($\times10^9$/L) [a]	11.6±6.8	9.8 (7.4-13.8) [2.3-35]	10.7±4.7	10.5 (7.6-13.8) [2.1-34.6]	0.361
WBC ($\times10^9$/L) [d]	9.7±6.1	8.5 (6-12.1) [2.4-33.4]	9.6±4.8	9.1 (6.6-12) [1.5-34]	0.953*
LYM ($\times10^9$/L)[a]	0.83±0.70	0.74 (0.46-0.95) [0.14-0.45]	0.66±0.35	0.58 (0.42-0.8) [0.19-2.0]	0.133
LYM ($\times10^9$/L)[d]	0.93±0.63	0.87 (0.43-1.2) [0.16-3.0]	1.2±0.74	1.0 (0.64-1.57) [0.17-3.90]	**0.007***
LYM (%)[a]	8.2±6.6	6.5 (3.9-10.1) [1.2-36.0]	7.0±4.4	6.0 (4.5-8.6) [1.2-27.5]	0.738
LYM (%)[d]	11.3±8.6	10.4 (5-14.7) [1.2-44]	14.8±10.7	13 (7.5-17.8) [1.8-60]	**0.021***
NEU ($\times10^9$/L)[a]	10.1±6.7	8.9 (5.7-11.6) [1.2-34.0]	9.6±4.5	9.3 (6.6-12.4) [1.8-32.7]	0.581
NEU ($\times10^9$/L)[d]	8.1±5.5	6.8 (4.5-10.6) [1.7-32.0]	7.6±4.6	7.1 (4.4-9.3) [0.56-31.6]	0.694*
NEU (%)[a]	83.7±12	87.5 (79-92) [45-96]	88.4±5.5	90 (86-92) [65-96]	0.107
NEU (%)[d]	80.4±12.1	81.5 (72-91) [45-96]	77±12.9	78 (70-86) [34-96]	**0.004***
NLR[a]	17.8±15.2	13.2 (7.4-24.5) [1.4-78.4]	17.5±11.9	14.7 (9.9-20.5) [2.4-79.1]	0.532
NLR[d]	15.2±17.1	7.7 (4.5-17.5) [0.9-77.5]	9.4±8.8	6.2 (4.2-11.7) [0.6-52.6]	**0.006***

ICU: intensive cae unit, ST Group: standard treatment group, TCZ Group: tocilizumab in addition to standard treatment group, SD: standard deviation, Q_1-Q_3: 25^{th}-75^{th} percentile, PCT: procalcitonin, CRP: C-reactive protein, FER: ferritin, FIB: fibrinogen, bLac: blood lactate, Cr: creatinine, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TG: triglyceride, WBC: white blood cell, LYM: lymphocyte, NEU: neutrophil, NLR: neutrophil-to-lymphocyte ratio, [a]: admission, [d]: discharge, *: adjusted for baseline value while comparing groups

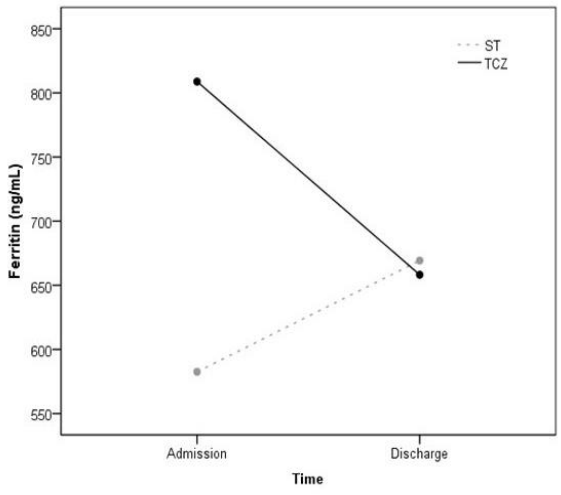

Figure 1. Ferritin on admission and discharge from ICU

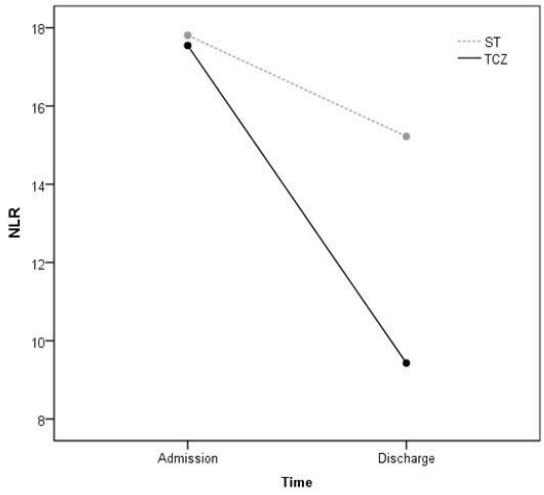

Figure 2. NLR on admission and discharge from ICU

The use of HFOT was significantly more frequent among the patients in the TCZ group (81.4%, n=83) as compared to the ST group (47.7%, n=21, p<0.001). The duration of MV was similar in the two groups (p=0.658), while the TCZ group had significantly longer total hospital stay and ICU stay (both p<0.001, Table 1).

The mortality rate in the ST group was 52.3% (n=23) versus 29.4% (n=30) in the TCZ group, indicating significantly lower mortality in patients receiving tocilizumab treatment (p=0.009) with a 2.63-fold increased risk of mortality in the absence of additional tocilizumab (Table 3).

DISCUSSION

This study analyzed the efficacy of an IL-6 receptor inhibitor, tocilizumab, in the treatment of COVID-19 patients developing moderate to severe ARDS. When the central role of IL-6 is in cytokine storm, it may be presumed that tocilizumab may represent a plausible therapeutic option in cytokine storm induced by COVID-19. Our clinical data showed that tocilizumab treatment was associated with an improved acute phase reactant profile and reduced mortality.

The severity of COVID-19 may range from mild symptoms to ARDS and death. Progression to ARDS and eventual death in COVID-19 patients is thought to result from an HLH-like condition, triggered by excessive release of proinflammatory cytokines (24). Until now, many studies have suggested that tocilizumab has beneficial effects in COVID-19 patients (19,25). In a recent study in Turkey, anakinra (IL-1 receptor antagonist), another anti-cytokine treatment, was compared with tocilizumab. The need for non-invasive MV requirements, HFOT, and the length of stay in the ICU were found to be lower in the group receiving tocilizumab treatment compared to the group receiving anakinra treatment (26). The American Infectious Disease Society guidelines recommend the use of tocilizumab in addition to standard treatment in hospitalized adult COVID-19 patients who have increased systemic inflammatory markers (27). Also, the National Institutes of Health guidelines endorse the use of tocilizumab (single intravenous dose up to 8 mg/kg, max. 800 mg) in conjunction with dexamethasone, in newly hospitalized patients who have rapid respiratory decompensation due to COVID-19 (28).

In a meta-analysis of 7 studies examining the effect of comorbid conditions on the course of COVID-19, a number of conditions such as COPD, CVD, and HT were found to be associated with an increased risk of ICU admission (29). In the current study, patients in the ST group were older, possibly due to the smaller sample size. The most common comorbidities in the patient group included HT, CVD, COPD, and DM. On the other hand, the two study groups were comparable with regard to APACHE II scores, which is a measure of the severity of the condition, as well as with regard to the CCI score, which measures the comorbidities.

Although vital parameters of MAP and DBP were lower in the ST group, this finding may be associated with the low number of patients in that group. On the other hand, although oxygenation parameters (SaO_2 and P/F ratio) were lower and respiratory rate was higher in the TCZ group, the mortality rates were lower, suggesting that tocilizumab was an effective therapeutic option. Furthermore, although the duration of MV was comparable in the two groups, the length of ICU and hospital stay was longer in the TCZ group. This may be due to the fact that lower mortality rates in the TCZ group vs. ST group may be related to a longer need for palliative care following ICU stay among patients receiving tocilizumab treatment.

Previous studies have underscored the prognostic importance of several laboratory parameters, including D-dimer, lymphocyte count, ferritin, CRP, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) in COVID-19 (21,33). In Sciascia et al.'s study (19), tocilizumab was shown to stabilize patients by reducing acute phase reactants in the treatment of COVID-19 related CRS, as well as to have efficacy in the treatment of cytokine storm. In the present study, CRP, an acute phase reactant, was similar on admission to ICU in both groups, while it decreased significantly on discharge among patients in the TCZ group. Also, ferritin that has significantly elevated on admission to ICU in the TCZ group was reduced to similar levels to those in the ST group on discharge. In another retrospective, multi-center study involving 150 COVID-19 patients, elevated ferritin and IL-6 levels were found to be associated with poor prognosis, suggesting that hyperinflammation of viral origin could be associated with mortality (32). Lower rates of mortality in the TCZ group of the current study despite higher ferritin levels suggest that tocilizumab may be effective in reducing mortality. In a study, tocilizumab was found to improve patients by reducing CRP, fibrinogen, and ferritin levels, and increasing lymphocyte count, similar to our observations. Again, in that same study, D-dimer levels remained elevated in patients receiving tocilizumab, which was explained on the basis of the lack of an effect of tocilizumab on coagulation (33). In parallel with these findings, patients in the TCZ group did not experience a significant decrease in D-dimer levels as compared to the ST group.

Numerous studies regarding hematological parameters in COVID-19 patients have been performed (36,37). Lymphocytopenia is a common finding in these patients, which has been purported to result from the destructive effect of SARS-CoV-2 on T lymphocytes (36). In a meta-analysis of 37 studies among COVID-19 patients, age was found to correlate negatively with lymphocyte count (37). The main three hematological findings that were associated with poor prognosis included leukocytosis, thrombocytopenia, and lymphopenia (38). In the present study, although patients in the TCZ group were younger, their lymphocyte count on admission was lower than that of patients in the ST group, although the difference was not significant. On the other hand,

Table 3. Mortality according to tocilizumab using

	ST (n=44)	TCZ (n=102)	p
Status, n (%)			
Death	23 (52.3)	30 (29.4)	**0.009**
Surviving	21 (47.7)	72 (70.6)	
OR (95% CI)	2.63 (1.27-5.45)		

ST Group: standard treatment group, TCZ Group: tocilizumab in addition to standard treatment group, OR: odds ratio, CI: confidence interval

lymphocyte count and percentage on discharge were significantly higher in the TCZ group vs. the ST group. Considering the role of lymphopenia in poor prognosis, this observation suggests a positive effect of tocilizumab on COVID-19. Many studies suggested that elevated NLR in COVID-19 may represent an independent biomarker for predicting poor prognosis and may be used to identify high-risk individuals (37,42). In the current study, NLR on admission was similar in both groups, while it was significantly lower in the TCZ group on discharge.

In a retrospective cohort study of 544 patients (TESEO study), intravenous or subcutaneous tocilizumab treatment was found to result in a decrease in the risk of MV and death (40). In the current study, the mortality rate in the ST group was 52.3% (23/44) vs. 29.4% (30/102) in the TCZ group, indicating a significant difference. Thus, lack of tocilizumab treatment was associated with a 2.63-fold increased risk of mortality. In another meta-analysis by Zhao et al. (41), involving a total of 1675 severe COVID-19 cases, 1000 patients received standard treatment and 675 also received tocilizumab. Similar to our observations, the mortality among patients receiving tocilizumab (132/675, 19.5%) was significantly lower than in controls (283/1000, 28.3%).

Conversely, tocilizumab was reported to offer no additional benefits in terms of clinical outcomes in severe COVID-19, based on a collective analysis of seven retrospective studies (42). However, none of these were randomized and controlled studies, and the clinical characteristics in the study groups were not homogeneously distributed. Also, there were significant differences in terms of tocilizumab dose, dose frequency, and anti-viral treatment regimens. Additionally, the delay between disease onset and initiation of treatment was not uniform (42). No consistent findings have been reported in these studies comparing tocilizumab and other treatment regimens. Most of these studies reported worse clinical outcomes with tocilizumab treatment, explaining why tocilizumab was not found to be useful. However, as emphasized earlier, these studies exhibit significant differences in terms of the characteristics of the study and control groups. Also, in a study by Klopfenstein et al. (43), although patients in the tocilizumab group had higher disease severity and lower survival than controls, their CCI was also higher.

The timing of tocilizumab treatment may be of high significance (17). Patients should be closely monitored for progression to ARDS and the development of CRS. Several studies have emphasized the importance of timely administration of tocilizumab with respect to treatment efficacy (17,44). In the present study, initiation of tocilizumab treatment within 48 hours of admission to ICU may have contributed to the observed efficacy.

This study has certain limitations. Firstly, it is a retrospective study. Secondly, the sample size in the ST group was small. Finally, IL-6 levels were not measured.

CONCLUSION

ARDS and CRS represent major causes of mortality in COVID-19. Despite the lack of curative treatment, patients are frequently given anti-viral agents, steroids, and heparin, in addition to anti-inflammatory agents. IL-6 inhibitors may represent a plausible therapeutic option in COVID-19, considering the role of IL-6 in the pathogenesis of CRS and ARDS. In this study, we conclude that tocilizumab can be administered to COVID-19 patients, based on the observed reduction in mortality. Proper selection of patients, the timing of treatment, and safety concerns should be considered when deciding on tocilizumab treatment. For further studies, we recommend the development of a scoring system for establishing treatment indications for tocilizumab that should include disease severity, the burden of lung injury, the presence of risk factors, and the level of inflammatory markers as well as IL-6. Also, further research should better elucidate the tolerability of tocilizumab treatment.

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