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Efficacy of tocilizumab in severe COVID-19: a retrospective study

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ABSTRACT

Aim: Coronavirus disease 2019 (COVID-19) is a pandemic with potential life-threatening outcomes. The current study aims to demonstrate the effect of tocilizumab in COVID-19 related cytokine storm.

Material and Method: This retrospective cross-sectional study evaluated the patients who received tocilizumab for COVID-19 related cytokine storm between March and August 2020. Demographic, clinical, and laboratory findings were recorded. Computerized tomography (CT) scans, which were performed before tocilizumab infusion were scored. The characteristics of the patients who survived versus those who did not survive were assessed.

Results: There was a total of 137 patients, 99 (72.3%) male and 38 (27.7%) female, with a median age of 62 years. Eighty-six (62.7%) patients had severe; 51 (37.2%) patients had critical disease course. The mortality rate was 24.1%. Higher mortality rates were present among patients older than 65 years, females, and with comorbid diseases (p=0.02, p=0.031, and p=0.01, respectively). The non-survived group had higher rates of mechanical ventilation (MV) support (85.2%) and admission to the intensive care unit (58.8%) (p<0.05). CT scores were higher in patients who did not survive compared with those who survived. Old age, critical disease, MV support, extended lung opacifications were associated with mortality according to multivariate logistic regression analysis (OR CI= 0.781, p=0.029, p=0.002, p=0.018, p=0.047, respectively).

Conclusion: We consider that due to the effect of tosilizumab in inhibiting the early stages of inflammation, it can be effective in the treatment of severe COVID-19 patients, especially under 65 years old, not requiring MV, and without extended pulmonary lesions.

Keywords: COVID-19, interleukin 6, tocilizumab, treatment

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INTRODUCTION

A 2019 novel coronavirus (2019-nCoV), also named the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV2), cause the Coronavirus disease 2019 (COVID-19), which was first appeared in Wuhan, China, in December 2019, has been spread rapidly all over the world and defined as a pandemic in March 2020. During COVID-19, a wide variety of symptoms may occur from mild to severe, including fever, cough, and dyspnea. However, the most important cause of mortality is respiratory failure due to severe acute pneumonia and acute respiratory distress syndrome (ARDS). Approximately 80% of COVID-19 patients may be asymptomatic or have a mild disease course. Fifteen percent of the patients who may need oxygen support have severe disease. The remaining 5% have critical COVID-19. Critical patients may require mechanical ventilation (MV) support due to ARDS (1). Being elderly, having comorbidities, and possessing impaired immunity are risk factors for higher susceptibility and higher mortality rates (2). COVID-19 has still been threatening human health all over the world regarding complications and death.

There is no effective prophylactic or post-exposure therapy that has been demonstrated in randomized controlled trials yet. Effects of lopinavir/ritonavir and remdesivir are not superior to those of standard care

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(3–5). Although favipiravir is the most widely used drug for COVID-19, the efficacy on severe and critical patients is limited (3,6). Data regarding the effectiveness of chloroquine/hydroxychloroquine are contradictory (3,7). For excessive pulmonary involvement, an approved treatment is necessary to prevent worsened outcomes.

Interleukin (IL)-6, tumor necrosis factor-alpha (TNF-a), and IL-12 are pro-inflammatory cytokines that may lead to cytokine storm in case of excessive production. Cytokine storm is responsible for COVID-19 associated acute respiratory failure that is more frequent in severe COVID-19. After the onset of cytokine storm, patients may progress to a rapid worsening that may lead to multiple organ dysfunction and death (8). Therefore, early diagnosis and treatment of cytokine storm are crucial for healing severe patients. Recent clinical experience has shown that IL-6 is one of the most important cytokines involved in the COVID-19 associated cytokine storm (1). Therefore, using the anti-human IL-6 receptor antibody tocilizumab has been a promising strategy for these patients.

However, the data regarding the efficacy of tocilizumab in COVID-19 is contradictory (2,9,10). There is still need to show the effect of tocilizumab in COVID-19 patients with severe lung involvement. This study aimed to evaluate the effectiveness of tocilizumab on the survival of COVID-19 patients with severe and critical diseases.

MATERIAL AND METHOD

The study was approved by University of Health Sciences Non-interventional Researches Ethics Committee (Date: 27.05.2020, Decision No: 2020-198). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design, Participants, and Data Collection

This retrospective cross-sectional study included the patients who received tocilizumab due to COVID-19 related cytokine storm, out of 2470 hospitalized COVID-19 patients at Gülhane Training and Research Hospital between March 2020 and August 2020.

All participants were diagnosed with COVID-19 according to the national COVID-19 Guideline case definition (11). The patients with a positive COVID-19 polymerase chain reaction (PCR) test, ≥18 years old, and who received tocilizumab for cytokine storm related COVID-19 included in the study. Patients who received other anti-cytokine therapies were excluded.

Clinical follow-up of the patients in the hospital was carried out under the coordination of chest medicine, infectious disease, internal medicine and intensive care unit physicians. In our center, rheumatology consultation is requested for patients who have been considered to be a candidate for tocilizumab treatment because of development of cytokine storm. Medical records have been used for obtaining demographic and clinical characteristics. IL-6, CRP, D-dimer, ESR, ferritin, liver enzymes, and complete blood count recorded from patients' files. The CT scans, within 72 hours before tocilizumab administration, were scored by a radiologist. Fleischner Society scoring system used to describe the lesions in CT scans (12). The presence and the spread of active infiltrations were recorded for each case. A semi-quantitative assessment method was applied to measure the degree of lung infiltration of COVID-19 in computed tomography (CT) (13). A total of five lobs in both lungs were evaluated. The extent of lesions in each lobe was estimated visually and scored. Scores were as follows; 0: none, 1: affecting less than 25% of the lobe, 2: affecting 26-50% of the lobe, 3: affecting 51-75% of the lobe, and 4: affecting more than 75% of the lobe. The total score between 0 and 20; was calculated by the sum of the scores of each lobe.

Definitions and treatment

The patients were classified as severe or critical COVID-19 according to the disease severity. The severe COVID-19 disease was defined as if the patient fulfills the following criteria of severe systemic inflammatory response and additionally respiratory rate >30/minute or oxygen saturation <93% on room air at rest. The critical COVID-19 disease was defined as fulfilling the criteria for the severe systemic inflammatory response in addition to at least one of the following: (1) respiratory failure requiring MV, (2) shock, and other organ failures, or a need for admission to the intensive care unit (ICU) (9,10).

Patients received the treatment agents in line with national COVID-19 treatment recommendations. The standard treatment included hydroxychloroquine (with/without azithromycin), favipiravir, and vitamin C alone or in combination. Low molecular weight heparin was administered to patients with high D-dimer levels. For patients with high procalcitonin levels or bacterial growth in the blood culture, parenteral antibiotic treatments were initiated. Corticosteroids, intravenous immunoglobulin, immune plasma, anakinra, and tocilizumab are treatment options for patients who were unresponsive to standard therapy. All patients received tocilizumab in an initial dose of 8 mg/kg. Whether the first dose was considered insufficient, according to national guidelines, a second dose within 24 hours was administered (11).

Statistical Analysis

All statistical analyses were performed using the IBM Statistical Package for Social Sciences, Statistics for Windows, Version 24.0 (IBM Corp.; Armonk, NY: USA, Released 2016). The normality assumption was assessed

by using the Kolmogorov-Smirnov test. The variables that do not have normal distribution were expressed as median (minimum-maximum) and interquartile range (IQR) (25th and 75th percentiles) and categorical variables were summarized as counts and percentages. The significance of the difference between the two groups was investigated by the Mann-Whitney U test for variables that were not normally distributed. Fisher's exact test and Chi-square test were used for categorical variables. Binary Logistic Regression (Nagelkerke R Square value was given) was used for logistic regression analysis. A p-value <0.05 was considered as statistically significant.

RESULTS

There were 137 patients (99 male and 38 female) with a median age of 62 years. The most common manifestations were cough (89.7%), fever (89.0%), shortness of breath (83.9%), weakness and fatigue (53.2%), myalgia (51.8%), nausea and vomiting (24.8%), headache (22.6%), diarrhea (16.0%), and loss of sense of taste and smell (11.6%). The median time between symptom onset and hospitalization was 5 (2-6.5) days, and the median duration between symptom onset and tocilizumab administration was 9 (6.5-12) days (**Table 1**). The comorbid diseases existed in 91 (66.4%) patients. Eighty-six (62.7%) patients had severe, 51 (37.2%) patients had critical disease (**Table 1**). Sixty-eight (49.6%) patients received hydroxychloroquine, and 135 (98.5%) received favipiravir as an antiviral treatment. The other treatments used for the patients were shown in Table 1. None of the patients received additional anti-cytokine treatments after tocilizumab treatment. The median dose of tocilizumab was 600 (ranges between 560-600) mg. Only three patients received a second dose of tocilizumab as 400mg within 24 hours due to continuing clinical symptoms.

CRP, ESR, fibrinogen, leucocyte, and LDH levels decreased within 24-72 hours after tocilizumab administration (**Table 2**). The median level of IL-6 on the tocilizumab administration day was 98 (ranges between 64.6-145.8). The median level of IL-6 after tocilizumab elevated to 417.6 (ranges between 190.6-1034.7) (**Table 2**).

Thirty-three (24.1%) patients died and were categorized as the non-survived group. The mortality rate was increasing with aging (p=0.001). The mortality rates were higher among patients who were older than 65 years, females, and patients with comorbidity (p=0.02, p=0.031, and p=0.01, respectively) (**Table 3**). The most common comorbidities were diabetes mellitus in 41 (30.0%) patients and hypertension in 37 (27.0%) patients. Twenty-four (17.5%) patients had chronic heart disease, 13 (9.5%) patients had chronic renal failure, 9 (6.6%) patients had chronic obstructive pulmonary disease, 8 (5.8%) patients had bronchial asthma, and 6 (4.4%) patients had

Table 1. Demographical and clinical characteristics of the study group

Characteristics	Patients (n=137)
Age, years, median (Q1-Q3)	62 (49.5-72)
Gender, n (%)	
Female	38 (27.7)
Male	99 (72.3)
Time between symptom onset and hospitalization, day, median (Q1-Q3)	5 (2-6.5)
Time between symptom onset and TCZ infusion, day, median (Q1-Q3)	9 (6.5-12)
Time from first symptom to TCZ infusion, n (%)	
≤6 days	34 (24.8)
7-12 days	73 (53.3)
≥13 days	30 (21.9)
Disease severity, n (%)	
Severe	86 (62.8)
Critical	51 (37.2)
Respiratory rate before TCZ infusion, n (%)	
≤20	19 (13.9)
21-30	94 (68.6)
≥31	24 (17.5)
SaO2 < 93% on TCZ day, n (%)	136 (99.3)
Precense of Comorbidity, n (%)	91 (66.4)
Concomitant treatment, n (%)	
Favipiravir	135 (98.5)
LMWH	128 (93.4)
Parenteral antibiotics	107 (78.1)
Hydroxychloroquine	68 (49.6)
Azithromycin	31 (22.6)
Corticosteroid	16 (11.7)
IVIG	3 (2.2)
TCZ dose, mg, median (Q1-Q3)	600 (560-600)
Second TCZ administration, n (%)	3 (2.2)

TCZ: Tocilizumab, IVIG: Intravenous Immunoglobulin; LMWH: Low-molecular-weight heparin

Table 2. Laboratory findings of COVID-19 patients on TCZ treatment day and after TCZ

	TCZ day	24-72 hours after TCZ
CRP, mg/dL	169.0 (118-237.8)	64.1 (23.7-117.7)
IL-6, pg/mL	98 (64.6-145.8)	417.6 (190.6-1034.7)
ESR, mm/h	76 (59.5-86)	60 (36-76.2)
Fibrinogen,mg/dl	638 (496-769)	474 (400-636)
Ferritin, ng/mL	563.6 (342.0-989.2)	587.2 (305.1-926.5)
D-dimer, mg/L	1.24 (0.6-1.9)	1.3 (0.8-3.0)
WBC, $x10^3/\mu L$	7100 (5400-9450)	5400 (3900-8001)
Hgb, g/dL	13 (11.8-13.8)	13 (11.6-14.0)
Lymphocyte, $x10^3/\mu L$	800 (600-1000)	800 (550-1200)
Platelet, $x10^3/\mu L$	234 (189.5- 299.5)	312 (227.5-397)
AST, IU/L	40 (30.5-65)	55 (33-81.5)
ALT, IU/L	30 (19.5-46)	49 (26-90)
LDH, IU/L	430 (326-577)	415 (25.5-555.5)

Variables were given as median (Q1-Q3). TCZ: Tocilizumab, CRP: C reactive protein, IL: Interleukin, ESR: Erythrocyte sedimentation rate, WBC: White blood cell, Hgb: Hemoglobin, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, LDH: Lactate dehydrogenase

congestive heart failure. The prevalences of hypertension, congestive health failure, and chronic renal failure were higher in the non-survived group than the survived group (p=0.000, p=0.003, and p=0.003, respectively) (Table 3). In the non-survived group, the rates of the patients on MV support (85.2%) and those with admission in the ICU (58.8%) were higher than the survived group (p<0.05) (Table 3). There was no statistically significant difference between survived and non-survived patients in terms of antiviral, anticoagulant, antibiotics, and the other treatment options used before tocilizumab. Statistically significant differences in CRP, IL-6, ESR, fibrinogen, d-dimer, leucocyte, LDH and lymphocyte levels were found between survived and non survived groups (p=0.016, p=0.000, p=0.031, p=0.016, p=0.000, p=0.000, p=0.000; p=0.049, respectively) (**Table 3**).

CT scans determined ground glass opacity in 135 (98.5%) patients, consolidation in 105 (76.6%) patients, ARDS in 104 (75.9%) patients, pleural effusion in 17 (12.4%) patients, interstitial lung disease in 7 (5.1%) patients. According to 78 CT scans performed within 72 hours before tocilizumab treatment, total CT scores were higher in the non-survived group than the survived group (p=0.01). The rate of patients with CT scores equal to and above 10 was higher in the non-survived group (p=0.019) (Table 3). There was no statistically significant difference between the survived and the non-survived group in terms of the presence of consolidation, pleural effusion, ground-glass opacity, interstitial lung disease, and acute respiratory distress syndrome in CT scans (p>0.05).

In multivariate logistic regression analysis, mortality showed a positive correlation with aging, disease severity, being under MV support and having extent lung opacifications (OR CI, p=0.029, p=0.002, p=0.018, p=0.047, respectively) (**Table 4**).

Table 3. Clinical characteristics of the survived and non-survived groups

Characteristics	Survived (n= 104)	Non-survived (n= 33)	p-value
Age, years, median (Q1-Q3)	58.5 (48.5-68.5)	70 (63-75)	0.001***
Age≥ 65, n (%)	40 (63.5)	23 (36.5)	0.020*
Gender, n (%)			0.031*
Female	24 (63.2)	14 (36.8)	
Male	80 (80.8)	19 (19.2)	
Precense of comorbidity, n (%)	63 (69.2)	28 (30.8)	0.010*
Hypertension, n (%)	19 (51.4)	18 (48.6)	0.000*
Congestive heart failure, n (%)	1 (16.7)	5 (83.3)	0.003**
Chronic kidney disease, n (%)	5 (38.5)	8 (61.5)	0.003**
Disease severity, n (%)			0.000*
Severe	83 (96.5)	3 (3.5)	
Critical	21 (41.2)	30 (58.8)	
MV requirement before TCZ, n (%)	4 (14.8)	23 (85.2)	0.000*
ICU admission before TCZ, n (%)	21 (41.2)	30 (58.8)	0.000*
C reactive protein, mg/dL, median (Q1-Q3)	163.7 (113.4-226.1)	210.9 (149.7-267.0)	0.016***
Interleukin-6, pg/mL, median (Q1-Q3)	83.5 (58.2-134.0)	150.7 (96.9-259.6)	0.000***
Erythrocyte sedimentation rate, mm/h, median (Q1-Q3)	70 (57-85)	83 (70-88)	0.031***
Fibrinogen, mg/dl, median (Q1-Q3)	623 (490.5-707)	726 (550-900)	0.016***
D-dimer, mg/L, median (Q1-Q3)	1.1 (0.6-1.7)	1.9 (1.2-2.5)	0.000***
White blood cell, x103/µL, median (Q1-Q3)	6800 (5100-8350)	9700 (7500-11800)	0.000***
Lymphocyte, x103/µL, median (Q1-Q3)	800 (600-1050)	700 (400-900)	0.049***
Lactate dehydrogenase, IU/L, median (Q1-Q3)	415.5 (322.5-509.5)	580 (416-672)	0.000***
Total CT Score (within 72 hours before TCZ infusion day), (n=78), median (Q1-Q3)	8 (6-12)	13 (8-16)	0.010*
Total CT Score (within 72 hours before TCZ infusion day), n (%) (n=78)			0.019*
<10	38 (60.3)	4 (26.7)	
≥10	25 (39.7)	11 (73.3)	

TCZ: Tocilizumab, MV: Mechanical ventilation, ICU: Intensive care unit, CT: Computerized tomography,*Pearson Chi-Square, **Fisher's Exact Test, ***Mann Whitney U Test

Table 4. Multivariate logistic regression analysis of the non-survived patients

	Unstandardized Coefficients		95% Confidence Interval for B		Standardized Coefficients	p-value
	B	Std.Error	Lower	Upper	Beta	
Gender	1.195	.928	.535	20.371	3.303	.198
Age	-2.522	1.156	.008	.774	.080	.029*
Comorbidity	-.973	.993	.054	2.648	.378	.327
HT	-.974	.910	.063	2.248	.377	.285
CHF	-4.345	2.949	.000	4.197	.013	.141
Disease severity	-3.171	1.032	.006	.317	.042	.002*
MV support	-3.969	1.677	.001	.505	.019	.018*
CT Score	-1.717	.866	.033	.981	.180	.047*

R2= 0.781(Nagelkerke), HT: Hypertension, CHF: Congestive Heart Failure, MV: Mechanical ventilation, CT: Computerized tomography, * p < 0.05

DISCUSSION

Cytokine storm syndrome mediated by the uncontrolled secretion of proinflammatory cytokines has been observed in most of the severe and critical COVID-19 patients. Cytokine storm may cause multiorgan failure, respiratory failure, and at last mortality. At this stage, stopping the cytokine storm before leading to life-threatening entities is one of the main aims of the treatment. In this situation, the object of the treatment should be either decreasing the proinflammatory cytokine release or affecting receptors of the released cytokines at the target organs. Recently, one of the most favored treatment options is the drug targeting IL-6. The current study found that tocilizumab decreases mortality in patients who have not been admitted to ICU, not under MV support, in the early stages of the disease without extensive lung lesions in pulmonary CT and younger than 65 years old.

Cytokine syndrome may occur during inflammatory, infectious, and iatrogenic causes. It may proceed with fever, hyperferritinemia, multiple organ failure, and mortality as a result of overwhelming systemic inflammation (8). During COVID-19, similar to the other diseases which promote cytokine storm, IL-6 plays a crucial role in the progress of the disease to cytokine storm (2,14–16). High levels of IL-6 inhibit perforin/granzyme-mediated apoptosis by preventing the cytotoxic T lymphocytes and natural killer cells. As a result, an increased antigenic presentation from virally infected target cells may bring about an accelerated cytokine release. Also, viral replication provokes IFN mediated toll-like receptor activation that may then stimulate cytotoxic T lymphocytes and macrophages to release cytokines while inhibiting cytolytic functions (17–19). Physiologically, due to not expressing the IL-6 receptor, most of the cells do not respond to IL-6. However, the amplification of IL-6 during the cytokine storm widely activates the signaling pathways. IL-6 uses transmembrane and soluble receptors and binds to gp130 to realize intracellular signal transduction and gene expression (14). Tocilizumab can inhibit cytokine releasing syndrome in various steps by binding transmembrane and soluble receptors of IL-6. Treatment with tocilizumab seems to be a promising option for patients with cytokine storm syndrome (20).

In the current study, the rate of mortality was 24.1% among patients receiving tocilizumab. There was an association between mortality and being elderly, needing MV support, having critical COVID-19, and an extensive pulmonary parenchymal disease. Recent studies in the literature presented a more severe disease course and higher rates of mortality in older and immunosuppressive patients (2,21). Also, being elderly has been found as an independent risk factor for mortality for the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) infections (22,23). Aging may impair normal functions of T and B lymphocytes and increase the response of type 2 cytokines (IL-4, IL-6, IL-10, and IL-15) that may cause prolonged inflammation related to uncontrolled viral replication (24). Besides older patients own a higher rate of comorbidities and use multiple drugs, they may have exaggerated clinical findings of the cytokine storm syndrome and increased viral load. In the current study, the number of comorbidities was increasing with aging. Patients with hypertension, chronic heart failure, and moderate-severe chronic renal failure had more severe disease courses and higher mortality rates, similar to the studies in the literature (25,26). Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers may extend SARS-CoV-2 viremia by increasing ACE2 protein secretion from epithelial cells due to ACE2 is a receptor of SARS-CoV-2. Concerning this, it is thought that patients with hypertension and who were using ACE inhibitors and angiotensin receptor blockers may have a more severe disease course and higher mortality rates (27). Additionally, a more intensified ACE2 protein secretion from alveolar epithelium in males may explain the more extensive and more severe disease course among male individuals (28). In the current study, the rate of male patients was statistically significantly higher, similar to the literature. Whereas, in the current study, the rate of mortality among female patients was higher than male patients.

To our knowledge of influenza and other viral respiratory infections, the mortality rates related to coronary artery disease may rise during the viremia (29). Also, new or worsening heart failure, arrhythmia, and myocardial infarction may occur (30). The present study found a higher mortality rate among patients with heart failure, also, an increased rate of comorbid coronary heart disease among all patients, similar to the study performed by Zhou et al. (30). Increased proinflammatory and procoagulant factors may prompt plaque rupture, ischemia, and thrombosis. Besides, secretion of ACE2 as a receptor of SARS-CoV-2 on cardiac myocytes and vascular endothelial cells may be a triggering factor for cardiac diseases (31).

In the current study, IL-6, CRP, ESR, LDH, fibrinogen, and D-dimer levels were statistically significantly higher in non-survived patients than the patients who survived on the day before tocilizumab administration. The lymphocyte count was significantly lower in the non-survived group than the survived group. Keske et al. (9) reported that after the onset of the cytokine storm, a progression in pulmonary involvement, a rapid decrease of oxygen levels, and a need for ICU admission may occur

within hours and days. Also, they found a relationship between mortality and high levels of CRP, ferritin, IL-6, and D-dimer in patients who were following up in ICU. Similarly, Xiaoling et al. (2) recommended the early administration of tocilizumab in patients with persistent fever, worsening clinical findings, and increasing IL-6 levels. Raising procoagulant factors, especially D-dimer levels higher than 1 μg/mL, was found to be associated with increased mortality (30). The elevation of acute phase reactants can be used as a sign of disease progression, also can be a sign of clinical deterioration. In consideration of the increased mortality risk of critical patients, before the critical stage of the disease tocilizumab should be administered to break the cytokine cycle. The current study also found critical patients who needed MV support had higher rates of mortality. When the time of tocilizumab administration is delayed, a lower survival rate may be observed among patients due to the increased need for MV support and a more severe disease course (32). Invasive MV support, immunosuppression, and extended lung lesions may increase the risk for secondary bacterial infections (10). Especially, in critical patients, instead of early MV, high flow oxygen support with a nasal cannula should be preferred.

The patients in the current study presented various stages and patterns of pulmonary parenchymal disease. Cough, fever, and dyspnea were the most prevalent symptoms determined. A recent study which compared clinical symptoms between the patients with and without pneumonia related to COVID-19 reported that the most frequent symptoms were cough, fever, and dyspnea, similar to our study (33). Wang et al. (26) reported that lung lesions, which were defined according to Fleischner Society, reach a peak between six to eleven days from the symptom onset and were seen as 83%-85% ground-glass opacity and consolidation. To evaluate the effect of lung lesions on mortality, CT performed at least six days after onset of the symptoms or within three days before tocilizumab was administered similarly to the study presented by Wang et al. (26). Stone et al. (34) performed a placebo-controlled randomized trial that showed tocilizumab had no benefit on having MV require and death. But, they did not compare the CT findings between the study groups. An association between mortality and the extent of lung opacifications was found in the current study, similar to the previous studies in the literature (35–37). In the current study, the mortality risk was being increased in patients with CT scores above 10. It was determined that for patients who thought to be in cytokine storm due to viremia, to influence survival rates, tocilizumab should be administered in early stages without diffuse pulmonary lesions on CT. In this context, 78.1% of patients received tocilizumab in the first 12 days after the symptom onset.

The crucial part of the treatment of COVID-19 related pneumonia is to prevent the mortality related to ARDS and multiorgan failure caused by the cytokine storm. General supportive treatments, oxygen support, anti-viral drugs (favipiravir, lopinavir, ritonavir, remdesivir, hydroxychloroquine), corticosteroids, anti-cytokine therapies (IL-1 and IL-6 inhibitors, ruxolitinib), intravenous immunoglobulin, and immune plasma can be used primarily (5,38,39). Tocilizumab was applied once in a maximum dose based on Chinese guidelines and a study performed by Keske et al (9). In a study performed to investigate the effectiveness of tocilizumab in the treatment of the cytokine releasing syndrome in cancer patients, it was stated that repetitive doses in certain intervals in line with the pharmacokinetic data is important for providing rapid acceleration of tocilizumab plasma levels and reaching appropriate plasma levels (40). Although there are no randomized controlled studies, the current data in the literature supports a dose of 400 mg (or 8 mg/kg) tocilizumab once can be sufficient for COVID-19 related pneumonia for decreasing mortality rate and preventing potential adverse events (2,9). The appropriate approach for tocilizumab treatment is adjusting the dose and repetition of the drug according to the severity of the disease, laboratory assessment, extent of pulmonary lesions, comorbidities, and additional treatments.

The current study has some limitations. A larger number of patients could have been included in a study on a pandemic virus. A control group containing non-severe patients or severe/critical patients who did not receive tocilizumab may be included. Further studies with prospective design may contribute by evaluating the clinical, laboratory, and radiologic values after tocilizumab treatment. No CT evaluation before tocilizumab day can be done in the patients under MV support or in ICU. Prospective studies performed with larger samples and had CT evaluation on the day of tocilizumab administration may give a worthwhile opinion to form specific cut-off values in scoring systems of CT evaluation and to choose the perfect time in terms of tocilizumab treatment.

CONCLUSION

In conclusion, the current study investigated the effect of tocilizumab treatment in COVID-19 and concomitant cytokine storm. Tocilizumab is effective on suppressing inflammation in the early phases, particularly among patients who are younger than 65 years old, have no need for MV, and have less parenchymal lung involvement. Mainly, in severe patients, considering increased levels of acute phase reactants and coagulation parameters, and deepened cytopenias may help for choosing the appropriate time for tocilizumab treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was approved by University of Health Sciences Non-interventional Researches Ethics Committee (Date: 27.05.2020, Decision No: 2020-198).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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