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Tocilizumab Treatment Affects Intensive Care Unit Admission Rates of COVID-19 Patients in a Dose-dependent Manner

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Abstract

Objective: COVID-19 led to a pandemic that continues to spread worldwide. Despite several studies, it is hard to perform a comprehensive study including a high number of patients. Critically ill patients need intensive care units (ICU) and with the increased cost of hospitalization in ICUs, the newly discovered drugs to treat COVID-19 must be cost-effective. We aimed to present the effect of Tocilizumab (TCZ) treatment at different doses on both mortality and days spent in ICU.

Methods: We conducted a retrospective study in the Medicana International Istanbul Hospital. We compared the outcome of patients treated with TCZ with the status of mortality and ICU admissions.

Results: There was a dramatic decrease in the duration of ICU stay for patients treated with a single 8 mg/kg TCZ dose ($P = .006$). In addition, the mortality rate decreased with 3 different doses (in a single 4 mg/kg dose, a single 8 mg/kg dose, and a divided 4 mg/kg dose), but increased in a divided 8 mg/kg dose ($P = .010$).

Conclusion: Despite the retrospective design of the study and the small sample size, our findings principally suggest that TCZ might reduce the rate of mortality and the need for ICU admissions in COVID-19 patients.

Keywords: COVID-19, Tocilizumab, intensive care unit, cytokine storm, dose dependence

Tocilizumab Tedavisinin COVİD-19 Hastalarında Yoğun Bakım Ünitesine Alınma Oranlarını Doza Bağımlı Olarak Etkileri

Öz

Amaç: COVİD-19 dünya çapında yayılmaya devam eden bir pandemiye yol açtı. Yapılan birkaç çalışmaya rağmen çok sayıda hastayı içeren kapsamlı bir çalışma gerçekleştirmek zordur. Durumu kritik olan hastalar, yoğun bakım ünitelerine (YBÜ) ihtiyaç duymaktadır ve YBÜ'lerde hospitalizasyonun artan maliyetiyle birlikte, COVID-19'u tedavi etmek için bulunan yeni ilaçların uygun maliyetli olması gerekmektedir. Biz, farklı dozlarda Tocilizumab (TCZ) tedavisinin hem mortalite hem de YBÜ'de geçirilen günler üzerine etkisini araştırmayı amaçladık.

Yöntemler: Medicana International İstanbul Hastanesi'nde retrospektif bir çalışma gerçekleştirdik. TCZ ile tedavi edilen hastaların sonuçlarını mortalite ve YBÜ'de yatış açısından karşılaştırdık.

Bulgular: 8 mg/kg tek doz TCZ ile tedavi edilen hastaların YBÜ'de yatış süresinde dramatik bir azalma oldu ($P = .006$). Ek olarak mortalite oranı üç farklı dozda azaldı (4 mg/kg tek doz, 8 mg/kg tek doz ve 4 mg/kg bölünmüş doz) ancak 8 mg/kg bölünmüş dozda arttı ($P = .010$).

Sonuç: Çalışmanın retrospektif tasarımına ve küçük örneklem boyutuna rağmen bulgularımız esasen TCZ'nin COVID-19 hastalarında mortalite oranını ve YBÜ'ye yatış ihtiyacını azalttığını düşündürmektedir.

Anahtar Kelimeler: COVID-19, tocilizumab, yoğun bakım ünitesi, sitokin fırtınası, doz bağımlı

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An epidemic caused by the new coronavirus–the "Severe Acute Respiratory Syndrome Coronavirus 2" (SARS-CoV-2 or COVID-19)–originated in Wuhan, China, in December 2019. It rapidly spread through China and across continents[1] and was declared a pandemic on March 12, 2020, by the World Health Organization (WHO).[2] As of June 8, 2020, almost 7 million infections with over 400 000 fatal cases have been reported globally. In 80% of the infected individuals, the prognosis of the disease is mild and the mortality rate is around 2.3%. However, this mortality rate is 8.0% in patients between 70 and 79 years of age and 14.8% in those older than 80 years.[3] In a study with 41 COVID-19 patients, pneumonia with ground-glass appearance was observed in the thorax CT of all the patients. In 29% of the patients, acute respiratory distress syndrome (ARDS) was observed, and 32% of the patients were hospitalized in the ICU; the mortality reported was 15% among these ICU patients.[2] Another study involving 2634 patients reported that 14% of the patients were treated in the ICU and 12% of these patients received mechanical ventilation. The mortality rate of patients who received mechanical ventilation was 88%.[4] Generally speaking, the pathogenesis of COVID-19 has not been clearly elucidated and a potent form of treatment has not been discovered yet. Current COVID-19 therapy is supportive, and ARDS is the leading cause of mortality in the presence of COVID-19 inflammation.[5]

In a SARS-Cov-2 study (2012), the occurrence of a cytokine storm characterized by the release of several proinflammatory cytokines including IL-6, TNF-α, and IL-12 was determined as the pathogenesis of the disease.[6] Similarly, in COVID-19 studies, high plasma cytokine levels, including IFN-γ, IL-10, IL-6, IL-2, and IL-7 have been identified in ICU patients. In another study, a group of patients with severe COVID-19 infection were diagnosed with cytokine storm syndrome.[7] The studies presented so far provide evidence that a cytokine storm might be an inevitable result of these diseases and directly related to the prognosis.[2,8]

Tocilizumab (TCZ) is a recombinant humanized IL-6 receptor (IL-6R) inhibitor commonly used in the treatment of rheumatic diseases and cytokine storm syndrome. It binds both soluble and membrane-bound IL-6R forms to inhibit IL-6R-mediated signal transduction.[9] The possible efficacy of TCZ for COVID-19 is being tested by randomized clinical trials.[10,11] Case reports and clinical studies have also confirmed the use of TCZ in COVID-19 patients.[2,7] In a study with 63 COVID-19 patients, improved survival rate and a remarkable decrease in ferritin, D-dimer, and C-reactive protein (CRP) levels were observed with TCZ administration.[12] In parallel with these findings, a recent study on TCZ treatment with a limited number of patients reported not only decreased CRP levels but also improvements in computed tomography (CT) opacities and hypoxia status.[13]

This study aims to contribute to this growing area of research by exploring the relationship of TCZ administration with the need for ICU stay and disease prognosis in COVID-19 patients.

Methods

Owing to time constraints, we chose to perform a retrospective study instead of a randomized controlled trial. The data of 42 patients who were admitted to the Medicana International İstanbul Hospital with a diagnosis of COVID-19 between March 1, 2020, and May 10, 2020, were retrospectively evaluated. Informed signed consent forms were taken from all of the participants or their guardians. The study was approved by the Ministry of Health of the Republic of Turkey (Decision Number: 2020-05-15T15_13_09) and Medicana International Istanbul Hospital Ethics Committee (Decision Number:12/05/2020-004). All of the applications in this study were performed under the ethical standards of the Institutional Ethics Committee and in keeping with the 1964 Declaration of Helsinki. Patient files were screened and the cases with sufficient medical records were included in the study, whereas patients with bacterial or fungal infections, chronic kidney failure, and previously diagnosed and/or treated malignancies, previous or ongoing hematological diseases and/or rheumatological diseases, or patients having kidney or other organ transplants were not included in the study. The diagnosis and the treatments of all the patients were determined according to the COVID-19 diagnostic criteria of the Turkish Republic Ministry of Health (March 2020). Following these guidelines, all of the patients were administered 2×400 mg dose of TCZ as the first treatment. Considering laboratory and clinical findings, if the health of the patients improved with TCZ administration, the treatment was continued, with 4 different TCZ doses. A single 400 mg dose (a), a single 800 mg dose (b), and a divided 400 mg dose (200 mg+200 mg after 12 hours)) (c), and a divided 800 mg dose (400 mg+400 mg after 12 hours) (d) were administered.[14]

Diagnosis

Severe Acute Respiratory Syndrome Coronavirus 2 qPCR positivity was the primary inclusion criterion for the study. The nasopharyngeal samples of the patients were analyzed for SARS-CoV qPCR positivity. If the SARS-CoV qPCR result was negative, the second criterion applied was the compatibility of the prognosis of the disease with radiological findings of possible viral pneumonia, if the clinical portrait could not be explained by another cause/disease. The suspicion of COVID-19 infection was not ruled out if the first sample was drawn from the upper respiratory tract and the SARS-CoV qPCR result of this sample was negative, if the patient's infection status was compatible with the case definition.

In addition, during the diagnosis, the following protocol was used: a) the presence of at least one of the signs and symptoms of fever or acute respiratory disease (cough and respiratory distress), if the clinical portrait could not be explained by another cause/disease; or b) travel abroad by the patient or a relative within 14 days prior the onset of symptoms, if the clinical portrait could not be explained by another cause/disease; or c) being in close contact with a confirmed case of COVID-19, if the clinical picture could not be explained by another cause/disease; or d) an acute respiratory infection developed in the past 14 days with fever, cough, dyspnea and tachypnea, hypoxemia, and hypotension, with supportive radiological findings and the need for hospitalization due to the change in consciousness, if the clinical portrait could not be explained by another cause/disease; or e) a sudden-onset fever, cough, or shortness of breath and the absence of nasal flow, if the clinical portrait could not be explained by another cause/disease.

The disease was described as severe if any of the conditions specified were met: 1) peripheral capillary oxygen saturation (SpO_2) <93% (while breathing ambient air); 2) respiratory rate >30 breaths/minute; or 3) PaO_2/FiO_2 ≤300 mm/Hg. Critical case definition was as follows: 1) the presence of respiratory failure requiring mechanical ventilation; 2) shock; 3) the failure of other organs. All critical cases had been hospitalized in the ICU.

Treatment and Observation

Being over the age of 50, having a chronic disease such as cardiovascular disease, diabetes, hypertension, cancer, chronic lung diseases, other immunosuppressive conditions, etc., meeting the criteria for severe pneumonia (confusion or tachycardia (>125/min) or respiratory problems or tachypnea (>30/min) or hypotension, increase the severity of the disease and risk of complications. Therefore, patients with any of these characteristics were followed up after hospitalization.

All patients received treatment as suggested by the Turkish Ministry of Health Guidelines for COVID-19 treatment in March 2020.

According to the Turkish Ministry of Health guidelines, TCZ treatment can be recommended in terms of ease of access to the drug in COVID-19 patients who develop macrophage activation syndrome (MAS). Tocilizumab can be administered at a dose of 8 mg/kg (up to 800 mg). Depending on the severity of the patient's symptoms, 400 mg or 800 mg can be administered at a time. If the first dose is administered as 400 mg, considering the changes in the clinical and laboratory findings, the dose can be repeated at 200-400 mg within 12-24 hours. Although a response to a total 800 mg dose has been received, patients who still have MAS symptoms should not be administered an extra 200 or 400 mg of TCZ, and a decision considering alternative treatment possibilities should be explored in consultation with rheumatology and/or hematology specialists.

Data Collection

We retrospectively screened the clinical data using the Medicana International Istanbul Hospital's database in May 2020. The inclusion/exclusion criteria specified in the materials and methods section and the status of TCZ usage were applied to select the patients for the study sample.

Statistical Analysis

The data were analyzed with IBM Statistical Package for the Social Sciences (IBM SPSS Corp., Armonk, NY, USA) version 24.0, and the results were evaluated within the 95% and 99% confidence intervals. The normal distribution of the quantitative variables in the study was analyzed using the Kolmogorov–Smirnov test. Differences in the measured parameters before and after drug administration were analyzed by the dependent groups *t*-test and the Wilcoxon test. The rate of change of the values before and after drug administration was calculated in terms of various variables that were analyzed with the *t*-test, Mann–Whitney U-test, ANOVA test, and Kruskal–Wallis test. The relationship between categorical variables was analyzed by the chi-square independence test, and the relationships between quantitative variables were analyzed with Pearson and Spearman correlation tests.

Results

Demographic Characteristics

The average age of the patients was 58.38 ± 14.51 years and ranged from 26 to 88 years. There were 31 (73.8%) males and 11 (26.2%) females in the group of 42 patients. Mortality was observed in 12/42 (28.6%) patients, whereas 30/42 (71.4%) patients were discharged. Only 15 (35.7%) patients were administered methylprednisolone (Table 1).

Laboratory Findings

Table 2 describes the laboratory data before and after TCZ administration. The data of the fifth day, following the last TCZ administration, were defined as "post-treatment." The statistically significant parameters compared to the pre-treatment group were PLT (259.06 ± 130.99); NE% (69.16 ± 18.24), LY% (22.72 ± 14.82), LY# (1.56 ± 0.83), MO% (6.37 ± 3.31), and Neu/LY# ratio (8.27 ± 12.08), ALT (205.13 ± 603.08), AST (135.11 ± 300.68), CRP (2.23 ± 3.18), and procalcitonin (0.58 ± 2.28) (Table 2).

Computed Tomography Findings

All patients had typical findings on thorax CT. In the study, 19 patients had bilateral, especially peripheral, multifocal plaque-style ground-glass opacities; 17 patients had bilateral multifocal plaque-like ground-glass opacity with focal consolidations, 4 patients had bilateral widespread ground-glass opacity, and 2 patients had unilateral ground-glass opacity with focal consolidation. No signs of pleural effusion or pulmonary embolism were observed. In 23 patients, in the first 5 days before treatment, increased ground-glass opacity and focal consolidated area size were monitored using CT (Figure 1a-e).

Tocilizumab Treatment

Out of the 42 patients treated with TCZ, 6 (14.3%) received dose a; 12(28.6%) received dose b, 9 (21.4%) received dose c, and 15 (35.7%) received dose d. Out of 15 patients, methylprednisolone was also administered. Statistically significant differences between the NE#, WBC, and D-dimer changes, were observed with different dose administrations of the drug.

The following relationship was observed between the different doses administered and patient status: If the drug administration was at dose a, then the mortality rate of patients was 16.7%, methylprednisolone administration rate was 50%, the rate of the total recovery observed by CT was 100%, and the rate of receiving ventilator support was 33.3%. If the drug administration was at dose b, then the mortality rate of patients was 8.3%, methylprednisolone administration rate was 33.3%, the rate of the total recovery observed by CT was 83.3%, and the rate of receiving ventilator support was 8.3%. If the drug administration was at dose c, then the mortality rate of patients was 11.1%, methylprednisolone administration rate was 11.1%, the rate of the total recovery observed by CT was 87.5%, and the rate of receiving ventilator support was 11.1%. If the drug administration was at dose d, then the mortality rate of patients was 60%, methylprednisolone administration rate was 46.7%, the rate of the total recovery observed by CT was 42.9%, and the rate of receiving ventilator support was 60% (Table 3).

Table 1. Demographic Presentation and the Clinical View of the Patients.

Characteristics	Patients (n = 42)
Age (range)	58.38 ± 14.51 (26-88)
Gender	
Male	31 (73.8%)
Female	11 (26.2%)
Outcome	
Worsened (Death)	12 (28.6%)
Discharge	30 (71.4%)
Chronic medical illness	
Hypertension	11 (26.2%)
Diabetes mellitus	11 (26.2%)
Chronic artery disease	2 (4.8%)
Chronic obstructive pulmonary disease	1 (2.4%)
Thromboembolic event	1 (2.4%)
Ischemic heart disease	1 (2.4%)
Hospitalization days	15.33 ± 7.53
Hospitalization status	
Ward	25 (59.5%)
Intensive care unit	17 (40.5%)
Orotracheal intubation	
Present	13 (31.0%)
Absent	29 (69.0%)
Symptoms	
Fever	29 (69.0%)
Cough	29 (69.0%)
Dyspnea	7 (16.7%)
Throat ache	7 (16.7%)
Headache	2 (4.8%)
Fatigue	2 (4.8%)
Emesis	1 (2.4%)
Syncope	1 (2.4%)
PCR test result	
Positive	33 (78.6%)
Negative	9 (21.4%)
Methylprednisolone administration	
Yes	15 (35.7%)
No	27 (64.3%)

Data are n/N (%) unless specified otherwise.

The results of ANOVA and Kruskal–Wallis tests performed to determine the difference of the clinical and the hospitalization status variables according to the dose status are summarized in Table 4. According to the results, there is a statistically significant difference between the intubation period (in days) of patients receiving different doses of medication (P = .015). The average period of intubation was 1.67 days with the administration of dose a, whereas it was 0.67 days at dose b, 0.44 days at dose c, and 5.40 days at dose d. Similarly, the average was 2.83 days at with the administration of dose a, whereas it was 0.92 days at dose b, 2 days at dose c, and 7.80 days at dose d administration with ICU time (days) mean values (Table 4).

Discussion

We screened the patients' laboratory, CT, and hospitalization findings with the 4 different TCZ dose administrations. The mortality rate and the need for ventilator support were high whereas the total recovery was low at dose d (400 mg+400 mg). Interestingly, when the exact dose was not divided as dose b (800 mg), the mortality rate and the need for ventilator support dramatically decreased, and the total recovery exceeded 80%. The ideal dose for each patient should be administered concerning individual clinical findings of each patient. In the current study, at the standard dose of TCZ (800 mg), the elevated parameters during the first admission to the hospital, such as neutrophil (NE) percent, CRP, and procalcitonin levels had decreased, as expected mild side effects. We also observed increased alanine aminotransferase (ALT), aspartate aminotransferase (AST), and D-dimer levels.

As SARS emerged for the first time in 2002, the studies on the infection exponentially increased, especially focusing on potential drug candidates. The up-to-date antiviral agents to be used in COVID-19 treatment include hydroxychloroquine (HQC), lopinavir–ritonavir, remdesivir, favipiravir, glucocorticoids, and TCZ. One of the most potent drugs, HQC, because of its low cost, availability, and proven safety and treatment success records, is commonly studied.[15,16] Remdesivir–a nucleotide analog–has been shown to inhibit not only COVID-19 but also MERS and SARS-related coronaviruses.[17] Although favipiravir, as a preliminary result, has been shown to be a more potent antiviral agent compared to the lopinavir–ritonavir combination, there is no confirmed evidence for COVID-19 treatment efficacy. TCZ appears to be the drug of choice for large-scale use due to its capability to block the cytokine storm, which is directly related to the severity of the disease.[18] TCZ, with its fewer side effects and direct intervention on IL-6 signaling, has gained importance as increased IL-6 blood level is associated with negative prognostic factors for survival.[19] Similar to HQC, TCZ usage is becoming widespread due to the increasing number of confirmed studies about its effectiveness on COVID-19.[12,20]

During the infection, the most common abnormalities are not only the PCR-positivity for COVID-19 but also increased CRP, D-dimer, and lactate dehydrogenase (LDH) levels.[21] The severity of the disease (the need for ICU) can be evaluated using such biochemical parameters. Increased neutrophil

Table 2. The Laboratory Findings of COVID-19 Patients Before and After Tocilizumab Treatment, According to the Ministry of Health Guidelines.

	Before TCZ		After TCZ		Rate of Change (%)		
	Average	SD	Average	SD	Average	SD	*P*
WBC	8.025	3.2	9.42	6.14	−1.39	5.86	.512
PLT	200.59	97.32	259.06	130.99	43.42	74.50	**.009**
NE%	80.45	10.36	69.16	18.24	−13.86	20.55	**.000**
NE#	6.65	3.17	9.10	14.13	43.34	212.80	.856
LY%	13.96	8.47	22.72	14.82	85.99	122.07	**.000**
LY#	0.95	0.44	1.56	0.83	86.09	101.33	**.000**
MO%	4.96	2.84	6.37	3.31	97.20	242.76	**.018**
MO#	0.37	0.22	0.45	0.23	67.65	118.32	.069
Neu/Ly# Ratio	9.62	10.34	8.27	12.08	4.11	144.16	**.018**
Ferritin	578.21	505.73	662.72	555.94	83.44	200.82	.586
ALT	34.71	26.11	205.13	603.08	643.90	1.963.23	**.000**
AST	46.95	29.51	135.11	300.68	230.98	593.15	**.000**
CRP	15.07	8.44	2.23	3.18	12.83	7.32	**.000**
Calcium	7.99	0.49	8.08	0.77	-0.87	0.76	.475
LDH	418.29	163.13	405.48	192.97	6.86	45.50	.886
BNP	735.84	1.210.87	419.15	515.22	41.51	158.42	.502
D-Dimer	5.848.85	17.187.54	7.116.61	18.599.09	651.40	2.429.78	.814
Procalcitonin	2.37	7.13	0.58	2.28	−14.08	72.27	**.004**

Data are n/N (%) unless specified otherwise. Statisticaly significant values are marked bold.
Abbreviations: HT, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease, CRP, C-reactive protein, ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase.

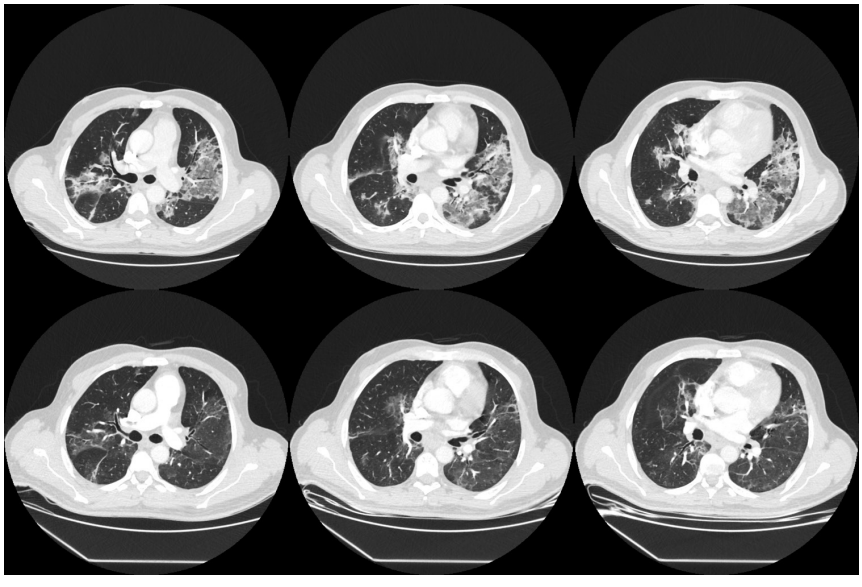

Figure 1. Thorax computed tomography (CT) images show significant improvement in findings in both lungs after tocilizumab (TCZ) treatment. (A-C) Ground-glass densities, focal consolidated areas with air bronchograms are observed in CT for both lungs before treatment. (D-F) A remarkable remission was observed in CT images in the findings in both lungs after treatment in thorax CT images.

Table 3. The Dose-dependent Clinical Status of the Patients.

	Dose Status								
	a		b		c		d		
	n	%	n	%	n	%	n	%	*P*
Death/discharge status									**.010**[Φ]
Death	1	16.7	1	8.3	1	11.1	9	60.0	
Discharged	5	83.3	11	91.7	8	88.9	6	40.0	
Methylprednisolone									**.293**[Φ]
Not administered	3	50.0	8	66.7	8	88.9	8	53.3	
Administered	3	50.0	4	33.3	1	11.1	7	46.7	
CT improvement findings									**.018**[Φ]
No improvement	0	0.0	2	16.7	1	12.5	8	57.1	
Improvement present	6	100.0	10	83.3	7	87.5	6	42.9	
Ward									**.007**
ICU	2	33.3	1	8.3	3	33.3	11	73.3	
Normal hospitalization	4	66.7	11	91.7	6	66.7	4	26.7	
Ventilator support									**.015**[Φ]
No	4	66.7	11	91.7	8	88.9	6	40.0	
Yes	2	33.3	1	8.3	1	11.1	9	60.0	

*$P < .05$. Statisticaly significant values are marked bold.
[Φ]The proportion of the cells whose expected value was less than 5 is more than 20%. For this reason, the analysis should be repeated by an increased number of observations. (a) A single 400 mg dose, (b) A single 800 mg dose, (c) A divided 400 mg dose (200 mg+200 mg after 12 hours), (d) A divided 800 mg dose (400 mg+400 mg after 12 hours).
Abbreviations: ICU, intensive care unit; CT, computed tomography.

count,[2,22] procalcitonin,[2,22] LDH,[2,22] ALT,[2,22] AST,[2,22] CRP,[22] and D-dimer levels[2,20,22] are associated with the severity of the disease and the need for ICU. In a survey conducted by Xu et al.,[13] 20 out of 21 patients were recovered and discharged within 2 weeks after TCZ administration. According to a systematic review conducted by Aziz et al.,[23] including 23 studies with 6279 patients, TCZ admission is associated with decreased mortality rates compared to standard treatment groups, whereas Lan et al.,[24] in their systemic review including 7 retrospective studies about TCZ treatment in

Table 4. The Change in Laboratory Findings with Different Tocilizumab Doses

	Dose Status								
	A		b		c		d		
	Avg.	SD	Avg.	SD	Avg.	SD	Avg.	SD	*P*
Hospitalization	16.67	5.24	12.83	3.66	15.89	10.06	16.47	8.97	.562
Intubation time (Days)	1.67	3.20	0.67	2.31	0.44	1.33	5.40	6.91	.015*
CPAP time (Days)	1.17	2.86	0.25	0.87	1.56	2.35	2.40	3.64	.169
ICU time (Days)	2.83	4.40	0.92	3.18	2.00	3.12	7.80	6.56	.006*
Time in ward (Days)	13.83	8.13	11.92	4.38	13.89	10.07	8.67	7.55	.317

*$P < .05$.
(a) A single 400 mg dose, (b) A single 800 mg dose, (c) A divided 400 mg dose (200 mg+200 mg after 12 hours), (d) A divided 800 mg dose (400 mg+400 mg after 12 hours).
Abbreviations: CPAP, continuous positive airway pressure; ICU, intensive care unit.

COVID-19 patients, reported decreased mortality rates but similar ICU admission periods compared to the standard care groups. In parallel with these findings, Guaraldi et al.,[25] in a retrospective cohort study, and Keske et al.,[26] in a research study, have associated TCZ treatment with decreased need for mechanical ventilation and rate of mortality. In addition to these findings, Perrone et al.[10] reported the reduced lethality rate through TCZ treatment among the patients not requiring mechanical ventilation support, whereas Rossotti et al.[27] and Somers et al.[28] suggested the usefulness of TCZ treatment among the patients requiring this support. In a recent study from Turkey, Borku Uysal et al.[29] reported that TCZ was more advantageous in preventing damage caused by the elevated cytokine response. Similarly, Günal et al.[30] suggested that an early TCZ administration at the beginning of the patient's SARS picture in severe COVID-19 patients might be effective in reducing the need for ventilatory support and improving lung functions. Conversely, in randomized trial involving 458 hospitalized patients, TCZ administration could not be associated with a better clinical status.[31]

Globally, ICU capacities are challenged to face this outbreak. To date, no treatment has yet been proven successful. More data are necessary to develop an improved and effective therapy to reduce mortality and the number of critically ill patients.[32] These patients require hospitalization, and because of the severity of the illness, almost 10% of them need ICU admission,[19] and this partial dependence on the ICU challenges the capacity of the health-care system of different countries, As the duration of ICU stay will increase the cost, optimal COVID-19 treatment strategies should be developed. Antinori et al.,[33] for example, reported that remdesivir usage might be effective in patients with non-critical conditions. Here, we suggest that earlier TCZ treatment decreases both the mortality rate and the ICU duration, if the required dose is administered.

Despite the retrospective nature of the work, the small sample size, and the lack of a control group and statistical power, our findings suggest that TCZ treatment may reduce the number of ICU admissions and/or mortality in patients with COVID-19. Owing to the lack of exact and definitive management protocols, several therapy regimens have been explored and tested in COVID-19 treatment. Although some have shown initial promise, many of them have been measures of desperation. ICU management requires the discovery of the actual drug for the treatment, but monitoring the adverse effects of the drug, screening the effects of these drugs on severely affected patients, and the potential mutations of the virus that may lead to the drug resistance of the virus should be considered.

The main disadvantage of the current findings is the impossibility of ruling out the unmeasured confounding factors, as the study samples were not randomized for comparisons. The knowledge of who was taking TCZ may have influenced the tendency of the staff to place a patient under invasive ventilation. Another disadvantage is the lack of time to investigate the long-term adverse effects of TCZ. However, monitoring the effect of TCZ at different drug doses was the strength of our study. Despite the non-randomized and preliminary results of this study, TCZ seems to be effective in treating the cytokine storm triggered by COVID-19. However, the study should be repeated with a larger-sized population to assess the optimum dose with fewer side effects.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Medicana International İstanbul Hospital (Date: May 12, 2020, Decision Number:12/05/2020-004).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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