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Original Article

Evaluation of hospitalized Covid-19 patients who received tocilizumab treatment in terms of clinical response, prognosis, and side effects

Ufuk Sonmez[1], Sabri Atalay[2], Alpay Ari[1], Murat Arslan[3], Huseyin Ozkarakas[3]

[1]Izmir Bozyaka Training and Research Hospital, Infectious Disease and Clinical Microbiology, Izmir, Turkey
[2]Izmir Tepecik Training and Research Hospital, Infectious Disease and Clinical Microbiology, Izmir, Turkey
[3]Izmir Bozyaka Training and Research Hospital, Anesthesiology and Reanimation Izmir, Turkey

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Corresponding Author: Ufuk Sonmez, Izmir Bozyaka Training and Research Hospital, Infectious Disease and Clinical Microbiology, Izmir, Turkey
Email: ufuksonmez87@gmail.com

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Abstract

Aim: In this study, we aimed to evaluate the clinical response, prognosis, and side effects of tocilizumab treatment among moderate, severe, and critical patients hospitalized due to coronavirus disease 2019 pneumonia.
Materials and methods: Retrospectively, 48 adult patients were included. Age, gender, co-morbid conditions, chest CT findings, and treatment modalities were recorded, and laboratory findings and the necessity of oxygen on the first, third and seventh day of tocilizumab were evaluated.
Results: While receiving tocilizumab, 34 (70.8%) of the patients were hospitalized in the intensive care unit, and 14 (29.1%) were in an inpatient clinic. On the seventh day, mean lymphocyte counts, mean C- reactive levels, and oxygen saturations were improved significantly (p: <0.001). All 14 patients whose tocilizumab treatment was initiated in an inpatient clinic survived, and none of them had needed an intensive care unit admission. The overall mortality rate was 45.8% (22/48). The average day of death was 16.6±12.6 (6 to 53). Among patients whose tocilizumab treatment was started in an intensive care unit, the mortality rate was 64.7% (22/34). Factors that were found to be significantly associated with mortality were as; hospitalization in an intensive care unit while receiving tocilizumab, receiving non-invasive/invasive mechanical ventilation, having bacterial superinfection, and high involvement in CT imaging (> 50%) at presentation. No serious side effects were observed during/after tocilizumab treatment.
Conclusions: In patients with moderate disease who have clinical signs of deterioration, starting early tocilizumab treatment may prevent admission to intensive care, reduce the necessity for supplemental oxygen, and improve clinical and laboratory response.

Keywords: SARS-CoV-2, tocilizumab, mortality

INTRODUCTION

In December 2019, a novel coronavirus causing pneumonia was identified in Wuhan city of China (1). This virological disease was referred to as coronavirus disease 2019 (COVID-19) by the World Health Organization in February 2020 (2).

Infection caused by COVID-19 may be asymptomatic, mild, moderate, or severe (3). In a report from China, of which 44.672 confirmed cases were involved, 81% of the patients were mild,14% were severe, 5% were critical, 1% were asymptomatic, and the overall fatality rate of the disease was found to be 2.3% (4). The first COVID-19 case in Turkey was reported on March 10, 2020, that has reached three million cases (5).

Although currently, none of the treatment regimens that are used have a definite effect on COVID-19 disease, some drugs are used for treating COVID-19 patients. These are anti-malarial drugs such as hydroxychloroquine, anticoagulant agents such as low molecular weight heparin, antiviral agents such as lopinavir/ritonavir, remdesivir, favipiravir, and anti-inflammatory agents such as corticosteroids (6).

Cytokine storm (CS) is an exaggerated systemic inflammatory

response with an evident expansion in many cytokines seen during a wide spectrum of diseases. Viral infections are among the major stimulators of CS. Elevated levels of pro-inflammatory cytokines such as interleukin-6 (IL-6) may cause cytokine release syndrome and macrophage activation syndrome (MAS), which both are extremely severe conditions that may end up in mortality among COVID-19 patients.

The clinical use of tocilizumab has been described in COVID-19 (7). Tocilizumab is an IL-6 receptor blocker agent mainly used to treat rheumatoid arthritis. As blocking the inflammatory pathway and using corticosteroids in COVID-19 prevents disease progression, pro-inflammatory cytokine blocking agents such as tocilizumab may also be conceivable to improve survival (8,9).

In this study, we evaluated the clinical response, prognosis, and side effects of tocilizumab treatment among moderate, severe, and critical patients hospitalized due to COVID-19 infection.

MATERIAL AND METHODS

Patients and Demographic Features

This retrospective study included hospitalized adult patients who received tocilizumab treatment between April 2020 and February 2021. Demographic features such as age, gender, concomitant co-morbid diseases, and treatment modalities of the patients were recorded. Approval was obtained from Izmir Bozyaka Training and Research Hospital Ethics Committee for our study on 21/05/2020 with the decision number of 14. The written informed consent form was obtained from the patients.

Treatment Modalities

Patients had received favipiravir 2x1600 mg as loading dose and 2x600 mg as maintenance for the total of 5 days and/or hydroxychloroquine 2x200 mg for the total of 5 days as antiviral regimens. Also, corticosteroid treatment (0.5-1 mg/kg methylprednisolone up to 10 days or pulse steroid, ≥ 250 mg) if they had received before tocilizumab were recorded. Patients with moderate to critical COVID-19 infection who had MAS and/or who were deteriorating in terms of clinical and laboratory assessment were started tocilizumab. The first dose of tocilizumab was given as 8 mg/kg (maximum 800 mg) intravenously. When the first dose was given as 400 mg, considering the change in clinical and laboratory findings, another 400 mg dose was repeated within 24 hours, if necessary.

Radiologic Assessment

All patients were scanned with low-dosage computerized chest tomography (CT) before they were hospitalized, and they were re-scanned with chest X-ray or chest tomography, if necessary. Chest-CT images with ground-glass opacification with/without consolidative abnormalities were evaluated. Five lung lobes were scored individually, and a semi-quantitative scoring system was used according to the pulmonary involvement (10). According to this scoring system percentage of the involvement of the lungs was described as <5%, 5-25%, 26-49%, 50-75%, and >75%.

Clinical Features

Clinical features such as oxygen saturation, the necessity of oxygen inhalation, non-invasive mechanical ventilation, or invasive mechanical ventilation were recorded on the first, third, and seventh day of tocilizumab treatment. Also recorded were any side effects during or after tocilizumab infusion and any proven secondary bacterial infections. Patients with dyspnea, respiratory frequency of ≥30/minute, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and/or >50% lung involvement were described as severe, and patients with respiratory failure, septic shock, and/or multiple organ dysfunction/failure were described as critical (3).

Laboratory Findings

Laboratory findings as C-reactive protein (CRP), white blood cell count, thrombocyte count, lymphocyte count, D-dimer, alanine aminotransferase (ALT), aspartate aminotransferase (AST) were analyzed on the first, third and seventh day of the tocilizumab treatment. The total days of hospitalization or mortality of the patients were recorded.

Statistical Analysis

All statistical data were analyzed by SPSS 15.0 program. Continuous variables were expressed as mean± sd (standard deviation) and median range (minimum-maximum). Categorical data were expressed as n (number) and percentage (%).

A T-test, otherwise Mann Whitney U test, was used if the distribution was homogeneous. Independent categorical variables were compared with each other with Pearson's Chi-Square Test or Fisher's Exact Test. Data were analyzed at a 95% confidence interval, and the p-value was considered significant as less than 0.05.

RESULTS

0f 48 patients, 34 were males (70.8%), and 14 were females (29.2%), with an average age of 56.46±13.5 (24 to 79). On the day of hospitalization, the clinical spectrum of the patients was 18 (37.5%) as moderate, 15 (31.25%) as severe, and 15 patients (31.25%) as critical.

Presenting clinical symptoms were as; dry cough (30/48, 62.5%), shortness of breath (29/48, 60.4%), fever (16/48, 33.3%), weakness (16/48, 33.3%), diarrhea (2/48, 4.1%), headache (1/48, 2%) and vomiting (1/48, 2%).

As co-morbidities: 21 (23.75%) patients had hypertension, 11 (22.9%) had diabetes mellitus, 4 (8.3%) had hematological malignancy, 4 (8.3%) had kidney transplantation, 3 (6.25%) had end-stage renal disease, 3 (6.25%) had asthma, 2 (4.1%) had chronic obstructive pulmonary disease, 2 (4.1%) had a rheumatological disease. Twelve (25%) patients did not have any co-morbid condition. Demographic features, clinical spectrum, and laboratory findings of the patients at presentation are given in Table 1.

Table 1. Demographic features, clinical spectrum, and laboratory findings of the patients at presentation

Parameter	Patients (n=48)	
Age (range)	56.46±13.5 (24-79)	
Gender		
Male	34 (70.8%)	
Female	14 (29.2%)	
Co-morbidities		
Hypertension	21 (23.75%)	
Diabetes mellitus	11 (22.9%)	
Hematological malignancy	4 (8.3%)	
Kidney transplantation	4 (8.3%)	
End stage renal disease	3 (6.25%)	
Asthma	3 (6.25%)	
Chronic obstructive pulmonary disease	2 (4.1%)	
Rheumatological disease.	2 (4.1%)	
None	12 (25%)	
Clinical spectrum of the patients		
Moderate	18 (37.5%)	
PaO2/FiO2	>300	
Severe	15 (31.25%)	
PaO2/FiO2	300-200	
Critical	15 (31.25%)	
PaO2/FiO2	<200	
Laboratory results	**Mean value**	**Normal range**
CRP (mg/L)	123.07±107.4 (5.9 – 461.4)	0-5
Ferritin (ng/mL)	552.4±496.1 (4.7-1500)	11-306.8

All patients had received 400 mg tocilizumab BID in 24 hours. None of them had any side effects during and after the infusion. On presentation, 36 (75%) patients were hospitalized in the inpatient clinic, and 12 (25%) were hospitalized in the intensive care unit before receiving tocilizumab. While receiving tocilizumab, 34 (70.8%) of them were hospitalized in the intensive care unit, and 14 (29.1%) of them had remained at the inpatient clinic. The mean day of starting tocilizumab treatment after COVID-19 diagnosis was 8.68± 4.38(2 to 18). Forty-seven patients (97.9%) had received favipiravir, 19 patients (39.6%) had received hydroxychloroquine, and 18 (37.5%) had received both. Twenty patients (41.6%) did not receive corticosteroids, 15 (31.25%) had received 0.5-1 mg/kg methyl-prednisolone up to 10 days and 13 (27%) had received pulse steroid.

The CT findings on the day of hospitalization were as follows; 5 (10.4%) patients had <5% involvement, 12 (25%) patients had 5-25% involvement, 19 (39.5%) patients had 26-49% involvement, 7 (14.5%) patients had 50-75% involvement and 5 (10.4%) patients had >75% involvement. Twenty-five (52%) patients had progress in imaging, in spite of treatment.

Laboratory test results, mean CRP values, white blood cell count, thrombocyte count, lymphocyte count, D-dimer, alanine aminotransferase, aspartate aminotransferase, mean values of oxygen saturations and on the first, third and seventh day of tocilizumab treatment are shown in Table 2. Improvement was statistically significant in mean lymphocyte count, CRP, and oxygen saturation (%) at the beginning and the seventh day of treatment.

A total of 10 patients died before the seventh day of tocilizumab treatment. Two of them died before the third day. Therefore, some data on these patients are missing.

The number of patients who needed oxygen support on the first, third, and seventh day of tocilizumab treatment is listed below in Table 3.

Nineteen (39.5%) patients had a secondary bacterial infection: 15 (31.25%) had secondary bacterial pneumonia, 2 (4.1%) had catheter-related infection, 1 (2%) had urinary tract infection, and 1 (2%) had bacteremia. Of the 15 patients who had secondary bacterial pneumonia, one received non-invasive mechanical ventilation, while the rest were intubated.

Twenty-six (54.2%) of all 48 patients were discharged from the hospital. These patients' mean length of stay was 21.4±11.4 (6 to 57) days.

The overall mortality rate was 45.8% (22/48). The average day of death was 16.6±12.6 (6 to 53). All 14 patients whose tocilizumab treatment was initiated at an inpatient clinic survived, and none of them had needed intensive care unit admission. Among patients whose tocilizumab treatment was started in the intensive care unit, the mortality rate was 64.7% (22/34).

Factors that were found to be significantly associated with mortality were as; hospitalization in the intensive care unit while receiving tocilizumab, receiving non-invasive/invasive mechanical ventilation, having bacterial superinfection, and high involvement in CT imaging (> 50%) at presentation, which is listed in Table 4.

The distribution of the patients between the inpatient clinic and intensive care unit and mortality results are presented in Figure 1.

Overall survival probability at the end of the follow-up period is shown in Figure 2 with the Kaplan-Meier curve.

Table 2. Laboratory test results and mean values of oxygen saturations

Parameter	1st day	3rd day	7th day	Normal range	p values
White blood cell count (x10³ /UL)	9.83±5.9 (0.09 - 40.05)	9.95±8.27 (0.49 - 43.89)	9.34±4.46 (3.23 - 21.77)	4.23-9.07	0.306
Lymphocyte count (x10³ /UL)	0.88±1.11 (0 - 7.83)	0.96±0.93 (0 - 5.92)	1.55±1.06 (0.17 - 6.34)	1.32-3.57	<0.001
Trombocyte count(x10³ /UL)	266.1±123.7 (13 - 481)	309.8±132 (15 - 555)	251.2±114.5 (48 - 553)	160-340	0.226
CRP (mg/L)	150.7±105 (2.8 - 424)	38.3±36.3 (1.3 - 150.8)	10.7±18 (0.5 - 89.5)	0-5	<0.001
D-dimer (ng/mL)	1452.6±1655.7 (205 - 6967)	2951.8±5418 (8.94 - 33664)	1898.9±2636.5 (94 - 13664)	0-240	0.501
Aspartate aminotransferase (U/L)	53.5±38 (6 - 201)	66.4±50.7 (8 - 301)	59.6±44.6 (10 - 219)	0-50	0.153
Alanine aminotransferase (U/L)	57±41.7 (7 - 165)	66.8±50.2 (5 - 249)	90.5±95.7 (10 - 508)	0-50	0.034
Oxygen saturation (%)	89.5±6.1 (65 - 99)	91.8±5.6 (80 - 98)	93.6±4.7 (81 - 99)	>95	<0.001
Total number(n)	48	46	38		

Table 3. The necessity of supplemental oxygen therapy

Oxygen therapy	1st day n (%)	3rd day n (%)	7th day n (%)
Nasal cannula	15 (31.25%)	10 (21.7%)	11 (28.9%)
Reservoir oxygen mask	3(6.25%)	5(10.8%)	5(13.1%)
Non-invasive mechanical ventilation	15 (31.25%)	7 (15.2%)	4 (10.5%)
Invasive mechanical ventilation	15(31.25%)	19(41.3%)	8(21%)
None	0	5 (10.8%)	10 (26.3%)
Total number(n)	48	46	38

Table 4. Factors associated with mortality

Parameter	Mortality n (%)			p values
	(+)	(-)	Total	
Clinic	0	14 (100)	14 (100)	<0.001
Intensive care unit	22 (64.7)	12 (35.3)	34 (100)	
Involvement in CT imaging				
>%50	10 (83.9)	2 (16.7)	12 (100)	0.002
<%50	11(31.4)	24(68.6)	35 (100)	
Non-invasive/invasive mechanical ventilation				
Received	20 (74.1)	7 (25.9)	27 (100)	<0.001
Not received	2 (9.5)	19 (90.5)	21 (100)	
Secondary bacterial infection				
Yes	15 (83.3)	3 (16.7)	18 (100)	<0.001
No	7 (23.3)	23 (76.7)	30 (100)	

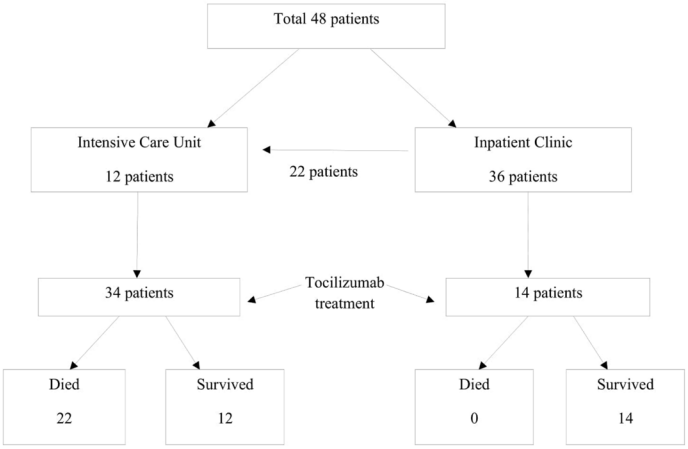

Figure 1. The distribution of the patients and mortality results

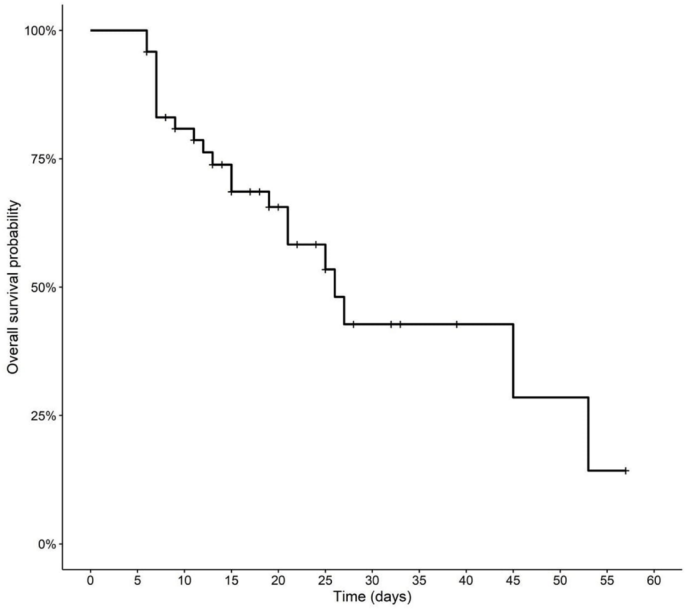

Figure 2. Overall survival probability-Kaplan Meier curve

DISCUSSION

COVID-19 is the cause of an ongoing pandemic. The search for effective treatment continues. In our retrospective study, we found out if tocilizumab treatment is effective among 48 patients who have COVID-19-related pneumonia with moderate to critical COVID-19 disease.

In our study, most of the patients were male (70.8%), and the mean age of patients was 56.46±13.5 (24 to 79). The most common onset symptoms were dry cough and shortness of breath, while the most frequently seen co-morbid conditions were hypertension and diabetes mellitus. Age, gender, and co-morbid conditions were not significantly associated with mortality.

In a study including 191 patients (mean age of 56 and male ratio of 62%), the most common co-morbid diseases were hypertension and diabetes mellitus. Parameters correlated with the severity of COVID-19 were as; high levels of serum IL-6, older age, D-dimer levels greater than 1 µg/mL, and lymphopenia (11).

Clinical data showed that tocilizumab treatment might provide clinical improvement by blocking IL-6. At the pandemic's beginning, some studies recommended tocilizumab treatment for severe patients (7,12). Although the issue of which patients should be received tocilizumab treatment is still controversial, it has been reported that in cases with persistent fever, clinical worsening, high involvement of CT imaging, and higher levels of IL-6, initiation of tocilizumab treatment at the earliest time may prevent clinical deterioration (7).

In the early stages of infection, clinical symptoms are mostly mild but may deteriorate in the following days. Studies have shown that clinical deterioration occurs within an average of 5-8 days (13,14). In our study, the mean day of starting tocilizumab treatment after COVID-19 diagnosis was 8.68±4.38 (2 to 18). In a study by Capra et al., 86 patients with COVID-19-related pneumonia and respiratory failure -but not needing mechanical ventilation- were included; tocilizumab treatment that had started in the first four days of admission significantly improved clinical outcome and had reduced the mortality rate (15). Thus, it seems relevant to start tocilizumab treatment within the first week after the COVID-19 diagnosis.

In our study, almost half of the patients died, and this rate was considerably higher among the patients who received tocilizumab treatment in an intensive care unit (64.7%). Factors that were found to be significantly associated with mortality were as; hospitalization in the intensive care unit while receiving tocilizumab, receiving non-invasive/invasive mechanical ventilation, having bacterial superinfection after tocilizumab treatment, high involvement in CT imaging (> 50%) at presentation. In fact, it should be considered that these factors are related to each other, especially related to an aspect of hospitalization in an intensive care unit. However, none of the patients who had moderate clinical features while receiving tocilizumab treatment were admitted to the intensive care unit or died. Thus, in one aspect, patients who have the necessary intensive care may be considered « delayed » in terms of receiving tocilizumab treatment.

In a retrospective cohort study of which 544 patients were included where tocilizumab treatment was compared to standard treatment, it was reported that tocilizumab treatment reduced the risk of death and the necessity of invasive mechanical ventilation in severe pneumonia cases (16). In another study of 96 patients, tocilizumab treatment was effective in selected patients with rapidly deteriorating severe COVID-19 pneumonia, and there was a significant reduction in the necessity for ventilatory support and supplemental oxygen therapy (17). Similarly, in our study, a significant decrease in the necessity of oxygen therapy after tocilizumab treatment was observed. While all patients were receiving oxygen therapy at the beginning of tocilizumab

treatment, 26.3% did not need any oxygen support on the seventh day. There was also a significant decrease in the number of patients who had needed non-invasive/invasive mechanical ventilation on the seventh day. However, it should be kept in mind that the loss of the severe patients before the seventh day may have influenced these results.

Decreased lymphocyte counts and higher CRP levels are parameters that were correlated with the severity of COVID-19. A significant increase in lymphocyte count and a decrease in mean CRP value were observed in our study by tocilizumab treatment.

In a study by Pan Luo et al., a rapid and significant decrease in the mean CRP levels were also found by tocilizumab treatment (18). However, they reported that a single dose of tocilizumab treatment, even with steroids, was insufficient in critically ill patients, and administration of an additional dose was found to be more beneficial.

A study by Uysal et al. showed a significant increase in the eosinophil averages and a significant decrease in mean CRP value after tocilizumab treatment (19). However, no statistically significant difference was observed between the averages of neutrophil, lymphocyte, ALT, AST, ferritin, troponin, and creatinine on the day of diagnosis, before the tocilizumab, after the tocilizumab, respectively.

In our study, tocilizumab did not cause any serious side effects, but, on the other hand, a significant increase in mean ALT values was found. This may be related to tocilizumab treatment and/or to other hepatotoxic agents such as favipiravir (20).

Although studies have shown that tocilizumab treatment is effective, some studies reported that tocilizumab treatment does not change the outcome of the disease. In a randomized, controlled, double-blind study of 243 hospitalized patients with COVID-19 pneumonia who were not receiving mechanical ventilation, standard therapy plus tocilizumab reduced the likelihood of progression to the composite outcome of mechanical ventilation or death. However, it did not improve survival compared with the placebo group who received standard therapy alone (21). In line with our results, no serious side effects related to tocilizumab were observed.

Limitations of the Study

The limitations of our study are; that it was conducted in a single center with a small group of patients with a retrospective design, and pre-treatment IL-6 levels were not measured.

CONCLUSION

As a result, in patients with moderate disease who have clinical signs of deterioration, starting early tocilizumab treatment may prevent admission to intensive care, reduce the necessity of supplemental oxygen, and improve clinical and laboratory response.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Approval was obtained from Izmir Bozyaka Training and Research Hospital Ethics Committee for our study on 21/05/2020 with the decision number of 14.

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