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Research Paper

Evaluating the Effects of Tocilizumab on the Recovery of Hospitalized Patients With Severe COVID-19 in the Cardiorespiratory Intensive Care Unit

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ABSTRACT

Background and Aim: In severe COVID-19, the vital organs of the body experience dysfunction, such as respiratory distress, which may lead to the death of the patient. This study investigates the effect of the tocilizumab drug on the recovery of patients with severe COVID-19.

Materials and Methods: This was a retrospective cohort study conducted in Kamkar-Arabnia Hospital, Qom, Iran, in the summer of 2021. The studied data, including age, sex, underlying disease, severity of pulmonary involvement, blood oxygen saturation percentage, duration of hospitalization, need for mechanical ventilation, etc. were extracted and compared with the files of patients with severe COVID-19 who were candidates for receiving tocilizumab according to the national protocol.

Results: 70(50%) patients were men and 70(50%) were women. The mean age of the patients was 55.96±14.18 years. No statistically significant difference was observed between the two groups ($P>0.05$) regarding clinical symptoms, the mean number of days dependent on a ventilator, the number of days receiving oxygen with a reservoir bag, and the number of days receiving nasal, the number of days hospitalized in the normal department, in the intensive care unit (ICU), as well as the outcome of the patients. No statistically significant difference was observed between the two groups among the laboratory variables of lymph flow and lactate dehydrogenase ($P>0.05$). However, the C-reactive protein level had a statistically significant difference ($P<0.05$). A statistically significant difference was observed between the two groups regarding blood oxygen saturation percentage in room air and blood oxygen saturation with auxiliary oxygen ($P<0.05$).

Conclusion: The results showed that the tocilizumab was effective in the recovery and increasing the amount of blood lymphocytes and blood oxygen of the patients; however, it did not have much effect in reducing the need for an intensive care unit and the outcome of death. For this reason, more clinical trials are required to prove the drug's effectiveness.

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Journal of Vessels and Circulation
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Introduction

In December 2019, a new coronavirus began in Wuhan City, China, quickly spreading and leading to an epidemic throughout China. It reached several continents in only one month. In late February 2020, China reported more than 78 631 confirmed cases of the virus and 2747 confirmed deaths caused by the virus [1]. In February 2020, the World Health Organization (WHO) called this disease caused by severe acute respiratory syndrome (SARS-CoV-2) COVID-19 [2-5]. During the COVID-19 pandemic, many people worldwide were affected by this disease with mild to severe symptoms. Meanwhile, the ways of transmission of the virus are not entirely known. Still, this virus, similar to the flu virus, is usually transmitted through respiratory droplets in close contact with person to person. In addition, the transmission of infection can also occur through contact with contaminated surfaces and touching the eyes, nose, and mouth. The incubation period of this disease is at least two days and, at most, 14 days, and its symptoms can vary from asymptomatic cases in 81% to respiratory distress syndrome in 5% of cases [6, 7]. The mortality rate is different in different countries and ages. Meanwhile, most of the deaths caused by this disease are seen in elderly patients with underlying risk factors [8, 9]. This virus is diagnosed using genomic tests (reverse transcription polymerase chain reaction [RT-PCR]) on nasopharyngeal samples to determine virus ribonucleic acid (RNA), and lung computed tomography (CT) scan helps diagnose this virus with a sensitivity of 98%, but it is not specific [10, 11]. Other paraclinical findings include lymphopenia, leukopenia, leukocytosis, thrombocytopenia, increased lactate dehydrogenase (LDH), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and D-dimer [12]. Also, during the infection with this virus, the plasma level of cytokines in the serum, including interleukin 2, 6, 7, 10, granulocyte growth factor, and tumor necrosis factors alpha increased in these patients, which is known as the cytokine storm phenomenon and is closely related to the severity of deterioration and is also effective on the prognosis of patients [12, 13]. The drugs used to treat this emerging virus include antivirals, such as interferon alpha, lopinavir, chloroquine phosphate, hydroxychloroquine, ribavirin, arbidol, and remdesivir [14]. Chloroquine phosphate and hydroxychloroquine phosphate were unsuitable for treatment due to the side effects of cardiac arrhythmia. The studies showed that oseltamivir did not affect improving COVID-19. In addition, lopinavir had a minimal impact [15]. On the other hand, studies have shown that remdesivir, as an antiviral drug, could reduce the duration of hospitalization and recovery; however, it did not significantly affect the mortality rate. Therefore, combined treatment with other drugs, especially in moderate to severe COVID-19, can be helpful, and further studies are required [16]. Tocilizumab is a recombinant human monoclonal antibody against the interleukin-6 receptor, which is commonly used in the treatment of rheumatoid arthritis binding to interleukin-6 receptor with high affinity and prevents the binding of interleukin-6 to the receptor and reduces the inflammatory response [17, 18]. In past studies, sufficient evidence has not been stated for the effectiveness of this drug in COVID-19 patients. Studies have recommended conducting further investigations on the effect of this drug in patients with COVID-19 through clinical trials [19] and considering the pandemic and the high prevalence of the COVID-19 virus, and the limited studies regarding the effectiveness of the tocilizumab to provide a strategic treatment to reduce the mortality caused by this virus in patients, this study investigates the effect of the tocilizumab on the recovery of hospitalized patients with severe COVID- 19 in Kamkar-Arabnia Hospital in Qom City, Iran in the summer of 2021.

Materials and Methods

This was a retrospective cohort study. The research population included patients with severe COVID-19 delta mutation referred to Kamkar-Arabnia Hospital in Qom City in the summer of 2021. Sampling was random, and the sample size was estimated at 140 patients based on similar studies. They were selected from the patients with severe COVID-19 at Kamkar-Arabania Hospital in Qom City, Iran, in the summer of 2021. These patients were candidates to receive tocilizumab and did not have contraindications for receiving the drug. These patients were divided into two groups: The case group with 70 patients from individuals who received the drug and the control group with 70 patients from subjects who did not receive the drug due to unavailability or lack of personal satisfaction. The patients who were candidates to receive the tocilizumab included hospitalized patients with severe and severe pulmonary involvement who had a progressive course despite treatment with a standard dose of corticosteroid during 24 to 72 h of admission and CRP >75 was reported or patients with rapid progression who need care and treatment in the intensive care unit (ICU) during 24 h. The exposed group included the files of 70 patients with severe COVID-19 referred to Kamkar-Arabniya Hospital in Qom City, Iran, who were candidates to receive tocilizumab, received 8 mg/

kg body weight (in case of no improvement, repeating another dose up to 48 h later) and the people of the non-exposed group included the files of 70 patients with severe COVID-19 referred to Kamkar-Arabniya Hospital in Qom City, Iran, who due to the patient's lack of personal consent or the unavailability of the drug in the hospital, have not received tocilizumab and in terms of age and gender and having an underlying disease (such as cardiovascular disease, diabetes, blood pressure, chronic lung disease, chronic kidney disease, age over 60, body mass index over 40, immunodeficiency and types of cancers) have been homogenized with the exposed group.

All patient information, clinical and paraclinical findings, and the disease included in the patient files and nursing reports were extracted. All information was entered into the SPSS software, version 22, and analyzed with the chi-square and the independent t-tests.

Results

In this study, 140 patients who had polymerase chain reaction (PCR) positive for delta mutation coronavirus were selected; the mean age in the exposed group was 79.55±13.99 years, and in the non-exposed group, it was 12.56±47.14 years. A total of 50% of patients were men and 50% were women. No significant difference was observed in the two groups regarding the underlying disease.

This study examined candidates for receiving tocilizumab using a lung CT scan at the beginning of hospitalization. In the exposed group, 27 patients had 38.5% relatively severe pulmonary involvement; in the non-exposed group, 29 patients had 4.41% relatively severe pulmonary involvement. In the exposed group, 43(5.61%) patients and 41(6.58%) patients had severe pulmonary involvement in the non-exposed group. The state of lung involvement in the two groups at the beginning of hospitalization was not statistically significant (P=0.73). In the examination of clinical symptoms in patients, no significant difference was observed between the two groups in terms of symptoms of cough (P=0.73), shortness of breath (P=1), cough (P=0.14), and fever (P=0.85) (Table 1).

The mean number of days elapsed from the onset of clinical symptoms when visiting the hospital was at least 5 days and at most 25 days. The mean days in the exposed group were 10.85 days; in the non-exposed group, it was 9.30 days. A statistically significant difference was observed between the two groups (P=0.007). This means that the mean number of days elapsed from the onset of clinical symptoms is higher in the exposed group, and the disease of the exposed group patients is more severe than the non-exposed group.

The results also showed no statistically significant difference between the two groups in the mean number of days of ventilator dependence, the number of days receiving oxygen with a reservoir bag, and the number of days receiving nasal oxygen (P>0.05) (Table 2).

The mean number of days of hospitalization in the normal department (P=0.27), in the intensive care (ICU) (P=0.97), as well as the outcome of the patients (P=0.43) did not have a statistically significant difference between the two groups (Table 3).

Table 1. Examination of the frequency of clinical symptoms among patients with and without medication

Variables		No. (%)		P
		Exposed	Non-exposed	
Cough	No	27(38.5)	29(41.4)	0.73
	Yes	43(61.5)	41(58.6)	
Shortness of breath	Yes	70(50)	70(50)	1
Cough	No	18(25.8)	11(15.8)	0.14
	Yes	52(74.2)	59(84.2)	
Fever	No	51(72.8)	50(71.4)	0.85
	Yes	19(27.2)	20(28.6)	

Table 2. Examining mean time of oxygen support among patients with and without medication

Variables	Mean±SD		P
	Exposed	Non-exposed	
Number of days dependent on ventilator	1.25±2.74	1.26±2.73	0.27
The number of days receiving oxygen with bag reservation	11.57±5.84	11.61±7.34	0.97
Number of days received with Nasal	1.56±0.71	1.16±0.54	0.72

Table 3. Examination of treatment course among patients with and without medication

Variables		Mean±SD/No. (%)		P
		Exposed	Non-exposed	
The mean number of days of hospitalization in the normal department of the hospital		1.25±2.74	1.26±2.73	0.27
The mean number of days of hospitalization in the intensive care unit		11.57±5.84	11.61±7.34	0.97
Follow-up death of patients	Death	17(24.28)	22(31.42)	0.43
	Discharge	53(75.71)	48(68.57)	

Table 4. Examining the course of inflammatory markers among patients with and without medication

Inflammatory Markers	Mean±SD		P
	Exposed	Non-exposed	
Lymph.0 (%)	797.20±329.32	962.41±680.30	0.07
Lymph.1 (%)	908.15±472.81	812.03±406.90	0.19
Lymph.2 (%)	1019.87±630.14	889.61±547.69	0.19
CRP.0 (nmol/L)	45.29±18.51	55.46±25.29	0.01
CRP.1 (nmol/L)	6.38±10.65	26.28±43.42	0.005
LDH.0 (IU/L)	852.83±240.55	830.62±368.47	0.70
LDH.1 (IU/L)	828.208±398.96	772.16±512.77	0.67

CRP: C-reactive protein; LDH: Lactate dehydrogenase; SD: Standard deviation.

A statistically significant relationship was observed in the two groups regarding the percentage of blood oxygen saturation in room air (P=0.00). The exposed group had an increasing course with a gentle slope during hospitalization, while the non-exposed group showed a significant drop in the blood oxygen saturation percentage; however, this difference is insignificant at the end of hospitalization. Also, a statistically significant relationship is observed between the two groups (P=0.00) in terms of the percentage of blood oxygen saturation with auxiliary oxygen, that the exposed group responded better to oxygen therapy after receiving the drug than the non-exposed group; however, this difference is insignificant in the last days of hospitalization (Figure 1 and Figure 2).

In this study, no statistically significant difference was observed between the two groups regarding the number of lymphocytes per microliter of blood during hospital-

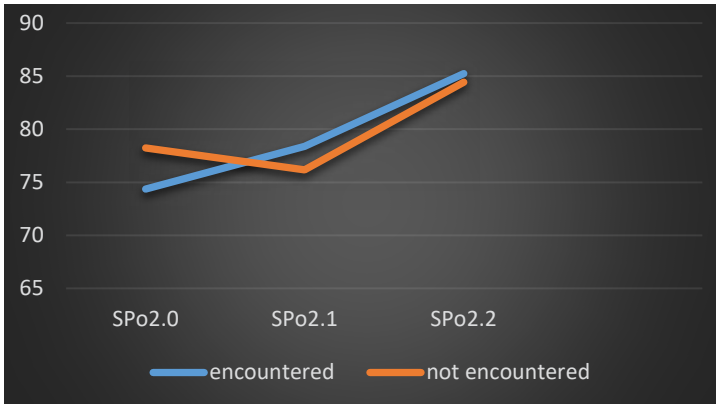

Figure 1. Oxygen saturation in room air among patients with and without medication

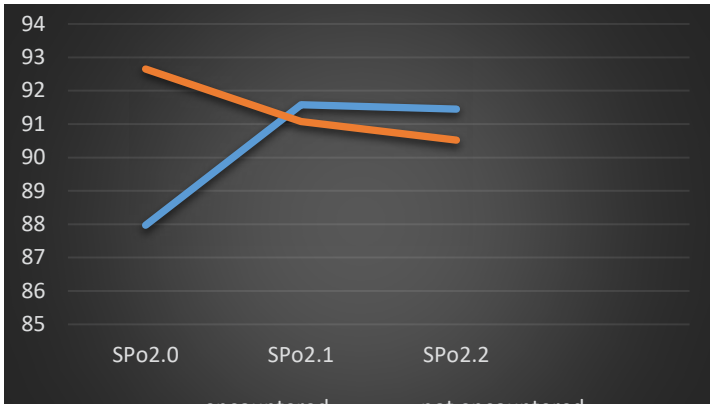

Figure 2. Oxygen saturation with supplemental oxygen among patients with and without medication

ization (P=0.07), the course of hospitalization (P=0.19), and discharge or death (P=0.19). Regarding the course of CRP, a statistically significant relationship was observed between the two groups (P=0.005), and the exposed group had a significant decrease in CRP levels compared to the non-exposed group. Regarding the LDH course, no statistically significant difference was observed between the two groups (P=0.67) (Table 4).

Discussion

In the conducted research, the effect of tocilizumab in the recovery of patients with severe COVID-19 has not yet been definitively confirmed, and several studies showed the lack of effect of the drug in the recovery of patients, and several others showed the effect of the drug in improving the conditions of patients. However, all studies recommend further research. The results of the present study showed that the mortality rate in the exposed group is 28.24%, and in the non-exposed group, it is 42.31% (P=0.34); therefore, no statistically significant difference is observed between the two groups. According to the cohort study conducted by Rosas et al. mortality on day 28 was 19.8% in the group receiving tocilizumab and 19.4% in the group receiving placebo (P=0.94) [20]. The difference between the two was insignificant, and the results are consistent with the present study. Also, in the study conducted by Lan et al. the mortality rate in the group receiving tocilizumab was 39(16.3%) people, and in the control group, it was 85(24.1%) people (P=0.69). The difference between the two groups was not significant in mortality, and the results of this study are consistent with the results of our study [19, 20]. In the present study, the mean number of days dependent on mechanical ventilation in the exposed group was 1.25. In the non-exposed group, it was 1.26 days (P=0.27), which was not statistically significant. The mean number of days requiring hospitalization in the ICU was 47.3 days in the exposed group and 91.2 days in the non-exposed group (P=0.59). According to the study by Lan et al. the risk of being hospitalized in the ICU was 35.1% in the group receiving tocilizumab and 15.8% in the control group (P=51.1), and the difference between the two groups was not significant. Also, the need for mechani-

Journal of Vessels and Circulation
Qom University of Medical Sciences

cal ventilation in the group receiving tocilizumab was 32.4%. In the control group, it was 28.6% (P=0.82), so the difference between the two groups in this variable was insignificant. Our results were also consistent with this study, which can be due to the more severe disease in the group receiving tocilizumab. Meanwhile, this study did not show evidence of the more significant benefits of using tocilizumab in patients with severe COVID-19. It recommended stopping the use of drugs until definitive evidence is found and controlled and high-quality trials are conducted. According to the study conducted by Kewan et al. the results showed that the need for mechanical ventilation in patients receiving tocilizumab was 68% and 22% in the control group. The mean recovery time in the group receiving tocilizumab was 8 days. In the control group, it was 13 days. The mean duration of support by mechanical ventilation in the group receiving tocilizumab was 7 days; in the control group, it was 10 days (P=0.11). It showed that the use of tocilizumab led to a reduction in the recovery time of tocilizumab compared to the control group; however, the relationship between the two groups was insignificant. This result is inconsistent with our study because, in our research, tocilizumab did not reduce the duration of hospitalization, which is probably due to the severity of the disease in the exposed group of our study [21]. In the present study, during the patients' hospitalization after receiving the medicine, the amount of oxygen therapy to a mean volume of 4 liters per min decreased only in 17 patients. The rest of the patients consumed more auxiliary oxygen until the last day of hospitalization, and this number was also 17 in the non-exposed group. No significant difference was observed between the two groups regarding reducing the amount of oxygen therapy. According to the study conducted by Xu et al. within 5 days after receiving the drug, the amount of oxygen therapy was reduced in 15(75%) patients, and 1 patient did not need oxygen therapy, which is inconsistent with the result of our study. In our study, the amount of oxygen therapy did not decrease after drug injection, which can be due to the more severe disease in delta mutation [22]. In our study, the mean number of final lymphocytes per microliter of blood in the exposed group is 1019; in the non-exposed group, it is 889 (P=0.19). Meanwhile, the patients were still in a lymphopenic state at the time of discharge or death. According to the study conducted by Xu et al., peripheral blood lymphocytes in 17 patients (85%), which decreased before injection, returned to normal 5 days after injection in 10 patients (52%), which is inconsistent with the result of our study, which is due to the more severe COVID-19 in the delta mutation, and our study, the patients did not get out of the lymphopenic state.

CRP decreased significantly in 16(84%) patients. In the present study, the mean final CRP in the exposed group was 38.6. In the non-exposed group, it was 28.26, which had statistically significant differences, and the exposed group had a significant decrease in CRP [22]. In the present study, the need for mechanical ventilation was 2.05 days in the exposed group and 1.25 days in the non-exposed group (P=27.0), and the meantime of discharge from the hospital in the exposed group was 14.87 days. The exposed group lasted 13.78 days, which is consistent with the study's results by Kewan et al. [21]. No significant relationship is observed between the two groups regarding reducing the duration of hospitalization and the need for mechanical ventilation.

Conclusion

Our retrospective study showed that the use of tocilizumab in patients with severe COVID-19 did not have an effect on improving the outcome, reducing the duration of hospitalization, reducing the need for hospitalization in the ICU and mechanical ventilation, and only in acute cases, after receiving the drug, they had a better clinical condition in terms of blood oxygen saturation and lymphocyte; however, no significant difference was observed between the two groups in terms of blood oxygen saturation and lymphocyte.

Ethical Considerations

Compliance with ethical guidelines

This study has been approved by the Ethics Committee of Qom University of Medical Sciences (Code: IR.MUQ.REC.1401.029).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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