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Tocilizumab Failed to Reduce Mortality in Severe COVID-19 Patients: Results from a Randomized Controlled Clinical Trial

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ABSTRACT

The severe coronavirus disease 2019 (COVID-19) is associated with increased levels of blood interleukin (IL)-6. Therefore, it is hypothesized that modulating the levels or effects of IL-6 could diminish airway inflammation and alter the course of COVID-19.

We conducted a controlled, randomized, double-blind clinical trial on hospitalized patients with severe COVID-19 in Iran. The patients were randomly distributed by block randomization to take either standard-of-care (SOC) plus 1 or 2 doses of tocilizumab 8 mg/kg or SOC alone. The endpoint was defined by clinical improvement and discharge.

We enrolled 40 patients (20 patients in each group) from 10 July to 10 December 2020. After randomization, 1 patient in the SOC arm and 3 patients in the tocilizumab arm refused to participate and were eliminated from the study.

The mean age of participants was 59.62±15.80 in the tocilizumab group (8 women and 9 men) and 63.52±12.83 years old in the SOC group (9 women and 10 men) groups. The number of patients

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who recovered did not differ significantly between the tocilizumab and SOC groups (12 [70.6%][70.6%] vs. 15 [78.9%]), respectively). Hospitalization rates were also similar between the groups (Log-rank test, p=0.615; hazard ratio, 0.83; 95% CI [0.39–1.78]). The results show that tocilizumab could not be a beneficial agent for treating severe cases of COVID-19 patients and would not significantly improve clinical outcomes.

Keywords: Coronavirus disease 2019 virus; Interleukin-6; Randomized controlled trial; Tocilizumab

INTRODUCTION

Since its emergence in late 2019, coronavirus disease 2019 (COVID-19) has become a global health concern.[1] COVID-19 presentations range from mild upper respiratory involvements to severe pneumonia, characterized by immunological abnormalities, hyperinflammation, and the cytokine storm.[2-4] The cytokine storm or excessive release of inflammatory cytokines can lead to acute respiratory distress syndrome, lung fibrosis, and lethal organ damage.[5]

Serum interleukin (IL)-10, IL-8, IL-6, and tumor necrosis factor (TNF-α) levels were shown to be significantly elevated in severe or deceased patients compared to moderate or recovered cases of COVID-19.[1,6] IL-6 is a pro-inflammatory and pro-fibrotic cytokine produced by immune cells such as monocytes and lymphocytes, as well as fibroblasts and bronchial epithelial cells, and plays a role in the pathogenesis of lung fibrosis.[7-9] IL-6 levels in critically ill patients are almost 10 times higher compared to moderate cases.[10] This elevated level of serum IL-6 is positively correlated with the SARS-CoV-2 RNAemia,[10] need for intubation,[11] and severity of the disease,[12] and can be used as prognostic and diagnostic markers for the severity of COVID-19. Therefore, it is suggested that the administration of IL-6 signaling inhibitors may have a beneficial impact on the resolution of cytokine storms and the treatment of COVID-19 patients in the pulmonary stage.

Tocilizumab is a monoclonal antibody against the IL-6 receptor and is primarily used in treating rheumatic diseases.[13] However, there have been contradictory results regarding its effectiveness in COVID-19 patients.[14-17] Therefore, in this randomized controlled trial, we investigated the effects of tocilizumab administration on recovery, oxygen therapy, and clinical and laboratory characteristics of hospitalized COVID-19 patients.

MATERIALS AND METHODS

Trial Design

This research was a phase-II double-blind, randomized, two-arm parallel, controlled trial conducted from 10 July to 10 December 2020. Forty cases from Imam Khomeini and Shariati Hospital, Tehran University of Medical Sciences (TUMS) were included in this research. The trial protocol was designed and implemented according to the Consolidated Standards of Reporting Trials (CONSORT) Guideline[18] and was approved by the Iranian Registry of Clinical Trials (ID: IRCT20081027001411N4) on 9 July 2020. In this study, all complete cases were analyzed, and a per-protocol approach was used .

Participants

COVID-19 infection in patients was confirmed by the confirmation of SARS-CoV-2 in nasopharyngeal swabs via polymerase chain reaction (PCR) and atypical computed tomography (CT) features, including subpleural, bilateral, and peripheral ground-glass opacities.

Patients 18 years of age or older were enrolled if they complied with all of the following conditions: 1) confirmed COVID-19 infection; 2) C-reactive protein (CRP) of >10 mg/L, IL-6 of >18 pg/mL, or lymphocyte counts of <1100 cells/μL); 3) at the pulmonary stage of the disease with blood oxygen saturation <93% or respiratory rate higher than 24; 4) not connected to a mechanical ventilator; and 5) not responding to standard COVID-19 treatments. All participants provided their informed consent before the enrollment.

Patients were excluded if they were allergic or intolerant to any therapeutic agent used in this study, had positive procalcitonin levels, had an active infection including latent or active tuberculosis, had a history of receiving immunosuppressive drugs or corticosteroids, or a had history of malignancies.

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Sample Size

Using the PASS software version 11, to achieve 80% power, 0.05 significance level, and detect a difference of 0.1 between the proportions of hospitalization in two groups based on a two-sided log-rank test, and also considering the proportion of patients lost during follow-up 1/10, the overall sample size was 40 subjects (equal in each group).

Randomization and Treatment

In this study, patients were randomly assigned to either the intervention group, receiving tocilizumab and standard of care (SOC), or the control group, receiving the SOC. Randomization was achieved using permuted blocks, with 10 blocks each containing 4 participants. Within each block, the 2 treatment combinations were evenly distributed (1:1) using a computer-generated random sequence. This method ensured random assignment to blocks and within each block. One patient in the SOC arm and 3 patients in the tocilizumab arm refused to participate and were excluded from the study before baseline measurements. Patients were allocated to receive SOC alone or SOC plus 8 mg/kg of tocilizumab (Actemra, Roche). Unstable patients received another dose of tocilizumab after 12 hours, with a maximum dose of 800 mg. The SOC was comprised dexamethasone plus remdesivir plus placebo. Patients, investigators, and outcome assessors were not informed of the assigned groups. Normal saline was used as a placebo in the control group.

Outcome

The clinical, demographic, and laboratory data of the patients were recorded before enrollment. Participants were followed for 40 days until improvement, discharge, or death. The primary outcome of this study was clinical improvement. Therefore, time to recovery was considered the event of interest, and survival analysis was performed by assuming death as an independent censoring event.

The clinical characteristics of the patients that were assessed included the respiratory rate, heart rate, blood pressure, fever, gastrointestinal symptoms, chest pain, dyspnea, cough, weakness, and myalgia. Oxygenation was assessed using oxygen saturation, the requirement for, and the type of oxygen support (i.e., nasal cannula, simple oxygen mask, non-rebreather mask, noninvasive, or invasive ventilation). All these characteristics were assessed once at enrollment and once after 3 to 5 days of initiating treatment.

CT findings, including the proportion of pulmonary involvement and radiological characteristics, were evaluated only in consenting individuals at baseline and 6 weeks after the treatment.

Laboratory parameters included complete blood count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), C-reactive protein, erythrocyte sedimentation rate (ESR), fasting blood sugar, venous blood gas parameters, IL-6, D-dimer, troponin, creatine phosphokinase, and ferritin at baseline, 3 to 5 days after the treatment, and at hospital discharge.

The patient's clinical and laboratory parameters were used to determine improvement and discharge if all of the following criteria were met: consciousness (using the Glasgow Coma Scale ≥14), amelioration of dyspnea (a respiratory rate <20 breaths per minute and not using the accessory or intercostal muscles to breathe), no fever for 3 days, oxygen saturation >93%, normal range of urinary output, tolerating oral regimen, blood pressure >100 mmHg, heart rate <90 beats per minute, reduced CRP to laboratory normal range, and no other side effects. All data were recorded on case report forms and an Excel spreadsheet. All adverse effects, whether or not related to the tocilizumab intervention, were assessed.

Statistical Analysis

All continuous variables are reported as the mean±standard deviation (SD), and categorical variables are expressed as numbers and percentages. The Kolmogorov-Smirnov test of normality was used for continuous variables. A repeated measures analysis of variance was performed to compare the groups over time. Mann-Whitney or Student's *t*-tests were applied to assess the statistical difference at each time point. In addition, Wilcoxon signed-rank or paired *t*-tests were performed to compare 2 time points in each study arm. The chi-square or Fisher's exact tests were applied to test the associations between two and categorical variables.

Kaplan-Meier curves and the log-rank test were applied to analyze the time to recovery. The multiple Cox regression model was used to adjust the effects of potential confounders in comparing hospitalization between the groups after assessing relevant assumptions. The false discovery rate was corrected using the Benjamini-Hochberg correction method for multiple comparisons.

Statistical significance was defined at $p<0.05$, and all statistical analyses were performed using the STATA software (Version 11.2).

RESULTS

Patients

Between 10 July and 10 December 2020, 40 eligible patients were randomly assigned to receive either the SOC alone (n=20), or the SOC plus tocilizumab (n=20). One patient in the SOC arm and 3 patients in the tocilizumab arm refused to participate in the trial and were excluded (Figure 1). The results of the outcomes were not significantly different from the results of the intention to treat (ITT), according to the analysis per protocol (Data are not presented). The enrollment, randomization, and assignment are summarized in Figure 1.

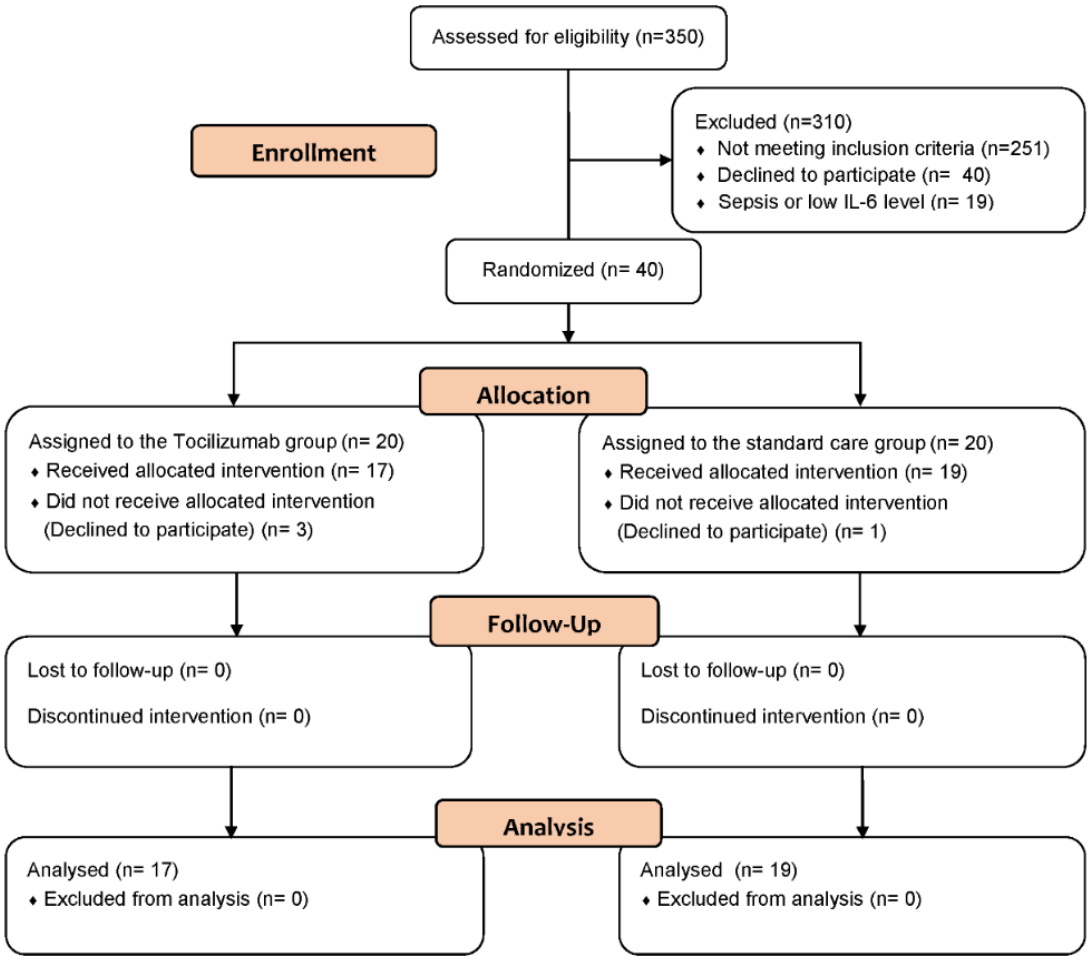

Figure 1. Randomization, enrollment, and treatment assignment

Women comprised 17 (47.2%) and men comprised 19 (52.8%) of the patients. The mean age of all participants was 61.74 ± 14.19 years old. There were no significant differences between the 2 arms regarding their gender (p=0.99) or age (p=0.426). In the tocilizumab group, 12 patients (70.6%) received 1 dose, and 5 patients (29.4%) received 2 doses of tocilizumab. The coexisting conditions and clinical characteristics of the patients at enrollment are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients at baseline

	Characteristic	Total (N=36)	Tocilizumab + SOC (N=17)	SOC (N=19)	*p*
Coexisting conditions	**Age (years)**	61.74 ± 14.19	59.62 ± 15.80	63.52 ± 12.83	0.426
	Male/female (%)	19/17 (52.77%)	9/8 (52.9%)	10/9 (52.6%)	0.99
	BMI	28.28 ± 4.25	29.08 ± 3.32	27.53 ± 4.96	0.29
	Tocilizumab dose 0	19 (52.8%)	-	19 (100%)	NA
	Tocilizumab dose 1	12 (33.3%)	12 (70.6%)	-	
	Tocilizumab dose 2	5 (13.9%)	5 (29.4%)	-	
	Crowded places, n (%)	24/29 (82.7%)	12/13 (92.3%)	12 (75%)	0.343
	Diabetes, n (%)	13 (36.1%)	8 (47%)	5 (26.3%)	0.196
	Hypothyroidism, n (%)	5 (13.9%)	3 (17.6%)	2 (10.5%)	0.650
	Respiratory disorder, n (%)	3 (8.3%)	1 (5.9%)	2 (10.5%)	0.99
	Renal diseases, n (%)	1 (2.8%)	0	1 (5.3%)	0.99
	Cardiovascular diseases, n (%)	16 (44.4%)	7 (41.1%)	9 (47.3%)	0.709
	Hypertension, n (%)	18 (50%)	9 (52.9%)	9 (47.3%)	0.738
	Gastrointestinal symptoms, n (%)	3 (8.3%)	1 (5.9%)	2 (10.5%)	0.99
	Cancer, n (%)	0	0	0	NA
	Autoimmune or neurodegenerative diseases, n (%)	0	0	0	NA
Other COVID-19 treatment	**Hydroxychloroquine, n (%)**	23 (63.9%)	9 (52.9%)	14 (73.3%)	0.196
	Atazanavir, n (%)	5 (13.9%)	3 (17.6%)	2 (10.5%)	0.65
	Corticosteroids, n (%)	12 (33.3%)	5 (29.4%)	7 (36.8%)	0.637
	Interferon, n (%)	1 (2.8%)	1 (5.9%)	0	0.472
	Lopinavir / Ritonavir, n (%)	3 (8.3%)	3 (17.6%)	0	0.095
	Body temperature, °C	37.29 ± 1.14	37.02 ± 1.50	37.51 ± 0.73	0.216
	Respiratory rate, breaths/min	20.25 ± 3.50	21.76 ± 3.81	18.89 ± 2.60	0.015*
	Respiratory rate >24 breaths/min, n (%)	9 (25%)	7 (41.1%)	2 (10.5%)	0.055
	Heart Rate, beats/min	91.94 ± 14.42	90.76 ± 14.92	93.0 ± 14.28	0.649
	Heart Rate >100 beats/min, n (%)	14 (38.9%)	5 (29.4%)	9 (47.3%)	0.27
	Systolic blood pressure, mmHg	127.75 ± 24.95	122.76 ± 24.77	132.21 ± 24.92	0.263
	Diastolic blood pressure, mmHg	74.05 ± 16.59	68.81 ± 17.37	78.47 ± 14.95	0.086
	Dyspnea, n (%)	31 (86.1%)	15 (88.23%)	16 (84.2%)	0.99
	GI Symptom, n (%)	12 (33.3%)	5 (29.4%)	7 (36.8%)	0.637
	Myalgia, n (%)	15 (41.7%)	5 (29.4%)	10 (52.6%)	0.158
	Chest pain, n (%)	5 (13.9%)	3 (17.6%)	2 (10.5%)	0.65
	Cough, n (%)	21 (58.3%)	9 (52.9%)	12 (63.1%)	0.535
	Weakness, n (%)	31 (86.1%)	14 (82.4%)	17 (89.5%)	0.65
	WBC count/µL	6995 ± 2699	7668 ± 2808	6428 ± 2539	0.179

Table 1. Continued...

WBC count	**4–10×10^3/µL, no (%)**	29/35 (82.9%)	13 (81.2%)	16 (84.2%)	0.99
	<4×10^3/µL, no (%)	4/35 (11.4%)	2 (12.5%)	2 (10.5%)	
	>10×10^3/µL, no (%)	2/35 (5.7%)	1 (6.3%)	1 (5.3%)	
	RBC count (×10^6) /µL	4.42 ± 0.932	4.43 ± 1.21	4.42 ± 0.639	0.984
	Lymphocyte count/µL	1079 ± 561	1212 ± 634	910 ± 421	0.188
Lymphocyte count	**800–5000/µL, n/N (%)**	14/25 (56%)	10/14 (71.4%)	4/11 (36.4%)	0.116
	<800/µL, n/N (%)	11/25 (44%)	4/14 (28.6%)	7/11 (63.6%)	
	>5000/µL, n/N (%)	0	0	0	
Platelet count	**Monocyte count/µL**	380.6 ± 224.9	395.8 ± 281.9	359.4 ± 116.5	0.704
	Platelet count/µL	200971 ± 70615	196625 ± 70727	204631 ± 72246	0.744
	<150×10^3/µL, n/N (%)	6/35 (17.1%)	2/16 (12.5%)	4/19 (21.1%)	0.666
	150–450×10^3/µL, n/N (%)	29/35 (82.9%)	14/16 (87.5%)	15/19 (78.9%)	
	>450×10^3/µL, n/N (%)	0	0	0	
VBG	**Neutrophils (%)**	76.24 ± 9.33	75.85 ± 9.98	76.27 ± 8.90	0.823
	Hemoglobin (g/dL)	12.38 ± 2.45	11.89 ± 3.13	12.78 ± 1.66	0.288
	Hematocrit (%)	36.44 ± 6.30	35.44 ± 7.26	37.39 ± 5.30	0.383
	PCO_2 (mmHg)	41.06 ± 8.77	40.06 ± 7.60	41.88 ± 9.78	0.561
	HCO_3 (meq/L)	24.74 ± 5.11	23.20 ± 5.42	26.10 ± 4.56	0.111
	pH	7.38 ± 0.107	7.36 ± 0.152	7.40 ± 0.047	0.224
	ALT (U/L)	37.65 ± 26.43	50.92 ± 34.74	27.33 ± 9.64	0.027*
	AST (U/L)	47.81 ± 18.02	52.64 ± 21.13	44.05 ± 14.71	0.186
	CPK (U/L)	160.3 ± 161.7	148.3 ± 89.9	167.5 ± 195.4	0.785
	FBS mg/dL	135.1 ± 53	139 ± 53.47	132.1 ± 54.31	0.745
	CRP (mg/L)	67.76 ± 40.10	71.78 ± 49.45	64.58 ± 31.98	0.611
	ESR (mm/hr)	56.75 ± 33.47	42.93 ± 28.06	68.27 ± 33.93	0.028*
	Ferritin (ng/mL)	507 ± 469	601.8 ± 653.7	433.3 ± 250.7	0.374
	IL-6 (pg/ml)	437.3 ± 619	622.9 ± 741.9	271.3 ± 440.4	0.471
	D-Dimer (µg/mL)	0.895 ± 0.963	0.69 ± 0.292	1.05 ± 1.25	0.784
	Troponin pg/mL	22.92 ± 55.71	31.73 ± 79.72	15.20 ± 18.87	0.759
	SARS-CoV-2 PCR positive, n (%)	36 (100%)	17 (100%)	19 (100%)	NA
	Procalcitonin negative, n (%)	36 (100%)	17 (100%)	19 (100%)	NA

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CPK, creatine phosphokinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; HCO_3, bicarbonate; LDH: lactic acid dehydrogenase; PCO_2, partial pressure of carbon dioxide; RBC, red blood cell count; SOC, standard of care; U/L, units per liter; VBG, venous blood gas; WBC, white blood cell count; NA, not available; *p value <0.05.

Nine patients (25%) had respiratory rates >24 breaths per minute, and 14 patients (38.9%) had a heart rate >100 beats per minute. Dyspnea, weakness, and cough were the most prevalent symptoms. Except for respiratory rate, which was higher in patients in the tocilizumab arm, there were no substantial differences in clinical features, comorbidity conditions, or standard medical care at enrollment. Furthermore, except for ALT, which was significantly elevated in the tocilizumab group, and ESR, which was notably elevated in the usual care group, we did not observe significant between-group differences regarding laboratory features at enrollment.

The mean blood O_2 saturation level was 84.6 ± 8.92 at the beginning of the study. All patients had peripheral ground-glass opacity on chest radiography at enrollment and the majority had 10% to 30% (38.8%) and 30% to 50% (27.7%) pulmonary involvements. All participants were receiving oxygen support at baseline with the majority (80%) receiving nasal cannulas. The level of pulmonary involvement and CT findings of patients in each group at baseline are summarized in Table 2.

Table 2. Pulmonary involvements at baseline

	Characteristic	Total (N=36)	Tocilizumab + SOC (N=17)	SOC (N=19)	*p*
Type of O_2 therapy, n (%)	**O_2 saturation (%)**	84.6 ± 8.92	84.8 ± 8.21	84.4 ± 9.73	0.881
	O_2 therapy requirement, n (%)	36 (100%)	17 (100%)	19 (100%)	NA
	Nasal cannula	18 (80%)	8 (47.1%)	10 (52.6%)	0.106
	Simple mask	11 (30.6%)	3 (17.6%)	8 (42.1%)	
	Non-rebreather mask	4 (11.1%)	3 (17.6%)	1 (5.3%)	
	Noninvasive ventilation	3 (8.3%)	3 (17.6%)	0	
Pulmonary involvement percent, n (%)	**A (<10%)**	4 (11.1%)	1 (5.8%)	3 (15.8%)	0.788
	B (10–30%)	14 (38.8%)	6 (35.3%)	8 (42.1%)	
	C (30–50%)	10 (27.7%)	5 (29.4%)	5 (26.3%)	
	D (50–70%)	3 (8.3%)	2 (11.8%)	1 (5.3%)	
	E (>70%)	5 (13.8%)	3 (17.6%)	2 (10.5%)	
Radiological properties, n (%)	**Peripheral ground glass**	36 (100%)	17 (100%)	19 (100%)	NA
	Alveolar consolidation	13 (36.1%)	8 (47.1%)	5 (26.3%)	0.196
	Crazy-paving pattern	6 (16.7%)	0	6 (31.6%)	0.020*
	Halo sign	0	0	0	NA
	Reverse halo sign	1 (2.8%)	1 (5.9%)	0	0.472
	Wedge-shaped	1 (2.8%)	0	1 (5.3%)	0.99
	Peribronchial infiltration	13 (36.1%)	7 (41.2%)	6 (31.6%)	0.549

NA, not available; SOC, standard of care; *p value <0.05.

Primary Outcome n Time To Event Analysis

In this study, the primary outcome was clinical improvement. Therefore, the time to recovery was considered as event time, and assuming death as an independent censoring event, the total median hospitalization time was 10 days (95% CI, 8–12). At the end of the study, 12 (71%) of patients in the tocilizumab group and 15 (79%) in the SOC groups were discharged from the hospital (p=0.563). Using the Kaplan-Meier estimator of time to discharge, we showed that during the follow-up time, the hospitalization probability did not significantly differ between the tocilizumab and SOC arms (log-rank test, p=0.615; Figure 2). Furthermore, the crude discharge risk was 17% lower in tocilizumab in comparison with the SOC group (hazard ratio [HR], 0.83; 95% CI, 0.39–1.78). Since the distribution of respiratory

rate, crazy-paving pattern, ALT, and ESR levels were not well-balanced between the two groups, the multiple Cox regression model was used to adjust for the effects of these potential confounders. The results in Table 3 showed that the adjusted discharge risk in the tocilizumab group was 1.90 times the SOC group (HR, 1.90; 95% CI, 0.63–5.75).

We also did not observe a significant difference in the time to improvement between participants assigned to either group (median (Q1, Q3): 10 (8, 15) days vs. 9 (6, 19) days; p=0.490).

The number of patients in each oxygen support group at baseline and after 3 to 5 days of starting the treatment and the primary outcomes are shown in Figure 3.

We did not observe a significant difference in mortality based on the type of oxygen therapy. Of the deceased patients, 55.5% (2 patients in the control arm and 3 patients in the tocilizumab arm) had pulmonary involvements of>70%, and 22% had pulmonary involvements between 50% and 70% (1 patient in each group).

Table 3. Crude and adjusted effect of tocilizumab on the improvement of patients

Group	Recover n=27	Death n=9	Crude HR (95% CI)	*p*	Adjusted HR (95% CI)	*p*
Tocilizumab + SOC	12 (44%)	5 (56%)	0.83 (0.39–1.78)	0.629	1.90 (0.63–5.75)	0.256
SOC	15 (56%)	4 (44%)				

HR: hazard ratio.

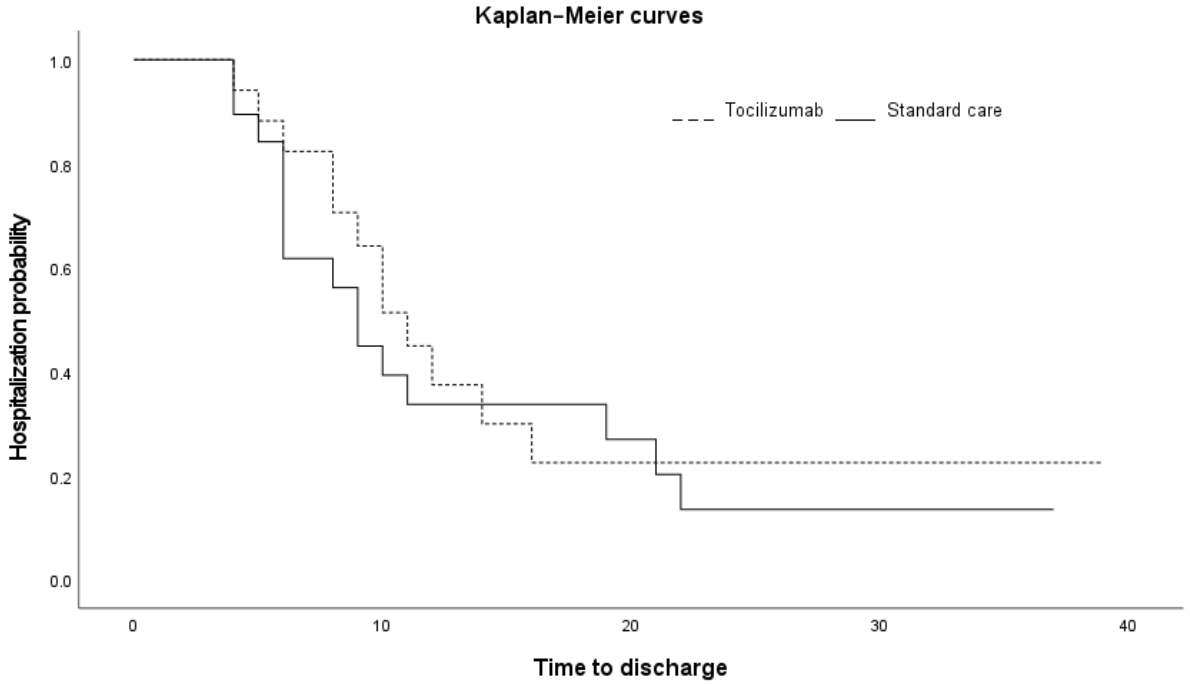

Figure 2. Kaplan-Meier curves for statistical comparison of time to discharge between groups (p=0.615).

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		Number of patients in oxygen support group at baseline (%)									
		Tocilizumab group					Standard care group				
		NIV (3)	Reserve Mask (3)	Simple Mask (3)	Nasal Cannula (8)	Negative (0)	NIV (0)	Reserve Mask (1)	Simple Mask (8)	Nasal Cannula (10)	Negative (0)
Number of patients in oxygen support group after 3-5 days of treatment (%)	Invasive Ventilation	1 (33.3%)	0	0	0	0	0	0	1 (12.5%)	0	0
	NIV	1 (33.3%)	1 (33.3%)	0	1 (12.5%)	0	0	0	1 (12.5%)	1 (10.0%)	0
	Reserve Mask	1 (33.3%)	0	0	0	0	0	1 (100%)	2 (25.0%)	0	0
	Simple Mask	0	1 (33.3%)	1 (33.3%)	0	0	0	0	3 (37.5%)	0	0
	Nasal Cannula	0	1 (33.3%)	1 (33.3%)	5 (62.5%)	0	0	0	1 (12.5%)	7 (70.0%)	0
	negative	0	0	1 (33.3%)	2 (25.0%)	0	0	0	0	2 (20.0%)	0
Outcome	Discharged	2 (66.6%)	2 (66.6%)	3 (100%)	5 (62.5%)	0	0	0	6 (75.0%)	9 (90.0%)	0
	Death	1 (33.3%)	1 (33.3%)	0	3 (37.5%)	0	0	1 (100%)	2 (25.0%)	1 (10.0%)	0

Figure 3. The patient's status regarding their oxygen support before and after tocilizumab treatment and the main outcome of each group. For each oxygen-support category (invasive ventilation, noninvasive ventilation (NIV), reservoir mask, simple mask, and nasal cannula), percentages were calculated with the number of patients at baseline and after 3 to 5 days of treatment in both groups. Improvement (green cells), no change (blue), and worsening (orange) in oxygen-support status are shown.

Secondary Outcome

The level of the participants' blood O_2 saturation substantially improved by 3 to 5 days into the treatment in both the tocilizumab (p=0.001) and SOC groups (p=0.002). Although body temperature was reduced in both groups after 3 to 5 days of treatment, the reduction was only significant in patients in the SOC arm. We did not observe significant differences in blood pressure, heart rate, or respiratory rate before and after 3 to 5 days of treatment, after which the number of patients with dyspnea significantly reduced in both the tocilizumab (p=0.012) and SOC (p=0.031) treatment groups. However, we did not observe significant beneficial effects of tocilizumab on the reduction of gastrointestinal symptoms, myalgia, and cough in patients, and the symptoms were significantly improved only in the SOC group. The clinical features of participants before and after treatment are summarized in Table 4.

Four of the 17 patients in the tocilizumab arm and 2 of the 19 patients in the SOC arm did not need oxygen supplements after 3 to 5 days of treatment. Oxygen support status improved in 7 of the 17 patients (41.1%) in the tocilizumab arm and 3 of the 19 patients in the control arm (15.7%) (Figure 3).

Laboratory Findings

The hemoglobin level was markedly reduced in the control group of patients 3 to 5 days after starting the treatment (p=0.002) and at discharge (p=0.025). Furthermore, the hematocrit was diminished at discharge in patients who received SOC. In contrast, the level of hemoglobin and hematocrit did not change in patients in the tocilizumab group. Tocilizumab also reduced the neutrophil percentage in patients; nevertheless, we did not detect a significant reduction in the percentage of neutrophils in patients who received SOC. In addition, although tocilizumab reduced IL-6 levels, the reduction was not significant. Except for hemoglobin and hematocrit levels, we did not detect significant differences in the other laboratory parameters in either group (Table 5).

Table 4. Clinical characteristics of patients before and after treatment measurements in each group

Characteristic	Before Treatment		After Treatment (Days 3–5)			
	Tocilizumab + SOC	SOC	Tocilizumab + SOC	*p*	SOC	*p*
	Mean ± SD	Mean ± SD	Mean ± SD		Mean ± SD	
O_2 saturation (%)	84.8 ± 8.21	84.4 ± 9.73	89.06 ± 6.89	0.001*	88.0 ± 10.05	0.002*
Systolic blood pressure, mmHg	122.76 ± 24.77	132.21 ± 24.92	121.4 ± 10.66	0.415	129.4 ± 18.46	0.526
Diastolic blood pressure, mmHg	68.81 ± 17.37	78.47 ± 14.95	72.0 ± 8.96	0.734	77.0 ± 12.45	0.668
Heart rate, beats/min	90.76 ± 14.92	93.0 ± 14.28	80.5 ± 24.32	0.077	88.47 ± 15.06	0.056
Respiratory rate, breaths/min	21.76 ± 3.81	18.89 ± 2.60	20.43 ± 4.56	0.211	18.15 ± 1.92	0.125
Body temperature, °C	37.02 ± 1.50	37.51 ± 0.73	36.8 ± 0.42	0.547	37.04 ± 0.32	0.007
	n (%), N=17	n (%), N=19	n (%), N=16	*p*	n (%), N=19	*p*
Dyspnea	15 (88.23)	16 (84.2)	6 (37.5)	0.012*	10 (52.6)	0.031*
Gastrointestinal symptoms	5 (29.4)	7 (36.8)	2 (12.5)	0.25	1 (5.3)	0.031*
Myalgia	5 (29.4)	10 (52.6)	1 (6.3)	0.125	3 (15.8)	0.016*
Chest pain	3 (17.6)	2 (10.5)	0	0.25	0	0.50
Cough	9 (52.9)	12 (63.1)	4 (25)	0.063	6 (31.6)	0.031*
Weakness	14 (82.4)	17 (89.5)	13 (81.3)	0.99	13 (68.4)	0.125
O_2 therapy requirement	17 (100)	19 (100)	14 (87.5)	0.103	17 (89.4)	0.486

**p value* <0.05, *p value* was calculated based on the after-treatment and before-treatment measurements in each of the studied groups; NA, not available; SOC, standard of care.

Table 5. Laboratory findings of patients before and after treatment in each group

Characteristic	Before Treatment		After Treatment (Days 3–5)				After Treatment (Discharge or Death)			
	Tocilizumab + SOC	SOC	Tocilizumab + SOC	*p*	SOC	*p*	Tocilizumab + SOC	*p*	SOC	*p*
	Mean ± SD	Mean ± SD	Mean±SD		Mean ± SD		Mean ± SD		Mean ± SD	
ALT (U/L)	50.92 ± 34.47	27.33 ± 9.64	57.85 ± 34.08	0.686	-	NA	61.6 ± 31.98	0.893	-	NA
AST (U/L)	52.64 ± 21.13	44.05 ± 14.71	47.14 ± 12.30	0.042*	-	NA	48 ± 19.83	0.50	-	NA
CPK (U/L)	148.3 ± 89.9	167.5 ± 195.4	130 ± 142.8	0.655	-	NA	-	NA	-	NA
FBS mg/dL	139 ± 53.47	132.1 ± 54.31	166.6 ± 62.82	0.686	-	NA	-	NA	-	NA
CRP (mg/L)	71.8 ± 49.45	64.58 ± 31.98	46.5 ± 48.09	0.155	40.38 ± 38.86	0.075	33.75 ± 27.18	0.068	40.66 ± 38.18	0.075
ESR (mm/hr)	42.9 ± 28.06	68.3 ± 33.9	66.2 ± 50.0	0.273	61.14 ± 31.06	0.753	41.5 ± 10.60	0.317	32.5 ± 10.6	0.317
Ferritin (ng/mL)	601.8 ± 653.7	433.3 ± 250.7	1026 ± 1217	0.207	762.4 ± 720	0.136	581 ± 226.4	0.066	553.6 ± 283.6	0.715
IL-6 (pg/mL)	622.9 ± 741.9	271.3 ± 440.6	251.1 ± 163.2	0.198	90.5 ± 75.87	0.062	220.2 ± 95.03	0.893	121.7 ± 96.11	0.99
D-Dimer (µg/mL)	0.69 ± 0.29	1.05 ± 1.25	1.43 ± 1.42	0.345	0.72 ± 0.49	0.735	1.85 ± 1.62	0.655	0.95 ± 0.64	0.99
Troponin	31.7 ± 79.7	15.20 ± 18.87	60.2 ± 43.32	0.514	25.2 ± 14.84	0.929	118.8 ± 113.3	0.99	65.1 ± 45.1	0.99
WBC count/MCL	7668 ± 2808	6428 ± 2539	10574 ± 8758	0.125	7716 ± 3882	0.396	8990 ± 5297	0.99	6984.6 ± 2530.3	0.807
RBC percent	4.43 ± 1.21	4.42 ± 0.64	4.61 ± 0.88	0.887	4.20 ± 4.15	0.067	4.58 ± 1.16	0.833	4.11 ± 0.80	0.152
Platelet count (×1000/MCL)	196.62 ± 70.72	204.63 ± 72.24	233.68 ± 85.61	0.191	234.15 ± 104.19	0.184	248.0 ± 88.41	0.263	270.23 ± 97.82	0.075
Hemoglobin (gm/dL)	11.89 ± 3.13	12.78 ± 1.66	12.5 ± 2.18	0.807	11.78 ± 1.50	0.002*	12.04 ± 2.65	0.944	11.59 ± 1.56	0.025*

Table 5. Continued...

Hematocrit (%)		35.44 ± 7.26	37.39 ± 5.30	38.6 ± 5.10	0.245	34.36 ± 3.73	0.099	36.45 ± 7.59	0.575	33.03 ± 3.13	0.017*
Neutrophil (%)		75.85 ± 9.98	76.27 ± 8.90	74.93 ± 14.10	0.814	80.66 ± 9.56	0.477	66.85 ± 14.26	0.042*	80.71 ± 7.02	0.397
Lymphocyte count/µL		1212 ± 634.3	910.3 ± 421.4	1385 ± 687.1	0.917	891.5 ± 446.9	0.878	1530.3 ± 719.5	0.225	887.8 ± 425.5	0.99
Monocyte count		395.8 ± 281.9	359.4 ± 116.5	571.2 ± 500.6	0.182	331.9 ± 208.1	0.917	452.1 ± 132.4	0.686	389.6 ± 220.1	0.686
VBG	**pH**	7.36 ± 0.15	7.40 ± 0.047	7.32 ± 0.14	0.213	7.40 ± 0.059	0.842	7.41 ± 0.047	0.173	7.39 ± 0.03	0.238
	HCO_3 (mEq/L)	23.20 ± 24.20	26.10 ± 4.56	26.34 ± 6.89	0.328	25.98 ± 3.94	0.955	26.34 ± 11.97	0.345	28.02 ± 3.71	0.388
	PCO_2 (mmHg)	40.06 ± 7.60	41.88 ± 9.78	49.8 ± 13.72	0.099	42.23 ± 7.98	0.776	46.57 ± 9.50	0.750	43.95 ± 8.02	0.463

*p value <0.05; the p values were calculated based on the after-treatment measurements compared with the before-measurement (as a reference) in each studied group. ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FBS, fasting blood sugar; HCO_3, bicarbonate; LDH, lactate dehydrogenase; PCO_2, partial pressure of carbon dioxide; RBC, Red blood cell; SD, standard deviation; U/L, units per liter; VBG, venous blood gas; WBC, white blood cell; NA, not available.

Safety

Although we did not see serious adverse events in the usual care arm, a total of 3 patients (17.6%) in the tocilizumab arm showed serious side events between the initiation of the intervention and the end of the trial. Two patients in the tocilizumab arm developed cardiogenic shock, while 1 patient developed both an infection and cardiogenic shock. The patients received antibiotics and inotrope agents. Of these 4 adverse events, 3 were considered to be related or possibly related, and 1 was considered unrelated to intervention by the site investigators. Table 6 displays all serious adverse events.

Table 6. Summary of adverse events in patients

Adverse Event	Tocilizumab + SOC (N=17)	SOC (N=19)	*p*
Infection, n (%)	1 (5.9%)	0	0.472
Edema, n (%)	0	0	NA
Cardiogenic shock, n (%)	3 (17.6%)	0	0.095
Kidney failure, n (%)	0	0	NA
Gastrointestinal bleeding, n (%)	0	0	NA

NA: not applicable; SOC, standard of care.

DISCUSSION

Critically ill COVID-19 patients commonly exhibit elevated levels of serum IL-6, which correlates with the severity of their illness.[1,6,12] The administration of IL-6 receptor inhibitors might prevent the progression of cytokine storms in COVID-19 patients in the pulmonary stage. Here, we aimed to investigate the effects of tocilizumab administration, as an IL-6 receptor blocker, on the treatment and clinical and laboratory characteristics of hospitalized COVID-19 patients. We did not find beneficial effects for tocilizumab administration in the treatment of severe COVID-19 patients. Although tocilizumab administration improved the oxygen support status of more patients in the intervention arm, it could not extend survival time, reduce mortality rate, or decrease the time to improvement. Except for the significant effects of tocilizumab treatment on the maintenance of hemoglobin levels and the reduction of neutrophil percentage in patients, we did not find any therapeutic effects of tocilizumab on the improvement of clinical and laboratory characteristics of patients. Similar to our results, previously, the effect of tocilizumab on the improvement of anemia and reduction of the neutrophil count was shown in patients with rheumatoid arthritis.[20,21]

Several observational and cohort studies have investigated the effect of tocilizumab on COVID-19 and reported contradictory results regarding its treatment efficacy.[14-17] In a case-control study by Marte et al, on severe to critical COVID-19 patients who received tocilizumab, no difference was observed in the mortality rate. However, they found that the treatment could reduce mortality in non-intubated patients.[14] Knorr et al, in an observational study, reported limited improvement effects for tocilizumab. In their study, 42% of patients receiving tocilizumab expired, and 49% improved.[17]

In contrast to our results, Rossotti et al, found tocilizumab to be potentially effective for COVID-19 patients and improve overall survival.[15] Moreover, results from an observational cohort of patients with severe COVID-19 pneumonia showed that intravenous or subcutaneous tocilizumab could reduce mortality and intubation rates.[22] A prospective study by Xu et al, also observed an immediate improvement with tocilizumab in clinical outcomes in COVID-19 patients, including fever, oxygen requirement, lymphocyte counts, and CRP levels.[23] In another cohort study,[24] tocilizumab was associated with reduced mortality but increased reinfection rates in intubated COVID-19 patients. An observational study by Jordan et al, showed the beneficial effects of tocilizumab in reducing COVID-19-associated mortality, inflammation, and oxygen support.[25]

Other studies include the RECOVERY clinical trial,[26] which evaluated the effects of intravenously 400 mg to 800 mg tocilizumab on 4116 hospitalized COVID-19 patients with systemic inflammation. In contrast to our results, they reported that tocilizumab improved clinical and survival outcomes. Tocilizumab improved clinical and survival outcomes, increasing the likelihood of patients being discharged from the hospital alive and reducing the risk of progression to requiring intubation or death.

Another clinical trial by Stone et al, assessed the effect of tocilizumab administration on 243 moderately ill hospitalized COVID-19 patients in hyperinflammatory states who were not intubated. In line with our results, they did not find tocilizumab to be an effective treatment for preventing death or mechanical invasive ventilation in patients.[27]

In line with our study, Veiga et al, conducted a clinical trial on 129 COVID-19 patients who received oxygen support or mechanical ventilation. They also did not observe a superior effect of tocilizumab compared to SOC in improving clinical features. Furthermore, they found an increase in the mortality rate in patients receiving tocilizumab.[28] Moreover, using systemic immunosuppression or a combination of various therapeutic agents might be more efficient than blocking a specific cytokine pathway.[29,30]

The effect of tocilizumab may vary in different populations based on the genetics of the studied population. The limitations of our study were probable biases including the shortness of the follow-up period and a small sample size. Therefore, further clinical trials on patients in different disease stages of COVID-19 and different populations are needed to determine the exact therapeutic effect of tocilizumab.

The results of this randomized, controlled, double-blind clinical trial showed no significant effect of tocilizumab intervention on the treatment of non-intubated, severe COVID-19 patients who had elevated IL-6 levels. Therefore, tocilizumab treatment is unlikely to change the recovery rate, survival time, or time to improvement significantly in COVID-19 patients.

STATEMENT OF ETHICS

This study was performed based on the Declaration of Helsinki guidelines and was approved by the ethics committee at the Tehran University of Medical Sciences (Approval ID:IR.TUMS.VCR.REC1399.290).

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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