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

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Research

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Abstract

Background

Severe COVID-19 is associated with an increased level of blood IL-6. It is suggested that adjusting the IL-6 level or its effects may diminish the inflammation of the airway and alter the course of the disease.

Methods

We performed a controlled, randomized, double-blind clinical trial including severe hospitalized COVID-19 patients in Iran. The patients were randomly distributed by block randomization to take usual care plus IL-6 inhibitor (tocilizumab 8mg/kg, 1 or 2 dosages) or usual care alone (ratio 1:1). The endpoint was defined by the clinical improvement and discharge or death. Main and safety analysis was performed in the overall population.

Results

We enrolled 40 eligible patients (20 patients in each group) from July 10, till October 10, 2020, in this study. After randomization, one patient in the usual care arm and three patients in the tocilizumab arm refused to participate in the study and were eliminated from the study and overall analysis. The mean age of participants was 59.62 ± 15.80 and 63.52 ± 12.83 years old in Tocilizumab (8 women and 9 men) and standard care (9 women and 10 men) groups respectively (P -value= 0.426). The number of recovered patients did not significantly differ between tocilizumab and usual care groups (70.6% (n=12) vs 78.9% (n=15) respectively) (P -value=0.563). Also, the survival time was not significantly varied between participants in the tocilizumab intervention and usual care group [Log rank test: $P=0.973$; Hazard ratio: 1.25; 95% CI: 0.249-4.209].

Conclusion

The study results recommended that tocilizumab could not be a beneficial agent for treating severe cases of COVID-19 patients and have not significantly affected patients' clinical improvement.

Clinical trial registration

This trial was registered in the Iranian Registry of Clinical Trials on 9 July 2020 (ID: IRCT20081027001411N4) (<https://www.irct.ir/trial/48396>).

Background

Severe acute respiratory syndrome coronavirus (SARS-CoV)-2 that generates a pandemic of coronavirus disease 2019 (COVID-19) viral infection, has threatened human health and become a global concern since its emergence in late 2019 (1). COVID-19 presentations may range from light upper respiratory involvements to severe pneumonia that is characterized by immunological abnormalities, hyper-inflammation, and cytokine storm (2-4). Cytokine storm or excessive release of inflammatory cytokines leads to lethal organ damages, lung fibrosis, acute respiratory distress syndrome (ARDS), and even patients' death (5).

It has been demonstrated that the level of serum interleukin (IL)-10, IL-8, IL-6, and tumor necrosis factor (TNF) was remarkably increased in severe or deceased patients compared to moderate or recovered cases (1, 6). IL-6 is a pro-inflammatory and pro-fibrotic cytokine that produce by immune cells including monocytes and lymphocytes as well as fibroblasts and bronchial epithelial cells and participates in the pathogenesis of lung fibrosis (7-9). It is found that IL-6 serum level in critically ill patients is almost 10 times more than in moderate cases (10). The elevated level of serum IL-6 is positively correlated with the SARS-CoV-2 RNAemia (10), need for intubation (11), and disease severity stages of patients (12) and can be used as prognostic and diagnostic markers for COVID-19 severity. Therefore, it is suggested that administration of IL-6 signaling inhibitors might have efficient effects on the resolution of cytokine storm and treatment of individuals affected with COVID-19 who are in the pulmonary stage. Tocilizumab is a monoclonal antibody to the IL-6 receptor and is mainly used for the treatment of rheumatic disease (13). There are contradictory results regarding tocilizumab efficacy on COVID-19 patients (14-17). Therefore, in this randomized controlled trial (RCT), we investigated the effects of tocilizumab administration on the recovery, oxygen therapy, clinical and laboratory features of COVID-19 inpatients.

Patients And Methods

2.1. Trial design

This research is a double-blind, randomized, two-arm parallel, phase-2, controlled trial that was performed from July 10 till October 10, 2020. 40 cases from Imam Khomeini and Shariati Hospital, Tehran University of Medical Sciences (TUMS) were included in this research. The trial protocol has been designed and mediated in adherence 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. According to the contradictory results about the effect of tocilizumab on COVID-19 patients, the lowest sample size with a 10% drop-out rate was estimated 40 patients according to the effect size of

tocilizumab on the pulmonary disease (19). The trial was conducted under the Declaration of Helsinki guidelines and was agreed by the Ethics Committee of the Tehran University of Medical Science (Approval Number: IR.TUMS.VCR.REC1399.290).

2.2. Participants

The confirmation of COVID-19 infection in patients was confirmed by the following specifications: 1. Confirmation of SARS-CoV-2 in nasopharyngeal swab via polymerase chain reaction (PCR) and 2. Atypical computed tomography (CT) features (subpleural, bilateral, peripheral ground-glass opacity). 18 years or older patients were eligible for enrollment in the trial if they [complied with the following conditions](#): 1. Confirmed COVID-19 infection; 2. Elevated C-reactive protein (CRP higher than 10mg/L) or IL-6 (higher than 18 pg/ml) or lymphopenia (lymphocyte count under 1100/ MCL); 3. At the pulmonary stage of the disease with blood oxygen saturation <93% or respiratory rate (RR) higher than 24; 4. Not connecting to the mechanical ventilator; 5. Not responding to standard COVID-19 treatment. All participants provided informed consent before enrollment. Patients were not eligible for enrollment in the trial if they [complied with the following conditions](#): 1. Were allergic or intolerant to any therapeutic factors used in this study; 2. With positive pro-calcitonin (PCT) and had an active infection (including latent or active tuberculosis (TB) infection); 3. Had a history of receiving immunosuppressive drugs and corticosteroids; 4. With a history of active malignancies.

2.3 Randomization and treatment

Eligible patients (one or two days after hospitalization) were randomly distributed to the control and intervention groups by block randomization (1:1 ratio). One patient in the standard care arm and three patients in the tocilizumab arm refused to participate and were excluded from the study and overall analysis before baseline measurements. Patients allocated to receive usual care alone or usual care plus 8mg/kg tocilizumab, (Actemra, Roche) (if the patient's conditions were not stable, 2 doses by 12 hours were administrated, maximum dose: 800 mg). All patients received usual care for the disease based on the Iranian protocol for diagnosis and treatment of COVID-19. The major standard medical cares that were received by COVID-19 patients are summarized in Table 1. In this study, patients, investigators, and outcome assessors did not inform which group received an intervention. Besides, a placebo was not used in the control group.

2.4. Outcome

The clinical, demographic, and laboratory data of the patients were recorded before their enrollment. Participants were followed through day 0 to 5, improvement, discharge, or death. The primary outcome was improvement and discharge or death after administration of intervention whichever came first. The 28 days' mortality rate, time to improvement, and time to the event were also evaluated in each group.

Clinical characteristics of the patients such as RR, heart rate (HR), blood pressure, fever, and general symptoms including gastrointestinal involvement (GI), thorax pain, dyspnea, cough, weakness, and myalgia were assessed at enrollment and after 3-5 days of starting the treatment. Besides, the degree of oxygen saturation (SO₂) and the necessity and type of oxygen supports including 1. Nasal cannula, 2. Simple oxygen mask, 3. Reservoir mask, 4. Noninvasive ventilation (NIV) and 5. Invasive ventilation were assessed at enrollment and after 3-5 days of starting the intervention. CT scan findings including pulmonary involvement percent and radiological properties were also evaluated at baseline and 6 weeks after treatment (only in participants who consented). Laboratory examinations to assess the level of complete blood count (CBC), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) liver enzymes, CRP, erythrocyte sedimentation rate (ESR), fasting blood sugar (FBS), vein blood gas (VBG) (containing PH, the partial pressure of carbon dioxide (PCO₂), and bicarbonate (HCO₃)), IL-6, D-dimer, troponin, creatine phosphokinase (CPK) and ferritin were done at baseline and by 3-5 days of starting the treatment and also at hospital discharge time.

Improvement and discharge were determined by the patients' clinical, general, and laboratory conditions and were determined by consciousness, ameliorated dyspnea, stopped fever for 3 days, SO₂ upper than 93%, normal range of urinary output, tolerated oral regimen (PO), blood pressure more than 10 millimeters of mercury (mm Hg), a respiratory rate less than 20 breaths per minute, heart rate less than 90 beats per minutes, and reduced CRP amount and no any other side effects. All data were assessed during the study were registered on case report forms (CRFs) and the Excel database.

2.5. Side events

All unfavorable adverse effects experienced by participants during this trial, whether or not related to tocilizumab intervention, were assessed and stored.

2.6. Statistical analysis

All continuous variables were reported as the mean $\pm$ standard deviation (SD) and categorical variables are expressed as N (%). The Kolmogorov-Smirnov (K-S) normality test was used for continuous variables. Repeated measures ANOVA was performed for comparison between both groups over time. Besides, Mann Whitney or Student's t-tests was applied to assess the statistical contrasts between two arms in each time point. Moreover, Wilcoxon signed-rank or paired t-tests was performed to test for statistical comparison between two-time points in each of the studied intervention arms. Two-sided Chi-square/Fisher's exact tests were applied to test the associations between two intervention

arms and the categorical variables. To analyze and draw the time-to-death curve between two intervention arms, Kaplan–Meier curve and the log-rank test were applied. Using the Benjamini-Hochberg correction method for multiple comparisons, the false discovery rate was corrected. Statistical significance was defined at $p < 0.05$ and all statistical analysis was done by STATA software (Versions 11.2).

Results

3.1. Patients

Between July 10 to October 10, 2020, 40 eligible patients were randomly assigned to receive usual care plus tocilizumab ($n=20$), or usual care alone ($n=20$). One patient in the standard care arm and 3 patients in the tocilizumab arm refused to participate in the trial and were excluded from the study and overall analysis. The results for the outcomes were not significantly distinct from the results of intention to treat (ITT), according to the analysis per protocol. The patients' enrollment, randomization, and assignment are summarized in Figure 1. The mean age of participants was 61.74 ± 14.19 years old (19 (52.8%) men and 17 (47.2%) women). There are no notable differences between the two arms regarding their sex and age ($P=0.99$ and $P=0.426$ respectively). In the tocilizumab group, 12 patients (70.6%) received one dose and 5 patients (29.4%) received two doses of tocilizumab. The coexisting conditions and clinical characteristics of patients at enrolment were shown in Table 1. Nine patients (25%) had RR upper than 24 breaths per minute and 14 patients (38.9%) had an HR of more than 100 beats per minute. Dyspnea, weakness, and cough were the most prevalent symptoms in patients. Except for RR which was higher in patients of the tocilizumab arm, there were no substantial between-group differences in clinical features, comorbidity conditions, and administrated standard medical care at enrollment. Besides, 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 enrolment.

The average blood SO_2 level was 84.6 ± 8.92 at baseline. All of the patients had peripheral ground-glass opacity at enrollment and the majority of them had 10-30% (38.8%) and 30-50% (27.7%) respiratory involvements respectively. All participants were receiving oxygen supports at baseline and the majority of them (80%) were received nasal cannula. Pulmonary involvement level and CT scan findings of patients in each group at baseline were summarized in Table 2.

3.2. Primary outcome

Mortality at 28 days was not considerably different between patients in the tocilizumab arm and standard care, with death reported in 5 (29.4%) and 4 (21.1%) patients respectively (Table 3). performing Kaplan–Meier estimator of time to death (day), we showed that the survival time was not significantly varied between patients in the tocilizumab intervention arm and usual care arm [Log rank test: $P=0.973$; Hazard ratio: 1.25; 95% CI: 0.249-4.209] (Figure 2).

We also did not observe a major difference in the time to event (improvement, or death) between participants assigned to the tocilizumab and standard care arms (median, 12.88 ± 9.05 days vs 12.05 ± 8.92 days; $P=0.784$). Also, the time to improvement was not considerably different between the two arms (median, 9.42 ± 3.55 days in the tocilizumab group vs 9.73 ± 6.05 days in the usual care group; $P=0.874$) (Table 3).

The number of patients in each oxygen support group at baseline and after 3-5 days of starting the treatment and the primary outcomes of them in both standard care and tocilizumab arms were shown in Supplementary Figure 1. We did not observe notable differences in the incidence of death according to the type of oxygen therapy in patients. Of the dead patients, 55.5% (2 patients in the control arm and 3 patients in the tocilizumab arm) had pulmonary involvement percent more than 70%, and 22% had pulmonary involvement percent between 50 to 70% (one patient in each group).

3.3. Secondary outcome

The level of participants' blood SO_2 was substantially ameliorated by 3-5 days of treatment in both groups ($P=0.001$ and $P=0.002$ in the tocilizumab and standard care respectively). Although the body temperature was reduced in both groups after 3-5 days of treatment, the reduction was only significant in patients in the usual care arm. We did not observe significant differences in the blood pressure HR and RR before and after 3-5 days of treatment in patients of both arms. After 3-5 days of starting the treatment, the number of patients suffered from dyspnea was significantly reduced in both the tocilizumab and standard care treatment group ($P=0.012$ and $P=0.031$ respectively). However, we did not observe significant beneficial effects of tocilizumab on the reduction of GI symptoms, myalgia, and cough in patients, and the symptoms only were significantly improved in the usual care arm. Clinical features of participants before and after treatment were summarized in Table 4.

4 of 17 patients in the tocilizumab arm and 2 of 19 patients in the standard care arm did not need oxygen supplement by 3-5 days of treatment. The oxygen support status was improved in 7 of 17 patients (41.1%) in the tocilizumab arm and 3 of 19 patients in the control arm (15.7%) (Figure S1).

3.4. Laboratory findings

The hemoglobin level was notably reduced in the control group of patients by 3-5 days of starting the treatment and also at discharge time ($P=0.002$ and $P=0.025$ respectively). Besides, the hematocrit percentage was diminished in patients who received standard care treatment at discharge time. While the level of hemoglobin and hematocrit percentage did not change in patients of the tocilizumab group. Tocilizumab also reduced neutrophil percentage in patients, nevertheless, we did not detect a significant reduction in the percentage of neutrophil in patients who received standard care. Besides, although tocilizumab reduced IL-6 level, the reduction was not significant. Except for hemoglobin and hematocrit levels, we did not detect any significant differences in the level of laboratory characteristics of patients during treatment in either group (Table 5).

3.5. Safety

Although we did not see serious adverse events in the usual care arm, a total of three patients (17.6%) in the tocilizumab arm showed serious side events between initiation of intervention and the end of the trial. Shock and infection developed in three and one patient in the tocilizumab arm respectively. Of these four adverse events, 3 were considered to be related or possibly related and one was considered to be unrelated to intervention by the site investigators. All serious adverse events are shown in Supplementary Table 1.

Discussion

It has been found that the level of serum IL-6 is elevated in critically ill COVID-19 patients and it is correlated with the severity of illness in patients (1, 6, 12). It is suggested that administration of IL-6 receptor inhibitor might prevent the progression of cytokine storm in COVID-19 patients who are in the pulmonary stage. Therefore, we aimed to investigate the effects of tocilizumab administration as an IL-6 receptor blockage, on the treatment and clinical and laboratory characteristics of hospitalized COVID-19 patients. We did not find beneficial effects for the administration of tocilizumab in the treatment of severe COVID-19 patients in our RCT. Although tocilizumab administration improved the oxygen support status of more patients in the intervention arm compared to the control arm by 3-5 days of treatment, it could not improve the survival time, reduce the mortality rate and decrease the time to discharge in the intervention group. Except for the significant effects of tocilizumab treatment on the maintenance of hemoglobin level and the reduction of neutrophil percent in patients, we did not find any therapeutic effects of tocilizumab on the improvement of clinical and laboratory characteristics of patients. Same as our results, previously the effect of tocilizumab on the improvement of anemia and reduction of the neutrophil count has been shown in rheumatoid arthritis (RA) patients (20, 21).

Some observational and cohort studies investigated the effect of tocilizumab on COVID-19 patients 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 in mortality rate has been found in all studied patients. However, they found that the treatment can reduce the mortality rate in non-intubated patients (14). PharmD et al., in an observational study, reported limited improvement effects for tocilizumab. In their study, from patients who received tocilizumab, 42% were expired and 49% were improved (17).

In contrast to our results, Rossotti et al. found tocilizumab as potentially effective care for COVID-19 patients which was associated with improved overall survival in patients compared to controls.(15) Moreover, results from an observational cohort research on patients with severe COVID-19 pneumonia showed that intravenous or subcutaneous tocilizumab may reduce the risk of mortality and the risk of intubation in patients (22). Xu et al. also prospectively observed tocilizumab effects on treating COVID-19 patients. They found that tocilizumab improved clinical outcomes including fever, oxygen intake, lymphocytes percentage, and CRP level immediately in patients (23). Besides, in a Cohort study by Somers et al., tocilizumab administration was associated with reduced mortality rate and increased reinfection occurrence in intubated COVID-19 patients (24). Moreover, according to the observational study by Jordan et al., tocilizumab might offer beneficial effects in reducing COVID-19 associated mortality, inflammation, and oxygen supports in patients (25).

Although there are several observational studies regarding the use of tocilizumab on the treatment of COVID-19 affected individuals, some randomized controlled clinical trials are required to determine the exact effect of treatment. Except for this study, there are other clinical trials regarding the effect of tocilizumab on COVID-19. In the RECOVERY trial by Horby et al., the effect of intravenously 400 mg to 800 mg tocilizumab was evaluated on 4116 hospitalized COVID-19 patients with systemic inflammation. In contrast to our results, they reported that tocilizumab treatment improved clinical characteristics and survival outcomes in patients. Patients who received tocilizumab had an increased chance of discharged from the hospital alive and a reduced chance of progressing to require intubation or death (26). In another clinical trial by Stone et al., the effect of tocilizumab administration was assessed on 243 moderately ill hospitalized COVID-19 patients at hyperinflammatory states who were not intubated. In line with our results, they did not find tocilizumab an effective treatment for preventing death or mechanical invasive ventilation in patients (27). in compliance with our study, Veiga et al. conducted a clinical trial on 129 COVID-19 patients who received support oxygen or mechanical ventilation. They also did not observe a superior effect for tocilizumab compared to standard care in improving clinical features. Besides, their result showed that tocilizumab may increase the mortality rate in patients (28).

Our study also has some limitations and weaknesses such as the possible existed bias, lack of placebo, and low sample size. Therefore, to determine the exact therapeutic effect of tocilizumab on COVID-19 patients, more clinical trials on COVID-19 patients on different disease stages are needed.

Conclusions

Our results in this randomized, controlled, double-blind clinical trial showed no significant effect for tocilizumab intervention on the treatment of non-intubated, severe COVID-19 patients who had elevated IL-6 levels. Tocilizumab treatment did not significantly change recovery rate, survival time, and time to event in affected individuals. Regarding the positive effects of corticosteroids administration on COVID-19 patients(29, 30), it seems that using systemic immunosuppression or a combination of various therapeutic agents might be more efficient than blocking a specific cytokine pathway.

Abbreviation List

ALT: Alanine aminotransferase; ARDS: Acute respiratory distress syndrome; AST: Aspartate aminotransferase; CBC: Complete blood count; CONSORT: Consolidated Standards of Reporting Trials; COVID-19: Coronavirus disease 2019; CPK: Creatine phosphokinase; CRF: Case report form; CRP: C-reactive protein; CT: Computed tomography; ESR: Erythrocyte sedimentation rate; FBS: Fasting blood sugar; GI: Gastrointestinal involvement; HCO₃: Bicarbonate; HR: Heart rate; IL: Interleukin; ITT: Intention to treat; mmHg: Millimeters of mercury; NIV: Noninvasive ventilation; PCO₂: Partial pressure of carbon dioxide; PCT: Pro-calcitonin; PO: Tolerated oral regimen; RA: Rheumatoid arthritis; RCT: Randomized controlled trial; RR: Respiratory rate; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SD: Standard deviation; SO₂: Oxygen saturation; TB: Tuberculosis; TNF: Tumor necrosis factor; VBG: Vein blood gas.

Declarations

Ethics approval

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).

Consent to participate

The written informed consent was signed by all patients before enrolling in the study.

Availability of data and materials

Data are available upon reasonable request.

Competing interests

The authors declare that they have no conflicts of interest.

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Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

Authors' contributions

MT, MJ, ASH, KS, KGM, HAT: Acquisition of clinical data and patient's diagnosis and treatment, interpretation of data, drafting the article, and final approval of the article.

MA, MM, SM, and AJ: The conception and design of the study, analysis and interpretation of data, revising the article critically for important intellectual content, and final approval of the article.

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Tables

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

	Characteristic	Total (N=36)	Tocilizumab (N=17)	Standard care (N=19)	P value
	Age (years)	61.74 ± 14.19	59.62 ± 15.80	63.52 ± 12.83	0.426
	Male/female, No (%)	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 Doses 0	19 (52.8%)	-	19 (100%)	NA
	Tocilizumab Doses 1	12 (33.3%)	12 (70.6%)	-	
	Tocilizumab Doses 2	5 (13.9%)	5 (29.4%)	-	
	Crowded places, n/N (%)	24/29 (82.7%)	12/13 (92.3%)	12/16 (75%)	0.343
Coexisting conditions	Diabetes, n/N (%)	13/36 (36.1%)	8/17 (47%)	5/19 (26.3%)	0.196
	Hypothyroidism, n/N (%)	5/36 (13.9%)	3/17 (17.6%)	2/19 (10.5%)	0.650
	Respiratory disorder, n/N (%)	3/36 (8.3%)	1/17 (5.9%)	2/19 (10.5%)	0.99
	Renal disorder, n/N (%)	1/36 (2.8%)	0	1/19 (5.3%)	0.99
	Cardiovascular disorder, n/N (%)	16/36 (44.4%)	7/17 (41.1%)	9/19 (47.3%)	0.709
	Hypertension, n/N (%)	18/36 (50%)	9/17 (52.9%)	9/19 (47.3%)	0.738
	GI, n/N (%)	3/36 (8.3%)	1/17 (5.9%)	2/19 (10.5%)	0.99
	Cancer, n/N (%)	0	0	0	NA
	Autoimmune & neurodegenerative diseases, n/N (%)	0	0	0	NA
Other COVID-19 treatment	Hydroxy Chloroquine, n/N (%)	23/36 (63.9%)	9/17 (52.9%)	14/19 (73.3%)	0.196
	Atazanavir, n/N (%)	5/35 (13.9%)	3/17 (17.6%)	2/19 (10.5%)	0.65
	Corticosteroids, n/N (%)	12/36 (33.3%)	5/17 (29.4%)	7/19 (36.8%)	0.637
	Interferon, n/N (%)	1/36 (2.8%)	1/17 (5.9%)	0	0.472
	Lopinavir / Ritonavir, n/N (%)	3/36 (8.3%)	3/17 (17.6%)	0	0.095
	Body temperature, °C, n/N (%)	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/N (%)	9/36 (25%)	7/17 (41.1%)	2/19 (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/N (%)	14/36 (38.9%)	5/17 (29.4%)	9/19 (47.3%)	0.27
	Systolic blood pressure, mm Hg	127.75 ± 24.95	122.76 ± 24.77	132.21 ± 24.92	0.263
	Diastolic blood pressure, mm Hg	74.05 ± 16.59	68.81 ± 17.37	78.47 ± 14.95	0.086
	Dyspnea, n/N (%)	31/36 (86.1%)	15/17 (88.23%)	16/19 (84.2%)	0.99
	GI Symptom, n/N (%)	12/36 (33.3%)	5/17 (29.4%)	7/19 (36.8%)	0.637
	Myalgia, n/N (%)	15/36 (41.7%)	5/17 (29.4%)	10/19 (52.6%)	0.158
	Chest pain, n/N (%)	5/36 (13.9%)	3/17 (17.6%)	2/19 (10.5%)	0.65
	Cough, n/N (%)	21/36 (58.3%)	9/17 (52.9%)	12/19 (63.1%)	0.535
	Weakness, n/N (%)	31/36 (86.1%)	14/17 (82.4%)	17/19 (89.5%)	0.65
	WBC count/MCL	6995 ± 2699	7668 ± 2808	6428 ± 2539	0.179
WBC count	4–10 ×1000/MCL, no (%)	29/35 (82.9%)	13/16 (81.2%)	16/19 (84.2%)	0.99
	<4 ×10×1000/MCL, no (%)	4/35 (11.4%)	2/16 (12.5%)	2/19 (10.5%)	

	>10 ×1000/MCL, no (%)	2/35 (5.7%)	1/16 (6.3%)	1/19 (5.3%)	
	RBC count (×1000) /MCL	4.42 ± 0.932	4.43 ± 1.21	4.42 ± 0.639	0.984
	Lymphocyte count/MCL	1079 ± 561	1212 ± 634	910 ± 421	0.188
Lymphocyte count	800-5000/MCL, n/N (%)	14/25 (56%)	10/14 (71.4%)	4/11 (36.4%)	0.116
	<800/MCL, n/N (%)	11/25 (44%)	4/14 (28.6%)	7/11 (63.6%)	
	>5000/MCL, n/N (%)	0	0	0	
	Monocyte count/MCL	380.6 ± 224.9	395.8 ± 281.9	359.4 ± 116.5	0.704
	Platelet count/MCL	200971 ± 70615	196625 ± 70727	204631 ± 72246	0.744
Platelet count	<150×1000/MCL, n/N (%)	6/35 (17.1%)	2/16 (12.5%)	4/19 (21.1%)	0.666
	150-450×1000/MCL, n/N (%)	29/35 (82.9%)	14/16 (87.5%)	15/19 (78.9%)	
	>450×1000/MCL, n/N (%)	0	0	0	
	Neutrophil Percent (%)	76.24 ± 9.33	75.85 ± 9.98	76.27 ± 8.90	0.823
	Hemoglobin (gm/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
VBG	PCO2 (mmHg)	41.06 ± 8.77	40.06 ± 7.60	41.88 ± 9.78	0.561
	HCO3 (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/N (%)	36/36 (100%)	17/17 (100%)	19/19 (100%)	NA
	Pro-calcitonin negative, n/N (%)	36/36 (100%)	17/17 (100%)	19/19 (100%)	NA

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; °C: Centigrade; CPK: Creatine phosphokinase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FBS: Fasting blood sugar; GI: Gastrointestinal; gm/dl: Grams per deciliter; HCO3: Bicarbonate; LDH: Lactic acid dehydrogenase; MCL: Microliter; µg/mL: Microgram per milliliter; mg/L: Milligrams per liter; meq/L: Milliequivalent per liter; min: Minute; mm Hg: Millimeter of mercury; mm/hr: Millimeters per hour; ng/ml: Nanogram per milliliter; PCO2: Partial pressure of carbon dioxide; pg/ml: Pictogram per milliliter; RBC: Red blood cell; U/L: Unit per liter; VBG: Venous blood gas; WBC: White blood cell; NA: Not available; *P-value <0.05.

Table 2. Pulmonary involvement level at baseline.

	Characteristic	Total (N=36)	Tocilizumab (N=17)	Standard care (N=19)	P-value
	SO2 percent	84.6 ± 8.92	84.8 ± 8.21	84.4 ± 9.73	0.881
	Need on oxygen therapy, n/N (%)	36/36 (100%)	17/17 (100%)	19/19 (100%)	NA
Type of oxygen therapy, no (%)	Nasal Cannula	18/36 (80%)	8/17 (47.1%)	10/19 (52.6%)	0.106
	Simple Mask	11/36 (30.6%)	3/17 (17.6%)	8/19 (42.1%)	
	Reservoir Mask	4/36 (11.1%)	3/17 (17.6%)	1/19 (5.3%)	
	Noninvasive ventilation (NIV)	3/36 (8.3%)	3/17 (17.6%)	0	
Pulmonary involvement percent, n/N (%)	A (<10%)	4/36 (11.1%)	1/17 (5.8%)	3/19 (15.8%)	0.788
	B (10-30%)	14/36 (38.8%)	6/17 (35.3%)	8/19 (42.1%)	
	C (30-50%)	10/36 (27.7%)	5/17 (29.4%)	5/19 (26.3%)	
	D (50-70%)	3/36 (8.3%)	2/17 (11.8%)	1/19 (5.3%)	
	E (>70%)	5/36 (13.8%)	3/17 (17.6%)	2/19 (10.5%)	
Radiological properties, n/N (%)	Peripheral ground glass	36/36 (100%)	17/17 (100%)	19/19 (100%)	NA
	Alveolar consolidation	13/36 (36.1%)	8/17 (47.1%)	5/19 (26.3%)	0.196
	Crazy paving pattern	6/36 (16.7%)	0	6/19 (31.6%)	0.020*
	Halo sign	0	0	0	NA
	Reverse halo sign	1/36 (2.8%)	1/17 (5.9%)	0	0.472
	Wedge-shaped	1/36 (2.8%)	0	1/19 (5.3%)	0.99
	Per-bronchial infiltration	13/36 (36.1%)	7/17 (41.2%)	6/19 (31.6%)	0.549

SO2, Oxygen saturation; NA, Not available; *P-value <0.05.

Table 3. Primary outcomes in Tocilizumab and standard care group.

Characteristic	Tocilizumab (N=17)	Standard care (N=19)	P-value
Time to the event (discharge or death), day	12.88 ± 9.05	12.05 ± 8.92	0.784
Time to improvement, day	9.42 ± 3.55	9.73 ± 6.05	0.874
The outcome, n/N (%)			0.563
Recover	12/17 (70.6%)	15/19 (78.9%)	
Death	5/17 (29.4%)	4/19 (21.1%)	

*P-value <0.05.

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

Characteristic	Before treatment		After treatment (Day 3-5)			
	Tocilizumab	Standard care	Tocilizumab	P-value	Standard care	P-value
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD		Mean $\pm$ SD	
SO2 percent	84.8 $\pm$ 8.21	84.4 $\pm$ 9.73	89.06 $\pm$ 6.89	0.001*	88.0 $\pm$ 10.05	0.002*
Systolic blood pressure, mm Hg	122.76 $\pm$ 24.77	132.21 $\pm$ 24.92	121.4 $\pm$ 10.66	0.415	129.4 $\pm$ 18.46	0.526
Diastolic blood pressure, mm Hg	68.81 $\pm$ 17.37	78.47 $\pm$ 14.95	72.0 $\pm$ 8.96	0.734	77.0 $\pm$ 12.45	0.668
Heart rate, beats/ min	90.76 $\pm$ 14.92	93.0 $\pm$ 14.28	80.5 $\pm$ 24.32	0.077	88.47 $\pm$ 15.06	0.056
Respiratory rate, breaths/min	21.76 $\pm$ 3.81	18.89 $\pm$ 2.60	20.43 $\pm$ 4.56	0.211	18.15 $\pm$ 1.92	0.125
Body temperature °C	37.02 $\pm$ 1.50	37.51 $\pm$ 0.73	36.8 $\pm$ 0.42	0.547	37.04 $\pm$ 0.32	0.007
	n/N (%)	n/N (%)	n/N (%)	P-value	n/N (%)	P-value
Dyspnea	15/17 (88.23)	16/19 (84.2)	6/16 (37.5)	0.012*	10/19 (52.6)	0.031*
GI Symptom	5/17 (29.4)	7/19 (36.8)	2/16 (12.5)	0.25	1/19 (5.3)	0.031*
Myalgia	5/17 (29.4)	10/19 (52.6)	1/16 (6.3)	0.125	3/19 (15.8)	0.016*
Chest pain	3/17 (17.6)	2/19 (10.5)	0	0.25	0	0.50
Cough	9/17 (52.9)	12/19 (63.1)	4/16 (25)	0.063	6/19 (31.6)	0.031*
Weakness	14/17 (82.4)	17/19 (89.5)	13/16 (81.3)	0.99	13/19 (68.4)	0.125
Need on Oxygen therapy	17/17 (100)	19/19 (100)	14/17 (76.4)	0.103	17/19 (89.4)	0.486

**P-value* <0.05, *P-value* was calculated based on the after treatment and before treatment measurements in each of studied groups, SO2, Oxygen saturation; mm Hg, Millimeter of mercury; min, Minute; °C, Centigrade; GI, Gastrointestinal; NA, Not available.

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

Characteristic		Before treatment		After treatment (Day 3-5)			After treatment (Discharge or death)				
		Tocilizumab	Standard care	Tocilizumab	P-value	Standard care	P-value	Tocilizumab	P-value	Standard care	P-value
		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*
Hematocrit Percent		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 Percent		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/ MCL		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
	HCO3 (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
	PCO2 (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, P-value was calculated based on the after treatment measurements compared with before measurement (as a reference) in each of studied groups, ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CPK: Creatine phosphokinase; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FBS: Fasting blood sugar; gm/dl: Grams per deciliter; HCO3: Bicarbonate; LDH: Lactic acid dehydrogenase; MCL:

Microliter; mg/L Milligrams per liter; meq/L: Milliequivalent per liter; mm Hg: Millimeter of mercury; mm/hr: Millimeters per hour; ng/ml: Nanogram per milliliter; PCO2: Partial pressure of carbon dioxide; pg/ml: Pictogram per milliliter; RBC: Red blood cell; SD, Standard deviation; U/L: Unit per liter; VBG: Venous blood gas; WBC: White blood cell; NA: Not available.

Figures

Figure 1

Randomization, enrollment, and treatment assignment.

Figure 2

Kaplan-Meier curves for statistical comparison of time to death between both groups (P-value=0.973).

Supplementary Files

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