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Efficacy of Tocilizumab in the treatment of severe COVID-19 patients with respiratory failure

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ABSTRACT

Objective: This study aimed to investigate the impact of tocilizumab, an IL6R inhibitor, on clinical features and laboratory tests of subjects admitted with severe COVID-19 and respiratory failure.

Material and Methods: A total of 30 patients with positive polymerase chain reaction for COVID-19 and respiratory failure were analyzed in a retrospective manner. All patients received 8mg/kg body weight tocilizumab i.v. once in addition to the standard COVID-19 treatment protocol, including Oseltamivir phosphate 75mg twice daily, hydroxychloroquine 200 mg twice daily, and azitromycine 250 mg once daily following a 500 mg loading dose. Demographic characteristics, and clinical features including oxygen saturation, the concentration of oxygen inhalation, body temperature, mean arterial pressure and heart rate, and SpO2, end-tidal CO2, and blood tests including complete blood count, procalcitonin, C-reactive protein (CRP), Troponin-I, D-dimer, and liver and kidney function tests were recorded before and after treatment with tocilizumab.

Results: A significant increase occurred in SaO2 on first and third days following treatment with tocilizumab (84.3 % and 90.3%, respectively, $p<0.001$ for both recordings compared to baseline). There was also a significant increase in end-tidal CO2. The increase in mean SaO2 after tocilizumab was followed by a decline in respiratory rate on the first and third days of treatment. A dramatic decline was observed in body temperature from the first day of treatment with tocilizumab. Lymphocyte count increased following tocilizumab and C-reactive protein and Troponin I levels were reduced.

Conclusion: Tocilizumab appears as an effective therapeutic option for improving oxygenation, symptoms and laboratory surrogates of ongoing inflammation in subjects with severe COVID-19.

Keywords: COVID-19, SARS-CoV-2, Tocilizumab, Cytokine storm

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INTRODUCTION

Several cases of pneumonia with unknown etiology have emerged in Wuhan, Hubei Province, China towards the end of 2019 (1). Fewer and cough, which were before an acute respiratory distress syndrome were the most prominent initial symptoms (2). Following the identification of a novel coronavirus in the throat swab sample of one patient by the Chinese Center for Disease Control and Prevention (CDC), World Health Organization (WHO) named the novel coronavirus as 2019nCoV (3). The rapid spread of pneumonia to other regions of China and overseas led World Health Organization (WHO) to declare this outbreak as the public health emergency of international concern (PHEIC). In February 2020, the virus was renamed as severe acute respiratory syndrome coronaviruse-2(SARS-CoV-2) by the International Committee on Taxonomy of Viruses (4). Epidemic disease caused by SARS-CoV-2 was further announced by the WHO as coronavirus disease 2019 (COVID-19).

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Coronavirus disease 2019 was the third coronavirus disease within the last two decades following severe acute respiratory syndrome coronavirus (SARS-CoV) which resulted in more than 8000 infections and 774 deaths in 37 countries, and Middle East respiratory syndrome coronavirus (MERS-CoV) which resulted in 2494 infections 858 deaths (**5, 6**). As of May 25, 2020, COVID-19 has been reported to affect about 5.5 million individuals and caused over 340.000 fatalities globally (**5**). Although nonspecific treatment has been shown to promote dramatic improvement in critical COVID-19 patients, several agents including opinavir, ritonavir, remdesivir, macrolides, hydroxychloroquine and colchicines are currently used for the treatment of COVID-19 (**6, 7**). Tocilizumab, a recombinant humanized anti-human IL-6 receptor monoclonal antibody which is commonly used in the treatment of rheumatic disorders (**8**). We hypothesized that tocilizumab could alleviate the cytokine storm which is directly associated with increased mortality in COVID-19 patients with respiratory failure. This study aimed to investigate the impact of tocilizumab on clinical features and laboratory tests of subjects admitted with severe COVID-19 and respiratory failure.

MATERIAL AND METHODS

A total of 30 patients meeting the inclusion criteria were enrolled in this retrospective study. Inclusion criteria were as follows: Age ⩾ years, definite SARS-CoV2 in presence of symptoms and positive polymerase chain reaction (PCR), and signs of severe respiratory failure including ambient air SpO2 ⩽ 92%, need of ⩾ 6l O2/min, need for NIV (non-invasive ventilation) or IMV (invasive mechanical ventilation). Subjects with severe hepatic failure (AST/ALT ⩾ 5x ULN), white blood cell count <2000/mm3/ µl, platelet count <50000/ mm3/ µl, concomitant severe bacterial infection, immunosuppressive treatment other than prednisolone ⩽10mg/d, sulfasalazine or hydroxychloroquine, active/chronic tuberculsosis, active/chronic hepatitis, known allergic reactions to tocilizumab. Written informed consent was obtained from all subjects included in the study. The study was approved by Institutional Ethical Committee and was conducted in accordance with the Helsinki Declaration.

All patients received 8mg/kg body weight tocilizumab (Roche Pharma [Schweiz] Ltd.) i.v. once in addition to the standard COVID-19 treatment protocol recommended by Science Advisory Board of Turkish Ministry of Health, including Oseltamivir phosphate 75mg twice daily, hydroxychloroquine 200 mg twice daily, and azitromycine 250 mg once daily following a 500 mg loading dose. Demographic characteristics, and clinical features including oxygen saturation, the concentration of oxygen inhalation, body temperature, mean arterial pressure and heart rate, and SpO2, end-tidal CO2, and blood tests including complete blood count, procalcitonin, C-reactive protein (CRP), Troponin-I, D-dimer, and liver and kidney function tests were recorded before and after treatment with tocilizumab. The change in clinical features and laboratory parameters before and after treatment with tocilizumab was the primary outcome measure of this study.

Statistical analysis: All analyses were performed on SPSS v21 (SPSS Inc., Chicago, IL, USA). Shapiro-Wilk test was used to determine whether variables are normally distributed. Data are given as mean ± standard deviation for continuous variables and frequency (percentage) for categorical variables. Repeated measurements of normally distributed variables were analyzed with two-way repeated-measures analysis of variances (ANOVA). Two-tailed p-values of less than 0.05 were considered statistically significant.

RESULTS

The mean age of the study group was 50 ± 6 years and 63.3 % were male. Comorbid diseases are presented in **Table 1**. The mean APCHE and SOFA scores were 26.6 ± 6.6, and 4.2 ± 0.9, respectively. The mean time from symptom onset to admission was 3.8 ± 0.8 days.

Table 1. Demographic and clinical features of the study group

	n=30, %
Age, years	50 ± 6
Gender, male	19 (63.3%)
Comorbid diseases	
Diabetes, n	8 (26.7%)
Hypertension, n	10 (33.3%)
Current smoking, n	8 (26.6%)
CAD, n	7 (23.3%)
Obesity, n	1 (3.3%)
Asthma, n	3 (10%)
COPD, n	7 (23.3%)
Heart failure, n	2 (6.7%)
CKD, n	2 (6.7%)
CVD, n	1 (3.3%)
FMF, n	2 (6.7%)
APACHE score	26.6 ± 6.6
SOFA score	4.2 ± 0.9
Time from symptom onset to admission, days	3.8 ± 0.8

The mean SaO2 was 79.7% before treatment with tocilizumab. A significant increase occurred in SaO2 on the first and third days following treatment with tocilizumab (84.3 % and 90.3%, respectively, p<0.001 for both recordings compared to baseline). There was also a significant increase in end-tidal CO2 (**Table 2**).

A dramatic decline was observed in body temperature from the first day of treatment with tocilizumab. Consistent with the improvement in SaO2, the mean heart rate decreased from 105.2/min to 97.8 /min on the first day and to 90.3 /min on the third day of treatment with tocilizumab. Mean arterial pressure was also observed to increase discordant with the decrease in HR. The increase in mean SaO2 after tocilizumab was followed by a decline in respiratory rate on the first and third days of treatment.

Changes in laboratory parameters following the administration of tocilizumab is given in **Table 2**. Hemoglobin, leukocyte count, platelet count, and neutrophil count were similar before and after tocilizumab. However, a significant increase occurred in lymphocyte count after administration of tocilizumab and lymphopenia returned to normal range on day 3. Although there were no significant

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changes in procalcitonin concentration, CRP significantly decreased from 15.5 ng/mL to 12.3 ng/mL on day 1 and 8.9 ng/mL on day 3. Troponin I level also decreased from 0.156 ng/mL to 0.119 ng/mL on day 3. ±

The number of intubated patients decreased from 22 to 17 on the first day and to 11 o the third day of treatment with tocilizumab. 96.6 of the subject have been discharged.

Table 2. Clinical findings and laboratory tests before and after tocilizumab

Parameters of patients (**n:30**)	**Before tocilizumab Mean±SD**	**Day 1 Mean± SD**	**Day 3 Mean± SD**	**P value**
Body temperature, degrees	37.9±0.61	37.1±0.77	36.8±0.79	0.687
Mean arterial pressure,mmHg	90.2±9.1	96.9±9.96	98.1±9.22	**0.001**
Heart rate, beats/min	105.2±13.1	97.8±16.5	90.3±14.2	**<0.001**
SaO2	79.7±4.3	84.3±5.3	90.9±3.5	**<0.001**
End-tidal CO2	36.3±1.7	39.4±2.3	40.3±6.2	**0.001**
O2 intake, lt/min	11.4±1.09	11.0±1.27	9.7±4.29	**0.037**
Respiratory rate, n/min	36.3±3.9	28.8±4.99	18.3±4.57	**<0.001**
Hemoglobin, mg/dL	11.9±1.63	11.9±1.84	12.0±1.99	0.965
Hematocrite, %	36.2±5.23	36.3±5.17	36.4±5.35	0.943
Platelet count, x10^3/ µL	220±109	242±72.3	255±142.8	0.242
Leukocyte count, x10^3/ µL	8.2±2.8	8.7±3.0	9.5±4.15	0.229
Neutrophil count, x10^3/ µL	80.1±14.2	80.1±11.2	77.9±15.2	0.290
Mena platelet volume, fL	9.4±0.92	9.3± 0,85	9.4± 1.01	0.687
Red cell distribution width, %	13.6±1.57	13.8±1,51	13.8±1.72	0.413
Lymphocyte count, x10^3/ µL	0.60±048	0.79±0.46	1.19±0.53	**<0.001**
Procalcitonin, ng/mL	0.61±1.26	0.76±1.09	0.84±1.54	0.548
CRP, mg/L	15.5±6.1	12.3±6.7	8.9±6.4	**<0.001**
GFR, %	90.8±33.0	81.6±32.1	82.4±33.3	**0.048**
BUN, mg/dL	22.4±23.1	25.0±22.1	28.0±23.6	0.110
CR, mg/dL	1.2±1.59	1.1±1.72	1.4±1.62	0.255
Na, mEq/L	136±7.6	142±8.4	145±6.7	**<0.001**
K, mEq/L	4.0±0.51	3.8±0.47	3.7±0.52	0.068
Calcium, mEq/L	7.5±0.64	7.3±0.63	7.5±0.65	0.455
HCO3, mEq/L	21.6±5.01	23.0±4.43	23.9±5.82	0.133
ALB, g/dL	3.2±0.48	3.0±0.51	3.1±0.42	0.683
INR1	1.25±0.59	1.3±0.47	1.4±0.66	0.849
TRP1, ng/mL	0.156±661	0.147±763	0.119±411	**<0.001**
AST, U/L	60.7±60	73.6±58	71.3±56	0.478
ALT, U/L	61.8±61	69.3±67	64.5±57	0.312
LDH, U/L	586±481	626±323	691±493	0.077
Total bilirubin, mg/dL	0.68±0.33	0.66±0.37	0.62±0.35	0.374
D-dimer, ng/mL	5.8±0.4.98	6.5±5.99	6.4±4.90	0.411
Fibrinogen, mg/d	626±223	577±221	541±250	0.115
Ferritine, mg/L	1875±1001	1468±1021	1266±936	**<0.001**
Triglyceride, mg/dL	180±138	169±127	187±143	0.725

DISCUSSION

This study retrospectively observed tocilizumab, an IL6R inhibitor, in the treatment of 30 severe COVID-19 patients with respiratory failure. Our findings show improvement in oxygenation and blood pressure and in blood tests including CRP and troponin I following the administration of tocilizumab. Lymphocyte count displayed a dramatic increase after tocilizumab. Concordant with the improvement in oxygenation a prominent decline occurred in oxygen volume delivered per minute and in respiration rate. These findings suggest that tocilizumab can be a valid therapeutic option in the treatment of severe COVID-19 patients.

COVID-19 is a novel coronavirus infection that predominantly affects the lungs and leads to rapidly progressing respiratory failure in a substantial amount of subjects. CT findings include multifocal ground-glass pattern, thickened interlobular and intralobular lines, vascular dilatation, and subpleural bands (**9, 10, 11, 12**). Subjects with lung involvement almost always require oxygen therapy and assisted ventilation. About 14% of patients infected by SARS-CoV-2 develop severe COVID-19 characterized by dyspnea, respiratory frequency ⩾30/min, blood oxygen saturation ⩽93% and PaO2 /FiO2 ratio 50% of the lung field and approximately 6% develop respiratory failure, septic shock, and multiorgan dysfunction (**13**).

In this study, following the administration of tocilizumab a significant improvement was observed in oxygenation and signs of hypoxia. Oxygen intake flow was reduced concordant to the improvement in oxygenation.

Emerging evidence indicates that CRP and troponin-I concentrations have prognostic value in COVID-19 patients and both are associated with the intensity of the ongoing inflammation (**14, 15, 16**). Our findings show that a significant reduction occurs in CRP and troponin-I following the administration of tocilizumab. The number of lymphocytes is also considered as an important indicator for the severity of COVID-19 (**1**). Results of the present study show that lymphocyte count rapidly returns to normal after treatment with tocilizumab. During the treatment, no adverse drug reactions and subsequent pulmonary infections were reported. These findings are consistent with the preliminary data demonstrating the efficacy of tocilizumab in the treatment of severe COVID-19 patients. Xu and colleagues have shown in their study on 21 severe COVID-19 patients that tocilizumab is associated with remarkable improvement in symptoms and oxygenation a few days after administration (**17**). A prospective, randomized, double-blind placebo-controlled trial is currently enrolling patients to evaluate the efficacy and safety of tocilizumab in patients with severe COVID-19 pneumonia (**18**). The findings of that study will provide valuable data regarding the role of tocilizumab in severe COVID-19.

Our findings indicate that tocilizumab provides promising improvement not only in oxygenation of the patients with severe COVID-19 but also reduces the blood concentrations of the inflammatory markers which are indicative for the cytokine storm. The recognition of SARS-CoV-2 by endothelial cells and alveolar macrophages triggers the generation of pro-inflammatory cytokines and chemokines which further attract monocytes, macrophages and T cells to the site of infection and promote a cytokine storm, in particular, in subjects with a defective immune response (**19, 20**). Although the mechanism of how tocilizumab improves symptoms and oxygenation in COVID-19 is unclear, it is considered that this agent can repress the cytokine storm which is responsible for alveolar damage in severe COVID-19. Results of this study also indicate that tocilizumab appears as a safe therapeutic option without adverse drug reaction.

The retrospective nature and relatively small sample size are the main drawbacks of this study. The lack of monitoring IL-6 levels during treatment with tocilizumab is also another limitation for this study.

CONCLUSION

In conclusion, tocilizumab appears effective in improving oxygenation, symptoms and laboratory surrogates of ongoing inflammation in subjects with severe COVID-19. These findings suggest that tocilizumab should be considered to repress the deterioration of severe COVID-19 patients.

Take home message: In COVID-19 pneumonia, it was observed that tocilizumab suppressed cytokine storm.

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