Efficacy of tocilizumab treatment in severe patients with COVID-19

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Abstract

Background: The aim of the study was to determine the effectiveness of tocilizumab treatment in patients with COVID-19. Methods: 60 patients infected with SARS-CoV-2 were enrolled in the study. The patients were divided into two groups according to whether they treated with tocilizumab or did not. Demographic and clinical features of the patients, laboratory findings, treatments, and clinical outcome were evaluated. Results: The mean age of 30 patients in group 1 was 63.6±16.3 years and male/female ratio was 3.2, whereas the mean age of 30 patients in group 2 was 59.4±11 years and male/female ratio was 2.7 (P=0.244 and P=0.766, respectively). pO2/FiO2 and lymphocyte count at baseline, 2nd day and 7th day were significantly lower in group 1 treated with standard treatment without tocilizumab than group 2 additionally treated with tocilizumab (P<0.05). D-dimer level at 7th day, ferritin and CRP levels at 2nd and 7th day were significantly higher in group 1 than group 2 (P=0.015, P<0.001, P<0.001, P<0.001, P<0.001, respectively). The patients in group 1 had higher intensive care unit need and mortality rate than the patients in tocilizumab group (P=0.015). 28-day survival was lower in group 1 than tocilizumab group (P=0.024). Conclusions: We observed clinical improvement and lower mortality rate in hospitalized patients with severe COVID-19 with tocilizumab treatment.

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Key words: Adult; COVID-19; SARS-CoV-2; tocilizumab

What is already known about this topic?

Modulating the levels of proinflammatory IL-6 or its effects may reduce the duration and severity of COVID-19 disease.

Tocilizumab was given in patients with inadequate response to standard treatment, progression of the disease and development of cytokine release syndrome

What does this article add?

Tocilizumab is an effective treatment if given early in severe patients of COVID-19 improving mortality, preventing ICU admission and shortening the duration of hospital stay

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic virus that emerged in late 2019 and later named 'coronavirus disease 2019' (COVID-19). It is characterized by a diverse clinical spectrum from asymptomatic or mild illness to life threatening disease, even death.[1]

To date, no effective specific treatment has been found yet. Cytokine release syndrome (CRS) was determined to be the major cause of morbidity in patients infected with SARS-CoV and MERS-CoV. [2,3]Interleukin (IL)-6 and IL-10 are among the core cytokines that are consistently found to be elevated in patients with CRS (4). Increased level of IL-6 has been reported in critically ill patients infected with SARS-CoV-2 and may be part of a larger cytokine storm associated with poor prognosis.[5]

Tocilizumab is a recombinant humanized anti-interleukin (IL)-6 receptor monoclonal antibody approved by the Food and Drug Administration (FDA) for the treatment of rheumatologic diseases and CRS. [6]It has been stated that modulating the levels of proinflammatory IL-6 or its effects may reduce the duration and severity of COVID-19 disease.[6,7]

The studies reporting experience with tocilizumab in COVID-19 patients have been limited. In this study, we aimed to determine the effectiveness of tocilizumab treatment in patients with COVID-19 and make comparison between the patients who treated with tocilizumab and who did not.

Materials and methods

A total of 60 patients infected with SARS-CoV-2 were evaluated prospectively from 2 April to 31 May 2020 at the department of Infectious Diseases. The patients were divided into two groups as group 1: who treated with standard treatment and group 2: who additionally treated with tocilizumab. Demographic features of the patients, chronic diseases, symptoms at admission, need for intensive care, laboratory findings, treatments, and clinical outcome were evaluated.

Diagnosis of COVID- 19 pneumonia was based on the World Health Organization interim guidance [8] and the New Coronavirus Pneumonia Prevention and Control Program (fifth edition) published by the National Health Commission of China.[9]Severe cases were defined as (i) respiratory rate $>$ 30 breaths/min, (ii) oxygen saturation [?] 93%, or (iii) PaO2/FiO2 ratio [?] 300 mm Hg. Critical severe cases were defined as including [?]1 of the following criteria: shock; respiratory failure requiring mechanical ventilation; combination with other organ failures; and admission to intensive care unit. [9]

Throat and nasopharyngeal swab samples for rRT-PCR were collected from only those patients showing symptoms suggestive of the disease. The laboratory diagnosis of COVID-19 was implemented by the RT-PCR assay in accordance with the protocol established by the World Health Organization. After RNAs were extracted by a commercial kit (Bio-Speedy nucleic acid extraction kit, Bioeksen, Turkey), another commercial RT-PCR kit (Bio-Speedy, COVID-19 RT-qPCR Kit, Bioeksen, Turkey) that targets RdRp gene of COVID-19 was used for detection of COVID-19 RNA in the samples. [10]

All of the patients with symptoms suspected COVID-19 had chest tomography (CT). The findings such as ground glass opacities, consolidations and cobblestone appearance were regarded typical for COVID-19. The

patients who had positive rRT-PCR for SARS-CoV-2 and/or typical findings of COVID-19 at chest CT were involved in this study.

Laboratory findings were defined according to the given normal ranges of the hospital laboratory as follows: lymphocyte count [?]800 µ/L, lymphopenia; platelets count <100 000 µ/L, thrombocytopenia; increased D-dimer >0.5 µg/ml; ferritin >400 µg/L; lactate dehydrogenase >214 and CRP >5 mg/L, respectively.

Oseltamivir (30 mg 1×1), hydroxychloroquine (2×200 mg loading and 1×200 mg maintenance dose), vitamin C (2×15 g) and azithromycin (1×500 mg loading and 1×250 mg maintenance dose) for a total of 5 days were given as suggested by National Ministry of Health Public Health Office. Favipiravir therapy (2x1600 mg loading and 2x600 mg maintenance dose) were added to the patients who continued to have symptoms or developed clinical and/or laboratory decompansation after 5 days of hydroxychloroquine treatment. Tocilizumab was given was at a dose of 400 mg and was repeated within 12-24 hours if needed in patients with inadequate response to standard treatment, progression of the disease and development of CRS.

Statistical analysis

SPSS 15.0 for Windows program was used for statistical analysis. Number and percentage were used for descriptive statistics and categorical variables. Mean, standard deviation, minimum, maximum and median were used for numerical variables. Independent groups were compared by Chi-Square test. When the normal distribution condition met, Student's t test was used for the numerical variables, otherwise the analysis of two independent groups was performed by using Mann Whitney U test. The correlations were analyzed by using Spearman Correlation analysis, since parametric test conditions were not met. P values of <0.05 were considered statistically significant.

Results

The mean age of 30 patients in group 1 was 63.6±16.3 years and 76.7% of them was male, whereas the mean age of 30 patients in group 2 was 59.4±11 years and 73.3% of them was male (P=0.244 and P=0.766, respectively). Seventeen patients (63%) in group 1 and 21 patients (72.4%) in group 2 had positive rRT-PCR. 83.3% patients in group 1 and 76.7% patients in group 2 had comorbidities, most commonly hypertension and diabetes mellitus. Sore throat was seen significantly higher in group 2 than group 1 (P=0.045). The mean fever was 38.4±0.7 in group 1 and was 37.9±0.7 in group 2 (P=0.01). The demographic and clinical characteristics of the patients are shown in table 1.

When the severity of the disease was compared between groups, severe disease was significantly higher in group 1 (P=0.002). The treatment with favipiravir, oseltamivir, and lopinavir plus ritonavir was given more commonly to the patients in group 1 (P=0.001). Corticosteroids were used significantly in group 1 (69% vs 23.3%, P<0.001, respectively) (Table 1).

pO2/FiO2 and lymphocyte count at baseline, 2nd day and 7th day were significantly lower in group 1 than group 2 (Table 2). Lymphocyte count statistically significantly decreased at 2nd day and increased at 7 th day in both of the groups (P=0.008,P=0.016 and P<0.001,P=0.004, respectively). D-dimer level at 7th day, ferritin and CRP levels at 2nd and 7th day were significantly higher in group 1 than tocilizumab group (P=0.015, P<0.001, P<0.001, P<0.001, P<0.001, respectively). CRP level higher than 50 mg/dl at baseline and 7th day was not statistically significant in group 1, whereas CRP level higher than 50 mg/dl at 7th day was lower than baseline in group 2 (P<0.007).

The patients in group 1 had higher intensive care unit need and exitus ratio, and lower 28-day survival than the patients in tocilizumab group (P=0.015, P=0.024, respectively) (Table 3). The mean lymphocyte count and pO2/FiO2 ratio were statistically significantly lower in non-survivors in both of the groups (P=0.004, P=0.028, P=0.021, and P=0.007, respectively). Acute respiratory distress syndrome (ARDS) was the leading cause of death.

Elevated transaminase levels were observed in 5 patients of tocilizumab group. No statistically significant difference was observed in alanine aminotransferase (ALT), aspartate aminotransferase (AST) levels, and

platelet count between the two groups. ALT levels at 7th day and platelet counts at 2nd and 7th day were higher than the levels at baseline in tocilizumab group (P=0.023, P<0.001, and P=0.011). Secondary bacterial and fungal infection, and neutropenia were not observed with tocilizumab treatment.

Discussion

Some of the hospitalized patients with COVID-19 develop symptoms of CRS including persistent high fever, clinical deterioration, and elevated serum inflammatory markers such as CRP, ferritin, and IL-6.[11,12] It has been stated that early treatment for inhibition of inflammatory process can be effective in clinical improvement and decreased mortality. [12-15]

Xu et al. [12] reported in their study that 85% of their patients had lymphopenia which returned to normal in 52.6% of those patients after tocilizumab treatment. It has been stated that elevated CRP also returned to normal after tocilizumab· [12,16,17] Similarly, Morena et al. [18] reported an increased lymphocyte count and decrease in inflammatory symptoms and markers after tocilizumab treatment. In our study, 78.3% of the patients (86.7% in group 1 and 70% in group 2) had lymphopenia and lymphocyte count returned to normal at 7th day. Increased level of IL-6 at baseline has been observed before treatment in all patients and improved with the tocilizumab treatment.[12,16]

The improvement in fever has been observed after tocilizumab treatment.[17-19] We also observed dramatically normalization of fever after tocilizumab treatment.

Although there are studies proposing that tocilizumab treatment was not associated with clinical improvement and mortality.[11,18,20,21] in contrast the other studies stated that ICU admissions, need for mechanical or noninvasive ventilation and mortality have decreased with tocilizumab treatment.[12,14,17,19,22,23]

Salama et al. [24] reported that tocilizumab reduced the progression to the composite outcome of mechanical ventilation or death, but it did not improve survival in hospitalized patients with Covid-19. No significant effect was reported in 28-day survival in COVID-19 patients who treated with tocilizumab. [20,21,23,24] In our study, the patients in tocilizumab group had lower intensive care unit need and exitus ratio, and higher 28-day survival.

Mo et al. [17] observed that 82% of nonventilated patients did not require mechanical ventilation during the hospital stay after tocilizumab administration. In our study, only 5 patients in tocilizumab group had received invasive mechanical ventilation.

Some researchers reported no side effects after tocilizumab treatment.[12,14] Campochiaro et al.[11] recorded serious adverse events in 25% patients, Salama et al.[24] in 15.2% of their patients treated with tocilizumab. Elevated liver enzymes and secondary infections were detected in the studies conducted by Mo et al. [17], Gupta et al. [15] and Morena et al.[18]. In our study, although 16.6% of the tocilizumab group had elevated transaminase levels, we observed no secondary bacterial and fungal infection, and neutropenia with tocilizumab treatment.

Mortality rate was 16.7% in our tocilizumab group, it has been reported 8-27.5% in other studies. [14,15,18,20,24]

The limitations of this study were limited number of patients and single center experience.

In conclusion, tocilizumab is an effective treatment if given early in severe patients of COVID-19 improving clinical symptoms and mortality, preventing ICU admission and shortening the duration of hospital stay.

References

1. Guan W, Ni Z, Hu Yu, Liang W, Ou C, He J. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med 2020;382:1708-1720. doi:10.1056/ NEJMoa2002032
2. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473-474. doi: 10.1126/science.abb8925.
3. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529-539. doi: 10.1007/s00281-017-0629-x.

4. Shimabukuro-Vornhagen A, Gödel P, Subklewe M, et al. Cytokine release syndrome. J Immunother Cancer. 2018;6(1):56. doi: 10.1186/s40425-018-0343-9.
5. Chen X, Zhao B, Qu Y, et al. Detectable Serum Severe Acute Respiratory Syndrome Coronavirus 2 Viral Load (RNAemia) Is Closely Correlated With Drastically Elevated Interleukin 6 Level in Critically Ill Patients With Coronavirus Disease 2019. Clin Infect Dis. 2020;71(8):1937-1942. doi: 10.1093/cid/ciaa449.
6. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health. Available at https://www.covid19treatmentguidelines.nih.gov/. Accessed [March 5, 2021].
7. REMAP-CAP Investigators, Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM,et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Feb 25:NEJMoa2100433. doi: 10.1056/NEJMoa2100433. Epub ahead of print.
8. WHO: Clinical management of severe acute respiratory infection when novel coronavirus (2019-nCoV) infection is suspected:interim guidance. January 28, 2020. https://www.who. int/docs/default-source/coronaviruse/clinical-management-of- novel-cov.pdf. Accessed Feb 15, 2020.
9. National Health Commission of China: New corona virus pneumonia prevention and control program,5th Ed., 2020. Available at:http://www.nhc.gov.cn/jkj/s3577/202002/a5d6f7b8c48c451c87dba14889b30147/files/3514cb996ae24e2faf65953b4ecd0df4.pdf. Accessed February 21, 2020.)
10. Trabulus S, Karaca C, Balkan II, et al. Kidney function on admission predicts in-hospital mortality in COVID-19. PLoS One. 2020;15(9):e0238680. doi: 10.1371/journal.pone.0238680.
11. Campochiaro C, Della-Torre E, Cavalli G, et al.; TOCI-RAF Study Group. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med. 2020;76:43-49. doi: 10.1016/j.ejim.2020.05.021.
12. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970-10975. doi: 10.1073/pnas.2005615117.
13. Campins L, Boixeda R, Perez-Cordon L, Aranega R, Lopera C, Force L. Early tocilizumab treatment could improve survival among COVID-19 patients. Clin Exp Rheumatol. 2020;38(3):578.
14. Capra R, De Rossi N, Mattioli F, et al. Impact of low dose tocilizumab on mortality rate in patients with COVID-19 related pneumonia. Eur J Intern Med. 2020;76:31-35. doi:10.1016/j.ejim.2020.05.009
15. Gupta S, Wang W, Hayek SS, et al., STOP-COVID Investigators. Association Between Early Treatment With Tocilizumab and Mortality Among Critically Ill Patients With COVID-19. JAMA Intern Med. 2021; 181(1):41-51.
16. Luo P, Liu Y, Qiu L, Liu X, Liu D, Li J. Tocilizumab treatment in COVID-19: A single center experience. J Med Virol. 2020;92(7):814-818. doi: 10.1002/jmv.25801. Epub 2020 Apr 15.
17. Mo Y, Adarkwah O, Zeibeq J, Pinelis E, Orsini J, Gasperino J. Treatment With Tocilizumab for Patients With COVID-19 Infections: A Case-Series Study. J Clin Pharmacol. 2021;61(3):406-411. doi: 10.1002/jcph.1787. Epub 2020 Nov 29. PMID: 33180360.
18. Morena V, Milazzo L, Oreni L, et al. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. Eur J Intern Med. 2020;76:36-42. doi: 10.1016/j.ejim.2020.05.011.
19. Sciascia S, Aprà F, Baffa A, et al.. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol. 2020;38(3):529-532.
20. Rosas IO, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021 Feb 25:NEJMoa2028700. doi: 10.1056/NEJMoa2028700.
21. Somers EC, Eschenauer GA, Troost JP,et al. Tocilizumab for treatment of mechanically ventilated patients with COVID-19. Clin Infect Dis. 2020 Jul 11:ciaa954. doi: 10.1093/cid/ciaa954.
22. Klopfenstein T, Zayet S, Lohse A, et al.; HNF Hospital Tocilizumab multidisciplinary team. Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. Med Mal Infect. 2020;50(5):397-400. doi: 10.1016/j.medmal.2020.05.001.
23. Hermine O, Mariette X, Tharaux PL, Resche-Rigon M, Porcher R, Ravaud P, CORIMUNO-19 Collaborative Group. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and

Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med. 2021; 181(1):32-40.
24. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med. 2021;384(1):20-30. doi: 10.1056/NEJMoa2030340. Epub 2020 Dec 17.

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