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Original Article / Orijinal Araştırma

Evaluation of Treatment with a Single (400 mg) versus Double Dose (800 mg) of Tocilizumab in Acute Respiratory Distress Syndrome Associated with COVID-19 Pneumonia

COVID-19 Pnömonisi ile İlişkili Akut Solunum Sıkıntısı Sendromunda tek doz (400 mg) ve çift doz (800 mg) Tocilizumab ile Tedavinin Değerlendirilmesi

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Abstract

Background: COVID-19 is a viral infectious caused by novel coronavirus called as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Recent studies have shown that the level of IL-6 in the severe infection group was higher than that in the moderate group, suggesting that IL-6 can be used as a biomarker for severity assessment. However, the correlation of IL-6 levels in critically ill patients is still unknown. Tocilizumab is a monoclonal antibody against the IL-6 receptor and commonly used for cytokine storm or macrophage activation syndrome (MAS) in COVID-19 patients.

Objective: In this study, we wanted to compare the clinical outcomes of single dose tocilizumab (400 mg) and double dose tocilizumab (800 mg) as treatment.

Material and Method: In this retrospective analysis we have included 120 patients with mild Acute Respiratory Distress Syndrome (ARDS) associated with COVID-19 pneumonia who received tocilizumab 400 mg once or twice daily. The two treatment groups were compared in terms of age, gender, comorbid diseases, arterial oxygen pressure (PaO_2), oxygen saturation (SaO_2) on room air, admission to the intensive care, length of stay in the intensive care unit, status of intubation, mortality, C reactive protein, white blood cell count, platelets, neutrophil, lymphocyte, ferritin, D-dimer, procalcitonin levels.

Results: There were no statistically significant difference between the two dosing regimens in gender, arterial oxygen pressure (PaO_2), oxygen saturation (SaO_2) on room air, comorbidities, need for intubation, mortality, requirement for intensive care, total length of hospital stay, length of stay in intensive care, CRP, WBC, platelets, neutrophils, lymphocytes, ferritin, D-dimer and procalcitonin levels.

Conclusion : Currently the short and long term adverse effects of tocilizumab have not been clearly reported in the literature. The clinical outcomes of once or twice daily tocilizumab did not differ significantly in terms of efficacy. Therefore a single dose of 400 mg once daily tocilizumab could be a rational treatment option.

Keywords: Tocilizumab, coronavirus, acute respiratory distress syndrome

Öz

Arka plan: COVID-19, şiddetli akut solunum sendromu koronavirüs 2 (SARS-CoV-2) olarak adlandırılan yeni koronavirüsün neden olduğu viral bir enfeksiyondur. Son çalışmalar, şiddetli enfeksiyon grubundaki IL-6 seviyesinin orta gruptan daha yüksek olduğunu göstermiştir, bu da IL-6'nın şiddet değerlendirmesi için bir biyobelirteç olarak kullanılabileceğini düşündürmektedir. Bununla birlikte, kritik hastalardaki IL-6 düzeylerinin korelasyonu hala bilinmemektedir. Tocilizumab, IL-6 reseptörüne karşı monoklonal bir antikordur ve COVID-19 hastalarında sitokin fırtınası veya makrofaj aktivasyon sendromu (MAS) için yaygın olarak kullanılır.

Amaç: Bu çalışmada tedavi olarak tek doz tosilizumab (400 mg) ve iki doz tosilizumab (800 mg) uygulamasının klinik sonuçlarını karşılaştırmak istedik.

Gereç ve Yöntem: Bu retrospektif analize, günde bir veya iki kez 400 mg tocilizumab alan COVID-19 pnömonisi ile ilişkili hafif Akut Solunum Sıkıntısı Sendromu (ARDS) olan 120 hastayı dahil ettik. İki tedavi grubu yaş, cinsiyet, eşlik eden hastalıklar, arteriyel oksijen basıncı (PaO_2), oda havasında oksijen satürasyonu (SaO_2), yoğun bakıma yatış, yoğun bakımda kalış süresi, entübasyon durumu açısından karşılaştırıldı. , mortalite, C reaktif protein, beyaz kan hücresi sayısı, trombositler, nötrofil, lenfosit, ferritin, D-dimer, prokalsitonin seviyeleri.

Bulgular: Cinsiyet, arteriyel oksijen basıncı (PaO_2), oda havasında oksijen satürasyonu (SaO_2), komorbiditeler, entübasyon ihtiyacı, mortalite, yoğun bakım gereksinimi, toplam hastanede kalış süresi açısından iki doz rejimi arasında istatistiksel olarak anlamlı bir fark yoktu. , yoğun bakımda kalış süresi, CRP, WBC, trombosit, nötrofil, lenfosit, ferritin, D-dimer ve prokalsitonin düzeyleri.

Sonuç: Halihazırda tocilizumabın kısa ve uzun dönem yan etkileri literatürde net olarak bildirilmemiştir. Günde bir veya iki kez tocilizumabın klinik sonuçları, etkinlik açısından önemli ölçüde farklılık göstermedi. Bu nedenle günde bir kez 400 mg'lık tek doz tocilizumab rasyonel bir tedavi seçeneği olabilir.

Anahtar Kelimeler: Tocilizumab, koronavirüs, akut solunum sıkıntısı sendromu

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was first detected in Wuhan City, China. COVID-19 was caused by novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has caused a worldwide pandemic.[1] Although the majority of patients survive the disease with mild to moderate symptoms, almost one third of the individuals are at risk of developing acute respiratory distress syndrome (ARDS) due to COVID-19. This group of severe patients may require mechanical ventilation (MV), intensive care, and their diseases may result in death.[2] A systemic inflammatory response develops in the body due to COVID-19 and in severe cases this inflammatory response induces damage to the lungs and other body organs.[2,3]

Cytokin storm plays an important role in critical patient groups with SARS-CoV-2 infection[4,5] which is mainly characterized by elevated plasma interleukin 6 (IL-6). According to recent COVID-19 studies it was elaborated that the level of IL-6 in the severe group was higher than that in the moderate group,[6,7] accordingly, it suggests that IL-6 can be used as a biomarker for severity assessment in COVID-19-related cytokin storm. However, the correlation of IL-6 levels in critically ill patients is still unknown. Tocilizumab, a monoclonal antibody against IL-6 receptor, has been previously used in the treatment of rheumatological diseases but with the outbreak of the COVID-19 pandemic it has been widely used in hospitals to treat COVID-19.[8]

In the context of ongoing pandemic, Xu et al. were the first to claim that tocilizumab could possibly leverage clinical outcomes on cytokine release syndrome (CRS) triggered by SARS-CoV-2. As of February 2020, they treated 21 severe or critical COVID-19 patients with tocilizumab and published that oxygen support decreased by 75% and CT images improved at a rate of 90.5%.[9]

Cytokine storm is a reaction state of the immune system that causes an uncontrolled release of proinflammatory cytokines. Indeed, under normal physiological conditions, cytokines are part of the body's immune response to infection, but their uncontrolled excess release can cause multisystem organ damage and death.[10] Cytokine storms can be caused by a range of infectious and non-infectious etiologies, including viral respiratory infections such as SARS-CoV-1 and SARS-CoV-2.[11-13]

In this retrospective study, we have analyzed patients with mild ARDS associated with COVID-19 pneumonia who were treated with a double dose of tocilizumab versus single dose and compared clinical outcomes.

MATERIAL AND METHOD

In this retrospective analysis we have included 120 patients with mild Acute Respiratory Distress Syndrome associated with COVID-19 pneumonia who received tocilizumab 400 mg once or twice daily between 01.06.2020 and 01.12.2020. The study protocol was approved by the Scientific Research Commission of the Turkish Ministry of Health. The study was approved by the Ethics Committee of the Harran University (protocole number:HRU/21.02.27). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

During the pandemic, the firstline treatment approach of our instution can be elaborated as: favipiravir, heparin, protein pump inhibitor and antibiotherapy. Tocilizumab 400mg/800 mg and other anti-inflammatory drugs were administered as secondline therapy in patients who developed cytokine storm due to COVID-19 and did not benefit from first-line treatment. We included patients with acute respiratory distress syndrome who did not benefit from first-line therapy and who received tocilizumab as second-line therapy.

The patients were divided into two groups according to the dosage of tocilizumab (800 mg versus 400 mg). The two groups were compared in terms of age, gender, comorbid diseases, arterial oxygen pressure (PaO_2), oxygen saturation (SaO_2) on room air, admission to the intensive care, length of stay in the intensive care, status of intubation, mortality, C reactive protein (CRP), white blood cell (WBC) count, platelet, neutrophil, lymphocyte, ferritin, D-dimer, procalcitonin levels. Age, gender, comorbid diseases, status of intubation, mortality, admission to the intensive care unit, length of stay in the intensive care, arterial oxygen pressure (PaO_2), oxygen saturation (SaO_2) on room air, C reactive protein (CRP), white blood cell (WBC) count have been analyzed in all patients. The mean calculation for platelets, neutrophils, lymphocyte, ferritin, D-dimer, procalcitonin levels have been conducted. In addition to this, regression analysis was performed on the factors affecting mortality.

The inclusion criteria were as follows:

1. PCR positivity or thorax CT consistent with COVID-19 pnemonia (14).
2. Age above 18 years
3. Mild ARDS manifestations related to COVID-19 pneumonia (200 mmHg<PaO_2/FiO_2<300mmHG+ PEEP or CPAP 200 mmHg<PaO_2/FiO_2<300mmHG+ PEEP or CPAP ≥5cm H_2O)

The exclusion criteria were as follows:

1. Patients who have received other anti-inflammatory drugs (steroid, anakinra)
2. Patients who receive treatment other than favipiravir, heparin, protein pump inhibitor and antibiotics in initial treatment.
3. Age under 18 years

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). The assumption of normal distribution of data was tested by kolmogorov-smirnov test. The patients were divided into two groups as those receiving tocilizumab 400 mg treatment and tocilizumab 800

mg treatment. Mann Whithney-U test was applied to numerical data and chi-square test was applied to nominal data. In addition, chi-square and student t tests were performed on the exitus and surviving groups to determine the factors affecting mortality.The hypotheses are two-sided and p≤0.05 was considered statistically significant at 95% confidence interval.

RESULTS

A total of 120 patients were retrospectively investigated between 01.06.2020 and 01.12.2020. The distribution of the individuals according to dosing regimen were as follows: 54 patients were treated with a single dose of tocilizumab 400 (400 mg), and 66 patients with a double dose of tocilizumab 400 (800 mg). The characteristics and parameters of two groups are provided in **Table 1** and **Table 2**.

There were no statistically significant differences between the groups receiving tocilizumab 400 or tocilizumab 800 in terms of gender, comorbidities, requirement for intubation, mortality, and need for intensive care (p>0.05) (**Table 1**).

No statistically significant differences were found between the groups receiving tocilizumab 400 or tocilizumab 800 in terms of age, oxygen saturation (SaO_2) on room air, PaO_2, total length of hospital stay, length of stay in intensive care, CRP, WBC, platelet, neutrophil, lymphocyte, ferritin, D-dimer and procalcitonin values (p>0.05) (**Table 2**).

Comparisons were made between discharged and deceased groups to identify factors affecting their mortality (**Table 3**).

When discharged and deceased patients were compared, it was found that the presence of additional disease, requirement for intensive care, requirement for intubation, length of stay, age, length of stay in the intensive care unit, increase in WBC, increase in neutrophils, increase in procalcitonin were found to be statistically higher in exitus patients. Oxygen saturation (SaO_2) was significantly lower in the group with on room air exitus (p≤ 0.05) (**Table 3**). Receiving tocilizumab 400 mg or 800 mg treatment had no effect on mortality.

Table 1. Comparison of the demographic parameters between the two groups

	Tocilizumab single dose (1x400 mg) n=54	Tocilizumab double dose (2x400 mg) n=66	All Patients n:120	P value
Gender				0.1
Female	26 (48.1%)	20 (30.3%)	46 (38.3%)	
Male	28 (51.9%)	46 (69.7%)	74 (61.6%)	
Hypertension				0.5
Yes	22 (40.7%)	32 (48.4%)	54 (45%)	
No	32 (59.3%)	34 (51.6%)	66 (55%)	
Diabetes mellitus				0.7
Yes	8 (14.8%)	12 (22.2%)	20 (16.6%)	
No	46 (85.2%)	54 (77.8%)	100 (83.3%)	
Chronic Renal Failure				0.6
Yes	2 (3.7%)	4 (6.06%)	6 (5%)	
No	52 (96.3%)	62 (93.94%)	114 (95%)	
Heart failure				0.8
Yes	4 (7.4%)	4 (6.06%)	8 (6.6%)	
No	50 (92.6%)	62 (93.94%)	112 (93.3%)	
Chronic obstructive pulmonary disease				0.7
Yes	6 (11.1%)	6 (9.09%)	12 (10%)	
No	48 (88.9%)	60 (90.91%)	108 (90%)	
Other chronic disorders				0.8
Yes	4 (7.4%)	6 (9.09%)	10 (8.3%)	
No	50 (92.6%)	60 (90.91%)	110 (91.6%)	
Comorbid disease				0.8
Yes	32 (59.25%)	38 (57.57%)	70 (58.3%)	
No	22 (40.75%)	28 (42.43%)	50 (41.6%)	
Need for intubation				0.2
Yes	4 (7.4%)	12 (18.18%)	16 (13.3%)	
No	50 (92.6%)	54 (81.82%)	114 (86.6%)	
Mortality				0.5
Yes	4 (7.4%)	8 (12.12%)	12 (10%)	
No	50 (92.6%)	58 (87.88%)	108 (90%)	
Need for intensive care				0.4
Yes	10 (18.51%)	18 (27.27%)	18 (23.3%)	
No	44 (81.49%)	48 (72.73%)	102 (76.6%)	

p≤ 0.05 was considered statistically significant

Table 2. Comparison of laboratory and other parameters between the two groups

	Tocilizumab single dose (1x400 mg) n=54 median (range min-max)	Tocilizumab double dose (2x400 mg) n=66 median (range min-max)	All patients n:120 median (range min-max)	P value
Age	67 (31 to 81)	64 (28 to 88)	65.50 (28 to 88)	0.5
Oxygen saturation (SaO_2) on room air (mean+/-sd)	83.92±2.26	83.84±2.25	83.88±2.24	0.8
PaO_2(mean+/-sd)	51.14±3.20	51.54±3.38	51.36±3.28	0.6
Total length of hospital stay	12 (6 to 25)	14 (7 to 41)	13 (6 to 41)	0.1
Length of stay in intensive care	0 (0 to 20)	0 (0 to 24)	0 (0 to 24)	0.3
C Reactive Protein (CRP)	66 (3 to 306)	79 (4 to 227.60)	68.95 (3 to 306)	0.1
White Blood Cell (WBC)	8.76 (2.77 to 20.42)	8.79 (1.50 to 22.80)	8.77 (1.50 to 22.80)	0.9
Platelets	186 (88 to 623)	208 (116 to 363)	208 (88 to 623)	0.5
Neutrophils	7.85 (0.27 to 19.22)	7.15 (0.54 to 20.99)	7.54 (0.27 to 20.99)	0.7
Lymphocytes	0.79 (0.27 to 3.33)	0.86 (0.23 to 5.90)	0.8 (0.23 to 5.90)	0.6
Ferritin	728 (71.10 to 3699)	807 (99.8 to 3625.50)	788.65 (71.1 to 3699	0.8
D-dimer	727 (188 to 4300)	666 (216 to 4420)	719.5 (188 to 4420)	0.8
Procalcitonin	0.22 (0.01 to 3.26)	0.12 (0.01 to 31.44)	0.2 (0.01 to 31.44)	0.4

p≤ 0.05 was considered statistically significant

Table 3. Factors affecting mortality

	Exitus n: 12	Discharged n: 108	p
Gender			0.7
Female	4 (33.3%)	42 (38.8%)	
Male	8 (66.6%)	66 (61.2%)	
Concomittant Disease			0.02
Yes	12 (100%)	50 (46.2%)	
No	0 (0%)	58 (53.8%)	
Requirement for intensive care			0.01
Yes	12 (100%)	16 (14.8%)	
No	0 (0%)	92 (85.2%)	
Requirement for intubation			0.01
Yes	12 (100%)	4 (3.7%)	
No	0 (0%)	104 (96.3%)	
Medication			0.5
Tocilizuman 400	4 (33.3%)	50 (46.2%)	
Tocilizumab 800	8 (66.6%)	58 (53.8%)	
	Exitus mean±sd	**Discharged mean±sd**	**p**
Hospital stay	20.33±8.82	14.29±6.59	0.04
Age	76.66±7.89	59.85±15.65	0.01
Intensive Care Unit Stay	11.16±8.77	1.50±4.58	0.01
Oxygen saturation (SaO_2) on room air	82±2.60	84.09±2.12	0.02
PaO_2	50.5±4.50	51.46±3.16	0.5
CRP	103.51±53.62	75.89±54.46	0.2
WBC	12.95±6.87	9.05±4.36	0.05
Platelets	194.66±89.22	217.5±86.12	0.5
Neutrophil	10.82±7.87	7.25±4.03	0.07
Lymphocyte	0.68±0.34	1.05±0.90	0.3
Ferritin	1123.51±904.99	917.97±743.82	0.5
D-dimer	936.5±388.38	1023.18±914.08	0.8
Procalsitonin	5.83±12.59	0.41±0.67	0.01

p≤ 0.05 was considered statistically significant

DISCUSSION

The present study showed that there was no difference between the double dose of tocilizumab (800 mg) compared to single dose therapy (tocilizumab 400 mg) in terms of their clinical outcomes. When discharged and deceased patients were compared, it was found that then presence of the presence of additional disease, the need for intensive care, the need for intubation, the length of stay, the age, the length of stay in the intensive care unit, the increase in WBC, the increase in neutrophils, the increase in procalcitonin were found to be statistically higher in exitus patients. Oxygen saturation (SaO_2) on room air was significantly lower in the exitus patients. Treatment with tocilizumab 400 mg or 800 mg had no effect on mortality. Undoubtedly, there are numerous controversial treatment options for COVID-19 which is a novel disease. Tocilizumab therapy has become prominent in COVID-19 pneumonia in patients who were unresponsive to treatment. Eimer J. et al. compared 29 patients receiving tocilizumab with 58 patients receiving only routine care and not only the ventilator-free days of the patients treated with tocilizumab were significantly more but also extubation was achieved at an earlier stage and in a higher number of patients. Both the length of stay in the ICU and the length of hospital stay were significantly shorter in patients treated with tocilizumab.[15] Similarly, in another study, mortality was 12% lower in COVID-19 patients treated with tocilizumab.[16] Although research on tocilizumab has increased with the pandemic, there is still no clear information about the dose of tocilizumab in COVID-19 pneumonia. According to Tonyati et al. and Colaneri et al. administered tocilizumab from 8 mg/kg to a maximum of 800 mg in most of the patients.[17,18] Alattar et al. used a median dose of 5.7 mg/kg/dose,[19] Luo et al. administeredlower doses of tocilizumab (80-600 mg per dose),[20] and Xu et al. targeted a dose of 4-8 mg/kg per dose. These varying dosing regimens make it complicated to perform a comparison between these studies and to evaluate the impact of this treatment.[21]

Farzaneh Dastan et al. have investigated the efficacy of asingle dose of tocilizumab 400 and reported that it was a promising agent for patients with severe or critical SARS-CoV-2 infection, if initiated immediately at the severe stage. In their study of 42 cases, 35 patients had clinical improvement while 7 patients died.[22] In our study, there were no statistically significant differences in the length of stay in the hospital and intensive care unit, intubation, need for intensive care and mortality among the patients receiving 400 mg and 800 mg tocilizumab therapy.

On the other hand, there are also studies that do not recommend the use of tocilizumab. Salvarani et al. published a randomized study of adults with a PaO_2/FiO_2 ratio of 200-300 mm Hg who were treated with tocilizumab showed no difference in progression compared to standard care.[23] In another systematic review, it was stated that there is insufficient evidence regarding the clinical efficacy and safety of tocilizumab in patients with COVID-19. Its use should be considered experimental, requiring ethical approval and clinical trial surveillance.[24]

Adverse effects of tocilizumab on COVID-19 patients are still uncertain. In a recently performed double-blind, randomized controlled study of patients with rheumatoid arthritis (RA), the principal adverse effects associated with tocilizumab were a transient decrease in leukocytes, elevated liver enzymes, dyslipidemia, and negativity associated with infection.[25] In our study, there were no groups of patients with moderate or severe ARDS, thus had no data on whether 400 mg or 800 mg tocilizumab use would have different effectsin these two groups. In addition, in our study, mortality was observed to be higher in the group treated with tocilizumab 800 mg, but it was not statistically significant. Although there is no difference between the clinical classifications of the groups, doctors may tend to give 800 mg tocilizumab treatment to more severe cases.

CONCLUSION

We do not have clear and adequate data about the short- and long-term adverse effects of tocilizumab. In this case, a single dose use of 400 mg would be more rational as the clinical outcomes between tocilizumab 400 mg and 800 mg are not different, Since it is difficult to accessevery drug during this pandemic conditions, we think that tocilizumab 400 mg treatment can serve a good alternative to tocilizumab 800 mg treatment. There is no doubt that comprehensive studies with large groups of patients are necessary.

Abbreviations: **ARDS**: Acute Respiratory Distress Syndrome, **CRP**: C reactive protein, **CRS**: cytokine release syndrome, **CT**: computerized tomography, **ICU**: intensive care unit, **IL**: interleukins, **MV**: mechanical ventilation, **PaO_2**: arterial oxygen pressure, **RA**: rheumatoid arthritis, **SARS-CoV-2**: severe acute respiratory syndrome coronavirus 2, **WBC**: White blood cell

ETHICAL DECLARATIONS

Ethics Committee Approval: Ethical approval was obtained from the ethics committee of the Harran University. Ethics committee number: HRU/21.02.27.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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