Research Article / Araştırma Makalesi
doi: 10.18678/dtfd.1084026

Duzce Med J, 2022;24(2):116-120
Düzce Tıp Fak Derg, 2022;24(2):116-120

Comparison of Tocilizumab and Anakinra in the Treatment of COVID-19: A Single-Center Experience

COVID-19 Tedavisinde Tocilizumab ve Anakinra'nın Karşılaştırılması: Tek Merkez Deneyimi

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Received / Geliş Tarihi : 07.03.2022
Accepted / Kabul Tarihi : 27.05.2022
Available Online / Çevrimiçi Yayın Tarihi : 05.07.2022

ABSTRACT

Aim: The aim of this study was to examine whether a difference between endotracheal intubation, non-invasive mechanical ventilation, high flow oxygen therapy requirements and 28-day mortality rate in severe and critical coronavirus disease 2019 (COVID-19) patients receiving anakinra and tocilizumab treatment.

Material and Methods: A total of 70 patients infected with COVID-19, who were treated with tocilizumab and anakinra from April 2020 to March 2021 at Karabük Training and Research Hospital, were recruited in this retrospective study. Data on patient demographics, comorbidities, treatments, clinical outcomes of the patients' and hemogram findings were retrieved from hospital records.

Results: The mean age of the patients was 61.34±11.8 years. Of the 70 patients, 12 (17.1%) were female and 58 (82.9%) were male. Severe and critical COVID-19 cases were evident in 48 (68.6%), and 22 (31.4%) patients, respectively. The mortality rate in 28 days was not statistically significantly different between the tocilizumab and anakinra groups (p=0.999). Both the necessity of high flow oxygen therapy and non-invasive mechanical ventilation were lower in the tocilizumab group than in the anakinra group (p<0.001, and p=0.002, respectively), while there was no statistically significant difference in the necessity of intubation between the two groups (p=0.999). The length of stay was also significantly shorter in the tocilizumab group (p=0.027).

Conclusion: High flow oxygen therapy, non-invasive mechanical ventilation requirements, and length of stay were significantly lower than anakinra in the tocilizumab group. Excessive inflammatory response with cytokine storm features causes severe disease course and worsens prognosis in COVID-19.

Keywords: Anakinra; COVID-19; tocilizumab.

ÖZ

Amaç: Bu çalışmanın amacı anakinra ve tocilizumab tedavisi alan ağır ve kritik koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) hastalarında; endotrakeal entübasyon, non-invaziv mekanik ventilasyon, yüksek akım oksijen tedavisi gereksinimleri ve 28 günlük mortalite oranları arasında bir farklılık olup olmadığının araştırılmasıdır.

Gereç ve Yöntemler: Bu geriye dönük çalışmaya, Nisan 2020 ile Mart 2021 tarihleri arasında Karabük Eğitim ve Araştırma Hastanesi'nde tocilizumab ve anakinra ile tedavi edilmiş olan COVID-19 ile enfekte 70 hasta dahil edildi. Hastaların demografik özellikleri, komorbiditeler, tedaviler, hastaların klinik sonuçları ve hemogram bulguları ile ilgili veriler hastane kayıtlarından alındı.

Bulgular: Hastaların ortalama yaşı 61,34±11,8 yıl idi. 70 hastanın 12 (%17,1)'si kadın ve 58 (%82,9)'i erkekti. Ağır ve kritik COVID-19 vakası sırasıyla 48 (%68,6) hastada ve 22 (%31,4) hastada görüldü. Tocilizumab ve anakinra grupları arasında; 28 gündeki mortalite oranı istatistiksel olarak anlamlı şekilde farklı değildi (p=0,999). Yüksek akım oksijen tedavisi ve non-invaziv mekanik ventilasyon gereksinimlerinin her ikisi de tocilizumab grubunda anakinra grubundan daha düşük (sırasıyla p<0,001 ve p=0,002) iken entübasyon ihtiyacı bakımından iki grup arasında istatistiksel olarak anlamlı bir farklılık yoktu (p=0,999). Tocilizumab grubunda hastanede kalış süresi de anlamlı olarak daha kısaydı (p=0,027).

Sonuç: Tocilizumab grubunda yüksek akım oksijen tedavisi, non-invaziv mekanik ventilasyon gereksinimleri ve hastanede kalış süresi anakinra grubuna göre anlamlı derecede daha düşüktür. COVID-19'da sitokin fırtınası, aşırı inflamatuar yanıt, ciddi hastalık seyrine neden olmakta ve prognozu kötüleştirmektedir.

Anahtar kelimeler: Anakinra; COVID-19; tocilizumab.

INTRODUCTION

Worldwide, more than 112 million cases of coronavirus and 3.8 million deaths have been reported (1). Nowadays only glucocorticoids are known to decrease mortality rates among severe coronavirus disease 2019 (COVID-19) infections (2,3). The corticosteroids' mechanism in critically ill patients is decreasing an excessive host inflammatory response which is responsible for serious illness and death from COVID-19.

Interleukin-1 and interleukin-6 are cytokines that are released into infection and stimulate acute-phase and fever responses (3,4). Anakinra is a recombinant monoclonal antibody and a slightly modified version of the human interleukin-1 receptor antagonist protein which received approval to treat rheumatoid arthritis, idiopathic pulmonary fibrosis and auto-inflammatory diseases such as the Familial Mediterranean Diseases (5,6). Tocilizumab is another monoclonal antibody that inhibits both membrane-bound and soluble interleukin-6 receptors (7). It is used to treat diseases such as rheumatoid arthritis and systemic-onset juvenile idiopathic arthritis (7). In the COVID-19 pandemic, anakinra and tocilizumab are used for the purpose of decreasing and managing host inflammatory responses in clinics worldwide (8,9). However, there is an inadequate number of research into severe COVID-19 patients between anakinra and tocilizumab usage that investigate the mortality rates from COVID-19. We aimed to investigate the mortality rate and mortality at day twenty-eighth of COVID-19 patients whose treatment includes anakinra and tocilizumab according to patients' genders, ages, other diseases, blood test results, and necessity of non-invasive mechanical ventilation (NIMV) or endotracheal intubation.

MATERIAL AND METHODS

Study Design and Participants

The patients infected with COVID-19, who were treated with tocilizumab and anakinra from April 2020 to March 2021 at Karabük Research and Training Hospital, were recruited in this retrospective study. All patients were anonymous.

The study was approved by both the Ministry of Health and the Local Ethics Committee (Karabük University Ethics Committee, dated June 2, 2021 and numbered 579). The patients were given an informed consent form and their written consent was obtained.

Procedures

Data on patient demographics (age, gender), comorbidities, treatments, clinical outcomes of the patients' blood biochemistry, and hemogram findings were retrieved from hospital records. Diabetes, hypertension, chronic renal failure, heart failure, chronic lung disease, and malignancy were noted in the patients. Only those treated with tocilizumab and anakinra while they were hospitalized were included in the study.

Eligibility criteria for tocilizumab and anakinra administration were: a diagnosis of COVID-19 confirmed upon reverse-transcriptase polymerase chain reaction (RT-PCR) positivity for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on nasopharyngeal swab; hyper-inflammation defined as an elevation in either C-reactive protein (CRP) or ferritin, in the presence of increased lactate dehydrogenase (LDH); severe respiratory involvement defined by typical radiological findings at chest X-Ray and /or computed tomography scan (10).

The severity of the COVID-19 was classified into four types: mild, moderate, severe, and critical (11). The serum levels of CRP, complete blood count, D-dimer, ferritin, and LDH were observed before tocilizumab and anakinra administration. The levels of pulse oxygen were observed before and after tocilizumab and anakinra administration. Hospitalization day, high flow oxygen therapy (HFOT) and mechanical ventilator needs, and mortality rate were evaluated in patients receiving tocilizumab and anakinra treatment.

Statistical Analysis

Statistical analysis was done with SPSS v.22.0. Normality assumption was examined with the Shapiro-Wilk test. Independent samples t-test or Mann-Whitney U test was used to compare groups whenever appropriate. Pearson chi-square or Fisher's exact test was used to analyze categorical variables. Data are presented as mean, standard deviation, or median (interquartile range) [min-max] for numerical variables, and as the number and percentage for categorical variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics

Of the 70 patients, 12 (17.1%) were female and 58 (82.9%) were male. The mean age of the patients was 61.34±11.8 years. Severe and critical COVID-19 cases were evident in 48 (68.6%), and 22 (31.4%) patients, respectively. All patients received high-dose steroids (250 mg/day). At the same time, 66 (94.3%) patients were treated with favipiravir. Considering biological agents 30 (42.9%) patients were treated with anakinra and 40 (57.1%) patients were treated with tocilizumab.

Comparisons of the patients receiving tocilizumab and anakinra revealed no statistically significant difference in age (p=0.271) and gender distribution (p=0.927). While chronic lung disease in the anakinra group was higher than in the tocilizumab group (n=13, 43.3% vs. n=7, 17.5%, respectively, p=0.018), there was no statistically significant difference between the groups in terms of diabetes mellitus (p=0.766), hypertension (p=0.580), chronic kidney disease (p=0.573), malignancy (p=0.420), and congestive heart failure (p=0.283, Table 1).

According to the disease severity, while 31 (64.6%) of the 48 patients with the severe disease received tocilizumab, and 17 (35.4%) received anakinra, of the 22 patients with the critical disease, 9 (40.9%) received tocilizumab, and 13 (59.1%) received anakinra (p=0.074).

Laboratory Results

When laboratory results of the tocilizumab and anakinra groups were compared; no statistically significant difference was found between the groups in terms of the CRP (p=0.233), D-dimer (p=0.075), LDH (p=0.194), procalcitonin (p=0.127) and hemoglobin (p=0.571) values. While ferritin (p=0.022), white blood cell count (p<0.001), and platelet count (p<0.001) were higher, a lower level of lymphocytes (p=0.013) was found in the anakinra group. Although the SpO_2 value was higher in the tocilizumab group before treatment (p<0.001), it was similar in groups after the treatment (p=0.234, Table 2).

Clinical Outcomes

The mortality rate in 28 days was not statistically significantly different between the tocilizumab and anakinra groups (p=0.999). Both the necessity of HFOT and NIMV were lower in the tocilizumab group than in the anakinra group (p<0.001, and p=0.002, respectively), while there was no statistically significant difference in the necessity of intubation between the two groups (p=0.999). The length of stay was also significantly shorter in the tocilizumab group (p=0.027, Table 3).

DISCUSSION

In this study, no significant difference was found between tocilizumab and anakinra groups in 28 days of mortality and intubation need. But; HFOT and NIMV requirements, and length of stay were significantly lower than anakinra in the tocilizumab group.

Observational studies have suggested that anakinra and tocilizumab are effective in reducing mortality and/or intubation in patients with severe COVID-19 (12,13). These good results led to this clinical trial, which suggests that tocilizumab, was administered very early in hospitalized patients with COVID-19 infection.

The first clinical experience of tocilizumab in COVID-19 patients have been reported at the end of 2020 in the Lancet Rheumatol (14). After that report, a single-center study including 100 unmatched COVID-19 patients with mechanical ventilation, showed an improvement in the respiratory severity using a disease-specific scale and a decrease in laboratory inflammation parameters after two intravenous administrations of tocilizumab (15). In another retrospective analysis, tocilizumab at the median dose of 5.7 mg/kg showed a significant reduction in invasive mechanical ventilation needs on day 14 (16). A retrospective study conducted on 29 patients treated with high-dose anakinra compared to 16 control, showed that high-dose anakinra was associated with a higher survival rate at 21 days with a reduction in CRP and with progressive improvement results of PaO_2/FiO_2 (17). Whereas in our study there was no reported clinical side effect of anakinra and tocilizumab.

In May 2021, Coloretti et al. (18) reported clinical results in an intensive care unit (ICU) admitted patients requiring mechanical ventilation for acute respiratory distress syndrome (ARDS) due to COVID-19. It was shown that both anakinra and tocilizumab seem to be well tolerated in hospital survival rates. In our study, the survival rates and toleration of medications are similar to the study by Coloretti et al. (18).

Anakinra and tocilizumab increase survival rates in COVID-19 patients. Both medicines decrease the severity and mortality of COVID-19. However, there is no clinical difference in mortality rates between anakinra and tocilizumab. One in 40 patients who received tocilizumab and one in 30 patients who received anakinra were dead until day 28.

Table 1. Demographic and clinical characteristics

	Tocilizumab (n=40)	Anakinra (n=30)	p
Age (years), mean±SD	62.7±11.1	59.5±12.7	0.271
Gender, n (%)			
Male	33 (82.5)	25 (83.3)	0.927
Female	7 (17.5)	5 (16.7)	
Diabetes mellitus, n (%)	12 (30.0)	10 (33.3)	0.766
Hypertension, n (%)	20 (50.0)	17 (56.7)	0.580
CLD, n (%)	7 (17.5)	13 (43.3)	**0.018**
CKD, n (%)	1 (2.5)	2 (6.7)	0.573
CHF, n (%)	7 (17.5)	2 (6.7)	0.283
Malignancy, n (%)	0 (0.0)	3 (10.0)	0.420

CLD: chronic lung disease, CKD: chronic kidney disease, CHF: congestive heart failure

Table 3. Comparison of clinical outcomes in groups

	Tocilizumab (n=40)	Anakinra (n=30)	p
Mortality in 28 days	1 (2.5)	1 (3.3)	0.999
Need for HFOT	2 (5)	13 (43.3)	**<0.001**
Need for NIMV	0 (0)	7 (23.3)	**0.002**
Need for intubation	3 (7.5)	2 (6.7)	0.999
Length of stay	13.5 (6.5) [5-56]	18 (17) [5-37]	**0.027**

HFOT: high flow oxygen therapy, NIMV: non-invasive mechanical ventilation

Table 2. Comparison of laboratory parameters in groups

	Tocilizumab (n=40)	Anakinra (n=30)	p
Ferritin (ng/mL)	1100 (1197) [160-1650]	1552 (571) [188-6797]	**0.022**
CRP (mg/L)	150.5 (111) [19-308]	164 (49) [67-331]	0.233
D-dimer (ng/mL)	1.46 (1.95) [0.31-24]	2.1 (4.5) [0.3-18]	0.075
LDH (U/L)	473 (208) [228-817]	537 (237) [240-930]	0.194
Procalcitonin (ng/mL)	0.09 (0.12) [0.01-5.3]	0.17 (0.25) [0.01-23.48]	0.127
WBC ($x10^3$, µl/mL)	10 (4.3) [2.5-19]	15 (8.3) [7.6-35.8]	**<0.001**
Platelets ($x10^3$, µL)	220 (112) [74-410]	328 (144) [110-959]	**<0.001**
Lymphocytes (µL)	735 (295) [290-2090]	555 (415) [180-5770]	**0.013**
Hemoglobin (g/dL)	13.4 (1.4) [9-16]	13.5 (2) [8.3-15.4]	0.571
SpO_2 (%), before treatment	88 (4.2) [80-96]	82 (6) [60-97]	**<0.001**
SpO_2 (%), after treatment	95 (3) [90-97]	94.5 (3) [90-97]	0.234

CRP: C-reactive protein, LDH: lactate dehydrogenase, WBC: white blood cell, SpO_2: peripheral oxygen saturation

Another study from Spain suggests that the use of anakinra in patients with moderate hyper inflammation associated with severe COVID-19 pneumonia after previous failure of corticosteroids alone or with tocilizumab therapy may be an alternative in the management of these patients, and may prevent deaths (19). However, in our study, there is no significant difference between the tocilizumab and anakinra groups in 28 days of mortality. But; HFOT and NIMV requirements were significantly lower than anakinra in the tocilizumab group.

In February 2021 a meta-analysis of non-randomized cohort studies across comparative reported that anakinra was safe and associated with significant reductions in both mortality and the need for mechanical ventilation (20).

A letter to editor analysis of non-randomized cohort studies is the first to investigate the effect of anakinra versus tocilizumab on the risk for COVID-19 death, showing a clear benefit of IL-1 versus IL-6 inhibition (21). According to our study, we have no evidence to verify this proposition.

One limitation of this study was the small patient population and was single-centered. The higher patient of chronic lung diseases in the anakinra group and the high ferritin value, which is one of the poor prognostic laboratory factors, may have affected our results.

CONCLUSION

High flow oxygen therapy, NIMV requirements, and length of stay were significantly lower than anakinra in the tocilizumab group. Excessive inflammatory response with cytokine storm features causes severe disease course and worsens the prognosis in COVID-19. Studies including larger numbers of patients are needed to comment on the efficacy of anti-inflammatory treatments.

Ethics Committee Approval: The study was approved by the Non-Invasive Clinical Research Ethics Committee of Karabük University (02.06.2021, 579).

Conflict of Interest: None declared by the authors.

Financial Disclosure: None declared by the authors.

Acknowledgments: None declared by the authors.

Author Contributions: Idea/Concept: MA, ÖÇ, BPA; Design: MA, ÖÇ, BPA; Data Collection/Processing: MA, ÖÇ, BPA; Analysis/Interpretation: MA, ÖÇ; Literature Review: MA, ÖÇ, AT, BPA; Drafting/Writing: MA, ÖÇ, AT, BPA; Critical Review: MA, AT, BPA.

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