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Effect of tocilizumab or anakinra use on prognosis in patients admission to intensive care due to COVID-19

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ABSTRACT

Aims: Anticytokine treatments may be beneficial in patients who do not benefit from glucocorticoid treatment, which is the first choice in systemic hyperinflammation cases caused by SARS-COV-2. Interleukin 6 receptor blocker tocilizumab and interleukin-1 receptor antagonist anakinra are anticytokines that have been granted off-label use permits by the Ministry of Health of the Republic of Turkiye. In this study, the effects of these two drugs on laboratory parameters used to evaluate mortality and clinical severity of the disease were investigated.

Methods: The files of patients who received tocilizumab (n:38) and anakinra (n:36) for the treatment of coronavirus disease-2019 between 01.07.2020-31.03.2022 in the Chest Diseases Intensive Care Unit of Adana City Training and Research Hospital were retrospectively reviewed.

Results: Mortality and mechanical ventilation requirement were found to be significantly lower in the tocilizumab group compared to the anakinra group (p=0.005, 0.01, respectively). In both groups, CRP pro BNP and fibrinogen values decreased, while WBC, D-dimer and neutrophil values increased. Unlike anakinra, tocilizumab decreased ferritin values and increased lymphocyte, platelet, INR, urea and aspartate transaminase, total bilirubin, red blood cell values (p=0.004, 0.035, 0.032, 0.09, p<0.001, p=0.002, p=0.006, p=0.008, respectively).

Conclusion: Tocilizumab was associated with significantly lower rates of mortality and mechanical ventilation compared to anakinra.

Keywords: Anakinra, COVID-19, intensive care, tocilizumab

INTRODUCTION

SARS-CoV-2 (COVID-19) can cause pneumonia, acute respiratory distress syndrome (ARDS), cardiovascular changes, and multiple organ failure.[1] Approximately 20% of patients experience severe pulmonary dysfunction. This disease, which affects the whole world, can be asymptomatic or severe. It is possible that SARS-CoV-2 infects cell types such as endothelial vessels, alveolar walls, or macrophages in the lung. The onset of local inflammation caused by SARS-CoV-2 infection activates macrophages in that area. In severe cases, local inflammation cannot be alleviated within the lung and systemic hyperinflammation called mastoid activation syndrome (MAS) may develop. A series of inflammatory pathways are triggered by cytokine release, including interleukin-6 (IL-6) and interleukin-1 (IL-1). Not only hypercytokinemia, but also increased serum levels of ferritin, C-reactive protein (CRP), and D-dimer indicate the development of inflammation and fibrinolysis in COVID-19 patients.[2] There is no specific treatment for this condition, which is described as a cytokine storm, and anticytokine treatments are being investigated.[3] It is difficult to alleviate severe MAS symptoms, and steroids and immunosuppressive drugs are used in treatment. Cytokine-targeted MAS therapy has been studied by various research groups. The IL-1 receptor antagonist anakinra and the IL-6 receptor blocker tocilizumab have been suggested to be effective in alleviating clinical symptoms.[2,4] In the COVID-19 treatment guideline prepared by the Ministry of Health of the Republic of Turkiye, the use of tocilizumab or anakinra with an off-label drug request was recommended in patients with MAS symptoms who did not respond to glucocorticoid treatment.[5] In this study, we aimed to examine the effects of anakinra and tocilizumab treatment on mortality and laboratory parameters in cytokine storm caused by severe COVID-19, for which there is no definitive treatment protocol. The results

may contribute to the development of complex COVID-19 treatment protocols.

METHODS

This study has been approved by the Clinical Researches Ethics Committee of Adana City Training and Research Hospital (Date: 01.07.2021, Decision No:1482). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The files of patients with positive COVID-19 PCR tests who did not improve with favipravir, enoxaparin, levofloxacin, pulse glucocorticoid therapy and tocilizumab (Actemra®) or anakinra (Kineret®) were retrospectively reviewed through the hospital information system between 01.07.2020 and 31.03.2022 in the Chest Diseases Intensive Care Unit of Adana City Training and Research Hospital.

With off-label use approval from the Turkish Medicines and Medical Devices Agency of the Ministry of Health, tocilizumab (8 mg/kg intravenous infusion within 1 hour, 2nd dose 400 mg or 200 mg within 24 hours) or anakinra (2-10 mg/kg subcutaneously twice a day for 4 days) were used. Patients diagnosed with acquired human deficiency syndrome, tuberculosis, and active hepatitis were excluded from the study. Patients' age, gender, comorbid disease, number of days of intensive care, need for mechanical ventilation (MV), mortality or survival status, Acute Physiology and Chronic Health Evaluation (APACHE) II scores procalcitonin, troponin, glucose, urea, creatinine, glomerular filtration rate (GFR), albumin, ferritin, CRP, alanine transaminase (ALT), aspartate transaminase (AST), total bilirubin, lactate dehydrogenase (LDH), pro B type natriuretic peptide (proBNP), D-dimer, white blood count (WBC), red blood count (RBC), platelet, neutrophil, lymphocyte, monocyte, international normalized ratio (INR), and fibrinogen values were recorded. Laboratory values immediately before administration of tocilizumab or anakinra (day 0) and on day 5 of treatment were compared.

Statistical Analysis

The data analyses were performed by SPSS 27 software (SPSS Inc, Chicago, IL, USA). Demographic differences between groups analyzed using Chi-square test for categorical variables and the Independent sample t-test for numaric variables, Fischer's exact test was used for the calculation of gender differences. Normality analysis was performed with the Shapiro-Wilk test. Independent Student's t-test and Mann-Whitney U test were used to analyze the differences between the tocilizumab and anakinra groups. Mortality rates and MV requirements were compared between the groups using the Pearson Chi-square test. Wilcoxon signed-rank test and Paired sample t-test were used to calculate differences in hematological and biochemical parameters, as repeated measures from day 0 to day 5 for the tocilizumab and anakinra groups. Significant p value was considered as $p<0.05$.

Limitations

The lack of a control group that did not use anticytokine treatment and the lack of comparison of laboratory values after the 5th day are the limitations of our study.

RESULTS

The study included 36 patients treated with anakinra (14 female, 28 male), 38 with tocilizumab (10 female, 28 male). The mean age of the anakinra group was 66.42±12 years, and the tocilizumab group was 58.03±13.4 years. There were 63.9% (23/38) comorbidities in the anakinra group and 57.9% (22/36) in the tocilizumab group. Both groups were different in terms of gender and mean age, and similar in terms of comorbid disease rates (p=0.048, p=0.006, p=0.598, respectively). Tocilizumab was administered on the 3.61±2.3rd day of the patient's admission to the intensive care unit, and similarly to anakinra on the 4.14±2.5th day (p=0.318). Mortality rates in the anakinra group (69.4% 25/36) were found to be significantly higher than in the tocilizumab group (36.8% 14/38) (p=0.005). The need for MV in the anakinra group (66.7% 24/36) was higher than in the tocilizumab group (36.8% 14/38) (p=0.01). There was no difference in the number of days of hospitalization after anakinra and tocilizumab treatment in surviving patients (16.97±9, 13.08±7.8, respectively) (p=0.064). The values of laboratory parameters on day 0 without tocilizumab and anakinra are given in **Table 1**.

On the 5th day of anakinra treatment, troponin, albumin, WBC, neutrophil, D dimer values increased, CRP, proBNP, fibrinogen values decreased. On the 5th day of tocilizumab treatment, procalcitonin, urea, AST, total bilirubin, D-dimer, WBC, RBC, platelet, neutrophil, lymphocyte, INR values increased significantly, ferritin, CRP, proBNP, fibrinogen values decreased (**Table 2**).

DISCUSSION

Previous studies have reported that anakinra or tocilizumab are beneficial or ineffective in COVID-19 disease.[6] Salama et al.[7] found that tocilizumab reduced the likelihood of progression to MV in patients with COVID-19 pneumonia who did not require MV, but did not affect survival. Dahms et al.[8] suggested that anakinra had no effect compared to standard care in terms of mortality and clinical improvement. Khani et al.[4] suggested that anakinra may be more beneficial in the early stages of the disease when high cytokine levels are not yet observed, thus preventing progression to severe disease and MV. When studies comparing the use of anakinra and tocilizumab were reviewed, no clear conclusion could be reached regarding the superiority of these two drugs in terms of survival and clinical improvement. There are studies in the literature that found anakinra use superior to tocilizumab[9,10] and reported that anakinra or tocilizumab provided clinical improvement without any difference.[11,12] There are studies reporting that tocilizumab is superior to anakinra, which supports our study.[13,14]

In addition, it has been shown that anakinra did not have a beneficial effect in patients who did not respond positively to tocilizumab treatment, which supports the superiority of tocilizumab treatment.[15]

During the course of COVID-19 disease, CRP, ferritin, and lymphocyte levels may provide insight into the viral load.[16] Continuing increases in CRP, ferritin, and D-dimer elevations, lymphopenia, thrombocytopenia, deterioration

Table 1. Values and comparison of laboratory parameters on day 0 in the anakinra and tocilizumab groups

Laboratory parameters	Reference range (unit)	Anakinra group (n=36)	Tocilizumab group (n=38)	p value
Procalsitonin	0-0.065(µg/L)	0.24±0.22	0.18±0.218	0.213
Troponin	0-16(ng/L)	83.58±326	19.13±24.73	0.147
Glukoz	74-106(mg/dl)	197.25±66.9	190.78±78.5	0.386
Ure	17-43(mg/dl)	64.89±23.85	43.87±16.5	<0.001
Serum creatine	0.67-1.17(mg/dl)	0.85±0.28	0.76±0.27	0.082
GFR	>90 ml/dk/1.7	83.92±22.43	98.89±21.02	0.003
Albumin	35-55(g/L)	28.45±3.36	29.76±3.7	0.116
Ferritin	23.9-336 (µg/L)	767±573	851.5±609	0.492
CRP	0-5 (mg/L)	95.47±57.2	101±82.2	0.825
ALT	5-50 (U/L)	38.86±24.8	70.92±64.76	0.028
AST	5-50 (U-L)	49.25±42.4	60.1±39.2	0.124
Total bilirubin	0.3-1.2 (mg/dl)	0.62±0.26	0.59±0.29	0.727
Lactate dehydrogenase	5-248 (U/L)	624±215	528±201.5	0.037
ProBNP	0-133 (µg/L)	2087±3459	864±1125	0.03
D-dimer	170-550 (µg/L)	2025±2359	1475±1438	0.439
WBC	3.8-11.8 (x10^3/µL)	11.1±3.78	9.98±4.39	0.255
RBC	3.63-4.92 (x10^6/ µL)	4.55±0.445	4.55±0.63	0.987
PLT	179-408 (x10^3/µL)	255±104	283±89	0.214
Neutrophil	1.9-8.2 (x10^3/µL)	10±3.65	8.97±4.27	0.171
Lymphocyte	1.1-3.1 (x10^3/µL)	0.47±0.29	0.54±0.43	0.772
Monocyte	0.2-0.9 (x10^3/µL)	0.522±0.4	0.413±0.25	0.382
INR	0.8-1.2	1.05±0.95	1.09±0.16	0.566
Fibrinogen	180-350 (mg/dl)	592±137.6	592±157	0.85
Interleukin 6	5.3-7.5 (pg/ml)	111±150.6	122.2±236.8	0.238
APACHE-II score		33.39±8.77	33.24±8.60	0.940

GFR: Estimate glomerular filtration rate, CRP: C-reactive protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, ProBNP: pro-B-type natriuretic peptide, WBC: White blood cell, RBC: Red blood cell, PLT: Platelet, INR: International normalized ratio

Table 2. Laboratory parameter values and comparison of anakinra and tocilizumab groups on days 0 and 5

	Anakinra group (n=36)			Tosilizumab group (n=38)		
	0. day	5. day	p value	0. day	5. day	p value
Prokalsitonin	0.24±0.22	1.39±4.23	p=0.673	0.18±0.218	0.819±4.52	p<0.001
Troponin	83.58±326	104.1±261	p=0.06	19.13±24.73	34.39±85.3	p=0.238
Glukoz	197.25±66.9	206.6±81.7	p=0.367	190.78±78.5	188.3±85.6	p=0.824
Ure	64.89±23.85	81.43±41.6	p=0.056	43.87±16.5	62.5±51.15	p<0.001
Serum creatine	0.85±0.28	0.95±0.67	p=0.851	0.76±0.27	0.95±0.96	p=0.267
GFR	83.92±22.43	83.4±29.5	p=0.712	98.89±21.02	95.45±27.15	p=0.267
Albumin	28.45±3.36	28.85±17.7	p=0.009	29.76±3.7	30.65±4.25	p=0.129
Ferritin	767±573	674±408.6	p=0.326	851.5±609	770.84±1537	p=0.004
CRP	95.47±57.2	61.33±88.1	p=0.015	101±82.2	10.06±18.33	p<0.001
ALT	38.86±24.8	48.34±30.35	p=0.091	70.92±64.76	111.8±250.3	p=0.523
AST	49.25±42.4	40.14±20.7	p=0.176	60.1±39.2	79.82±253.8	p=0.002
Total bilirubin	0.62±0.26	0.748±0.394	p=0.169	0.59±0.29	0.758±0.318	p=0.006
LDH	624±215	632.6±320.8	p=0.174	528±201.5	662.6±656	p=0.592
Pro BNP	2087±3459	567.5±648	p=0.008	864±1125	617.3±1146	p=0.035
D-dimer	2025±2359	4030±4376	p=0.053	1475±1438	3106±4114	p=0.094
WBC	11.1±3.78	13.78±5.29	p=0.005	9.98±4.39	14.96±6.18	p<0.001
RBC	4.55±0.445	4.37±0.717	p=0.215	4.55±0.63	4.73±0.79	p=0.008
PLT	255±104	255±139.5	p=0.933	283±89	321.1±125.8	p=0.032
Neutrophil	10±3.65	12.97±5.3	p=0.003	8.97±4.27	13.14±6.42	p<0.001
Lymphocyte	0.47±0.29	0.44±0.37	p=0.403	0.54±0.43	0.726±0.39	p=0.035
Monocyte	0.522±0.4	0.466±0.39	p=0.403	0.413±0.25	0.558±0.49	p=0.208
INR	1.05±0.95	1.05±0.163	p=0.408	1.09±0.16	1.036±0.193	p=0.009
Fibrinogen	592±137.6	393.8±154.9	p<0.001	592±157	243.4±101	p<0.001

GFR: Estimate glomerular filtration rate, CRP: C-reactive protein, ALT: alanine aminotransferase, AST: aspartate aminotransferase, LDH: Laktat dehidrogenaz, ProBNP: pro-B-type natriuretic peptide, WBC: White blood cell, RBC: Red blood cell, PLT: Platelet, INR: International normalized ratio

in liver function tests, and hypofibrinogenemia suggest that the course of the disease is worsening.[17] Ozdemir et al.[18] reported that the lymphocyte count and percentage increased on the third day of tocilizumab treatment, similar to our results. Increased D-dimer levels in COVID-19-associated MAS are a result of pulmonary infiltration and inflammatory response to damage.[19] High D-dimer levels may be a sign of developing MAS.[16] In this study, D-dimer levels increased by 300-400% and it was observed that tocilizumab and anakinra could not stop the increase in D-dimer levels on the 5th day, and the increase continued. Vural et al.[20] reported that serum CRP levels can effectively assess disease severity in COVID-19 disease. Since it does not directly inhibit CRP synthesis like tocilizumab, CRP can be used as a safe test to monitor the acute phase response in patients receiving anakinra treatment.[5] In this study, CRP levels decreased in both the anakinra and tocilizumab groups. Similar to our results, Aljuhani et al.[21] found that mortality decreased with tocilizumab treatment, and D-dimer peak levels did not change. Saruhan et al.[22] found that tocilizumab treatment decreased CRP and ferritin levels and increased urea, AST, D-dimer, and procalcitonin levels, supporting our study results. In our results, the decrease in fibrinogen levels and the increase in D-dimer levels in both groups indicate that laboratory indicators evaluated as MAS continued on day 5. Unlike anakinra, tocilizumab decreased ferritin levels on day 5 and increased lymphocyte, monocyte, platelet, and INR levels. These results suggest that tocilizumab is more beneficial than anakinra in correcting the deteriorated laboratory values in MAS. However, the increase in total bilirubin, AST, procalsitonin and urea are undesirable negative results in the tocilizumab group. An increase in procalcitonin may indicate secondary infection. Therefore, monitoring procalcitonin levels after treatment and obtaining blood and other tissue culture samples is recommended.[5] Liver and kidney function should also be monitored. In the anakinra group, no improvement was achieved in laboratory values different from tocilizumab, Increased troponin values in both groups may be a direct result of coronary thrombotic events, sepsis-related myocardial injury, or the inflammatory surge.[23]

Wang et al.[24] reported that there is no confirmed antiviral drug with a specific effect against SARS-CoV-2, and IL-6 targeted treatments can be used in pandemics where the virus is present. Hyperinflammation associated with COVID-19 is found in only a fraction of all patients, but no specific treatment has been reported for this population.[20] Langer et al.[25] emphasized that the timing of anticytokine treatment is more important than the choice of anticytokine. Clinical trials are ongoing for tocilizumab and anakinra.[26] Further studies are needed to clarify the indications and timing of drug administration.

Limitations

The lack of a control group without anticytokine treatment and the retrospective, single-center design with a limited sample size are the factors limiting our study.

CONCLUSION

As a result, tocilizumab was associated with significantly lower rates of mortality and MV and improvement of laboratory parameters compared to anakinra. In COVID-19 disease developing MAS, but liver and kidney functions should be monitored after tocilizumab treatment. However, the risk of developing secondary infection appears to be higher after use of tocilizumab. Anakinra may be preferred in patients who develop secondary infection or myocarditis.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study has been approved by the Clinical Researches Ethics Committee of Adana City Training and Research Hospital (Date: 01.07.2021, Decision No:1482).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

The authors received no financial support for the conduct or publication of this research.

Author Contributions

All authors contributed significantly to the study's conception, design, data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

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