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ORIGINAL ARTICLE

Effectiveness of Anakinra Therapy on COVID-19 Patients in ICU

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Abstract

Background: There is no consensus on effective treatments for COVID-19 disease yet. Our aims are to observe the clinical and laboratory results of anakinra treatment on intensive care patients and to contribute to the literature on its usefulness.

Methods: The characteristics of the patients receiving Anakinra treatment in the COVID ICU of xx were retrospectively reviewed. The patient's laboratory values and the corticosteroid doses (high dose(≥250 mg), low-dose (<250 mg)) and they received in addition to Anakinra treatment were also evaluated. Patients taking other corticosteroid derivatives were excluded from the study. Furthermore, the data of the patient group who did not receive Anakinra but received high-dose methylprednisolone (MP) treatment were compared with the present patient data and evaluated in terms of treatment effectiveness. And also patients receiving Anakinra+high dose MPZ and Anakinra+low-dose MPZ were compared.

Results: The patient group that receiving Anakinra+high-dose MPZ has significantly higher mortality rate (P=0.038) and significantly longer MV and hospitalization days in the intensive care unit (p=0.001, p=0.004). As the mean hospitalization days were longer in group receiving Anakinra + low-dose (<250mg) MPZ than the group receiving Anakinra + high-dose steroids (p=0.018), there was no significant difference in terms of MV time and mortality rates.

Conclusions: In our study, the patients who received Anakinra treatment had a longer hospitalization day and MV period, and the higher mortality rate was attributed to this patient group that had a more severe course. It was observed that the use of anakinra treatment after low-dose and high-dose MPZ treatment did not cause a significant difference in mortality rates.

Keywords: Anakinra Treatment, COVID-19 Disease, Cytokine Storm.

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INTRODUCTION

COVID-19 disease causes a serious pandemic all over the world. As the pandemic grows, the pathophysiology of the disease becomes clearer and new treatment regimens are put on the agenda. It has been reported that COVID-19 disease is associated with both immunodeficiency and hyperinflammation, and hyperinflammation manifests itself with a cytokine storm (1). Although Tocilizumab treatment was used in 2020 when the disease first appeared, its use has gradually decreased, considering that the current treatment may prolong the period of immunosuppression and increase the risk of secondary infection in later periods (2). Due to the side effects of tocilizumab treatment, Anakinra treatment, which has a short duration of action and provides IL-1 blockade, has come to the fore.

Anakinra, as an IL-1 receptor antagonist, is one of the treatments used in rheumatoid arthritis, cryopyrin-associated periodic syndrome (CAPS) and Still disease (3). In 6 studies, it has been suggested that Anakinra treatment can have a beneficial role especially for selected patients with COVID-19 who have moderate or severe pneumonia accompanied by increased inflammatory marker levels (4).

In a study conducted in 21 patients receiving anakinra treatment; despite the significant decrease in fever, white blood cell count, ferritin, procalcitonin, creatinine and bilirubin values compared to the group that did not receive treatment, no difference was observed in terms of mechanical ventilation time or length of stay in the intensive care unit (5). In another study conducted in Italy, patients were divided into 3 groups: high-dose Anakinra (5 mg/kg twice daily, 29 patients), low-dose Anakinra (100 mg twice daily, 7 patients) and patients receiving standard therapy (16 patients). When the group receiving high-dose Anakinra and the group receiving standard treatment were compared, it was found that the respiratory functions of the patients receiving Anakinra treatment were improved and the 21-day life expectancy was significantly higher (p=0.009) (6).

Studies on the effectiveness of Anakinra treatment are continuing. For example; in SAVE-MORE double-blind studies, twenty-eight-day mortality decreased (hazard ratio = 0.45, P = 0.045), and the hospital stay was shorter (7). In this study, we aimed to investigate the significance of clinical and laboratory findings of the research between patients who received Anakinra treatment and those who did not receive Anakinra treatment, but who received high-dose MP (methylprednisolone).

MATERIALS AND METHODS

Study Sample

254 COVID-19 patients followed up in Ankara City Hospital COVID Intensive Care Unit between 01.03.2020-01.03.2021 were included in the study. 24 patients were excluded from the study due to insufficient data. 30 patients were excluded from the study due to length of stay less than 3 days. 6 patients were excluded due to pregnancy. 114 patients were excluded due to not receiving MP (Figure-1). The remaining 80 patients were evaluated.

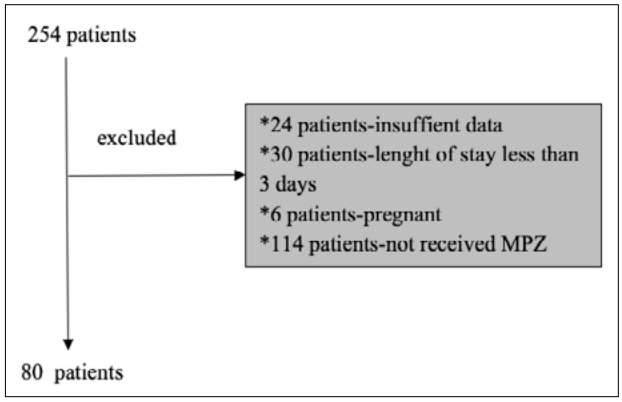

Figure-1: Study design

Study design

80 patients' data were recorded by examining patients files and charts. All treatments, the number of days in the intensive care unit, the days after the symptom onset (symptom duration), mechanical ventilation days, mortality rates, and secondary infection data were recorded. Symptom durations of the patients were recorded in two groups as shorter and longer than 7 days. At the same time, C-reactive protein (CRP), interleukin-6 (IL-6), lymphocyte count, AST, ALT, LDH, D-dimer, procalcitonin, ferritin and fibrinogen values were also recorded as helpful parameters in the diagnosis of macrophage activation syndrome. In addition, "cytokine storm score" (SFS) was calculated according to the laboratory values of the patients in our study. Based on IL-6 ≥40 pg/ml and/or two of the following as criteria: CRP ≥100 mg/L, D-dimer ≥1000 ng/ml, ferritin ≥500 ng/ml and lactate dehydrogenase ≥300 U/L , each criterion was evaluated as 1 point. (8).

Firstly; the patients were divided into 2 groups as Anakinra + high-dose MP (≥250 mg) and received only high-dose MP. Secondly; the patients were divided into

Anakinra + low-dose MP (<250 mg) and Anakinra + high-dose MP (≥250 mg), and the above-mentioned data were compared between these groups.

Anakinra doses were determined in collaboration with the Rheumatology Clinic. A cytokine storm that was both laboratory and clinically unresponsive to MP, including increased oxygen demand and tachypne, was the indication for treatment. Accordingly, doses were started at 600 mg/day (200 mg 3x1 for the first 3 days, then 100 mg 4x1 for 3 days, then 100 mg 3x1 for 3 days, then 100 mg 2x1 for 3 days, completed in 9 days in total) or 400 mg/day (reducing by 100mg every 3 days, completed in 9 days in total). Only 6 patients received 600 mg of Anakinra and it was thought that it would not be statistically significant.

Secondary infection rates were positive consultation results from Infectious Diseases Clinic mentioned in the patients' record. As the aim of our study was not to determine the infection rate of the patients, we found this information sufficient.

Ethics committee approval

Ethical committee approval was obtained for the study from Ankara City Hospital Ethical Committee (Approval date: 25.08.2021, Approval number: E1-21-1961)

Statistical Analyze

The compatibility of numerical features of the normal distribution was examined via Shapiro-Wilks test. The independent samples t-test was used to compare various groups in terms of normally distributed features, and the Mann-Whitney U test was used to compare various groups in terms of non-normally distributed features. Categorical features and intergroup relations were analyzed using the Pearson chi-square test. Statistical significance level was accepted as P <0.05 and SPSS (ver. 25) program was used for calculations.

RESULTS

80 patients diagnosed with COVID19 pneumonia in Ankara City Hospital Intensive Care Clinic were included in the study. 40 patients who received anakinra treatment and 40 patients who did not receive anakinra treatment were compared in terms of demographic data, numerical characteristics and mortality rates (Table-1). All patients receiving anakinra had previously received MP therapy. In addition, the group receiving Anakinra was divided into 2 groups as 10 patients with low-dose (<250 mg) MP and those who received high-dose (≥250 mg) MP.

Table-1: Comparison of demographic and numerical characteristics of patients who received and did not receive anakinra

	Patients receiving anakinra (n=40)	Patients not receiving Anakinra (Receiving high-dose MP (≥250 mg) (n=40)
Age (Year)	58±12	61±13
Sex(Male)	30 (%75)	28 (%70)
APACHE score	7.8±3.7	8.1±5.5
SOFA score	3.6±1.3	4.1±2.8
Day of hospitalization	17±9.8	11±5
Day of intubation	7.2±8	2.9±4.3
Rate of intubation	27 (%67.5)	17 (%42.5)
The rate of discharge	16(%40)	26 (%60)
Diabetes mellitus (n=20)	11(%27.5)	9(%22.5)
Hypertension (n=34)	20 (%50)	14 (%35)
Coronary artery disease (n=15)	10 (%25)	5(%12.5)
Chronic pulmonary disease (n=5)	1(%2.5)	4(%10)
Chronic renal disease (n=5)	2(%5)	3(%7.5)
Neurological disease (n=6)	4(%10)	2 (%5)
Malignancy (n=6)	4(%10)	2(%5)
Ferritin (μg/L)	1244±900	780±581
C-reactive protein (g/L)	119±61	146±78
IL-6 (pg/mL)	58±95	87±165
D-dimer (mg/L)	3.7±7.6	2.3±2.8
LDH (U/L)	585±194	557±293
Lymphocyte counts(10^9/L)	0.5±0.2	0.6±0.2
Procalcitonin (μg/L)	0.4±0.6	1.01±2.3

The duration of symptoms of the patients included in the study were noted. It was divided into two as <7 days and >7 days. There was no statistically significant difference

in terms of length of stay in the intensive care unit, mechanical ventilation days, and mortality between those who received anakinra and those with symptom duration >7 or <7 (P=0.293, p=0.293, p=0.182).

Hospitalization characteristics of patients who received Anakinra+ high/low-dose MPZ and only high-dose MPZ treatments are given in Table-1. Ferritin levels were significantly higher in the Anakinra treatment group (p=0.01). IL-6 value was higher in the other group (p=0.01). There was no significant difference between the two groups in CRP, procalcitonin, D-dimer and LDH values (p=0,09, p=0,4, p=0,96, p=0,2). When cytokine storm score was calculated with all values, no significant difference was observed (p=0.7).

When the patients receiving Anakinra+high-dose MPZ were compared with the patient group receiving only high-dose MPZ, the mortality rate was significantly higher (p=0,038) and the days of mechanical ventilation and hospitalization in the intensive care unit were significantly longer (p=0.001, p=0.004) in patients receiving Anakinra. However, the secondary infection rates has no significant difference (P=0.484) (Table-2), IL-6 and AST values were significantly higher of that patients received high-dose MPZ (p=0.01, p=0.01).

Table-2: Comparison of mortality, intensive care unit stay, MV days and secondary infection rates of patients who received Anakinra + high-dose MPZ and those who received only high-dose MPZ

	Patients receiving anakinra+high dose MPZ (n=30)	Patients not taking anakinra (Those who take high-dose MPZ (≥250 mg) (n=40)	p value
Day of hospitalization in ICU	18.6±9.9	11.4±5.6	0.001
Day of mechanical ventilation	8.23±8.6	2.9±4.3	0.004
Exitus rate	18 (%60)	14 (%35)	0.038
Secondary infection rate	19 (%63.3)	22 (%55)	0.48

The group receiving Anakinra + high-dose steroids and the group receiving Anakinra + low-dose steroids were compared, the average hospitalization day was significantly longer in the group receiving Anakinra + high-dose steroids (p=0.018), while the mean duration of mechanical ventilation was longer in the group receiving Anakinra + low-dose steroids. There was no significant difference in mortality rates between these groups (p=1.0) (Table-3).

Table-3 : Comparison of mortality, intensive care unit stay, MV day rates of patients receiving Anakinra + high-dose MPZ and those receiving Anakinra + low-dose MPZ

	Patients receiving anakinra + high-dose MPZ (n=30)	Patients receiving anakinra + low dose (<250 mg) MPZ (n=10)	p value
Day of hospitalization in ICU	18.6±9.9	12.1±5.8	0.018
Mechanical ventilation day	8.23±8.6	4.4±4.9	0.193
Exitus rate	12 (%40)	4 (%40)	1.0

DISCUSSION

In this study, we evaluated the characteristics of patients who received Anakinra treatment, which acts on IL-1 blockade in the case of cytokine storm in COVID-19 disease, and the differences between the group who received high-dose steroids and did not receive Anakinra. And also patients receiving Anakinra+high dose MPZ and Anakinra+low-dose MPZ were compared.

Studies on anakinra treatment in intensive care are very limited. The first case report about the treatment; A 47-year-old female patient who could not use glucocorticoid therapy due to neuropsychiatric complaints. In this patient, clinical and laboratory stabilization was detected on the 10th day after the use of 100 mg s.c. Anakinra every 6 hours. On the 19th day, it was observed that there was no oxygen support (9). In other studies, it was stated that IL-6 and IL-1 blockade treatments reduced the rate of mechanical ventilation and were safe for inpatients who were followed up with severe COVID-19 pneumonia. In

a case series of 9 patients; it was observed that 8 patients went into a fever-free period within 3 days. They showed clinical and laboratory improvement. It was observed that CRP values started to decrease on the 5th day, and at the same time, it completely returned to normal on the 11th day in 5/8 patients. The regression of CT findings were noticed on the 5th-8th days (10).

In a study conducted in Italy,120 patients diagnosed with COVID-19 were examined. 65 patients were evaluated for hyperinflammation (Ferritin 1000 ng/ml, CRP 10 mg/dl) and respiratory failure, and then treated with pulse methylprednisolone (1 mg/kg, tapering to 14 days) and Anakinra (200 mg 3x1 for the first 3 days, then 100 mg 3x1, completed in 14 days). The 28-day mortality rate was found to be significantly lower in the treated group, p=0.005). There was no significant difference between the two groups in terms of infection rate and laboratory changes (11). In our study, there was no significant difference in the secondary infection rates between the patient groups who received and did not receive Anakinra.

Although, in a study conducted by Cavalli and his colleagues, the survival time without mechanical ventilation was 72% in the Anakinra group (5 mg/kg, 2 times a day) and 50% in the other group, there was no significant difference (p=0.15) (6). In another study comparing the patient group who received 52 Anakinra treatment (2x100 mg, 3 days, followed by 1x100 mg for 7 days) and the two groups who received 44 standard treatments (oral steroids were not given, but it as stated that some patients received 500 mg MPZ), the mortality rate and intubated patients number in the Anakinra group was found to be significantly less (12). Patients with saturation 93% or 3% oxygen therapy loss and saturation less than 93% under oxygen therapy greater than 6 lt/min were used as criteria in this study. It was observed that the mortality rate was higher in the patient group receiving Anakinra + high-dose MPZ, the duration of mechanical ventilation and the length of stay in the intensive care unit were longer. However, this may be due to the fact that the patients in our study were on high flow oxygen therapy and were in a more severe patient group.

In a SAVE-MORE double-blind randomized controlled trial enrolled 594 patients with suPAR (soluble urokinase plasminogen activator receptor) ≥6 ng ml^{-1}, as an indicator of progressive respiratory failure. In this study, shorter hospital stays and a lower mortality rate were found in the group that received anakinra treatment as a secondary endpoint. (7). In another study, it was suggested that respiratory failure could be prevented and pro/anti-inflammatory balance could be achieved compared to Anakinra treatment given according to suPAR level (13).

A total of 128 patients were analyzed in a single-center study. 63 of these patients were given early rescue therapy (30 of them Anakinra only (3x100 mg, 3 days, tapering off)), 33 of them Anakinra + steroid (1-2 mg/kg/day, tapering off) and 44 of the remaining 65 patients were given standard treatment. While being followed up with treatment, late rescue therapy (Anakinra/Tocilizumab) was started in 22. Indications for early treatment are (1) positive CT or PCR result with severe COVID-19 involvement, (2) PaO2/FiO2<300 and CRP or ferritin value is more than 3 times the normal range, (3) lymphocyte value is 1000/mm3 and D-dimer or LDH value is 3 times the normal value. Results showed that early rescue treatments reduced the mortality rate by 74% (p=0.04). There was no significant difference between delayed rescue treatment and standard treatment (14). In our study, as criteria, IL-6 ≥40 pg/ml and/or two of the following: CRP ≥100 mg/L, D-dimer ≥1000 ng/ml, ferritin ≥500 ng/ml and lactate dehydrogenase ≥300 U/L based on each criterion, 1 point was evaluated. Those with a score of ≥2 were considered to be in cytokine storm. Those with a score of <2 were given treatment according to their clinical status. After the patients received MPZ treatment, Anakinra treatment was given if there was no clinical improvement. When all patients were evaluated, there was no significant difference in terms of length of stay in the intensive care unit, mechanical ventilation days and mortality between those who received Anakinra and those with >7 or <7 symptom duration.

In a meta-analysis of 6 studies, it has been suggested that Anakinra treatment can have a beneficial role especially for selected patients with COVID-19 who have moderate or severe pneumonia accompanied by increased inflammatory marker levels (4).

As a result; it is found that the patients who received Anakinra treatment had a longer hospitalization day and mechanical ventilation period, and the higher mortality rate was attributed to the fact that this patient group had more severe course in our study. It is observed that the administration of anakinra treatment after low-dose and

high-dose MPZ treatment did not cause a significant difference in mortality rates. In addition, adequate data on the time of administration of Anakinra treatment could not be provided. The limitations of the study are the small number of patients and its retrospective nature. Therefore, more comprehensive, randomized, and controlled studies are needed.

Conflict of interest

The authors have no conflicts of interest to declare and no funding.

Declarations

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

This study was approved by Ankara City Hospital Ethical Committee (Approval date: 25.08.2021, Approval number: E1-21-1961)

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