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Anakinra treatment in COVID-19 pneumonia.

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Abstract

Background: Cytokine Storm Syndrome (CSS), characterized by overproduction of proinflammatory cytokines in the course of severe Coronavirus Disease (COVID-19), has been defined as the major cause of mortality. Anakinra inhibits the pro inflammatory cytokines Interleukin (IL)-1α and IL-1β. It also poses a therapeutic option for the treatment of CSS leading to severe acute respiratory syndrome. We aimed to report our experience of anakinra therapy in this single-centre retrospective study.

Methods: We conducted a single-center retrospective study to reveal the outcome of anakinra on COVID19 patients. Anakinra 100 mg 3 × 1 sc was administered to 15 patients who had pneumonia findings on Thorax CT, had O2 saturation levels below 90%, a ferritin value above 1000 ng/mL, a progressively increased CRP value, a lymphocyte count below 1000 mm3, and a normal procalcitonin value.

Results: All fifteen patients (median age: 47,3 ± 11,2 years) were male. Four patients had diabetes history. The clinical and laboratory parameters improved 5 days following anakinra use. No patient was admitted to the intensive care unit. Also, no mortality was reported in the one-month follow-up of the patients.

Conclusions: The cases with Covid-19 pneumonia should be followed closely in terms of CSS findings. We have demonstrated that the early administration of anakinra therapy during the course of CSS leads to positive results.

Keywords: Anakinra, Covid-19, Cytokine Storm Syndrome

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Introduction

There is still no known treatment proven to be effective in yielding reliable results for COVID-19 disease caused by the new type of Coronavirus (nCOV-2019). Efficient treatments and vaccines are currently being investigated in our country and all over the world to control the disease. However, the very short duration of this pandemic period makes it impossible to develop a new specific drug that is approved for use. Effectiveness of the drugs that have already been included in the treatment schemes as an emergency option for this disease are not fully known, but proven to be safe due to their use in many diseases, such as other coronavirus infections (such as SARS-CoV, MERS-CoV, HIV infection), [1,2].

COVID-19 deaths are primarily caused by Acute Respiratory Distress Syndrome (ARDS) and by Cytokine Storm Syndrome (CSS), a state of hyperinflammation leading to a multiorgan failure [3].

Cytokine storm complicating Macrophage Activation Syndrome (MAS) that is associated with rheumatic disease shares considerable biochemical overlap with the hyperinflammation observed in patients with COVID-19 [4].

Anakinra inhibits the proinflammatory cytokines interleukin (IL)-1α and IL-1β and has been used with some success for MAS caused by various inflammatory conditions in patients with COVID-19 in several small studies. The dose and route of administration of anakinra are especially relevant given its short plasma half-life, with both intravenous and subcutaneous routes being considered [5,6].

There is no consensus on when and in which doses anakinra treatment should be given to patients with a diagnosis of covid-19 [7].

Its half-life is 4-6 hours. A dose of 2-10 mg/kg can be administered subcutaneously (sc) or intravenously with a pre-filled syringe. Depending on the severity of the patient's clinical findings, it can be adjusted from 2-3 × 100 mg (sc) daily to 3x200 mg (sc) (maximum) dose. It might be preferred for MAS conditions in pregnancy [8].

There are studies published on the effects of anakinra use in COVID-19, and we aimed to report our experience of anakinra therapy in this single-center retrospective study.

Methods

Adult patients with SARS-CoV-2 infection who received anakinra at Istinye University Faculty of Medicine, Department of Pulmonology, between March 30 and May 20, 2021 were included. Diagnosis of COVID-19 Journal Pre-proof 6 was established based on clinical, laboratory, and radiological findings and confirmed by detection of SARS-CoV-2 RNA in oro-nasopharyngeal swab samples using Reverse Transcriptase–Polymerase Chain Reaction (RT-PCR).

The presenting signs and symptoms, vital signs and oxygen saturation levels on room air (SO2R), and laboratory findings including complete blood count, C-reactive Protein (CRP), procalcitonin, ferritin, and D-dimer levels along with information on comorbidities and medications were obtained from patient files.

Chest Computerized Tomography (CT) scan was performed in all patients carrying risk factors or in the existence of any clinical evidence for pneumonia. We excluded patients for whom there is a suspicion of bacterial infection.

The patients' management was carried out according to the recommendations of Turkish Ministry of Health [9]. Initial treatment with favipiravir and enoksaparin sodium was given to all patients usually for 5-10 days depending on the clinical severity.

Patients with a progression to CSS despite antiviral treatment were considered as candidates for initiating anakinra treatment.

Anakinra 100 mg 3 × 1 sc was started in 15 patients, in whom oxygen saturation fell below 90%, the ferritin value was over 1000 ng/mL, CRP value increased progressively, lymphocyte count was below 1000 mm3, and procalcitonin value was normal.

Statistical Analysis

Statistical Package for the Social Sciences (version 21) software was used to analyze the data. Normally distributed continuous variables were evaluated by t-test, whereas nonparametric variables were analyzed by Mann–Whitney U test. P-value less than 0.05 was considered statistically significant.

Results

The mean O2 saturation of 15 all-male patients (100%) was 87±1.06 and the mean age was 47.3 ± 11.2. Four patients had type-2 diabetes. The laboratory findings of the patients obtained on the day of initiation of anakinra and on the 5th day of treatment are shown in Table 1.

Figure 1. *Demographic and laboratory parameters of patients.*

	The day anakinra initiated	**5th day of the treatment of Anakinra**	**P-value**
	Mean ± SD	Mean ± SD	P-value
Ferritin (ng/mL)	2198,9 ± 1225	937 ± 722	<0.001
WBC (K/uL)	10,7 ± 2,9	12,08 ± 5,1	0,221
Neutrophile (K/uL)	9,6 ± 2,7	14,3 ± 5,9	0,294
Lymphocyte (mm3)	TGM	TGM	TGM
0,59 ± 0,17	1.3 ± 0,6	0.001	TGM
CRP (mg/dL)	12,7 ± 3,8	1,9 ± 3,2	<0.001
Plt (mm3)	184 ± 63,1	382,6 ± 111,9	<0.001
O2 Saturation (%)	87 ± 1,06	93,2 ± 1,5	<0.001
Ddimer (ng/mL)	843,5 ± 263,1	292,9 ± 168,4	<0.001

Fifteen patients of whom 100% were male (median age: 47,3 ± 11,2 years) were included. A significant improvement was observed in clinical and laboratory parameters 5 days following the initiation of anakinra. The decrease in ferritin, CRP, d-dimer values, the increase in oxygen saturation, and lymphocyte values were statistically significant. No patients were admitted to the intensive care unit. Also, no mortality was observed in the one-month follow-up of the patients.

Discussion

Anakinra is an immunosuppressive drug that carries out the theoretical risk of harm in the wrong patient group by potentially targeting beneficial inflammation; however, the positive effects might also be overlooked if the correct patient group is not ascertained. Therefore, it is important to target this treatment to the individuals considered to have hyperinflammation [7].

Depending on the severity of the patient's clinical findings, it might be adjusted from 2-3 × 100 mg (sc) daily to 3x200 mg (sc) (maximum) dose, and it might be used for 3 days according to the clinical response. CRP might be utilized during the follow-up [8]. In our study, anakinra treatment was applied for five days. None of our patients required intensive care.

Achille Aouba et al. administered anakinra 2x100mg to 9 patients with moderate and severe covid-19 pneumonia. After treatment, CRP values of the patients have regressed on the 6th day and none of the patients died [10]. In our study, CRP and ferritin values decreased on the 5th day of treatment, whereas lymphocyte counts increased. Our patients who received anakinra treatment did not die.

Millan et al. demonstrated that in the early period of cytokine storm where acute hypoxemic respiratory failure begins, the need for mechanical ventilation of

patients reduces following anakinra treatment [11]. Also, O2 saturations increased in our patients. A decline was detected in respiratory failure results.

In a retrospective study published in Italy, in which high-dose anakinra treatment (5 mg/kg twice a day or 100 mg/ twice a day) was administered, the clinical improvement rate was reported as 72% in moderately severe ARDS patients. No serious side effects attributable to anakinra treatment were observed [6].

Similarly, five patients with severe COVID-19 pneumonia in Italy were successfully treated with a high-dose (300 mg/day) anakinra infusion. It has been reported that there were no complications or side effects in these patients [12]. We did not observe any drug-related side effects in our patients who received anakinra treatment. Thus, we demonstrated that anakinra treatment in the early phase of cytokine storm reduces the need for intensive care.

The cellular mechanisms triggered by COVID-19 and the pathophysiology of diabetes make individuals with diabetes more susceptible to a cytokine storm resulting in potential organ damage [13]. Type 2 diabetes was detected in four of our patients who were treated with anakinra.

Conclusion

Anakinra is a highly plausible drug candidate for COVID-19 disease. We recommend initiating anakinra therapy to reduce the need for intensive care and mortality in patients with progressive covid-19 disease, cytokine storm findings, and oxygen saturation levels below 90%.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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