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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

The Factors Affecting the Efficacy of Interleukin-1 Receptor Antagonists in COVID-19 Patients

COVID-19 Hastalarında İnterlökin-1 Reseptör Antagonistlerinin Etkinliğini Etkileyen Faktörler

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Abstract

Objectives: Coronavirus disease-2019 (COVID-19) spreads quickly all over the world. Interleukin-1 (IL-1) is a proinflammatory cytokine associated with SARS-CoV-2, causing lung damage. Anakinra is an IL-1 receptor antagonist. In this study, we aimed to describe the characteristics of COVID-19 patients who survived after anakinra treatment.

Materials and Methods: Forty-four patients who did not respond to pulse steroid treatment and were given 8 mg/kg Anakinra were included in this study. The clinical, laboratory, and imaging [thorax computed tomography (CT)] findings of survivors and non-survivors who received anakinra treatment were compared.

Results: Most of the patients were male (81.8%), the median follow-up period was 19.5 (IQR 15.5) days. Of the patients, 40.9% died. The median age was higher ($p<0.001$), and diabetes mellitus was more common ($p<0.034$) in non-survivors. In multivariate cox regression analysis, the presence of underlying hypertension ($p=0.017$) and pure ground glass opacity (GGO) on thorax CT at first admission to hospital ($p=0.04$) were found to be independent risk factors for mortality in COVID-19 patients treated with anakinra.

Conclusion: The presence of hypertension in COVID-19 patients and the presence of pure GGO on thorax CT at first admission to the hospital are the findings that may reduce the response to anakinra treatment. Prospective studies with larger patient populations are needed to demonstrate the validity of this finding.

Key Words: COVID-19, Anakinra, Hypertension

Öz

Amaç: Koronavirüs hastalığı-2019 (COVID-19) tüm dünyaya hızla yayılmaktadır. İnterlökin-1 (IL-1), akciğer hasarına neden olan SARS-CoV-2 ile bağlantılı proinflamatuar bir sitokindir. Anakinra, bir IL-1 reseptör antagonistidir. Bu çalışmada anakinra tedavisi sonrası hayatta kalan COVID-19 hastalarının özelliklerini açıklamaya hedefledik.

Gereç ve Yöntem: Pulse steroid tedavisine yanıt vermeyen ve 8 mg/kg Anakinra verilen 44 hasta çalışmaya dahil edildi. Anakinra sonrası sağ kalan ve yaşamayan hastaların klinik, laboratuvar ve görüntüleme [toraks bilgisayarlı tomografi (BT)] bulguları karşılaştırıldı.

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Bulgular: Hastaların çoğu erkekti (%81,8), medyan takip süresi 19,5 (IQR 15.5) gündü. Hastaların %40,9'unda ölüm meydana geldi. Yaşamayan grupta ortanca yaş daha yüksek (p<0,001) ve diabetes mellitus daha yaygındı (p<0,034). Çok değişkenli cox regresyon analizinde, anakinra ile tedavi edilen COVID-19 hastalarında altta yatan hipertansiyon varlığı (p=0,017) ve hastaneye ilk başvurusundaki akciğer bilgisayarlı tomografisinde saf buzlu cam görünümünün (p=0,04) bağımsız mortalite risk faktörleri olduğu bulundu.

Sonuç: COVID-19 hastalarında hipertansiyon varlığı ve hastaneye ilk başvuruda akciğer BT'sinde saf buzlu cam varlığı anakinra tedavisine yanıtı azaltabilecek durumlardır. Bu bulgunun geçerliliğini göstermek için daha büyük hasta popülasyonları ile ileriye dönük çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: COVID-19, Anakinra, Hipertansiyon

Introduction

Most people with coronavirus disease-2019 (COVID-19) have only mild symptoms, but about 10-15% of patients have moderate or severe disease, and 3-5% require admission to an intensive care unit (ICU) (1). In severe cases, COVID-19 may be complicated by acute respiratory distress syndrome. During this phase patients have excessive increases in proinflammatory cytokines, especially interleukin-1 (IL-1), and IL-6, finally leading to hyperinflammation (2).

IL-1 is an extremely important proinflammatory cytokine, that has been linked to the lung-damaging COVID-19 and may work as a therapeutic target for COVID-19 pneumonia (3,4). Anakinra, an IL-1 receptor antagonist, was finally reported as a potential therapeutic option (5).

Anakinra blocks the activity of IL-1a and IL-1b and is an accepted agent in the treatment of some rheumatologic diseases. Anakinra has also been shown to contribute to reduction in mortality in patients with secondary hemophagocytic lymphohistiocytosis or macrophage activation syndrome caused by viruses (6). The preliminary data from some observational studies and one prospective study suggest that anakinra is effective for mild-to-moderate, and severe COVID-19 patients (7-14). However, some other studies reported contrary results (15-17). These conflicting results propound that there may be some clinical, and laboratory features that affect the results of anakinra treatment in COVID-19 patients.

We consider that it is important to determine the clinical and laboratory data to affect the treatment, beyond the efficacy of the treatment itself. In this study, we aimed to determine the clinical differences of COVID-19 survivors and non-survivors following the anakinra treatment.

Materıals and Methods

Patients admitted to Hatay Training and Research Hospital between October 1 and December 31, 2020, diagnosed with hyperinflammation due to COVID-19 and hospitalized in the ICU were analyzed. All patients met two of the following laboratory criteria: C-reactive protein >90 mg/L, ferritin level >500 µg/L, D-dimer level >0.5 mg/L. All patients had severe pneumonia. Severe pneumonia was considered present when basal oxygen saturation was <93%. Forty-four patients who did not respond to pulse steroid treatment (250 mg-1000 mg methylprednisolone per day for three consecutive days) and given 8 mg/kg of Anakinra therapy were included in the study. Anakinra treatment was administered until clinical benefit, defined as sustained improvement of respiratory parameters, was achieved. The clinical, laboratory, and thorax computed tomography (CT) findings of survivors and non-survivors who received anakinra treatment were compared. In laboratory and clinical data, the data on the day when Anakinra was initiated were analyzed. Thoracic CT scans of the patients at their first admission to the hospital were examined.

Thorax CT images were categorized as first, ground glass opacification (GGO) which hazy areas of increased attenuation without obscuration of the underlying vessels, the second crazy-paving pattern, GGO with interlobular and intralobular septal thickening, and the last one consolidation, homogeneous opacification of the parenchyma with obscuration of the underlying vessels. We used the total severity score to determine the severity of lung involvement due to COVID-19. According to the total severity score, each of the five lung lobes was assessed for degree of pulmonary involvement, which was classified as none (0%), minimal (1-25%), mild (26-50%), moderate (51-75%), or severe (76-100%). No lobe involvement was scored as 0, minimal involvement 1, mild involvement 2, moderate involvement 3, and severe involvement 4. An overall lung total severity score was reached by summing the five lobe scores (range of possible scores, 0-20). If the score is 7 and below, we defined it mild, 8-17 is moderate, 18 and over is severe (18).

Pulmonary artery enlargement was visually assessed according to the categories as 0% (absent); 1-25% (minimal); 26-50% (mild); 51-75% (moderate); over 75% (severe) (18). When possible, with respect to their state of mindfulness, all patients were informed of the possible effects and adverse events of anakinra treatments. Written informed consent for the off-label use of steroids and Anakinra were obtained from all patients. Mustafa Kemal University Faculty of Medicine, Clinical Research Ethics Committee approval was provided for the study (approval date/no: 4.2.2020-02).

Statistical Analysis

The statistical analyzes were performed with SPSS version 25 (SPSS, Chicago, USA) software. Categorical data were presented as frequency and percentage. Quantitative data were not normally distributed, expressed as median and interquartile range (IQR). When comparing the surviving and non-surviving groups, chi-square or Fisher's exact test was selected for categorical data. Mann-Whitney U test was used when comparing the quantitative data. Hazard ratio (HR) of survival were estimated using Cox regression models with enter method. Results of the Cox regression model are presented as HR with 95% confidence interval (CI). Variables with a p-value <0.25 on univariate analysis were subsequently entered into the final multivariate model. P-values <0.05 were considered statistically significant.

Results

A total of 44 patients who were treated with steroid and anakinra together or sequentially were included in our study. Most patients were male (81.8%), and 93.2% of patients received continuous positive airway pressure and high-flow nasal oxygen as main oxygen support. Demographic, clinical, laboratory, and radiographic characteristics are shown in Table 1. The median follow-up period was 19.5 (IQR 15.5) days. Of the patients, 40.9% died. The median age was higher (p<0.001), and diabetes mellitus was more common in the non-survivor group (p<0.034) (Table 1).

In the non-survivor group, the need for mechanical ventilator respiratory support before anakinra treatment was more frequent (p<0.001), and the time to start treatment was

Table 1: Baseline demographic and clinical characteristics

n, (%)	Survived (N=26)	Non-survived (N=18)	P
Gender, male	22 (84.6)	14 (77.8)	0.697
Age, years	46.35 (12.7)	60.78 (15.45)	**<0.001**
Comorbidities			
Hypertension	5 (19.2)	7 (38.9)	0.183
Diabetes mellitus	1 (3.8)	5 (27.8)	**0.034**
Chronic obstructive lung disease	2 (7.7)	1 (5.6)	>0.999
Cardiovascular disease	1 (3.8)	0	>0.999
Clinical findings			
Mechanical ventilatory support (CPAP or IMV) before treatment	8 (30.8)	17 (94.4)	**<0.001**
Time from hospitalization to initiation of treatment, days	5 (3)	8.5 (6.25)	**<0.001**
Thorax computed tomography findings			
Involvement pattern			
Pure ground glass opacity	9 (40.9)	10 (71.4)	0.074
Consolidation + Ground glass opacity	5 (22.7)	1 (7.1)	0.370
Crazy pattern	8 (36.4)	3 (21.4)	0.467
Diffusiveness			
Mild	4 (18.2)	1 (7.1)	0.628
Moderate	8 (36.4)	2 (14.3)	0.255
Severe	10 (45.5)	11 (78.6)	**0.049**
Main pulmonary artery diameter increase			
None	19 (86.4)	7 (50)	**0.026**
Mild	2 (9.1)	4 (28.6)	0.181
Moderate	1 (4.5)	2 (14.3)	0.547
Severe	0	1 (7.1)	0.389
Laboratory findings			
Lymphocyte number	575 (287.5)	335 (292.5)	0.025
LDH (mg/L??)	458 (357)	613 (322)	**0.008**
CRP (mg/L??)	100.98 (94.7)	101 (63.08)	0.784
Ferritin (mg/L??)	926 (752.75)	1109.5 (580.25)	0.952
D-dimer (IU/L??)	0.566 (1.04)	1.675 (3.10)	**0.004**

LDH: Lactate dehydrogenase, CRP: C-reactive protein, CPAP: Continuous positive airway pressure, IMV: Invasive mechanical ventilation

longer (p<0.001). The presence of severe lung involvement was more common (p=0.049) and the increase in the diameter of the main pulmonary artery was higher (p=0.026) in thorax CT images of the non-survivors. The non-survivor group had higher serum levels of D-dimer, lactate dehydrogenase (LDH) and lower lymphocyte count (Table 1).

In multivariate cox regression analysis, presence of underlying hypertension (HT) [p=0.017; HR=5,587 (95% CI, 1,368-22,810)] and pure ground glass appearance at the first admission [p=0.04; HR=4,477 (95% CI, 1,069-18,742)] were found to be independent risk factors for mortality in COVID-19 patients treated with Anakinra (Table 2).

Discussion

In some studies on the development of hyperinflammation due to COVID-19, a lower mortality rate was observed in the group treated with biological agents compared to the standard supportive therapy (19-21). On the contrary, some studies have shown that biological agents have no effect on mortality (8,16). In our study, our aim is to describe the characteristics of COVID-19 patients who survived after the anakinra treatment.

In a study by Della-Torre et al. (21), COVID-19 related mortality was independently associated with older age, high concentration of LDH, and low PaO2/FiO2 ratio at the time of drug infusion. Plasmapheresis was performed to improve oxygenation in patients with increased thrombo-inflammatory markers (LDH >800, D-dimer >1000 mg/L) (22). In this study, we did not find correlation between mortality and age or LDH levels. Patients who underwent plasmapheresis were not included in our study which may have affected our result.

Previous studies in patients with COVID-19 have shown that the presence of HT increased mortality (23,24). Franzetti et al. (25) reported that HT, ischemic heart disease, and older age were predictors of lower probability of survival in patients with COVID-19 treated with Anakinra. In our study, the presence of HT was found to be independent predictor of mortality in patients receiving anakinra [p=0.017, HR 5,587; (95% CI 1,368-22,810)]. In fact, inflammation and coagulopathy have been identified as risk factors for COVID-19 infection. We treat only inflammation by means of Anakinra, and maybe we should research treatment options for coagulation disorders in COVID-19 patients with HT. All our patients were given low-molecular- weight-heparin and antiaggregant treatment as standard therapies. There exists no objective criteria for following coagulation and a treatment plan, such as the inflammation criteria. In patients with COVID-19, the coagulation cascade is disrupted along with inflammation. However, this situation was not followed up with a change in the treatment regimen or a specific plan. On the contrary, IL-1 and IL-6 blockers were added to the treatment in the presence of hyperinflammation.

Previous studies have reported GGO and consolidation were more common findings in patients with COVID-19 requiring admission to the ICU. These findings suggest that thorax CT scan can be a useful tool for risk stratification (26). In additon, the thorax CT scan can predict the prognosis of patients. Some studies have informed us that the GGO pattern was more valuable than a consolidation pattern in predicting the prognosis of patients with COVID-19 (27). However, Hajezi et al. (28) reported GGO was less common than consolidation in patients with COVID-19 associated mortality. We found that GGO was an independent risk factor for mortality in patients treated with Anakinra. Results of the current study was not compatible with the literature. In our study, thorax CT at the time of hospitalization was used. Thorax CT was not performed on the day Anakinra was started.

Table 2: The factors affecting survival with Anakinra treatment after multivariate analysis

	HR (95% CI) Univariate analysis	p	HR (95% CI) Multivariate analysis*	p-value
Age	1,050 (0.999-1,105)	0.055	1.056 (0.988-1,129)	0.108
Diabetes mellitus	3,517 (1,227-10,081)	0.019	1,531 (0.384-6,105)	0.546
Hypertension	3,117 (1,191-8,158)	0.021	5,587 (1,368-22,810)	**0.017**
Mechanical ventilation before Anakinra treatment	4,049 (0.512-32,042)	0.185	1,981 (0.238-16,504)	0.527
Time between hospitalization and onset of Anakinra treatment (day)	1.002 (0.937-1.071)	0.964	-	-
Pure ground glass opacity	2,773 (0.828-9,285)	0.098	4,477 (1.069-18,742)	**0.040**
Severe lung ınvolvement	1,581 (0.437-5,717)	0.485	-	-
Main pulmonary artery diameter increase	1,258 (0.432-3,663)	0.674	-	-
Lymphocyte number	1 (0.998-1.003)	0.639	-	-
Lactate dehydrogenase	1.001 (0.999-1,003)	0.251	-	-
D-dimer	0.993 (0.898-1,098)	0.892	-	-
PCT	0.237 (0.005-11,952)	0.472	-	-

HR: Hazard ratio, CI: Confidence interval, PCT: Procalcitonin

Due to the rapid progression of the lung findings in the nature of the disease, the lung findings may have changed at the time the drug was started. The small number may affected this result. Our results may have been affected by this situation. However, the presence of GGO at hospital admission may help us to predict that anakinra may be less effective.

In these patient groups (who has HT or GGO), other treatment options may be considered instead of anakinra. Disturbances in the coagulation pathway and treatment options can be investigated.

Study Limitations

The small number of our patients, and the fact that we have assessed the thorax CT performed at hospitalization instead of the day anakinra was administered are the main limitations of our study.

Conclusion

The presence of HT and GGO on Thorax CT at hospital admission are findings that reduce the clinical benefits of Anakinra treatment in COVID-19. Prospective studies on larger patient populations are needed to demonstrate the validity of this information.

Ethics

Ethics Committee Approval: Mustafa Kemal University Faculty of Medicine, Clinical Research Ethics Committee approval was provided for the study (approval date/no: 4.2.2020-02).

Informed Consent: Written informed consent for the off-label use of steroids and anakinra were obtained from all patients.

Peer-reviewed: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: E.U.Y., V.A., M.S., M.E., Concept: E.U.Y., Design: E.U.Y., Data Collection or Processing: E.U.Y., V.A., M.S., M.E., L.B., Analysis or Interpretation: M.E.Y., Literature Search: E.U.Y., L.B., Writing: E.U.Y., M.E.Y., D.M.K.

Conflict of Interest: There is no conflict of interest.

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