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Clinical consequences of tocilizumab consumption time on COVID-19 patients

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Abstract

***Background & Aims*:** Studies have shown that treating COVID-19 with tocilizumab is associated with lower death risks and mechanical ventilation needs. However, the definite effectiveness of this drug based on the timing of its use is still controversial due to various findings. Some studies have shown that the timing of consumption can impact the drug's effectiveness.

***Materials & Methods*:** This retrospective study was conducted on all COVID-19 patients who were treated with tocilizumab (Actemra) from August 2020 to August 2021 at Firoozabadi Hospital, Tehran. Demographic, laboratory, and clinical information of the patients were extracted from patient records. SPSS v22 software was used for data analysis.

***Results*:** In this study, we analyzed data from 344 patients with an average age of 57.31 ± 14.75 years (range: 19-95). The cohort included 186 men (54.06%) and 158 women (45.94%). Most patients (70.9%) received the drug between the second and fifth day of hospitalization. Overall, 104 patients (30.2%) died during their stay. Among those who received the medication twice, 38 out of 118 died, while 66 out of 224 died after a single dose. The highest mortality rate was observed in patients who received the drug after five days (39 deaths), and the age group of 60-95 had the highest percentage of deaths, totaling 58 (55.76%). Female patients also exhibited a higher mortality rate at 60.57% (63 deaths).

***Conclusion*:** Therefore, it seems that the best time to prescribe tocilizumab to COVID-19 patients is between the 2nd and 5th day of hospitalization. Additionally, the timing of drug consumption and the treatment process in elderly women with abnormal laboratory parameters should be evaluated more carefully.

***Keywords*:** Actemra, COVID-19, Outcome, Tocilizumab, Treatment

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which leads to COVID-19 disease, is associated with cytokine release syndrome (CRS) (1). Cytokine release syndrome is recognized as one of the main causes of increasing COVID-19 severity and mortality rate, and it is also one of the main causes of COVID-19 patients not responding to treatment (2). It seems that CRS leads to hyperinflammation in the first 10 days after the initial symptoms start appearing (1, 3).

CRS overactivates macrophages and Tcells by over activating immune responses. As a result, the production of pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6, tumor necrosis factor-α (TNFα), and interferon-γ (IFN-γ) are overproduced (4, 5). This leads to tissue damage, respiratory distress syndrome, organ and coagulation system failure, and ultimately death (6). Studies have shown that IL-6, which is found in both mild and severe COVID-19 patient groups, is a key cytokine and has a direct relationship with disease severity (7).

IL-6 activates intracellular transcription pathways through membrane receptors (classical signaling pathway) or soluble receptors (transsignaling pathway). IL-6 overproduction through the classical signaling pathway stimulates fibroblasts and releases procollagen and fibronectin, playing an important role in the pathogenesis of pulmonary fibrosis (8). On the other hand, by increasing the expression of vascular endothelial growth factor (VEGF) through transsignaling, vascular permeability increases. As a result, blood pressure, hypoxia, peripheral edema, and organ damage are all reduced (9).

One of the treatments that have been used to manage CRS in COVID-19 patients is interleukin-6 blocking drugs such as tocilizumab. This drug is a human IL-6 receptor inhibitory monoclonal antibody (10).The FDA approved it for the treatment of some rheumatic diseases, such as rheumatoid arthritis, systemic juvenile idiopathic arthritis (SJIA), polyarticular juvenile idiopathic arthritis (PJIA), confirmed giant cell arteritis, and severe CRS caused by chimeric antigen receptor T cell (CAR-T) immunotherapy (11-13). This drug has an irreversible effect on both transmembrane and soluble (sIL-6R) receptors with a long half-life (14, 15). The definitive effectiveness of this drug for the treatment of COVID-19 is still controversial due to various findings. Some studies have shown that consumption time can impact its effectiveness (14-16). The purpose of this study is to investigate the consequences of tocilizumab consumption timing on patients with COVID-19.

Materials & Methods

This descriptive cross-sectional study was performed on patients over the age of 18 with COVID-19 who were treated with tocilizumab (Actemra). Disease diagnosis in this study was done by PCR test or imaging findings. This study was approved by the ethics committee of Iran University of Medical Sciences with the ethics code IR.IUMS.FMD.REC.1401.024.

The sampling method in this study was census. Therefore, 345 patients with COVID-19 who were treated with tocilizumab (Actemra) at Firouzabadi Hospital, in Tehran from 2020 to 2021 were included in the study. Exclusion criteria included patients with incomplete records.

Patients with the following criteria were candidates to receive tocilizumab: patients with interstitial pneumonia and severe respiratory distress, patients who needed ventilation or ICU hospitalization, and patients with systemic inflammation (interleukin over 40 pg/ml and D-dimer over 1500 ng/ml).

The list of COVID-19 patients who were treated with tocilizumab (Actemra) between August 2020 and August 2021 was obtained from the hospital pharmacy. The information taken from the patients included demographic information (sex, age), the patient's hospital record number, and the exact time of hospitalization and tocilizumab administration. Using the patient's hospital record number in the comprehensive hospital information system, other necessary information, including laboratory findings and disease outcomes, were extracted. Patients were

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divided into three groups based on the timing of the drug's administration. The groups included patients who received the medicine on the first day of hospitalization, patients who received the medicine between the 2nd to 5th day of hospitalization, and patients who received the medicine after the 5th day of hospitalization. The outcome of tocilizumab administration was examined based on the timing of its use. Data analysis was performed using SPSS v.22 software. A significance level of less than 0.05 was considered.

In this study, data from 344 patients with an average age of 57.31 ± 14.75 years (range: 19-95) were analyzed. The gender breakdown included 186 men (54.06%) and 158 women (45.94%). Most patients received the drug between the second and fifth day of hospitalization, with 244 patients (70.9%) receiving it during this period. Additionally, 104 patients (30.2%) died during their hospitalization. Among those who received the medication twice during their hospitalization, 38 out of 118 died, while among those who received it once, 66 out of 224 died. Among the different groups who received this medicine, the highest death rate belonged to the group that received the drug after 5 days since their admission time (39 people). Additionally, the highest percentage of deaths occurred in the 60-95 age group, with 58 people (55.76%). The female group also had the highest mortality rate at 60.57% (63 people).

Results

This study included 186 males (54.06%) and 158 females (45.94%). The average age of the patients was 57.31 ± 14.75 years. The frequency distribution of medication consumption time on the 1st day, 2nd to 5th day, and after the 5th day was 10.8% (37 patients), 70.9% (244 patients), and 18.3% (63 patients), respectively. A total of 30.2% (n = 104) of hospitalized patients died.

Table 1 shows the frequency distribution of medication consumption time, laboratory parameters, sex, and age according to the disease outcome in the participants. A significant relationship was observed between medication consumption time and disease outcome, as well as laboratory parameters (WBC, LYMPH, PMN, Troponin, BUN, and LDH, and D-dimer).

The highest mortality rate was related to women (n = 63, 57.60%) and the 60-95 age group. There was a significant correlation between the outcome of the disease and gender, but there was no significant relationship between the disease outcome and age.

Table 1. Frequency distribution of the medication consumption time, Laboratory parameters, sex and age according to the disease outcome

		Living people	Dead people	P-value
Medication consumption time	1 day	19 (51.35%)	18 (48.65%)	0.006
	2-5 day	181 (74.48%)	62 (25.52%)	
	> 5 day	24 (38.09%)	29 (61.91%)	
Labrotary parametrs	WBC	7.601	8.528	0.044
	LYMPH	14.201	12.100	0.028
	PMN	80.324	82.630	0.049
	PLT	201.22	203.41	0.787
	Hb	13.619	12.984	0.443
	RDW	13.759	13.954	0.34
	ESR	49.81	46.85	0.501
	CRP	66.209	68.276	0.045
	Troponin	16.907	36.299	0.06

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		Living people	Dead people	P-value
	Ddimer	1385.77	3602.04	0.001
	FBS	199.73	210.25	0.44
	BS	170.38	170.93	0.96
	AST	67.42	70.51	0.73
	ALT	53.79	46.35	0.33
	LDH	832.35	1007.44	0.69
	BUN	16.43	20.72	0.044
	Cr	1.089	1.125	0.028
Sex	Male	144 (60.25%)	41 (39.42%)	0.001
	Female	95 (39.74%)	63 (60.57%)	
Age	18-29 y	35 (76.08%)	11 (23.91%)	0.086
	40-59 y	101 (74.26%)	35 (25.73%)	
	60-59 y	102 (63.75%)	58 (36.25%)	

Table 2 shows the frequency distribution of laboratory parameters and age according to the medication consumption time. A significant relationship was observed between medication consumption time and age, but only creatinine had a significant relationship with the consumption time.

Table 2. Frequency distribution of the Laboratory parameters and age according to the medication consumption time

		1 day	2-5 day	➢ 5 day	P-value
Labrotary parametrs	WBC	8.956	7.766	7.660	0.201
	LYMPH	11.61	13.802	13.516	0.283
	PMN	81.22	80.884	81.394	0.929
	PLT	204.43	201.19	203.34	0.95
	Hb	13.011	13.550	13.192	0.87
	RDW	14.131	13.788	13.767	0.52
	ESR	51.30	49.85	43.93	0.47
	CRP	65.431	66.483	68.530	0.77
	Troponin	21.952	20.719	31.544	0.44
	Ddimer	2620	2186.43	1670.003	0.73
	FBS	191.42	205.66	195.84	0.68
	BS	173.32	162.73	194.04	0.13
	AST	93.63	64.46	67.85	0.097
	ALT	65.11	49.45	51.66	0.38
	LDH	960.81	886.44	842.53	0.39
	BUN	20.78	17.12	18.27	0.09
	Cr	1.670	1.032	1.029	0.001
Age	18-29 y	3 (0.81%)	38 (15.63%)	5 (7.9%)	
	40-59 y	18 (49.64%)	103 (42.38%)	16 (25.39%)	
	60-59 y	5 (7.9%)	16 (25.39%)	42 (66.66%)	

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Discussion

This study includes the clinical results of COVID-19 patients treated with tocilizumab. The aim of this study was to investigate whether the timing of medication consumption effects disease outcomes. To our knowledge, very few studies have been conducted in this field.

During the first wave of the COVID-19 pandemic, tocilizumab was frequently used as a treatment despite the limited evidence and trial studies (17). In our study, only consumption time of this medication was examined. The results showed that using this drug after the 5th day of hospitalization increases patients mortality. The optimal time to prescribe this drug is between the 2nd and 5th day of hospitalization, which has the highest percentage of survival. A study conducted by Diaz et al. showed that taking this medication 10 days after the onset of symptoms may reduce the death rate (16). Previous studies have shown that corticosteroids were the only drugs that could reduce mortality (17). In the mentioned study, corticosteroids use was not considered a confounding variable, although 68% of the patients were taking this drug, which likely influenced the final result (16).

In the present study, all participants were included based on laboratory and radiological criteria for COVID-19. Unlike other studies, the age range examined was much broader (19-95 years vs. 47-73 years) (18-21).

Gender analysis, similar to other studies, showed a higher male-to-female ratio, but the mortality rate in female patients in our study was higher than in other studies (18, 19, 22).

It has been shown that patients had elevated levels of inflammatory proteins, LDH, and D-dimer at the time of tocilizumab administration and were in the inflammatory phase of the disease (16). In this study, diseases outcome was significantly related to LDH and D-dimer, but the medication consumption time only showed a significant relationship with creatinine. Other laboratory variables, including lymphocytes, WBC, PMN, troponin, and BUN, also influenced disease outcome. In Diaz et al's study, there was no significant relationship between CRP levels and medication administration time.

The mortality rate in our study was higher than in other studies (23, 24). This difference can be attributed to our study method. In experimental studies conducted in this field, the mortality rate varied between 10% and 20% (23-26). a More precise criteria were likely applied to include patients in this study, and confounding variables have also been taken into account in the statistical analyses. A study conducted by Gupta et al. reported almost the same mortality rate as our study (27).

Salvarani et al.'s study had a similar mortality rate to ours, but their results were not suitable for comparison since patients hospitalized in the ICU were excluded from their study (28). A meta-analysis study conducted on COVID-19 patients using tocilizumab reported a 16% mortality rate (29), while a study in Spain reported a 21% in-hospital mortality rate (19). The difference in mortality rates between the Spanish study and ours can be explained by the number of examined samples. The Spanish study included 6,424 patients, while our sample size was 181 patients.

In this study, the best time to prescribe tocilizumab was between the 2nd and 5th day of hospitalization. However, another study showed high clinical improvement after prescribing this medication on the 6th day of hospitalization. Other descriptive studies have reported similar results (22, 30-34).

In our study, average LDH decreased in patients who received the drug on the 1st day, the 2nd to 5th day, and after 5 days of hospitalization, respectively, but CRP and lymphocytes increased, although none of these had a significant relationship. Studies have shown that LDH and CRP decrease and lymphocytes increase significantly after the administration of tocilizumab from the 1st to the 6th day (20, 35). The amount of D-dimer was decreased with increased drug consumption time, whereas other studies showed that this factor increased significantly (14, 35, 36).

In our study, liver enzymes decreased with increasing drug consumption time, but this decrease was not significant. Other studies showed an increase

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in liver enzymes, but this increase did not cause any clinical complications for the patients (17, 27, 37, 38, 39).

In this study, confounding variables such as underlying diseases and duration of hospitalization were not investigated. Additionally, due to the retrospective nature of the study, some laboratory parameters could not be measured. It is recommended that future studies be conducted as clinical trials with control groups.

Thus, it seems that the best time to prescribe tocilizumab in COVID-19 patients is between the 2nd and 5th day of hospitalization. The timing of medication consumption and the treatment process in elderly women, along with the results of disturbed laboratory parameters should be evaluated more carefully. The early use of tocilizumab in hospitalized COVID-19 patients can have beneficial effects. Based on this, the treatment process can improve, contributing to better public health during the pandemic.

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Author contribution

Shahin Keshtkar Rajabi: writing the paper

Amir Ziaee: conception and designing the analysis

Farshad Divsalar: data collection

Elnaz Hemmati: data collection

Mohammad Amin Abbasi: Analysis and supervision

Data availability

The data that support the findings of this study are available upon request from the corresponding author.

Conflict of interest

The authors declare no conflict of interest.

Ethical statement

The proposal for this study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.FMD.REC.1401.024). The researchers adhered to all the principles recommended by the Helsinki Convention on Ethics in Research. Patients' personal and attributable information were kept confidential.

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