Rational Use of Tocilizumab in Critically Ill COVID-19 Patients: A Two-Center Observational Study in the Intensive Care Unit

Atefeh Afzali[1], Shadi Farsaei[1,2*], Rasool Soltani[1]

[1]*Department of Clinical Pharmacy, School of Pharmacy, Isfahan University of Medical Sciences, Isfahan, Iran.*

[2] *Isfahan Pharmaceutical Sciences Research Center, School of Pharmacy, Isfahan University of Medical Sciences, Isafahan, Iran.*

Received:2025-06-15, Revised:2025-08-25, Accepted: 2025-08-27, Published:2025-12-30

Abstract

Background: Tocilizumab (TCZ) is a key treatment for severe COVID-19 but poses risks due to immunosuppression and limited evidence. Concerns about misuse and limited supply necessitate a thorough assessment. This study investigates the utilization patterns and appropriateness of tocilizumab use in critically ill COVID-19 patients.

Methods: Over nine months, this prospective, cross-sectional, observational study evaluated TCZ use in adult COVID-19 patients at the intensive care unit (ICU) of two referral hospitals in Isfahan, Iran, from February 2022 to April 2023. Data on TCZ dosing, duration, and concomitant treatments were collected to evaluate the rational use of TCZ as the primary outcome. Clinical outcomes, APACHE scores, inflammatory markers, and adverse effects were monitored on days 3 and 5 post-TCZ administration. We aimed to explore the associations between appropriate TCZ administration and both clinical and laboratory outcomes as secondary endpoints. Statistical analyses were set at $P < 0.05$

Results: After excluding 10 patients due to incomplete data from the 118, 108 patients were analyzed for TCZ use. The mean age was 64.3 years, with 58.3% males. Notably, 39.8% of patients did not meet TCZ indication criteria, and only 7.5% received rational use of TCZ according to clinical guidelines regarding indication, dose, and dosing intervals. CRP levels significantly decreased after TCZ treatment ($P < 0.001$). The rational prescription group had higher APACHE scores five days post-treatment ($P = 0.05$), and appropriate TCZ use was significantly more common among intubated patients ($P = 0.02$).

Conclusion: While rational use correlated with higher APACHE scores, no significant differences in other outcomes were observed, possibly due to sample size. Tocilizumab's mechanism in reducing inflammation and CRP is well-established. Still, limitations include incomplete data on out-of-hospital prescriptions and patients who needed but did not receive TCZ, which necessitate further investigations.

J Pharm Care 2025; 13(4): 253-259.

Keywords: COVID-19; Tocilizumab; Intensive Care Unit

Introduction

Since the onset of the COVID-19 pandemic, approximately 30 drugs have been developed, with tocilizumab (TCZ) emerging as a key treatment for severe cases. Tocilizumab, a recombinant monoclonal antibody targeting interleukin-6 receptors, has effectively reduced intensive care unit (ICU) admissions and mortality, particularly in patients with elevated C-reactive protein (CRP) levels (1,2). Cytokine release syndrome, particularly involving interleukin-6 (IL-6), significantly contributes to COVID-19 mortality. Targeting IL-6 with specific therapies may mitigate the disease's effects. Researchers are hopeful that TCZ can improve lung inflammation in COVID-19 patients. However, the low level of evidence from observational studies calls for caution regarding its impact on mortality (3,4).

*** Corresponding Author:** Shadi Farsaei
Address: Department of Clinical Pharmacy, School of Pharmacy, Isfahan University of Medical Sciences, Hezar jarib Ave., Isfahan, Iran.
Email: sh.farsaei@gmail.com, Farsaei@pharm.mui.ac.ir

In Iran, where severe COVID-19 cases have significantly strained healthcare resources, TCZ has demonstrated potential in improving clinical outcomes by modulating the inflammatory response. Ongoing research in the region has focused on assessing TCZ's efficacy in attenuating lung inflammation and preventing the progression to critical illness, underscoring its potential therapeutic benefit in the local context of the pandemic (5-7). Additionally, the indiscriminate use of TCZ poses limitations due to the associated immunosuppression and heightened risk of infection. Despite its demonstrated efficacy in reducing CRP levels and potential benefits for many severely ill patients, there is a growing concern about irrational prescribing practices (8).

Regardless of its encouraging efficacy, the judicious use of TCZ in COVID-19 treatment necessitates ongoing evaluation and refinement of clinical protocols to address safety concerns and optimize patient outcomes (9,10). Current data on the drug utilization evaluation of TCZ in COVID-19 patients is lacking. Most studies focused on evaluating the efficacy of TCZ in treating COVID-19, with the most comprehensive analysis employing a causal inference approach to assess its application, demonstrating a 3.1% absolute reduction in 28-day mortality, along with an extra 8.6% absolute risk reduction linked to its use (11).

In light of the World Health Organization (WHO)'s warnings about the global shortage, high costs, and limited availability of TCZ, it seems that an evaluation of the rational usage of TCZ is necessary. However, no study evaluates the percentage of rational TCZ administration in critically ill patients during the treatment of COVID-19. This study was conducted to assess the proportion of critically ill COVID-19 patients receiving TCZ in accordance with established rational use criteria as the primary outcome. Additionally, we aimed to explore the associations between appropriate TCZ administration and both clinical and laboratory outcomes as secondary endpoints.

Methods

Study Design

This cross-sectional, observational study investigated the patterns of tocilizumab (TCZ) use among hospitalized COVID-19 patients at the intensive care unit (ICU) of two major referral hospitals in Isfahan (Alzahra and Amin hospitals), from February 2022 to April 2023.

Ethical Consideration

The methodologies employed in this study were approved by the institutional review board, which assigned the ethical code IR.ARI.MUI.REC.1400.077. Since this was an observational study, informed consent was not required and was accordingly waived.

Population

This study investigated the administration pattern of TCZ in adult patients aged 18 years and older diagnosed with COVID-19 and admitted to the ICU over nine months. Patients with incomplete medical reports of TCZ administrations or other clinical or laboratory data during their follow-up were excluded. A COVID-19 diagnosis is confirmed by detecting the SARS-CoV-2 virus through PCR or antigen tests. Disease severity is classified as mild (mild symptoms without pneumonia), moderate (pneumonia without hypoxia), severe (low oxygen saturation below 90%, respiratory distress), and critical (respiratory failure, septic shock, or multiorgan failure). Assessment of severity includes clinical symptoms like shortness of breath, comorbidities, laboratory markers such as lymphopenia and elevated inflammatory markers (CRP, ferritin, D-dimer), and imaging findings. The sample size was determined based on a 14-month study period, with a minimum of 100 patients.

Data Collection

Eligible patients were closely followed from enrollment to assess the percentage of TCZ rational prescribing and related outcomes, with key measures including ICU length of stay and intubation rates. The Pharm.D. meticulously recorded data regarding the prescription of TCZ, including dose, duration of infusion, and any concomitant medications administered for the treatment of COVID-19. The study was blinded to rational-use status, and then two clinical pharmacists evaluated the data and reported the percentage of rational TCZ use based on the standards (12). In addition to demographic information, underlying diseases and other pertinent medical records were collected. APACHE score was also meticulously calculated and recorded upon entering the study.

During the study, patient progress was evaluated on days 3 and 5 following the initial dose of TCZ by assessing changes in APACHE scores, arterial oxygen saturation (SaO2), and C-reactive protein (CRP) levels. Finally, these data and other clinical outcomes were compared between the two patient groups categorized by rational and irrational indications for TCZ administration.

Also, serial measurements of alanine aminotransferase (ALT) level, white blood cell count (WBC), and platelet count were performed to monitor for potential adverse reactions associated with TCZ administration.

Statistical Analysis

The Shapiro-Wilk test assessed the normality of continuous variables, reported as mean ± standard deviation (SD) or

median (interquartile range), and categorical variables were presented as frequencies (%). Mann-Whitney test was used to compare continuous variables between the groups, while Chi-square or Fisher's exact tests were employed to compare categorical data. The Friedman test also revealed significant changes in the measured parameters within each group over time, indicating within-subject variability across the repeated assessments. Additionally, Quade nonparametric ANCOVA was conducted between groups, using the baseline parameter as a covariate. Analyses were performed using SPSS (SPSS Inc., version 20, Chicago, IL, USA), with significance set at $P < 0.05$.

Results

Patient Characteristics

A total of 118 patients from two referral hospitals were initially included in the study. After excluding 10 patients (due to incomplete data), the analysis of tocilizumab (TCZ) consumption patterns and rational prescribing was conducted on 108 patients. The mean age of the population was 64.3 ± 16.40 years, with males accounting for 58.3% of patients. The average number of chronic complications in past medical history was 1.84 (SD = 1.27), and 70.5% of participants had not been intubated (Table 1).

Table 1. Baseline demographic characteristics and vital signs of the study population

Patients' Characteristics (N = 108)		
Age†		16.4 (64.3)
Gender*	Male	63 (58.3%)
	Female	45 (41.7%)
Diabetes*		38 (35.2%)
High blood pressure*		44 (40.7 %)
Atherosclerotic cardiovascular disease*		14 (12%)
Heart failure*		10 (9.3%)
Hyperlipidemia*		14 (12%)
Chronic kidney disease*		4 (1.9%)
Other chronic comorbidities*		55 (50.9%)
PMH number*		2 (1-3)
Intubated patients*		31 (29.5%)
Heart rate#		82(75-93)
Respiratory rate#		22(20-24)
Blood pressure#		120/80 (110/75-130/80)

† Mean (Standard Deviation), *Number (Percent), #Median (IQ1-IQ3).

Regarding the concurrent administration of medications, all patients received systemic corticosteroids, 78.7% were given antibiotics concurrently (mostly carbapenems, cephalosporins, and fluoroquinolones, which were prescribed in almost half of the patients), and 81.5% received remdesivir.

TCZ Utilization

Table 2 summarizes the data on the administration of TCZ. According to the TCZ administration guidelines, it is indicated for hospitalized COVID-19 patients who have significant oxygen requirements and those with lower but increasing oxygen needs accompanied by evidence of systemic inflammation (12). In our study population, 39.8% of patients did not meet the criteria for TCZ administration. Furthermore, TCZ was contraindicated for five patients. For one patient (0.9%), the TCZ dose exceeded the reasonable limit based on weight, accounting for over 120%; for eight patients (7.4%), the doses were appropriate at 8 mg/kg (12); and for 99 patients (91.7%), the doses were below the recommended threshold, representing less than 80% of the rational dose. As per the guidelines, if clinical signs and symptoms worsen or do not improve, a second dose of TCZ may be administered after a minimum interval of 8 hours following the initial injection (12). In our study, 47.2% of patients received a single dose, while 50% received two doses at least 12 hours between the first and second injections. Additionally, 1.85% of patients received three doses, and 0.93% received four doses of tocilizumab. In our study, all tocilizumab infusions were administered over a duration exceeding 2 hours, ranging from 2 to 6 hours, which aligns with the guideline recommendation of infusion over approximately 60 minutes (12). Considering all parameters of TCZ administration, including indication, dosage, number of doses, and dosing intervals, only 7.5% of patients received TCZ in accordance with rational clinical guidelines.

Table 2. Tocilizumab administration data in the study population (N = 108)

Variable				Number (Percent)
Indication	Rational	Hospitalized COVID-19 patients who have significant oxygen requirements and those with lower but increasing oxygen needs accompanied by evidence of systemic inflammation		65 (60.2%)
	Irrational	No significant or worsening oxygen dependency		6 (15.8%)
		No evidence of systemic inflammation, demonstrated by non-elevated CRP levels		26 (68.4%)
		Both of above criteria		6 (15.8%)
		Contraindication	ALT ≥ 10 times the ULN	2 (1.9%)
			Immunocompromised	3 (28%)
Dose	Irrational	More than 120% of the recommended dose		1 (0.9%)
		Less than 80% of the recommended dose		99 (91.7%)
	Rational	Recommended dose: 8 mg/kg once (maximum dose: 800 mg)		8 (7.5%)

CRP: C-reactive Protein, ALT: Alanine Aminotransferase, ULN: Upper Limits of Normal.

Laboratory and Clinical Outcomes

As outlined in the methodology, the patients enrolled in the study were monitored, and specific clinical and laboratory parameters were recorded on the third and fifth days following the TCZ injection, as presented in Table 1. According to the Friedman test, C-reactive protein (CRP) levels significantly decreased during the follow-up after TCZ administration (P-value < 0.001). The results of the Mann-Whitney test revealed that CRP levels before TCZ administration were considerably higher in the rational prescription group (P-value < 0.001). Additionally, Quade's nonparametric ANCOVA analysis between groups indicated that the APACHE score in the rational prescription group was significantly higher five days after TCZ administration, with baseline APACHE considered the covariate (P-value = 0.05) (Table 3).

Table 3. Clinical and laboratory data of patients during study follow-up of tocilizumab administration

Variable	Phase*	All patients (N=108)	Rational (N=70)	Irrational (N=38)	P-value
APACHE score#	1	7 (5-10)	7(4.5-10)	8(4.75-10)	0.99[a]
	2	7 (5-10.25)	7(5-12)	7.5(5-10)	0.73[b]
	3	6 (5-10.5)	6(5-15)	6(4.5-10.25)	0.05[c]
O2 saturation (%)#	1	90 (85-93)	90(86-92)	90(85-94)	0.07[a]
	2	91 (86-94)	90(86.5-94)	91.5(85-95)	0.54[b]
	3	92 (88-95)	91(88-95)	93(85.5-95)	0.94[c]
CRP (mg/L)#	1	81 (63.25-91.75)	87.5(80-97)	55.5(28.75-66)	<0.001[a]
	2	34 (20-53)	37(25-56)	19.5(10-45)	<0.001[b]
	3	12 (6-22)	13(7-27.25)	9 (4.25-15)	0.66[c]
ALT (U/L)#	1	30.5 (21-44.5)	30(21-45)	29.5(20-48)	0.35[a]
	2	37 (28-62)	36(27-68)	43.5(30.5-50.5)	0.42[b]
	3	46 (31-93)	48.5(34.25-105.5)	46(29-64)	0.48[c]
WBC (WBCs per microliter × 10^3)#	1	10.6 (8.1-12.85)	9.9(6.55-12.7)	10.75(8.895-12.9)	0.004[a]
	2	10.700 (9-14.25)	10.7(8.9-14.5)	10.75(9-13.9)	0.80[b]
	3	11.75 (9.225-15.05)	12.1(9.15-16.45)	11.6(9.5-14.1)	0.33[c]
Platelets (platelets per microliter × 10^3)#	1	212 (159-271)	180(15.825-255)	247(191-298)	<0.001[a]
	2	245 (203-328)	242(203.5-322.5)	252(197-339.5)	0.016[b]
	3	227 (153-318)	227(149.5-315)	130.5(156.75-347)	0.23[c]

APACHE: Acute Physiology and Chronic Health Evaluation, #median (IQ1-IQ3).

* 1: Before TCZ administration, 2: Three days after TCZ administration, 3: five days after TCZ administration.

[a] The analysis is based on Friedman's test for within-subject changes across all patients, [b] Mann-Whitney analysis was conducted between groups prior to TCZ administration, [c] Quade nonparametric ANCOVA was performed between groups five days after TCZ administration, using the baseline parameter as a covariate.

Comparative analysis between patients with rational versus irrational indications for TCZ revealed that appropriate prescriptions were significantly more frequent among intubated patients (P = 0.02) (Table 4).

Table 4. Clinical and laboratory data of patients with rational and irrational Tocilizumab indications

Variable	All patients (N=108)	Rational (N=70)	Irrational (N=38)	P-value
Duration from ICU Admission to TCZ administration[#]	3 (2-5)	3 (2-4)	4 (2-6)	0.133
PMH number[#]	2 (1-3)	2 (1-3)	2 (1-3)	0.439
Intubation †	32 (29.6%)	25 (37.3%)	6 (15.8%)	0.02
Hospital Length of stay (days) *	14.7 (7.7)	8.56 (15.39)	5.59 (13.63)	0.615
ICU Length of stay (days) *	6.5 (5.8)	6.1 (7.18)	4.82 (5.28)	0.081
Death †	35 (32.4%)	24 (34.3%)	11 (28.9%)	0.571

APACHE: Acute Physiology and Chronic Health Evaluation. * Mean (Standard Deviation), [#]Median (IQ1-IQ3), †Number (percent).

Discussion

Medication Use Evaluations (MUEs) for tocilizumab were conducted during the COVID-19 pandemic to assess its real-world implementation and effectiveness. These studies concentrated on patient selection, dosing protocols, and clinical outcomes within hospital settings (13-15). A 2024 study analyzed electronic health record (EHR) data from a large medical center before and after tocilizumab's inclusion in COVID-19 guidelines. The findings revealed that 69% of eligible patients received tocilizumab post-implementation of the formulary policy. A 3.1% absolute risk reduction in 28-day mortality was associated with adopting the guidelines, along with an additional 8.6% risk reduction directly linked to tocilizumab administration (with a number needed to treat of 12 to prevent one death) (13).

Current literature lacks comprehensive analyses comparing real-world tocilizumab (TCZ) prescribing patterns with established treatment guidelines, particularly regarding dosing accuracy and rationale for administration. Our multicenter evaluation at two academic referral centers in Iran (Isfahan) revealed 60.3% guideline-concordant TCZ initiation, yet 91.2% of recipients received subtherapeutic doses (< 80% recommended dosage). Given the high rate of irrational use, we propose the implementation of actionable institutional protocols to enhance adherence to clinical guidelines. Key factors contributing to dosing errors in our study included the high medication cost, challenges in safely storing remaining amounts in the vial, and medication shortages within a limited timeframe.

Notably, the primary reason for irrational prescribing was not elevated C-reactive protein (CRP) levels, which failed to meet the criteria for TCZ administration. Consequently, the lower CRP levels observed in cases of irrational indication were expected. Additionally, the higher number of intubated patients in the rational indication group highlighted significant or worsening oxygen dependency, indicating that the criteria for irrational indications were not met in this group, which was the second most common reason for irrational prescribing. Furthermore, comparing patient outcomes between the rational and irrational indications following TCZ administration revealed a higher APACHE score in the rational prescribing group. While the APACHE score is a crucial prognostic factor in COVID-19 patients, we did not observe any significant impact of rational indications on other clinical outcomes. A larger sample size may be needed to demonstrate these differences as statistically significant.

Predictably, C-reactive protein (CRP) levels will decrease significantly in the study population. The systemic inflammation associated with COVID-19 and hypoxemic respiratory failure can increase the secretion of various cytokines. This systemic inflammation is evidenced by elevated blood levels of interleukin-6 (IL-6), CRP, D-dimer, and ferritin. In the liver, IL-6 stimulates the production of CRP, serum amyloid A, fibrinogen, and hepcidin while reducing albumin synthesis. Tocilizumab is the first monoclonal antibody that selectively binds to the interleukin-6 receptor, preventing IL-6 from attaching to its receptor (IL-6R) and subsequently decreasing CRP levels (16, 17).

Our study has limitations as the findings were based exclusively on data from the hospital pharmacy. Some patients may have received tocilizumab (TCZ) through prescriptions filled outside the hospital pharmacy, which introduces potential selection bias and design constraints. Additionally, we did not evaluate patients who required TCZ but did not receive it, which limits our ability to assess the causal inference of the guidelines. Moreover, certain hard endpoints, including 28-day mortality, were not reported

.

Conclusion

Medication Use Evaluations during the COVID-19 pandemic highlighted tocilizumab's real-world use, showing improved mortality with guideline-based administration. However, our study found frequent subtherapeutic dosing and 39.7% irrational prescribing, mainly due to low CRP levels and oxygen requirements not being met. While rational use correlated with higher APACHE scores, no significant differences in other outcomes were observed, possibly due to sample size. Tocilizumab's mechanism in reducing inflammation and CRP is well-established, but limitations include incomplete data on out-of-hospital prescriptions and patients who needed but did not receive TCZ.

Conflict of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

This study was financially supported by the Isfahan University of Medical Sciences, Isfahan, I.R. Iran, through Grant No. 3400857.

References

1. Wei Q, Lin H, Wei RG, Chen N, He F, Zou DH, et al. Tocilizumab treatment for COVID-19 patients: a systematic review and meta-analysis. Infect Dis Poverty. 2021;10(1):71.
2. Salo JLM, Marcelo LJN, Sanchez ACA, Marcelino CP, Hazel Anne LC, Miranda KJA, et al. Effectiveness of Tocilizumab in COVID-19 Patients with Pneumonia: A Systematic Review. Acta Med Philipp. 2025;59(2):72-80.
3. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55(5):105954.
4. Moore JB, June CH. Cytokine release syndrome in severe COVID-19. Science. 2020;368(6490):473-474.
5. Talaschian M, Akhtari M, Mahmoudi M, Mostafaei S, Jafary M, Jalali SM, et al. Tocilizumab Failed to Reduce Mortality in Severe COVID-19 Patients: Results from a Randomized Controlled Clinical Trial. Iran J Allergy Asthma Immunol. 2024;23(1):82-96.
6. Shafieipour S, Rezaei Zadeh Rukerd M, Shamsizadeh Meymandi T, Sinaei R, Sarafzadeh F, Abu Saeedi H, et al. The Effect of Intravenous Tocilizumab Therapy on the Prognosis of Patients with COVID-19: A Case-Control Study. Iran J Med Microbiol. 2023;17(2):243-250.
7. Aringale V, Daswani B, Fernandes M. Retrospective Observational Analysis of Tocilizumab Outcomes in COVID-19 Patients at a Tertiary Care Hospital. J Pharm Care. 2024;12(1):24-31.
8. Verma AA, Pai M, Saha S, Bean S, Fralick M, Gibson JL, et al. Managing drug shortages during a pandemic: tocilizumab and COVID-19. CMAJ. 2021;193(21):E771-E776.
9. Campochiaro C, Della-Torre E, Cavalli G, De Luca G, Ripa M, Boffini N, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. Eur J Intern Med. 2020;76:43-49.
10. Hafez W, Ziade MA, Arya A, Saleh H, Abdelshakor M, Fadl Alla O, et al. Treatment Outcomes of Tocilizumab in Critically-Ill COVID-19 Patients, Single-Centre Retrospective Study. Antibiotics (Basel). 2022;11(2):241.
11. Landewé RBM, Ramiro S, Mostard RLM. COVID-19-induced hyperinflammation, immunosuppression, recovery and survival: how causal inference may help draw robust conclusions. RMD Open. 2021;7(1):e001638.
12. Tocilizumab. In: UpToDate lexidrug [Internet]. [Place unknown]: UpToDate Inc; Updated 2024. Accessed April 20, 2025. Available from: http://online.lexi.com
13. Goriacko P, Moskowitz A, Ferguson N, Khalique S, Hopkins U, Quinn N, et al. Medication use evaluation of tocilizumab implementation in COVID-19 treatment guidelines: A causal inference approach. Am J Health Syst Pharm. 2024;81(21):e700-e710.
14. Anci C, Solavallone V, Cardone R, Orlando JM. Use of tocilizumab in COVID-19 pneumonia hospitalized patients. Cohort study. Acta Colombiana de Cuidado Intensivo. 2023;23(2):105-112.
15. Petrelli F, Cherri S, Ghidini M, Perego G, Ghidini A, Zaniboni A. Tocilizumab as treatment for COVID-19: A systematic review and meta-analysis.

World J Methodol. 2021;11(3):95-109.

16. Calderón-Ochoa C, Plamenov-Donchev N, Hernández-Quiñones F, Mendoza-López O, Hinojos-Gallardo Luis C, Longino-Gómez Asunción J, et al. Tocilizumab demonstrates superiority in decreasing C-reactive protein levels in hospitalized COVID-19 patients, compared to standard care treatment alone. Microbiol Spectr. 2024;12(6): e0249823.
17. Soliman EMR, Wageh KM, Mohamed MM, Mohamed HA. The effect of tocilizumab administration on inflammatory markers in COVID-19 patients. Egypt J Bronchol. 2024;18(1):65.

PLEASE CITE THIS PAPER AS:

Afzali A, Farsaei S, Soltani R. Rational Use of Tocilizumab in Critically Ill COVID-19 Patients: A Two-Center Observational Study in the Intensive Care Unit. J Pharm Care. 2025; 13(4):253-259.