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Impact of tocilizumab on clinical outcomes in severe COVID-19 patients and risk of secondary infection: A case-control study

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ABSTRACT

Objective: This study aimed to identify the effect of tocilizumab (TCZ) on clinical outcomes in severe COVID-19 patients.

Material and Methods: We included hospitalized COVID-19 patients with an initial WHO scale ≥4. We matched the patients with baseline characteristics by using propensity scores. Then, we selected patients with C-reactive protein levels above 30 and showing an upward trend. We assessed the effect of TCZ in patients on clinical outcomes by using Mann – Whitney U and Chi-square tests.

Results: Of 200 patients who had an initial WHO scale ≥ 4, 42 (21%) were given TCZ in addition to standard of care (SOC). Twenty-five patients (50%) needed mechanical ventilation (MV) in the TCZ group, compared with 35 (21%) of 158 patients with SOC ($p<0.01$). Nineteen (45%) and 37 (23%) patients died in 30 days in these groups, respectively ($p <0.01$). The secondary infection rate was significantly higher in the TCZ group ($p=0.004$). However, no difference was observed in all these parameters in the propensity score-matched cohort (14 patients in TCZ and 14 in the SOC group) ($p=0.45$, 0.45, 1.0 respectively).

Conclusions: Tocilizumab does not provide a beneficial effect on MV requirement and mortality in severe COVID-19, and it does not increase the risk of secondary bacterial infection.

Keywords: COVID-19, IL-6, SARS-CoV-2, Tocilizumab

1. INTRODUCTION

Since the end of December 2019, the infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused the death of more than 1.7 million people all around the world [1]. Although, many potential drugs and vaccines are under clinical evaluation, an effective treatment of the disease has not been found so far. Many severe patients developed cytokine release syndrome (CRS), which played a crucial role in the pathogenesis of the coronavirus disease 2019 (COVID-19) [2, 3]. The elevated production of pro-inflammatory cytokines including interleukin 6 (IL-6) is considered to be the main factor in the development of CRS and respiratory failure [4, 5]. Furthermore, increasing plasma IL-6 levels have been observed in the intensive care unit (ICU) patients with COVID-19 and this has been associated with high mortality [4, 6]. Although, there is no proven treatment for COVID-19, inhibition of this inflammation at the right time suggests that the clinical outcome may be improved [7]. Tocilizumab (TCZ), a humanized anti-IL-6 receptor monoclonal antibody, blocks the IL-6-mediated pro-inflammatory cytokines and has been approved for the treatment of rheumatoid arthritis and systemic juvenile arthritis [8-10].

Following the COVID-19 outbreak, several studies have described the use of TCZ in COVID-19 pneumoniae [5, 11-14]. However, most of these studies are not randomized controlled

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trials (RCT) and have a small number of patients [11, 12]. The impact of TCZ on clinical outcomes in severe COVID-19 patients was found to be different in previous studies. While some studies have demonstrated that TCZ is associated with better overall survival [15-17], others have shown no additional benefit [18, 19].

Besides its life-saving effect, inhibition of IL-6 may have undesirable consequences. One of the most important complications of anti-IL-6 agents is secondary infections. In many safety studies, it was shown that TCZ increases secondary infection rates in patients with COVID-19 [15, 16, 20].

The Republic of Turkey Ministry of Health has allowed for compassionate use of tocilizumab in the event of cytokine storm or macrophage activation syndrome in patients with severe COVID-19 since the beginning of the pandemic. In this study, we aimed to evaluate the impact of TCZ on mortality and the need for mechanical ventilation (MV), in hospitalized severe COVID-19 patients using propensity score matching in two centers. Secondly, we evaluated the infection rates in matched patients.

2. MATERIAL and METHODS

This retrospective two-center case-control study was performed between March 22 and June 5, 2020 (the last follow up was on July 25) at Marmara University, Pendik Training and Research Hospital and Umraniye Training and Research Hospital. The participants of the matched case-control study were selected from a hospitalized COVID-19 real-time polymerase chain reaction (RT-PCR) positive patient population pool. We analyzed the data of patients who were World Health Organization (WHO) scale 4 and above [21].

We obtained the following data from computer-based patient records: gender; age; comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease (COPD), asthma, immunosuppression, cardiovascular system disease, chronic renal and liver disease); serum inflammatory markers (Lymphocyte count and percent, C-reactive protein (CRP), ferritin, d-dimer); symptom onset dates; baseline clinical status (SpO_2/FiO2 ratio, need for O_2); length of hospital stay; requiring ICU; clinical outcomes (requiring MV and 30 days mortality) and secondary infections.

Severe cases were defined as saturation of oxygen <94% on room at sea level, a ratio of arterial PaO_2/FiO_2 <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50% according to National Institutes of Health (NIH) classification at the same time [22].

Tocilizumab was initiated in patients with worsening respiratory parameters and/or suspected cytokine storm, despite standard therapy, according to the evaluation of the attending physicians. TCZ dose was 8 mg/kg (up to a maximum 800 mg) infused over 60 min intravenously; in some patients, a second dose was applied after 24 hours in case of persistence of respiratory distress and high inflammatory markers. The choice and indication of TCZ treatment depended on attending physicians.

Propensity score matching

After analyzing data of patients with WHO scale ≥ 4, a propensity score matching was performed [23]. Propensity scores with a caliper width of 0.1 were calculated by using the variables of age, gender, and the number of comorbidities with an allocation ratio target of 1 to 3. According to the duration from the onset of symptoms to the initiation of TCZ treatment (in days), the patients were divided into 3 strata, namely 7 to 10 days, 11 to 13 days and more than 14 days. The control patients and three measurements or each ferritin, CRP, procalcitonin, lymphocyte count, SpO2/FiO2 ratio values. Among three measurments in distinct time periods, the measurement temporarily matched to the first day of TCZ treatment of respective case patient was selected for each control patient. For the selection of temporarily matched measurement, the aforementioned strata were used. Afterwards, two additional criteria two additional criteria or CRP value were used for matching, including: an increase in CRP value relative to CRP level at admission and a CRP value above 30 mg/L during the first day of TCZ treatment for cases and during the corresponding stratum for controls.

This study was approved by the Institutional Review Board of Marmara University, School of Medicine (approval number 092020.718). The necessary permission was obtained from the Republic of Turkey Ministry of Health.

Statistical Analysis

The normality assumption of numerical variables was tested with histogram, skewness kurtosis and Shapiro-Wilk tests [24]. The numeric variables without normal distribution were presented with median, interquartile range, minimum and maximum values. The categorical variables were presented with frequencies and percentages. The distributions of numerical variables among two independent groups (namely case and control groups) were tested with Mann-Whitney U test. The categorical variables were analyzed with Chi-squared test and Fisher's exact test. A p-value less than 0.05 was considered statistically significant. Microsoft Excel 2007 and Stata 15.1 software were used for data analysis.

3. RESULTS

Overall, 407 consecutive hospitalized adult patients (≥18 years) whose RT-PCR was positive for COVID-19 were enrolled in the study. Of 407 patients, 200 patients with WHO scale 4 and above at admission were analyzed. Of 200 patients, 158 (79%) received standard of care (SOC) (hydroxychloroquine (HQ) and/or favipiravir and/or azithromycin) and 42 (21%) received TCZ in addition to SOC. Baseline characteristics of both groups were summarized in Table I. The median age was similar, and the majority of the patients were male in both groups (78.6% in TCZ and 58.9% in SOC group, p= 0.02). Total 40 cases matched to 120 controls were selected with propensity score matching method. Of the matched cases and controls, 6 cases and corresponding 18 control patients were excluded, since their tocilizumab treatment started before day 7. After

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using CRP criteria, 14 cases and 14 controls were included in this study (Figure 1).

When we analyzed a data of 200 patients, ferritin and procalcitonin were higher, and lymphocyte count and SpO_2/FiO_2 ratio were lower at admission in the TCZ+SOC group compared to the SOC group (Table I). All repurposed antivirals except HQ and steroid were used statistically more frequently in the TCZ group (Table I). Length of hospital stay (TCZ+SOC group 15.5 (18%) vs SOC group 12 (11%) days), mechanic ventilation requirement (n=25 (59.5%) vs n=35 (22.2%) cases), and 30-day mortality (7 (45.2%) vs 5 (23.4%) days) were found significantly higher in the TCZ+SOC group ($p < 0.01$ for all).

The secondary infection rates were higher in the TCZ group than in the SOC group (n=12 (28.5%), n=17 (10.7%) respectively, p=0.004). The most common infection was pneumonia in both groups: 9 of 12 patients in the TCZ group and 11 of 17 patients in the SOC group. *Acinetobacter baumanii* and other multiple drug resistant gram-negative bacteria were cultured in 15 tracheal aspirates. Bacteremia was detected in 7 patients in each group. Candidemia was detected only in two patients in the SOC group.

Propensity-score matched case-control

A total of 28 patients were matched; 14 patients were in the TCZ + SOC group, and 14 in the SOC group. The median age, sex, number and types of comorbidities, laboratory parameters, and concomitant use of antivirals and steroids were similar in each group (Table I). Compared with the SOC group, TCZ group had higher ferritin levels (p= 0.01).

Seven of 14 patients (50%) in TCZ group and 5 of 14 patients (35.7%) in SOC group died after intubation and there was no statistical difference (p=0.45). The secondary bacterial infections were detected in 4 patients in the TCZ group and 3 in the SOC group. Similarly, there was no significant difference in this parameter. The most common infection was pneumonia in both groups.

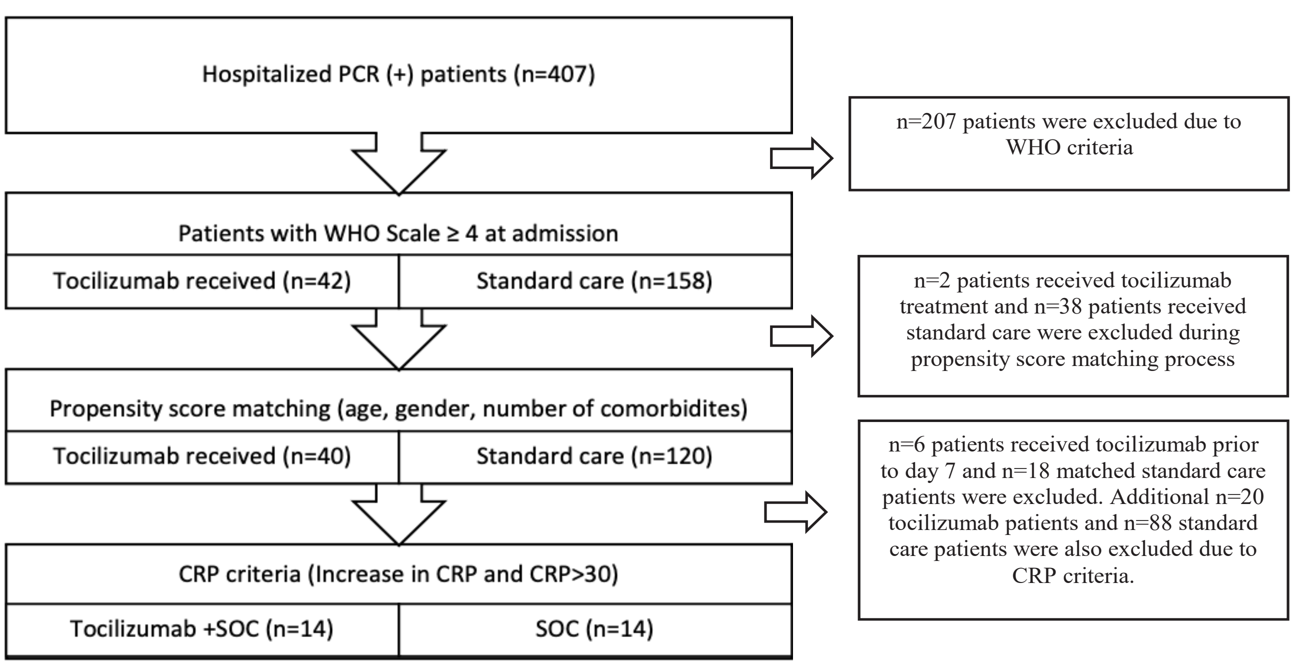

Figure 1. *Flowchart for patient selection*

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Table I. *Characteristics of patients receiving TCZ + SOC or only SOC, before and after propensity score matching*

		Total			Match		
Variable	**Statistics**	**TCZ + SOC**	**SOC**	**p**	**TCZ + SOC**	**SOC**	**p**
Observation	*n (%)*	42 (21.0)	158 (79.0)	n/a	14 (50.0)	14 (50.0)	n/a
Patient characteristics							
Age	*Median (IQR)*	61 (16.9)	60.8 (25)	0.63	61 (17)	59 (25)	0.43
	Min-Max	30-81	20-95		30-81	44-80	
Gender							
Male	*n (%)*	33 (78.6)	93 (58.9)	**0.02**	11 (78.6)	11 (78.6)	1.00
Female	*n (%)*	9 (21.4)	65 (41.1)		3 (21.4)	3 (21.4)	
Number of comorbidities	*Median (IQR)*	2(2)	1(3)	0.80	1 (2)	1 (2)	0.76
	Min-Max	0-6	0-5		0-4	0-3	
Comorbidity							
Hypertension	*n (%)*	22(52.4)	81 (51.3)	0.90	7 (50.0)	6 (42.9)	0.71
Diabetes	*n (%)*	14 (33.3)	58 (36.7)	0.69	2 (14.3)	2 (14.3)	1.00
COPD/Asthma	*n (%)*	8 (19.1)	33 (20.9)	0.79	3 (21.4)	3 (21.4)	1.00
Coronary artery disease	*n (%)*	10 (23.8)	46 (29.1)	0.50	5 (35.7)	4 (28.6)	1.00
Immuno-suppression	*n (%)*	4 (9.5)	16 (10.1)	1.00	1 (7.1)	1 (7.1)	1.00
Chronic kidney disease	*n (%)*	4 (9.5)	14 (8.9)	1.00	1 (7.1)	1 (7.1)	1.00
Chronic liver disease	*n (%)*	2 (4.8)	0 (0.0)	**<0.01**	0 (0.0)	0(0.0)	n/a
Laboratory							
Ferritin on admission	*Median (IQR)*	734.3 (823.7)	318.6 (450.9)	**<0.01**	751.6 (716.86)	278.05 (507.1)	0.09
	Min-Max	43.6 – 2939.2	5.2 – 9427		43.6 – 2676.11	13 – 3000	
Ferritin matched	*Median (IQR)*	n/a	n/a	n/a	1075 (1097)	564 (553)	**0.01**
	Min-Max	n/a	n/a		245-3295	50-1411	
CRP on admission	*Median (IQR)*	61.1 (130.8)	37.5 (82.3)	0.08	19.1 (67.7)	63.9 (78.1)	0.06
	Min-Max	0.2-412.4	0-391		0.2-255	18.5-250	
CRP matched	*Median (IQR)*	n/a	n/a	n/a	195 (108)	155 (236)	0.78
	Min-Max	n/a	n/a		40-274	56-381	
Procalcitonin on admission	*Median (IQR)*	0.27 (1.05)	0.1 (0.16)	**<0.01**	0.165 (0.9)	0.135 (0.17)	0.55
	Min-Max	0.03-22.57	0.03 – 100		0.05-13.42	0.04 – 3.43	
Procalcitonin (maximum, matched)	*Median (IQR)*	n/a	n/a	n/a	0.53 (0.73)	0.11 (1.25)	0.41
	Min-Max	n/a	n/a		0.05-3.8	0.04 – 15.02	

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Lymphocyte count	*Median (IQR)*	710 (700)	1000 (740)	**<0.01**	935 (970)	1000 (300)	0.82
	Min-Max	100 – 9600	0 – 7200		100-9600	500-2100	
Lymphocyte count matched	*Median (IQR)*	n/a	n/a	n/a	680 (360)	850 (800)	0.66
	Min-Max	n/a	n/a		100 – 9600	100 – 1700	
SpO_2/FO_2 ratio on admission	*Median (IQR)*	233.5 (186)	404 (184)	**<0.01**	243 (138)	333.5 (226)	0.12
	Min-Max	90-471	92-476		98-466	111-476	
SpO_2/FiO_2 ratio matched	*Median (IQR)*	n/a	n/a	n/a	161.5 (162)	281 (110)	0.054
	Min-Max	n/a	n/a		80-457	100-476	
Treatment							
Favipiravir	*n (%)*	38 (90.5)	105 (66.5)	**<0.01**	12 (85.7)	11 (78.6)	0.62
	Days of treatment						
	Median (IQR)	5(0)	5(0)	0.19	5(0)	5(0)	0.35
	Min-Max	0-6	0-9		0-6	5-5	
Hydroxychloroquine	*n (%)*	39 (92.9)	155 (98.1)	0.08	14 (100.0)	14 (100.0)	n/a
	Days of treatment						
	Median (IQR)	10(2)	9(5)	0.11	10(2)	10(2)	0.83
	Min-Max	0-10	0-10		5 – 10	5-10	
Macrolide	*n (%)*	35 (83.3)	100 (63.3)	**0.01**	13 (92.9)	8 (57.1)	0.08
	Median (IQR)	5(0)	5(1)	0.54	5(0)	5(0)	0.63
	Min-Max	0-6	0-7		3-6	5-5	
Steroid	*n (%)*	22 (52.4)	34 (21.5)	**<0.01**	10 (71.4)	5 (35.7)	0.06
ICU admission	*n (%)*	34 (80.95)	53 (33.5)	**<0.01**	10 (71.4)	6 (42.9)	0.13
Outcome							
Length of hospital stay	*Median (IQR)*	15.5 (18)	12 (11)	**0.01**	16 (18)	13 (14)	0.49
	Min-Max	2-67	3-69		2-53	3-31	
Secondary infection	*n (%)*	12 (28.57)	16 (10.13)	**0.002**	4 (28.57)	3 (21.43)	1.00
Requiring MV	*n (%)*	25 (59.52)	35 (22.15)	**<0.01**	7 (50.00)	5 (35.7)	0.45
30-day mortality	*n (%)*	19 (45.2)	37 (23.4)	**<0.01**	7 (50.0)	5 (35.7)	0.45
Discharge	*n (%)*	23 (54.8)	121 (76.6)		7 (50.0)	9 (64.3)	

Abbreviations: COPD: Chronic obstructive pulmonary disease, CRP: C-reactive protein, ICU: Intensive care unit, IQR: Interquartile Range, MV: Mechanical ventilation, SOC: Standard of care, TCZ: Tocilizumab

4. DISCUSSION

In the present study, we found that TCZ did not improve the clinical outcome (need for MV or 30-day mortality) in severe COVID-19 patients. Also, TCZ did not increase secondary bacterial infections in severe COVID-19 patients. According to our early institutional policy, HQ was started for all patients except for some contraindications, and other antivirals and steroids were added in the absence of clinical improvement. Given the higher use of favipiravir, macrolide, and steroid in the TCZ group, this indicates that TCZ was given to patients with more severe conditions. As a result of this, ICU admission, length of hospitalization, requiring MV, mortality, and secondary infection rate were found significant in this group. Similarly, previous studies demonstrated that elevated serum IL-6, CRP, ferritin, and procalcitonin levels are correlated to poor outcomes and the development of secondary bacterial infection as prognostic factors [25, 26]. The lymphocyte count, another important prognostic factor in COVID-19, decreases depending on damage to the cytoplasmic component of lymphocyte, and this was also found associated with severe COVID-19 [27-29].

The RCTs relating to the impact of TCZ on clinical outcomes were limited and results are variable [11, 12]. In a recent study, Stone et al. showed that TCZ has no impact on preventing intubation and death [30]. Some case-control studies demonstrated that TCZ reduces the need for MV and mortality in severe patients with COVID-19 [13, 16, 31]. However, Campochiaro et al. showed that there is no difference in clinical improvement and mortality between TCZ and SOC [32]. In another study, it was demonstrated that severe to critical COVID-19 patients treated with TCZ have lower mortality, but it is not statistically significant [33]. In our study, after propensity score matching with baseline characteristics, we matched the patients by using CRP (above 30 mg/L and increasing trend), a covariate that most likely affects treatment assignment, to allow an appropriate matching. The severity of both groups may be considered quite similar to each other at treatment assignment period. However, ferritin levels were found higher in the TCZ group. This may reflect a greater hyperinflammation.

The higher WHO scale category is independently associated with the development of critical disease [34]. We included patients who needed oxygen (WHO scale 4 and higher) at admission to the study and found the SpO_2/FiO_2 ratio of the patients taking TCZ was lower in both overall and matched groups. Although, it was not statistically significant in the matched group, lower levels of SpO2/FiO2 ratio were observed in TCZ group. Previous studies showed that steroid treatment improves clinical outcomes in severe patients requiring supplemental oxygen, with or without the need for MV [35, 36]. In our study, although not statistically significant, steroid use was higher in the TCZ group correlated with oxygen need. At least we did not show worse outcomes in this group. However, we were unable to demonstrate any benefit of using TCZ in severe COVID-19 patients.

Some studies demonstrated that a combination of TCZ and steroids have better outcomes [37]. However, some studies support an association between steroid or TCZ use and the development of secondary infections [20]. Hill et al., also demonstrated that TCZ has no impact on outcomes and increases infection rates in hospitalized COVID-19 patients [18].

In a recent meta-analysis, it was demonstrated that the bacterial infection rate ranged from 5.9% to 8.1% in critically ill patients with COVID-19 [38]. In our study, the overall secondary bacterial infection rate was significantly higher in the TCZ group. Although, overall initial procalcitonin values were also found higher in this group, only 3 of 28 infections were observed within 48 hours after admission (2 cases in SOC, 1 in TCZ group). Other 25 of 28 infections developed after 48 hours. When cases were matched, despite the higher steroid use in the TCZ group, there was no difference in secondary infection between both groups. The procalcitonin values were already similar.

Limitations

There are some limitations to our study. First, the number of propensity score-matched cases were very limited. Second, we matched only CRP as a laboratory parameter at the treatment assignment period. We could not measure IL-6 levels, one of the most important pro-inflammatory cytokines, because it was unavailable at that time in our centers. Third, coinfection with other viral respiratory pathogens could not be demonstrated. This study was conducted in two centers, there may be a center effect in our results.

Conclusion

The present study showed that TCZ has no beneficial effect on the need for MV and 30-day mortality in patients with severe COVID-19. Besides, no significant association of TCZ on secondary bacterial infections has been demonstrated. Detailed randomized studies are needed in terms of TCZ's efficacy in the treatment of COVID-19 and its contribution to the development of superinfections.

Compliance with Ethical Standards

Ethical approval: This study was approved by the Institutional Review Board of Marmara University, School of Medicine (approval number 092020.718). The necessary permission was obtained from the Republic of Turkey Ministry of Health.

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Conflict of interest: The authors have no potential conflicts to declare.

Authors' contributions

Conception and design of the study, drafting the article: BES, Data collection and writing: SO, LNA and FG, Analysis and interpretation of data: CI and US, Data collection and drafting the article: FTT, Data collection and interpretation of data: FK, Revising: MA, Revising the article critically for intellectual content: IC and ZO, Conception and design of the study, revising the article critically for intellectual content: VK. All authors read and approved the final version of the article.

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