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International Journal of Antimicrobial Agents 57 (2021) 106265

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Early clinical outcomes with tocilizumab for severe COVID-19: a two-centre retrospective study

Steven M. Smoke[a,*], Karan Raja[b,*], Patrick Hilden[c], Nicole M. Daniel[b]

[a] Pharmacy Department, Saint Barnabas Medical Center, 94 Old Short Hills Road, Livingston, NJ 07039, USA
[b] Pharmacy Department, Clara Maass Medical Center, 1 Clara Maass Dr., Belleville, NJ 07109, USA
[c] Biostatistics Department, Saint Barnabas Medical Center, Livingston, NJ, USA

ARTICLE INFO

Article history:
Received 20 May 2020
Accepted 5 December 2020

Editor: J. Gray

Keywords:
COVID-19
SARS-CoV-2
Tocilizumab
IL-6 inhibitor
Immunomodulatory agents

ABSTRACT

Severe COVID-19 (coronavirus disease 2019) is associated with elevated inflammatory markers, consistent with cytokine release syndrome (CRS). Tocilizumab is an interleukin-6 (IL-6) inhibitor effective in treating CRS secondary to chimeric antigen receptor T-cell (CAR T-cell) therapy. The efficacy of tocilizumab in treating COVID-19 is unknown. This was a retrospective cohort study conducted at two hospitals in northern New Jersey (USA). All patients treated with tocilizumab for confirmed or suspected COVID-19 between 10 March 2020 and 9 April 2020 at the study sites were included. The primary endpoint was clinical improvement on Day 7 after treatment as assessed by respiratory status. Univariate analysis compared data between those who improved and those who did not. A total of 45 severe and critically ill patients treated with tocilizumab for COVID-19 were evaluated. Of the 45 patients, 11 (24.4%), 22 (48.9%) and 12 (26.7%) patients improved, had no change or worsened by Day 7 after treatment, respectively. Lower white blood cell count and lactate dehydrogenase at the time of drug administration as well as shorter time from supplemental oxygen initiation to dosing were significantly associated with clinical improvement in the univariate analysis. In conclusion, tocilizumab administration was associated with a low rate of clinical improvement within 7 days in this cohort of severe and critically ill patients with COVID-19.

1. Introduction

COVID-19 (coronavirus disease 2019), a disease caused by the novel coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2), has swept across the globe unlike any disease seen in decades. According to the World Health Organization (WHO), nearly 47 million cases and 1.2 million deaths have been reported worldwide as of 3 November 2020 [1]. The rapid spread and considerable mortality has clinicians desperate for therapeutic options to improve patient outcomes.

Evidence has suggested that severe viral infections may be associated with cytokine release syndrome (CRS), a hyperinflammatory state that can result in multiorgan failure. Retrospective reports from China have demonstrated that severe COVID-19 is associated with elevated inflammatory markers, similar to CRS [2]. In particular, elevated interleukin-6 (IL-6), D-dimer, C-reactive protein, cardiac troponin and procalcitonin have been identified as predictors of mortality in COVID-19 [3–6]. This has led to speculation that treatment with immunomodulatory agents may yield positive outcomes by lessening hyperinflammation and minimising acute and long-term end-organ damage [7].

Tocilizumab is a monoclonal antibody that functions as an IL-6 receptor antagonist. Initially approved for the treatment of autoimmune disorders, it was subsequently found to be effective for the treatment of CRS secondary to chimeric antigen receptor T-cell (CAR T-cell) therapy [8]. Given its efficacy for this indication as well as the apparent role of IL-6 in COVID-19, interest in its role for severe manifestations of COVID-19 has grown.

A variety of observational studies and randomised controlled trials (RCTs) have investigated this question. Two meta-analyses of observational studies came to conflicting conclusions regarding the efficacy of tocilizumab [9,10]. Aziz et al. evaluated 23 studies with 6279 patients and found that tocilizumab use was associated with lower mortality [risk difference (RD), −0.06; 95% confidence interval (CI) −0.12 to −0.01] and decreased need for mechanical ventilation (RD, −0.11; 95% CI −0.19 to −0.02) [9]. However, Lan et al. assessed seven studies with 592 patients and found no difference in mortality [risk ratio (RR), 0.62; 95% CI 0.31–1.22] or need for

* Corresponding authors. Tel.: +1 973 322 2879; fax: +1 973 322 5185
E-mail addresses: steven.smoke@rwjbh.org (S.M. Smoke), karan.raja@rwjbh.org (K. Raja).

https://doi.org/10.1016/j.ijantimicag.2020.106265
0924-8579/

mechanical ventilation (RR, 0.82; 95% CI 0.14–4.94) between those treated with tocilizumab and the control group [10]. More recently, Gupta et al. conducted a multicentre cohort study of nearly 4000 patients and found that those treated with tocilizumab had a lower adjusted risk of death compared with patients not treated with tocilizumab [hazard ratio (HR), 0.71; 95% CI 0.56–0.92] [11].

Results from RCTs have been similarly inconsistent. Stone et al. conducted a randomised, double-blind, placebo-controlled study and found no benefit of tocilizumab with respect to intubation or death (HR, 0.83; 95% CI 0.38–1.81) or disease worsening (HR, 1.11; 95% CI 0.59–2.10) [12]. An open-label RCT conducted by Salvarani et al. also found no differences in outcomes with tocilizumab compared with placebo, with a rate ratio for clinical worsening at 14 days of 1.05 (95% CI 0.59–1.86) [13]. Hermine et al. found no difference in respiratory status at Day 4 [median posterior absolute risk difference, −9.0%; 90% credible interval (CrI) −21.0 to 3.1] but a reduction in death or need for ventilation with tocilizumab at Day 14 (median posterior HR, 0.58; 90% CrI 0.33–1.00) [14].

The availability of some RCT results prior to peer-reviewed publication has further clouded this issue. Two such randomised, double-blind, placebo-controlled studies of tocilizumab have reported conflicting results. The COVACTA trial in patients with severe or critical COVID-19 found no difference in clinical status at Day 28 (odds ratio, 1.19; 95% CI 0.81–1.76) [15]. The EMPACTA study conducted in patients with severe COVID-19 only found reduced death or need for mechanical ventilation at Day 28 (HR, 0.56, 95% CI 0.32–0.97) [16].

In the setting of unclear evidence and increasing cases of COVID-19 worldwide, interest in the role of tocilizumab as a therapeutic option persists. The purpose of this study was to assess the characteristics and clinical outcomes of patients treated with tocilizumab for COVID-19.

2. Materials and methods

This was a retrospective cohort study conducted at two community medical centres located in northern New Jersey (USA). Both hospitals are members of a health system that shared identical institutional guidance regarding COVID-19 treatment recommendations during the study period. This guidance recommended consideration of tocilizumab as a treatment option for severe COVID-19 based on elevated inflammatory markers, increasing oxygen requirement and elevated temperature without specific thresholds. The recommended dose was 8 mg/kg (maximum 800 mg) once. This dose could be repeated for patients who did not respond within 8–12 h of the initial dose. The treatment and dosing strategy for tocilizumab, as well as use of other antivirals and corticosteroids, were based upon provider discretion. All patients treated with tocilizumab for confirmed COVID-19 between 12 March 2020 and 9 April 2020 at the study sites were included. COVID-19 was diagnosed by real-time PCR detection of SARS-CoV-2 from nasopharyngeal swabs.

The primary endpoint was clinical improvement on Day 7 after treatment as assessed by respiratory status. Respiratory status was assessed at the end of the day according to the following ordinal scale recommended by the WHO R&D Blueprint Expert Group [17]: death (7); hospitalised on invasive mechanical ventilation (6); hospitalised on non-invasive ventilation or high-flow oxygen device (5); hospitalised requiring supplemental oxygen (4); hospitalised not requiring supplemental oxygen (3); not hospitalised, limitation on activities (2); and not hospitalised, no limitations on activities (1). Clinical improvement was defined as any decrease in score on Day 7 compared with the day of treatment initiation. Data were collected from admission until 7 days following tocilizumab administration. Data on baseline demographics, medical history, oxygen requirements and COVID-19 therapy were collected. Additionally, vital signs and laboratory data immediately prior to tocilizumab therapy were collected. Data were compared between those who improved and those who did not. Differences between patients who improved and did not were assessed using the Wilcoxon rank-sum test for continuous variables and the χ^2 test or Fisher's exact test for categorical variables as appropriate. This study was approved by the central Institutional Review Board.

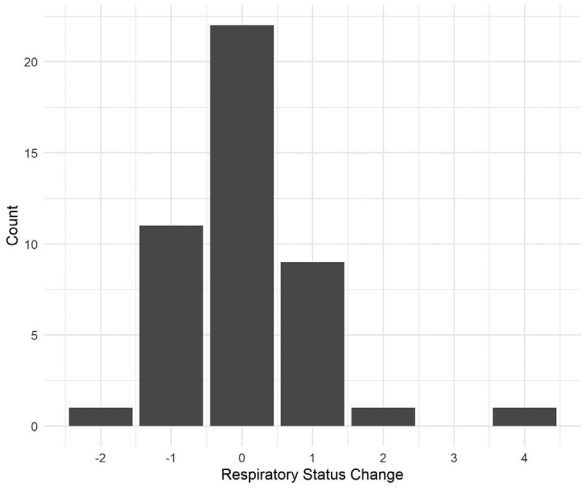

Fig. 1. Histogram plot of respiratory status change at Day 7. Negative values indicate clinical worsening, whereas positive values indicate improvement.

3. Results

A total of 46 patients received tocilizumab at the study sites during the 4-week study period. One patient was transferred to an outside hospital prior to the Day 7 assessment and was excluded from the analysis. Table 1 outlines the baseline and clinical characteristics of the 45 patients included for analysis as well as the results from the univariate analysis comparing characteristics of those who improved and those who did not. Overall, 29 patients (64.4%) were male, the median patient age was 55.0 years [interquartile range (IQR) 48.0–63.0 years] and the median body mass index (BMI) was 30.0 kg/m^2 (IQR 26.6–36.7 kg/m^2). The most common co-morbidities were hypertension (51.1%) and type 2 diabetes mellitus (31.1%).

Patients received tocilizumab a median of 11.0 days (IQR 7.0–15.0 days) after symptom onset and 112.2 h (IQR 51.5–155.8 h) after admission. Of the 45 patients, 32 (71.1%) were intubated (score of 6 on the respiratory status scale) on the day of tocilizumab administration, and an additional three patients were intubated within the 7-day follow-up period. Moreover, 31 patients (68.9%) had documented acute respiratory distress syndrome (ARDS) at the time of dosing. All patients received hydroxychloroquine, two (4.4%) received lopinavir/ritonavir and 27 (60.0%) received corticosteroids. Of the 45 patients, 11 (24.4%) improved by Day 7 after treatment, 22 (48.9%) had no change and 12 (26.7%) worsened. Fig. 1 illustrates the respiratory status change at Day 7 for the entire cohort. Lower white blood cell (WBC) count ($P = 0.038$) and lactate dehydrogenase (LDH) ($P = 0.015$) at the time of drug administration as well as shorter time from initiation of supplemental oxygen to dose ($P = 0.044$) were significantly associated with clinical improvement.

4. Discussion

In this small retrospective cohort study, we found low rates of early clinical improvement in patients with severe or critical

Table 1
Baseline and clinical characteristics of 45 patients included in the analysis, and results of the univariate analysis comparing characteristics of those who improved and those who did not.

Variable	Missing data	Group	Entire cohort (n = 45)	Not improved (n = 34)	Improved (n = 11)	P-value
Site						>0.999
		Site 1	14 (31.1)	11 (32.4)	3 (27.3)	
		Site 2	31 (68.9)	23 (67.6)	8 (72.7)	
Demographics						
Age (years)			55.0 (48.0–63.0)	57.0 (49.8–63.8)	53.0 (44.5–56.0)	0.149
BMI (kg/m^2)			30.0 (26.6–36.7)	29.5 (26.5–36.1)	35.0 (28.6–37.7)	0.457
Sex						0.067
		F	16 (35.6)	15 (44.1)	1 (9.1)	
		M	29 (64.4)	19 (55.9)	10 (90.9)	
Co-morbidities						
ESRD						>0.999
		No	44 (97.8)	33 (97.1)	11 (100.0)	
		Yes	1 (2.2)	1 (2.9)	0 (0)	
Malignancy						>0.999
		No	43 (95.6)	32 (94.1)	11 (100.0)	
		Yes	2 (4.4)	2 (5.9)	0 (0)	
Hypertension						0.141
		No	22 (48.9)	14 (41.2)	8 (72.7)	
		Yes	23 (51.1)	20 (58.8)	3 (27.3)	
Diabetes mellitus type 2						0.132
		No	31 (68.9)	21 (61.8)	10 (90.9)	
		Yes	14 (31.1)	13 (38.2)	1 (9.1)	
Heart disease						0.558
		No	41 (91.1)	30 (88.2)	11 (100.0)	
		Yes	4 (8.9)	4 (11.8)	0 (0)	
COPD						>0.999
		No	44 (97.8)	33 (97.1)	11 (100.0)	
		Yes	1 (2.2)	1 (2.9)	0 (0)	
Asthma						0.143
		No	42 (93.3)	33 (97.1)	9 (81.8)	
		Yes	3 (6.7)	1 (2.9)	2 (18.2)	
Medication use						
Cumulative tocilizumab dose (mg/kg)			7.3 (5.5–7.9)	7.3 (6.2–8.3)	7.1 (4.7–7.8)	0.552
Re-dose						>0.999
		No	37 (82.2)	28 (82.4)	9 (81.8)	
		Yes	8 (17.8)	6 (17.6)	2 (18.2)	
Corticosteroid use						0.304
		No	18 (40.0)	12 (35.3)	6 (54.5)	
		Yes	27 (60.0)	22 (64.7)	5 (45.5)	
Vasopressor use (pre-dose [a])						0.482
		No	27 (60.0)	19 (55.9)	8 (72.7)	
		Yes	18 (40.0)	15 (44.1)	3 (27.3)	
Vital signs						
Respiratory rate (pre-dose [a], breaths/min)			25.0 (22.0–31.0)	25.5 (22.0–31.8)	25.0 (22.5–29.5)	0.905
Heart rate (pre-dose [a], beats/min)			110.0 (98.0–122.0)	114.0 (104.2–123.8)	107.0 (92.0–115.5)	0.110
Temperature (pre-dose [a],°F)			100.9 (100.2–102.2)	100.9 (100.0–102.2)	100.7 (100.4–102.2)	0.989
Laboratory parameters						
Neutrophils (admission, × 10^3/mm^3)			5.6 (4.2–8.2)	5.5 (4.4–7.6)	7.4 (4.0–9.8)	0.905
Lymphocytes (admission, × 10^3/mm^3)			0.8 (0.5–1.1)	0.8 (0.5–1.2)	0.8 (0.5–0.9)	0.730
Neutrophil-to-lymphocyte ratio (admission)			8.0 (4.9–13.0)	7.8 (5.0–12.1)	8.2 (4.7–14.5)	0.653
WBC count (pre-dose [a], × 10^3/mm^3)			9.4 (8.1–12.0)	10.1 (8.3–12.3)	8.1 (5.8–9.4)	0.038
Platelets (pre-dose [a], × 10^3/mm^3)			250.0 (209.0–362.0)	249.0 (210.2–358.5)	325.0 (207.0–364.5)	0.812
Lymphocytes (pre-dose [a], × 10^3/mm^3)	5 (11.1)		0.8 (0.5–1.2)	0.8 (0.5–1.4)	0.7 (0.6–0.9)	0.696
Ferritin (pre-dose [a], mg/L)	18 (40.0)		1303.0 (763.8–1786.0)	1303.0 (684.6–1777.0)	1397.0 (1066.8–1922.8)	0.622
Creatinine (pre-dose [a], mg/dL)			1.0 (0.7–1.4)	1.0 (0.7–2.3)	1.0 (0.9–1.0)	0.682
Bilirubin (pre-dose [a], mg/dL)	5 (11.1)		0.6 (0.4–1.0)	0.6 (0.4–1.1)	0.5 (0.4–0.7)	0.549
Lactate dehydrogenase (pre-dose [a], units/L)	21 (46.7)		497.0 (369.8–660.8)	599.0 (425.0–684.5)	354.0 (320.0–394.0)	0.015
C-reactive protein (pre-dose [a], mg/dL)	21 (46.7)		16.0 (9.4–25.6)	20.3 (8.1–27.5)	12.4 (10.7–12.9)	0.251

(*continued on next page*)

Table 1 (*continued*)

Variable	Missing data	Group	Entire cohort (n = 45)	Not improved (n = 34)	Improved (n = 11)	P-value
Respiratory status [b]						
Baseline respiratory status			6.0 (5.0–6.0)	6.0 (6.0–6.0)	6.0 (4.5–6.0)	0.136
Baseline respiratory status						0.251
		<6	13 (28.9)	8 (23.5)	5 (45.5)	
		6	32 (71.1)	26 (76.5)	6 (54.5)	
Timing variables						
Time from symptom onset to dose (days)			11.0 (7.0–15.0)	10.5 (7.0–13.8)	13.0 (8.5–15.5)	0.218
Time from admission to dose (h)			112.2 (51.5–155.8)	116.4 (85.6–170.8)	82.2 (38.5–114.6)	0.055
Time from admission to intubation (h)	10 (22.2)		87.2 (37.8–121.8)	87.8 (45.5–121.9)	34.7 (23.4–89.6)	0.146
Time from initiation of oxygen supplementation to dose (h)	1 (2.2)		113.6 (74.3–151.8)	117.2 (88.4–177.3)	80.7 (41.2–115.4)	0.044
Time from initiation of high-flow oxygen to dose (h)	6 (13.3)		76.2 (26.3–112.8)	93.8 (33.8–113.2)	35.0 (28.9–55.7)	0.123
Time from ARDS to dose (h)	14 (31.1)		75.8 (37.3–98.7)	87.3 (40.0–107.6)	49.5 (32.3–63.3)	0.091
Time from intubation to dose (h)	16 (35.6)		51.1 (25.0–93.8)	60.0 (28.6–93.8)	24.6 (11.7–41.4)	0.114

NOTE: Data are presented as n (%) or median (interquartile range).
BMI, body mass index; ESRD, end-stage renal disease; COPD, chronic obstructive pulmonary disease; WBC, white blood cell; ARDS, acute respiratory distress syndrome.
[a] Pre-dose, collected within 24 h (vital signs, vasopressor use) or 48 h (laboratory values) prior to the dose.
[b] Respiratory status was assessed at the end of the day according to the ordinal scale recommended by the WHO R&D Blueprint Expert Group [17].

COVID-19. In fact, worsening respiratory status was common and was observed in 27% of patients by Day 7 after treatment. These findings are similar to those reported by Salvarani et al. who found that 28.3% of patients randomised to tocilizumab experienced clinical worsening by Day 6 [13]. Results from Hermine et al., which found positive outcomes compared with standard of care at Day 14 but not Day 4, further suggest that any benefits with tocilizumab are uncommon within the first week after treatment [14].

Evidence made available after this study period has demonstrated the efficacy of corticosteroids in treating severe and critical COVID-19 [18,19]. Corticosteroid use was common but not universal in this cohort. Their use was not associated with clinical improvement and was numerically more common in those who did not improve (64.7% vs. 45.5%; $P = 0.304$). This is a question of particular importance given that the benefit of the incremental immunomodulatory impact of tocilizumab combined with corticosteroids may be different than the benefit of tocilizumab or corticosteroids alone. This is precisely the issue that Rodríguez-Baño et al. sought to answer in their multicentre cohort study [20]. Ultimately, those authors found that tocilizumab alone (HR, 0.32; 95% CI 0.22–0.47) and pulse-dose corticosteroids alone (HR, 0.61; 95% CI 0.43–0.86) were associated with decreased intubation and death but the combination of both was not (HR, 1.17; 95% CI 0.86–1.58) [20]. In contrast, the RCT conducted by Hermine et al. found a signal of potentially improved outcomes in the subgroup of patients who received corticosteroids (HR, 0.38; 90% CrI, 0.13–1.11), although this was not statistically significant [14]. The interaction of the effects of tocilizumab and corticosteroids in the management of COVID-19 will require careful examination in order to determine the optimal deployment of these therapies.

Importantly, the lack of a control group in our study prohibits an assessment of the efficacy of tocilizumab for COVID-19. This is better assessed with the aforementioned RCTs, which have thus far failed to yield consistent findings. In light of such conflicting data, it would seem that dramatic benefits in a broad range of patients with COVID-19 are unlikely with tocilizumab. However, glimpses of possible clinical benefits warrant critical evaluations of specific subpopulations or patient characteristics that may predict benefit.

Factors that have been independently associated with poor outcome in COVID-19 include older age, neutrophil-to-lymphocyte ratio, and organ and coagulation dysfunction [21–23]. Our analysis identified that only lower WBC count and LDH at the time of drug administration as well as shorter time from initiation of supplemental oxygen to dose were associated with clinical improvement. Zhou et al. previously identified that elevated WBC count ($>10 \times 10^9$/L) and elevated LDH (>245 U/L) were associated with higher mortality among inpatients with COVID-19 [21]. However, neither of these associations were significant in their multivariable analysis. Salvarani et al. also evaluated outcomes in the subgroup of patients with baseline LDH < 250 U/L and found numerically lower clinical worsening among those who received tocilizumab (23.1% vs. 36.45%; RR, 0.6; 95% CI 0.2–2.2) [13]. This imbalance in our study may simply be a reflection of differences in illness severity or it may support that the role of tocilizumab is earlier in the disease course.

C-reactive protein (CRP) is another biomarker that has been subject to considerable attention with respect to tocilizumab. Martínez-Sanz et al. found lower mortality (adjusted HR, 0.34; 95% CI 0.17–0.71) with tocilizumab in the subgroup of patients with baseline CRP > 15 mg/dL in their multicentre cohort study [24]. Similarly, Biran et al. evaluated a subgroup of patients with baseline CRP > 15 mg/dL and found that tocilizumab was associated with decreased mortality (HR, 0.48; 95% CI 0.30–0.77) [25]. Salvarani et al. found numerically lower clinical worsening among those with baseline CRP > 15 mg/dL that was not statistically significant (RR, 0.4; 95% CI 0.1–1.9) [13]. We did not find differences in median baseline CRP among those who did and did not improve [12.4 (IQR 10.7–12.9) mg/dL vs. 20.3 (IQR 8.1–27.5) mg/dL; $P = 0.251$]. Biomarkers predictive of clinical response could be highly useful for clinicians considering the use of this medication. Further research into these and other laboratory values is required to resolve this question.

The association between response and drug timing relative to the initiation of supplemental oxygen could have important implications for the use of this drug. Given its mechanism, it is plausible that there may be a critical window where tocilizumab can blunt excessive inflammation and yield positive outcomes. It has been suggested that suppressing the immune response prior to an excessive immune response is unlikely to provide benefit and may be detrimental [26]. Our data further suggest that tocilizumab administration after a dramatic immune response has mounted may be too late to reverse end-organ damage. Similarly, Sciascia et al. found that tocilizumab administration within 6 days from admission in the hospital was associated with an increased likelihood of

survival (HR, 2.2; 95% CI 1.3–6.7) [27]. Nevertheless, the published RCTs to date have enrolled patients early relative to hospitalisation with a median of 2 days [13] and 1 day [14] from admission to randomisation. The lack of consistent benefits demonstrated in these studies does not support routine use of tocilizumab in this time window. Further study is required to determine whether an optimal time window for drug administration exists.

Important limitations in our study include the design, which is subject to selection bias. Differences identified between those who improved and those who did not may be reflective of the natural disease course and unrelated to tocilizumab use. Additionally, the small sample size and short follow-up period limit the implications of these results. Other questions regarding tocilizumab for COVID-19, including assessments of long-term safety and efficacy, are beyond the scope of this study.

In conclusion, tocilizumab administration was associated with low rates of clinical improvement within 7 days in this cohort of severe and critically ill patients with COVID-19. Further study is required to determine the optimal role of tocilizumab in the management of COVID-19.

Acknowledgments

The authors would like to thank Alison Brophy, PharmD, Christopher Makosiej, PharmD, and Vasyl Zybrak, PharmD, for their contributions to data collection and analysis.

Funding: None.

Competing interests: None declared.

Ethical approval: This study was approved by the central Institutional Review Board [FWA # 00003433].

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