Tocilizumab in the Management of COVID-19: A Preliminary Report

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ABSTRACT

Importance: Pneumonia due to COVID-19 can lead to respiratory failure and death due to the development of the acute respiratory distress syndrome. Tocilizumab, a monoclonal antibody targeting the interleukin-6 receptor, is being administered off-label to some patients with COVID-19, and although early small studies suggested a benefit, there are no conclusive data proving its usefulness.

Objective: To evaluate outcomes in hospitalized patients with COVID-19 with or without treatment with Tocilizumab.

Design, setting, participants: Retrospective study of 1938 patients with confirmed COVID-19 pneumonia admitted to hospitals within the Jefferson Health system in Philadelphia, Pennsylvania, between March 25, 2020 and June 17, 2020, of which 307 received Tocilizumab.

Exposures: Confirmed COVID-19 pneumonia.

Main outcomes and measures: Outcomes data related to length of stay, admission to intensive care unit (ICU), requirement of mechanical ventilation, and mortality were collected and analyzed.

Results: The average age was 65.2, with 47% women; 36.4% were African-American. The average length of stay was 22 days with 26.3% of patients requiring admission to the ICU and 14.9% requiring mechanical ventilation. The overall mortality was 15.3%. Older age, admission to an ICU, and requirement for mechanical ventilation were associated with higher mortality. Treatment with Tocilizumab was also associated with higher mortality, which was mainly observed in subjects not requiring care in an ICU with estimated odds ratio (OR) of 2.9 ($p = 0.0004$). Tocilizumab treatment was also associated with higher likelihood of admission to an ICU (OR = 4.8, $p < 0.0001$), progression to requiring mechanical ventilation (OR = 6.6, $p < 0.0001$), and increased length of stay (OR = 16.2, $p < 0.0001$).

Conclusion and relevance: Our retrospective analysis revealed an association between Tocilizumab administration and increased mortality, ICU admission, mechanical ventilation, and length of stay in subjects with COVID-19. Prospective trials are needed to evaluate the true effect of Tocilizumab in this condition.

Key Indexing Terms: COVID-19; Treatment; Outcomes; IL-6. **[Am J Med Sci 2021;361(2):208–215.]**

INTRODUCTION

Since December 2019, the world has grappled with a global pandemic caused by the novel coronavirus SARS-CoV-2. Infection with SARS-CoV-2 encompasses a continuum of disease from asymptomatic infection to respiratory failure due to the acute respiratory distress syndrome (ARDS).[1] Mortality from COVID-19-related ARDS in critically ill patients cared for in an intensive care unit (ICU) is reported to be in the range of 26–70%.[2–4]

Considering the aggressive nature of the disease, caregivers around the world have opted to try off-label and unproven interventions. Hydroxychloroquine, vitamin D, corticosteroids, angiotensin converting enzyme inhibitors, convalescent plasma, and the anti-viral agents lopinavir and ritonavir, among others, have been tested, but none has proven effective and many have potential to cause harm.[5] To date, only the anti-viral Remdesivir has been approved for use in this condition in the U.S.[6] Tocilizumab is another agent that has been used in the management of COVID-19.[7] This antibody acts against the interleukin-6 (IL-6) receptor. IL-6 levels have been notably high in some COVID-19 patients and it has been believed to be involved in the exuberant inflammatory response or

cytokine storm triggered by SARS-CoV-2 infection that might lead to ARDS.[7] On this basis, physicians at our hospitals have administered Tocilizumab to COVID-19 patients with severe respiratory impairment off-label and outside of a clinical trial hoping to improve outcomes by preventing or ameliorating the development or progression of the COVID-19 related cytokine storm, thereby inhibiting the development of ARDS in both the intensive care unit (ICU) and non-ICU settings. Considering that the role of Tocilizumab in the treatment of patients with COVID-19 remains undefined, and that data from large, well-controlled randomized trials are not available, we retrospectively collected and analyzed data on our patients and report preliminary results that question the usefulness of Tocilizumab in this population.

METHODS

Patient population

This retrospective study was approved by the Jefferson Institutional Review Board (#20E.234). Included were COVID-19 patients admitted between March 12, 2020 and June 17, 2020. The patients were identified using the Jefferson Health electronic record (EPIC). There were a total of 115,696 hospital-based patient encounters that originated in the relevant time period from Jefferson Center City facilities (Thomas Jefferson University Hospital, Methodist Hospital, Jefferson Health Care Center, and Jefferson Hospital Neuroscience) and Jefferson New Jersey hospital facilities (Jefferson Cherry Hill Hospital, Jefferson Stratford Hospital, and Jefferson Washington Township Hospital). Of these encounters, COVID-19 positive patients were identified by at least one of the three following criteria: 1) a positive COVID-19 test result within 21 days of the hospital admission or during the admission, 2) a COVID-19 confirmed infection status added to their chart within 21 days of a hospital admission or during the admission, or 3) an ICD-10 U07.1 code listed as any one of the patient's final coded diagnoses from the admission. A total of 1938 patients were hospitalized with COVID-19 infection. Of these, 307 patients had Tocilizumab administered during their hospitalization, whereas 1631 did not (Figure 1). Criteria for inclusion in the Tocilizumab treatment group included: 1) age of 18 years or older with a clinical presentation consistent with COVID-19 (e.g., fever, respiratory symptoms, and new pulmonary infiltrates), 2) laboratory confirmation of SARS-CoV-2 infection by an RT-PCR test, and 3) outcome data available. Subjects without a COVID-19 diagnosis and patients recruited to a formal Tocilizumab clinical trial or administered drug for reasons other than for COVID-19 were excluded.

Most patients were initially hospitalized on the non-ICU service cared for by hospitalists or pulmonologists. Some were then transferred to the ICU if deterioration in clinical picture was noted. For the most part, transfer to the ICU was triggered by deterioration of hypoxemia in the setting of increased work of breathing not improved by high flow oxygen supplementation, non-invasive ventilation, and proning (if possible). In other words, significant attempts were made to treat patients non-invasively prior to transfer to the ICU for more careful monitoring or mechanical ventilation. A smaller group of patients was directly hospitalized into the ICU from the Emergency Room depending on their level of hypoxemia, hemodynamics, and other parameters.

Our institution defined the following guideline for considering the administration of Tocilizumab to a given patient. The case was to be consulted to Infectious Diseases and Rheumatology or Hematology for consideration and ultimately approval of the therapy. Consultation of a case was at the discretion of the attending physician. Baseline laboratory work to evaluate for inflammatory markers and possible cytokine storm was required. If approved, the patients were given the drug once at 4−8 mg/kg intravenously.

Outcomes

Inpatient mortality was considered the primary outcome variable. We also evaluated mortality in subjects requiring ICU care versus non-ICU patients. For secondary outcomes, we considered admission to the ICU, mechanical ventilation, inpatient length of stay (LOS), ICU LOS and duration of mechanical ventilation. Given that duration outcomes are continuous measures with long tails, we also created dichotomous (0,1) measures to indicate long duration (e.g., 3 days or more vs. shorter duration was chosen arbitrarily);

Data analysis

This is a retrospective observational study that evaluated the impact of Tocilizumab therapy on mortality and other outcomes for hospitalized patients with severe disease treated in the ICU versus those not requiring ICU management. Use of Tocilizumab was analyzed against other parameters such as age, gender, race, ICU care, and mechanical ventilation, and length of stay. Patient characteristics were compared using Fisher exact or chi-square test, and t-test as appropriate. These data include those still hospitalized, or discharged, or those who expired while in the hospital. Multivariate logistic regression analysis was performed to predict inpatient mortality, ICU admission, LOS, ICU duration, need for ventilation and ventilation duration.

We compared baseline characteristics of the Tocilizumab treated group (TCZ) with the group not treated with Tocilizumab (non-TCZ) in the overall cohort. Categorical variables were compared by using the χ^2 test and continuous variables were compared by using the t-test. The multivariate logistic regression was used for identified factors that predict different bivariate outcome variables with control variables included as appropriate and sample volume allowed. The strengths of associations of the predictors were expressed as the odds ratio (OR) estimates, 95% confidence intervals (CIs) and P-value.
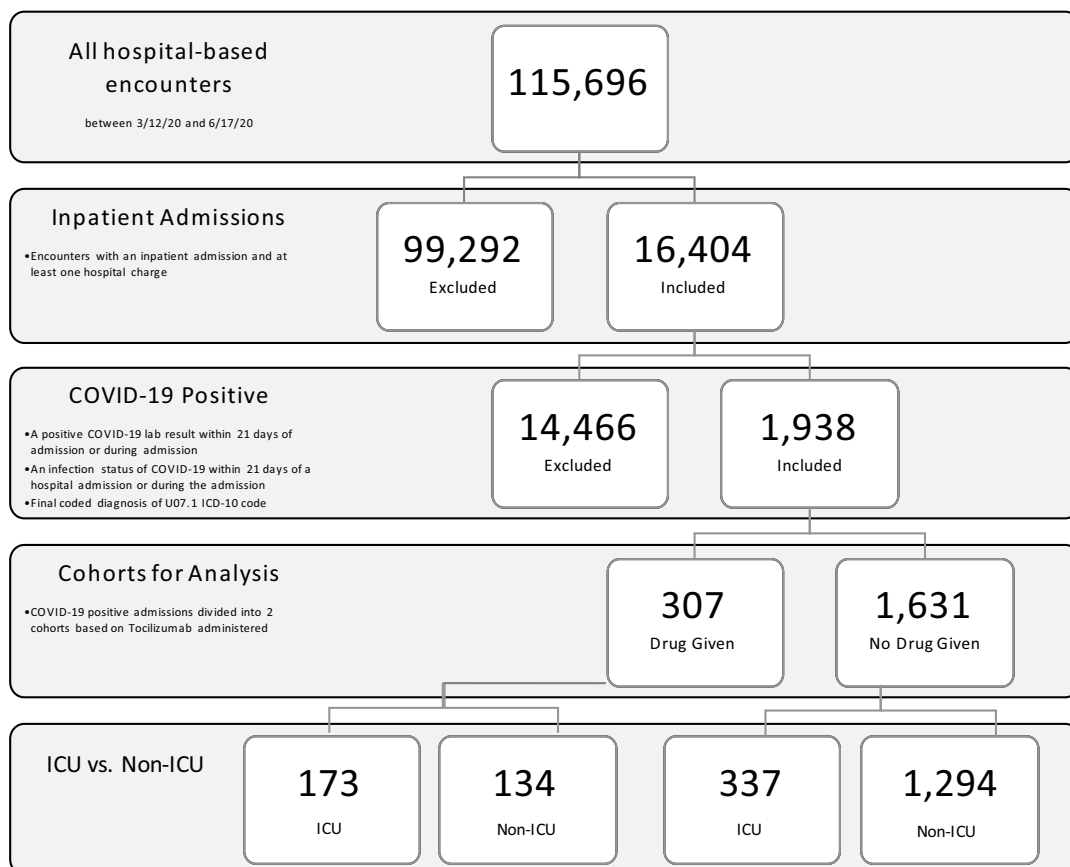
FIGURE 1. COVID-19 Patient Selection for Study.

$P < .05$ was considered statistically significant. Model discrimination was assessed by using C-statistics, the values of which are equivalent to the area under a corresponding receiver-operating characteristic curve, which measures a model's predicting power with 0.5 as no predicting power and 1.0 as perfect prediction. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Tocilizumab (TCZ) was administered in 307 (15.8%) of 1,938 hospitalized patients with a COVID-19 diagnosis. There were more males (53%) than females (47%) in the overall group, and a higher proportion of males (65%) vs. females (35%) was administered TCZ (Table 1). White and Asian race groups were more represented in the TCZ treated group than in the non-treated group when compared to Blacks and Hispanics. The average patient age was 65.2, which was similar between the TCZ and non-TCZ groups. However, a higher percentage of patients in the 60−69 age group received TCZ treatment when compared to the non-treatment group (P-value = 0.0032). In general, patients over age 80 and,

to a lesser degree, younger subjects had relatively less TCZ treatments.

Figure 2A provides the total COVID-19 patient distribution by ICU admission and survival status. As expected, there was higher mortality in the ICU group when compared to the non-ICU settings (the latter includes patients who received the drug in a non-ICU setting, but could have been transferred to an ICU later). Figure 2B provides the total COVID-19 patient distribution by their TCZ use, ICU admission, and survival status. As shown in Table 1, the overall mortality rate was 15.3%, while there was a 26.3% ICU admission rate and 14.9% of mechanical ventilation rate. Notably, the TCZ treatment group had a higher mortality rate (26.1% vs. 13.2%), higher ICU admission rate (56.4% vs. 20.7%) and higher mechanical ventilation use (33.6% vs. 11.4%) when compared with the non-TCZ treatment group. Patients in the TCZ treatment group had a shorter LOS (average 14.3 days vs. 23.5 days). However, TCZ treatment group had a longer ICU stay (average 10.8 days vs. 7.3 days) and longer mechanical ventilation duration (average 14.2 days vs. 10.1 days). The TCZ treatment group had a lower rate of discharge disposition to home (26.7% vs. 41.9%) compared to the non-TCZ treatment group.

TABLE 1. Patient Characteristics by Tocilizumab Treatment.

| Variable	Total (N = 1938)		No TCZ Treatment (N = 1631)		TCZ Treatment (N = 307)		Chi-square Test
	N	%	N	%	N	%	P-value
Female	911	47.0%	805	49.4%	106	34.5%	<.0001
Male	1027	53.0%	826	50.6%	201	65.5%	<.0001
Race - White	871	44.9%	717	44.0%	154	50.2%	0.0451
Race - Black	706	36.4%	611	37.5%	95	30.9%	0.0295
Race - Hispanic	148	7.6%	136	8.3%	12	3.9%	0.0073
Race - Asian	168	8.7%	133	8.2%	35	11.4%	0.0637
Age	65.2 *	17.9 **	65.2 *	18.2 **	65.2 *	15.8 **	0.9821 ***
Age less than 50	374	19.3%	325	19.9%	49	16.0%	0.1063
Age: 50−59	302	15.6%	252	15.5%	50	16.3%	0.711
Age: 60−69	397	20.5%	315	19.3%	82	26.7%	0.0032
Age: 70−79	400	20.6%	331	20.3%	69	22.5%	0.3863
Age: 80−89	326	16.8%	282	17.3%	44	14.3%	0.2037
Age: 90+	139	7.2%	126	7.7%	13	4.2%	0.0297
Discharge - Home	765	9.8%	683	41.9%	82	26.7%	<.0001
Discharge - SNF	340	17.5%	288	17.7%	52	16.9%	0.761
Discharge -Home Care	190	9.8%	158	9.7%	32	10.4%	0.6907
Inpatient LOS	8.6 *	9.1 **	7.5 *	8.3 **	14.3 *	10.8 **	<.0001 ***
Days in ICU	2.3 *	6.1 **	1.5 *	5.0 **	6.1 *	9.3 **	<.0001 ***
Days on Ventilation	1.7 *	6.3 **	1.2 *	4.9 **	4.8 *	10.7 **	<.0001 ***
Mortality	296	15.3%	216	13.2%	80	26.1%	<.0001
ICU Admission	510	26.3%	337	20.7%	173	56.4%	<.0001
On Ventilation	289	14.9%	186	11.4%	103	33.6%	<.0001
LOS >= 3 Days	1549	79.9%	1250	76.6%	299	97.4%	<.0001
TCZ therapy	307	15.8%	0	0%	307	100%	-

Note:
* Mean.
** Standard deviation.
*** P-value for t-test assuming unequal variances.

The effect of TCZ treatment on all COVID inpatient mortality was assessed using multivariate logistic regression with gender, age, inpatient length of stay (LOS), ICU admission and ventilation as control variables. The model covariates were selected *a priori* based on clinical relevance or data availability. We considered LOS, ICU admission, and mechanical ventilation as measures of disease severity. We used male gender, White or Caucasian race, and age group of 49 and younger as default for comparison. Table 2 shows that TCZ therapy had a marginally positive association with mortality (OR 1.4, p = 0.081). Age had significant effects on mortality as older age groups had progressively higher odds ratios compared to the baseline age group (less than 50). Both ICU admission and mechanical ventilation had significant positive relationship with mortality (OR 3.4 and 5.2 with p < 0.0001). Gender, race and LOS had no significant effects.

When mortality was evaluated in subjects with severe condition (i.e., ICU patients) vs. non-severe condition (or non-ICU patients), TCZ correlation with mortality became much clearer. For ICU patients, TCZ treatment was not significantly correlated with mortality (p = 0.2344). However, for non-ICU patients, TCZ treatment was positively correlated with mortality (OR 2.9, p = 0.0004). The age effect pattern in both ICU and non-ICU groups remained similar; i.e., older age groups had bigger odds ratios for mortality. However, for non-ICU COVID-19 patients, there were no significant differences in mortality among the three younger age groups, less than 50, 50−59 and 60−69 group. For the non-ICU group, Black race had a marginally negative correlation with mortality (OR 0.6, p = 0.0531).

Using the same multivariate logistic model, we tested TCZ treatment effects on several other outcomes in the patient groups. TCZ effects on different outcomes are summarized in Table 3 without showing all control variables. Using all 1938 hospitalized COVID-19 patients, we found that TCZ treatment was positively correlated with ICU admission (OR 4.8, p = 0.0001) and positively correlated with mechanical ventilation (OR 6.6, p = 0.0001). For the 1642 subjects that survived, the inpatient LOS of 3 days or more was positively correlated with TCZ treatment (OR 16.2, p = 0.0001). Similarly, for the 1321 non-ICU patients that survived, the inpatient LOS of 3 days or more was positively correlated with TCZ treatment (OR 40.7, p = 0.0002). For the 321 subjects requiring ICU care, TCZ treatment was positively correlated with the
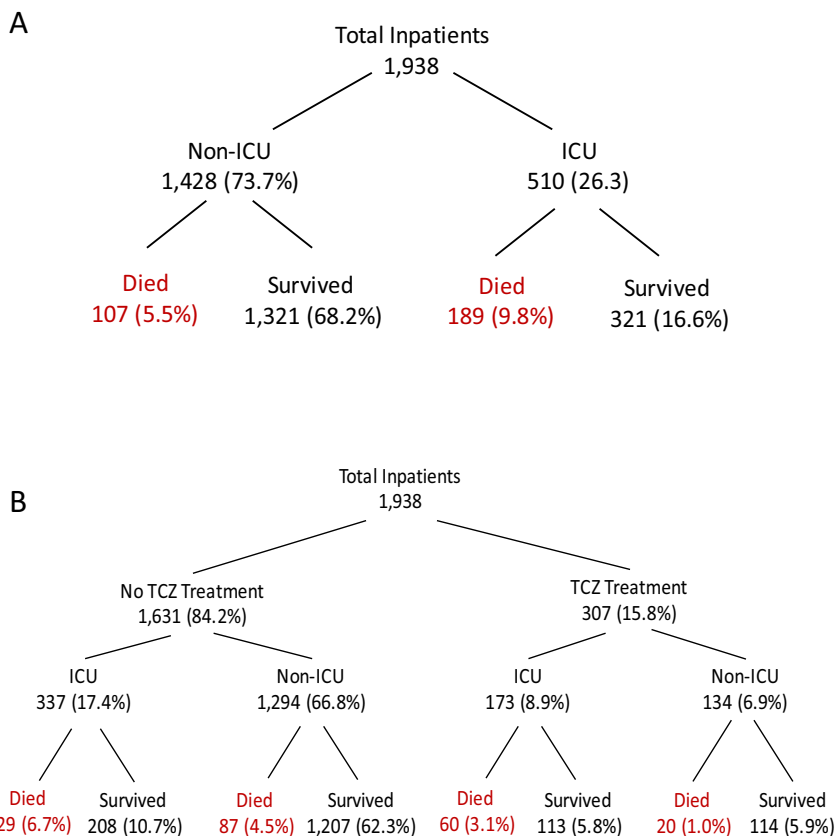
FIGURE 2. Outcomes in Patients with COVID-19.

ICU duration 3 days or more indicator (OR 6.1, p = 0.0001). For the 160 subjects that required mechanical ventilation and survived, TCZ treatment was positively correlated with the ventilation duration of 3 days or more indicator (OR 2.8, p = 0.0224). For three duration measures, we also used the 4 days and 5 days indicator to test the logistic models and reached similar results. Finally, it is recognized that multicollinearity between

TABLE 2. Multivariate Mortality Analyses of TCZ Treatment.

Measure	All Inpatients (N = 1938, MOT = 296)		Non-ICU Inpatients (N = 1428, MOT = 107)		ICU Inpatients (N = 510, MOT = 189)	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
TCZ therapy	1.4 (1.0, 2.0)	0.081	2.9 (1.6, 5.1)	0.0004	1.3 (0.8, 2.1)	0.2344
Female	0.9 (0.7, 1.2)	0.6181	0.7 (0.5, 1.1)	0.1547	1.0 (0.6, 1.5)	0.8434
Race - Black	0.9 (0.6, 1.2)	0.4053	0.6 (0.3, 1.0)	0.0531	1.0 (0.7, 1.6)	0.9308
Age: 50−59	2.4 (1.1, 5.3)	0.0355	−	−	2.0 (0.8, 5.1)	0.1247
Age: 60−69	5.1 (2.4, 10.4)	<.0001	−	−	3.4 (1.5, 7.7)	0.0043
Age: 70−79	7.5 (3.6, 15.3)	<.0001	4.5 (2.2, 9.5)	<.0001	6.3 (2.7, 14.8)	<.0001
Age: 80−89	15.5 (7.4, 32.2)	<.0001	11.2 (5.6, 22.3)	<.0001	7.3 (3.0, 17.7)	<.0001
Age: 90+	62.1 (28.4, 135.6)	<.0001	35.1 (17.3, 71.4)	<.0001	39.4 (8.9, 174.1)	<.0001
Inpatient LOS	1.0 (1.0, 1.0)	0.3525	1.0 (1.0, 1.0)	0.6524	0.9 (0.9, 0.9)	<.0001
On Ventilation	3.4 (2.3, 5.2)	<.0001	−	−	6.3 (3.8, 10.3)	<.0001
ICU Admission	5.2 (3.5, 7.8)	<.0001	−	−	−	−
Outcome: Mortality	15.3%		7.5%		37.1%	
C-Statistics	0.86		0.836		0.813	

Note: OR: Odds ratio estimate. CI: 95% Wald confidence limit.

TABLE 3. TCZ Treatment Effects on Secondary Outcomes.

Outcome	OR (95% CI)	P-value	Sample Size	Outcome #	Outcome %	C-Statistics
ICU Admission: for all patients	4.8 (3.7, 6.2)	<.0001	1938	510	26.3%	0.651
On Ventilation: for all patients	6.6 (4.7, 9.3)	<.0001	1938	289	14.9%	0.751
LOS 3 days or more: Survived patients	16.2 (5.1, 51.9)	<.0001	1642	1311	79.8%	0.747
LOS 3 days or more: Survived non-ICU patients	40.7 (5.6, 203.3)	0.0002	1321	1004	76.0%	0.674
ICU 3 days or more: Survived patients	6.1 (3.0, 12.3)	<.0001	321	211	65.7%	0.869
On Vent 3 days or more: Survived patients	2.8 (1.2, 6.8)	0.0224	160	122	76.3%	0.690

TCZ use, ICU admission, and mechanical ventilation could affect the association between treatment and mortality, among other variables. Therefore, we ran multicollinearity tests on these independent variables. The variance inflation factors of the independent variables were all below 2, which indicated no multicollinearity concern in the multivariate model.

DISCUSSION

The mortality in patients with COVID-19 requiring hospitalization because of hypoxemia associated with bilateral pulmonary infiltrates has been reported as high as 70% although more studies that are recent report a lower mortality[3−5]; our overall mortality was 15.3%. The development of a cytokine storm leading to ARDS is considered a major cause of death in such patients. IL-6 is considered an important driver of the cytokine storm and therefore has become a target for intervention. This seemed justified as IL-6 levels were found elevated in patients with Severe Acute Respiratory Syndrome (SARS), a related disease linked to another coronavirus, and correlated with disease severity.[8] Similar observations have been made in subjects with COVID-19.[9] This prompted interest in several agents targeting IL-6 and its receptor.

Tocilizumab binds to soluble and membrane-bound IL-6 receptors, inhibits IL-6-mediated signaling, and is approved by the Federal Drug Administration for the treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and cytokine release syndrome.[10−12] Early case reports, case series, and relatively small pilot single-arm non-randomized clinical trials (including a range of 20 to 100 patients) suggested the safety and benefit of Tocilizumab in the setting of COVID-19.[10−19] Because of some of these data, the agent was recommended by China's National Health Commission for use in COVID-19 patients with elevated IL-6 levels.[20] However, other reports failed to show improved mortality[21] and highlighted the potential adverse effects of Tocilizumab including toxic erythema, candidemia, and bowel perforation.[22−24] An "Interim Guidance on Management Pending Empirical Evidence Report published by the American Thoracic Society on April 3, 2020 did not make a recommendation in favor of or against Tocilizumab considering the limited and conflicting data available.[25] Meanwhile, formal multi-center clinical trials testing the effectiveness of Tocilizumab in the treatment of COVID-19 have started (NCT04320615 and NCT04315298), but data are pending.

Considering that the role of Tocilizumab in the treatment of patients with COVID-19 remains undefined, we felt the need to report data retrospectively collected at our institution in the hope of adding to the accumulating literature regarding this agent in order to assist providers with their management of these patients. Consistent with other studies, we confirmed an increased mortality for COVID-19 related to age. However, the main finding from this observational correlation analysis is that Tocilizumab treatment may not reduce COVID-19 related mortality, and was associated with increased mortality for non-severe condition (non-ICU) COVID-19 patients. Our study findings also show that TCZ therapy may promote ICU admission, progression to requiring mechanical ventilation, and increased LOS, ICU duration, and mechanical ventilation duration. Interestingly, Tocilizumab was not associated with increased mortality in ICU patients, perhaps because of the severity of the condition and duration of disease. Although these findings require confirmation in large prospective well-randomized clinical trials, the consistency of the negative impact of Tocilizumab on several parameters should prompt pause when considering this agent for all hospitalized COVID-19 patients.

IL-6 acts on important physiological processes in many organs including liver, muscle, bone, and kidney, as well as in glucose and lipid metabolism.[26] In the setting of severe infections, IL-6 appears to drive inflammation as indicated by the now well-known increase in C-reactive protein, a downstream secondary massager for IL-6.[26] However, IL-6 might only serve as a marker of disease severity, instead of an important driver of

disease progression. This concept is consistent with data generated in experimental murine models of sepsis where complete lack of IL-6 was not found to alter mortality.[27] Another consideration is that IL-6 is likely to affect cells in different ways and that targeting this molecule may have simultaneous beneficial and deleterious effects depending on the cell involved. This is highlighted in an animal model of ventilator-associated lung injury where IL-6 from hematopoietic cells appeared to limit alveolar barrier disruption, thereby reducing neutrophil-mediated injury to the endothelium.[28] This suggests that cell type-specific targeting of IL-6 might represent a better approach in COVID-19. Finally, the dosing of the agent and timing of administration may influence its effectiveness as dosing regimens for COVID-19 have not been standardized and vary considerably in published studies.

The retrospective nature of the study has inherent limitations, as it is difficult to include in the analysis differences in practice patterns, which likely affected choice of patients for drug administration, timing of drug administration, considerations for transfer to an ICU, and the management of co-morbidities during the hospitalization, among other confounding factors. For example, in our study 56.3% of TCZ-treated patients required ICU admission compared with only 20.7% of non-TCZ-treated patients that speaks to a sicker population and a likely selection bias toward TCZ use in the ICU group. Nonetheless, we found that it is the non-ICU patients that seemed to do worse with TCZ treatment rather than ICU patients. Another study confounder was that the inclusion of patients cared for at several hospitals within a single healthcare network might have produced bias as the patients were cared for by different providers. Our inability to determine the timing of the drug is an important limitation as it is difficult to ascertain an effect on outcome parameters without this information. Another limitation is due to 'bias by indication', which could prompt the administration of an agent to sicker patients. This could not be ascertained with the data available.

In conclusion, this preliminary retrospective observational analysis indicates that Tocilizumab therapy was not associated with improved inpatient mortality rate for COVID-19 patients. In fact, for non-ICU patients, Tocilizumab was positively associated with inpatient mortality. This study further indicates that Tocilizumab therapy may also be associated with ICU admission, ventilation use, longer inpatient length of stay, longer ICU duration, and longer ventilation duration. Due to the retrospective nature of the study, we cannot confidently conclude that Tocilizumab therapy had negative effects or was not effective for COVID-19 patients. More clinical data measures, patient specific comorbidities, larger sample size and, most importantly, treatment randomization are needed to understand the effect of Tocilizumab therapy in treating patients with COVID-19.

REFERENCES

1. **Li X, Ma X.** Acute respiratory failure in COVID-19: Is it 'typical' ARDS? *Crit Care*. 2020;24:198. https://doi.org/10.1186/s13054-020-02911-9
2. **Graselli G, Zangrillo A, Zanella A, et al.** Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. *JAMA*. 2020;3233:1574–1581. https://doi.org/10.1001/jama.2020.5394
3. **Wang D, Hu B, H C, et al.** Clinical charateristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323:1061–1069. https://doi.org/10.1001/jama.2020.1585
4. **Bhatraju PK, Ghassemieh BJ, Nichols M, et al.** Covid-19 in critically ill patients in the Seattle region — case series. *N Engl J Med*. 2020;382:2012–2022.
5. **Pascarella G, Strumia A, Piliego C, et al.** COVID-19 diagnosis and management: a comprehensive review. *J Intern Med*. 2020. https://doi.org/10.1111/joim.13091
6. FDA approves emergency use of Remdesivir for COVID-19. Available at: https://www.drugs.com/news/fda-approves-emergency-remdesivir-covid-19-89997.html. Accessed May 18, 20120.
7. **Di Giambenedetto S, Ciccullo A, Borghetti A, et al.** Off-label use of Tocilizumab in patients with SARS-CoV-2 infection. *J Med Virol*. 2020. https://doi.org/10.1002/jmv.25897
8. **Sarzi-Puttini P, Giorgi V, Sirotti S, et al.** COVID-19, cytokines and immunosuppression: what can we learn from severe acute respiratory syndrome? *Clin Exp Rheumatol*. 2020;38:337–342.
9. **Cheng G, Wu D, Guo W, et al.** Clinical and immunologic features in severe and moderate Coronavirus disease 2019. *J Clin Investig*. 2020;130:2620–2629. https://doi.org/10.1172/JCI137244
10. **Calabrese C, Rajendram P, Sacha G, et al.** Practical aspects of targeting IL-6 in COVID-19 disease. *Cleveland Clin J Med*. 2020:1–5. https://doi.org/10.3949/ccjm.87a.ccc018
11. **Scott LJ.** Tocilizumab: a review in rheumatoid arthritis. *Drugs*. 2017;77:1865–1879.
12. **Mazzitelli M, Arrighi E, Serapide F, et al.** Use of subcutaneous Tocilizumab in patients with COVID-19 pneumonia. *J Med Virol*. 2020. https://doi.org/10.1002/jmv.26016
13. **Allan SR, Dao A, Madhrira, et al.** Interleukin-6 receptor antagonist therapy to treat SARS-CoV-2 driven inflammatory syndrome in a renal transplant recipient. *Transpl Infect Dis*. 2020:e13326. https://doi.org/10.1111/tid.13326.
14. **Capra R, De Rossi N, Mattioli F, et al.** Impact of low dose Tocilizumab on mortality rate in patients with COVID-19 related pneumonia. *Eur J Intern Med*. 2020;76:31–35. https://doi.org/10.1016/j.ejim.2020.05.009
15. **Klopfenstein T, Zayet S, Lohse A, et al.** Tocilizumab therapy reduced intensive care unit admissions and/or mortality in COVID-19 patients. *Med Mal Infect*. 2020. https://doi.org/10.1016/j.medmal.2020.05.001. Pii: S0399-077X(20)30129-3
16. **Toniati P, Piva S, Cattalini M, et al.** Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. *Autoimmune Rev*. 2020;19(7):102568. https://doi.org/10.1016/j.autrev.2020.102568
17. **Xu X, Han M, Li T, et al.** Effective treatment of severe COVID-19 patients with Tocilizumab. *Proc Natl Acad Sci USA*. 2020;117:10970–10975. https://doi.org/10.1073/pnas.2005615117. Pii: 202005615.
18. **Sciascia S, Apra F, Baffa A, et al.** Pilot prospective open, single-arm multicentre study on off-label use of Tocilizumab in patients with severe COVID-19. *Clin Exp Rheumatol*. 2020;38:529–532
19. **Guaraldi G, Meschiari M, Cozzi-Lepri A, et al.** Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol*. 2020. https://doi.org/10.1016/S2665-9913(20)30173-9
20. China approves use of Tocilizumab for coronavirus patients. March 4, 2020. Available at: https://www.the-rheumatologist.org/article/china-approves-use-of-Tocilizumab-for-coronavirus-patients/. Accessed November 18, 2020.
21. **Colaneri M, Bogliolo L, Valsecchi P, et al.** Tocilizumab for treatment of severe COVID-19 patients: preliminary results from SMAtteo COvid19 Registry (SMACORE). *Microorganisms*. 2020;8(5):695. https://doi.org/10.3390/microorganisms8050695

22. **Sernicola A, Carnicelli G, Di Fraia M, et al.** "Toxic erythema" and eosinophilia associated to Tocilizumab therapy in a COVID-19 patient. *J Eur Acad Dermatol Venereol*. 2020. https://doi.org/10.1111/jdv.16620

23. **Antinori S, Bonazzetti C, Gubertini G, et al.** Tocilizumab for cytokine storm syndrome in COVID-19 pneumonia: an increased risk for candidemia? *Autoimmun Rev*. 2020;19(7):102564. https://doi.org/10.1016/j.autrev.2020.102564

24. **Zie F, Yun H, Bernatsky S, et al.** Risk of gastrointestinal perforation among Rheumatoid Arthritis patients receiving Tofacitinib, Tocilizumab, or other biologics. *Arthritis Rheum*. 2016;68:2612–2617. https://doi.org/10.1002/art.39761

25. **Wilson KC, Chotirmall SH, Bai C, et al.** COVID-19: Interim guidance on management pending empirical evidence. From an American Thoracic Society – led International Task Force. Available at: https://www.thoracic.org/about/newsroom/press-releases/journal/2020/ats-publishes-new-guidance-on-covid-19-management.php. Accessed May 20, 2020.

26. **Calabrese LH.** Rose-John S. IL-6 biology: implications for clinical targeting in rheumatic disease. *Nat Rev Rehumatol*. 2014;10:720–727. https://doi.org/10.1038/nrrheum.2014.127

27. **Remick DG, Bolgos G, Copeland S, et al.** Role of interleukin-6 in mortality from and physiologic response to sepsis. *Infect Immun*. 2005;73: 2751–2757.

28. **Wolters PJ, Wray C, Sutherland RE, et al.** Neutrophil-derived IL-6 limits alveolar barrier disruption in experimental ventilator-induced lung injury. *J Immunol*. 2009;182:8056–8062. https://doi.org/10.4049/jimmunol.0801323