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Clinical Outcomes Following Tocilizumab Administration in Mechanically Ventilated Coronavirus Disease 2019 Patients

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Objectives: Effective treatments for the critically ill patient with novel coronavirus disease 2019 are desperately needed. Given the role of cytokine release syndrome in the pathogenesis of coronavirus disease 2019-associated respiratory distress, therapies aimed at mitigating cytokine release, such as the interleukin-6 receptor-inhibiting monoclonal antibody tocilizumab, represent potential treatment strategies. Therefore, we examined the outcomes of critically ill coronavirus disease 2019 patients treated with tocilizumab and factors associated with clinical improvement.

Design: A retrospective cohort analysis of 21-day outcomes for consecutive mechanically ventilated patients treated with tocilizumab from March 24, 2020, to May 4, 2020.

Setting: Nine ICUs at six hospitals within a hospital system in Houston, Texas, United States.

Patients: The first 62 coronavirus disease 2019 patients on invasive mechanical ventilation who were treated with tocilizumab, which was considered for all patients with severe disease.

Interventions: Tocilizumab was administered either at a weight-based dose of 4–8 mg/kg or at a flat dose of 400 mg, with repeat administration in some patients at the physician's discretion.

Measurements and Main Results: The primary outcomes were mortality and clinical improvement, defined as extubation. By day 21 post-tocilizumab, clinical improvement occurred in 36 patients (58%) and 13 patients (21%) died. In both univariable and multivariable analyses, age less than 60 years was associated with clinical improvement. Transient transaminitis was the most common adverse reaction, occurring in 25 patients (40%).

Conclusions: Based on clinical outcomes and mortality rates seen in previous reports of mechanically ventilated patients, tocilizumab, as part of the management strategy for severe coronavirus disease 2019, represents a promising option. These findings support the need for evaluation of tocilizumab in a randomized controlled trial.

Key Words: anti-interleukin-6; cytokine release syndrome; respiratory distress syndrome, adult; severe acute respiratory syndrome coronavirus 2 infection

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The clinical presentation of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) associated coronavirus disease 2019 (COVID-19) varies widely, and acute respiratory distress syndrome (ARDS) represents a severe manifestation of the disease and ultimately may result in death (1, 2). Preliminary reports from China were highly discouraging, indicating mortality rates of 81–97% in those with severe ARDS requiring invasive mechanical ventilation (1, 2). In the United States, mortality rates of 24–67% have been observed in critically ill cohorts (3–5). Patients with greater disease severity have been shown to express elevated concentrations of proinflammatory cytokines, implicating cytokine release syndrome (CRS) or cytokine storm in the pathogenesis of COVID-19 induced ARDS (2, 6–8). Thus, among the numerous treatment modalities being

evaluated, those targeting cytokine dysregulation are of major interest as a management strategy for COVID-19 (9).

The level of interleukin (IL)-6 expression is thought to have a prominent role in distinguishing between patients with severe disease and a high likelihood of mortality, compared with those with milder disease (9). Tocilizumab is a recombinant humanized monoclonal antibody against the IL-6 receptor, inhibiting subsequent IL-6-mediated signaling and thereby potentially mitigating CRS. Tocilizumab is Food and Drug Administration (FDA) approved for the treatment of several conditions including severe chimeric antigen receptor T cell-induced CRS (10). Therefore, tocilizumab may be a suitable therapy for the management of critically ill COVID-19 patients.

Based on the potential role of tocilizumab in modulating CRS as well as its established clinical and safety profile, our center included tocilizumab as part of its COVID-19 treatment algorithm since early March 2020. While several reports on tocilizumab treatment in COVID-19 patients now exist, data pertaining specifically to tocilizumab use in a large cohort of critically ill patients on invasive ventilation is lacking (11, 12). Thus, in this report, we describe the 21-day outcomes of mechanically ventilated patients with severe COVID-19 who received tocilizumab as part of their management strategy.

MATERIALS AND METHODS

Study Design and Patients

This retrospective review of COVID-19 patients managed within the Houston Methodist Hospital System from March 24, 2020, to May 4, 2020, used data from electronic medical records and the institution's clinical surveillance program. Patients were critically ill (i.e., requiring invasive mechanical ventilation) and received tocilizumab after intubation or within 24 hours before intubation. SARS-CoV-2 infection was confirmed by reverse transcriptase polymerase chain reaction assay performed on nasopharyngeal or sputum specimens. Retrospective review was approved by the Institutional Review Board of the Houston Methodist Research Institute.

Institutional Patient Management Algorithm

Beginning early March 2020, a consensus treatment algorithm for the management of hospitalized COVID-19 patients was developed at the institution level. The algorithm used a disease severity classification to guide supportive measures and pharmacologic treatment. Management consisted of supportive care only for patients with mild disease, consideration of hydroxychloroquine for patients with moderate disease, and consideration of hydroxychloroquine with or without ribavirin for patients with severe disease (defined as oxygen saturation < 94%, respiratory rate > 30 breaths per minute, > 4 L of oxygen by nasal cannula, or imminent respiratory failure). All patients were screened for inclusion in ongoing industry-sponsored clinical trials or compassionate use programs for investigational antiviral agents. Given the rapidity of the spread of the virus as well as emerging data regarding potential treatment options, additional off-label or investigational agents were administered at the medical team's discretion.

Tocilizumab Administration

Tocilizumab administration was considered in patients with moderate disease and risk factors for worse COVID-19 outcomes and in all patients with severe disease, according to the institutional algorithm. All patients receiving tocilizumab were screened for contraindications prior to administration. Initially, tocilizumab (Genentech, San Francisco, CA) was administered intravenously at a dose of 4–8 mg/kg. During evolution of the treatment algorithm, a flat dose of 400 mg was adopted to prevent medication shortage within the hospital system. A repeat dose was administered at the discretion of the treating physician.

Outcomes Assessed

The primary outcomes of interest were mortality and clinical improvement, defined as extubation, at 21 days post-tocilizumab administration. Additional outcomes included changes in inflammatory markers (IL-6, C-reactive protein [CRP], lactate dehydrogenase [LDH], and ferritin) and respiratory markers (ratio of the Pao_2/Fio_2 and positive end-expiratory pressure [PEEP]) in those who remained ventilated over the first week post-tocilizumab. In addition, Radiographic Assessment of the Quality of Lung Edema (RALE) score was calculated daily over the first week and at days 10, 14, and 21 when available. Hospital discharge status and serious adverse events potentially associated with tocilizumab according to the product labeling were also collected (13).

Statistical Analysis

Patient characteristics were reported as frequency and proportion for categorical variables and as median and interquartile range or mean and SD for continuous variables. Differences across groups were determined by chi-square or Fisher exact tests for categorical variables and Wilcoxon rank-sum test or *t* test for continuous variables as appropriate. The distribution of markers was depicted by box plots and the mean change over time assessed by linear mixed modeling. Post hoc marginal pairwise comparisons were performed to determine the adjusted means and 95% CIs of the changes in each continuous variable. Cox regression analyses were used to determine the characteristics associated with clinical improvement. Variables for the multivariable models were selected based on clinical importance and Stata's Lasso technique with the cross-validation selection option. Model performance was determined by the *C*-statistic. Good calibration was determined by a nonsignificant Hosmer-Lemeshow goodness-of-fit test. The likelihood ratio test was used to reduce model subsets. Analyses were performed on Stata Version 16.1 (StataCorp LLC, College Station, TX). A *p* value of less than 0.05 was considered statistically significant.

RESULTS

Patients and Treatment Characteristics

A total of 69 patients who initially presented to six different hospitals within the hospital system received at least one dose of tocilizumab. Of these, seven patients were excluded from the analysis as they were not critically ill. Baseline characteristics and tocilizumab dosing for the first 62 consecutive patients with severe disease who

required invasive ventilation and received tocilizumab are shown in **Table 1**. The cohort was primarily male (59.7%), had a mean age of 59.7 years (\pm 13.9 yr), and 63% were obese. The median times from symptom onset to hospital admission and from hospital admission to intubation were 6 days (3–9 d) and 1.5 days (0–3 d), respectively. Thirty-two patients (51.6%) underwent prone ventilation and eight (12.9%) required venovenous extracorporeal membrane oxygenation (ECMO) prior to tocilizumab administration.

Laboratory markers and indicators of respiratory status are shown in **Table 2**. Median IL-6 and CRP values pre-tocilizumab were 82 pg/mL (22–221 pg/mL) and 25.1 mg/dL (15.7–36.8 mg/dL), respectively. Baseline mean PaO₂/FIO₂, PEEP, and RALE scores were 181.5 (\pm 89), 12.1 cm H₂O (\pm 3.2 cm H₂O), and 20.3 (\pm

9.3), respectively. Sixty-nine percent of patients received corticosteroids, and nearly all patients (95%) received additional off-label or investigational viral-directed therapy (**Table S1**, Supplemental Digital Content, <http://links.lww.com/CCX/A368>). The mean weight-based tocilizumab dose was 4.8 mg/kg (\pm 0.9 mg/kg) and 24% of patients received a repeat infusion. The median time from symptom onset to tocilizumab administration was 9 days (7–14 d), and the time from hospital admission to tocilizumab administration was 3.5 days (2–6 d).

Clinical Course

Of the 62 patients, clinical improvement occurred in 36 patients (58%) by 21 days post-tocilizumab. Twenty of these patients were

TABLE 1. Baseline Characteristics of Tocilizumab-Treated Coronavirus Disease Patients Stratified by Achievement of Clinical Improvement Based on World Health Organization Ordinal Scale

Characteristics	Total (n = 62)	Clinical Improvement at 21 d		p
		No (n = 26)	Yes (n = 36)	
Age (yr), mean (\pm sd)	59.7 (\pm 13.9)	65.5 (\pm 13.6)	55.6 (\pm 12.8)	0.01
Age < 60 yr	30 (48.4)	7 (26.9)	23 (63.9)	0.004
Male gender	37 (59.7)	19 (73.1)	18 (50.0)	0.11
Race				0.94
White	34 (54.8)	16 (61.5)	18 (50.0)	
Black	20 (32.3)	8 (30.8)	12 (33.3)	
Asian	3 (4.8)	1 (3.8)	2 (5.6)	
Native American	1 (1.6)	0 (0.0)	1 (2.8)	
Declined	4 (6.5)	1 (3.8)	3 (8.3)	
Hispanic ethnicity ^a	17 (27.9)	9 (34.6)	8 (22.9)	0.39
Weight (kg), mean (\pm sd)	96.0 (\pm 26.2)	98.4 (\pm 23.1)	94.3 (\pm 28.4)	0.55
Body mass index (kg/m ²), median (IQR)	31.5 (27.6–38.4)	31.9 (28.2–37.8)	31.1 (26.5–38.7)	0.78
Body mass index \geq 30 kg/m ²	39 (62.9)	16 (61.5)	23 (63.9)	0.85
Diabetes	28 (45.2)	14 (53.8)	14 (38.9)	0.24
Hypertension	39 (62.9)	21 (80.8)	18 (50.0)	0.02
Chronic obstructive pulmonary disease	6 (9.7)	3 (11.5)	3 (8.3)	0.69
Asthma	4 (6.5)	1 (3.8)	3 (8.3)	0.63
Smoking history	15 (24.2)	7 (26.9)	8 (22.2)	0.67
Cancer history	9 (14.5)	7 (26.9)	2 (5.6)	0.03
Days from symptom onset to admission, median (IQR)	6.0 (3.0–9.0)	5.0 (3.0–7.0)	6.5 (3.0–9.0)	0.88
Hospital admission to intubation (d), median (IQR)	1.5 (0.0–3.0)	2.0 (0.0–3.0)	1.0 (0.0–3.0)	0.60
Sequential Organ Failure Assessment total score, mean (\pm sd)	9.3 (\pm 3.4)	9.8 (\pm 3.7)	8.8 (\pm 3.1)	0.25
Prone ventilation	32 (51.6)	12 (46.2)	20 (55.6)	0.46
Venovenous extracorporeal membrane oxygenation	7 (11.3)	4 (15.4)	3 (8.3)	0.44

IQR = interquartile range.

^aEthnicity was not available in one patient.

Unless specified, data shown as n (%).

TABLE 2. Pre-Tocilizumab Laboratory Markers, Respiratory Indicators, and Radiographic Assessment of the Quality of Lung Edema Scoring

Characteristics	Total (n = 62)	Clinical Improvement at 21 d		p
		No (n = 26)	Yes (n = 36)	
Absolute lymphocyte count (cells/ μ L), median (IQR)	752.5 (505.4–1,112.8)	655.5 (491.2–1,019.0)	871.1 (542.0–1,123.1)	0.28
Interleukin-6 (pg/mL), median (IQR)	82.0 (22.0–221.0)	90.0 (37.0–230.0)	49.0 (21.0–151.0)	0.35
C-reactive protein (mg/dL), median (IQR)	25.1 (15.7–36.8)	29.9 (13.9–39.0)	24.9 (16.9–35.0)	0.79
Ferritin (ng/mL), median (IQR)	1,349.5 (723.5–2,423.0)	1,895.5 (723.5–4,853.5)	1,285.5 (791.0–2,071.0)	0.20
Lactate dehydrogenase (U/L), median (IQR)	465.0 (353.0–592.0)	499.0 (409.0–617.5)	393.5 (349.0–563.0)	0.19
Pao ₂ /Fio ₂ ratio, median (IQR)	163.0 (110.0–220.0)	168.5 (110.0–237.5)	163.0 (113.0–218.0)	0.88
Positive end-expiratory pressure (cm H ₂ O), mean (\pm sd)	12.1 (\pm 3.2)	12.7 (\pm 3.2)	11.7 (\pm 3.2)	0.24
Radiographic Assessment of the Quality of Lung Edema score, mean (\pm sd)	20.3 (\pm 9.3)	20.5 (\pm 11.6)	20.1 (\pm 7.6)	0.90

IQR = interquartile range.

discharged from the hospital and 16 patients remained hospitalized at day 21 (two requiring noninvasive ventilation, six on nasal cannula, and eight on room air). At last follow-up, all 16 patients were subsequently discharged alive from the hospital. Mean time to extubation was 9.6 days (\pm 4.3 d) post-tocilizumab. Time to extubation is shown by Kaplan-Meier analysis in **Figure 1A**. Thirteen out of the 62 patients (21%) remained intubated 21 days following tocilizumab administration.

By day 21 post-tocilizumab, 13 patients (21%) died. Time to death is shown by Kaplan-Meier analysis in **Figure 1B**. In 11 patients, life support measures were withdrawn in the presence of irreversible hypoxemic respiratory failure and concomitant multisystem organ failure. In one case, resuscitation was performed in a patient with severe bradycardia and subsequent pulseless electrical activity. In another case, life support was withdrawn following intraventricular hemorrhage in a patient on venovenous ECMO.

Factors Associated With Clinical Outcomes

Factors associated with clinical improvement or mortality were evaluated using logistic regression. Age less than 60 years was significantly associated with clinical improvement at 21 days, whereas hypertension and history of cancer were associated with lack of clinical improvement (**Table 3**). Male gender and ribavirin administration approached significance ($p < 0.2$) and were therefore included in the multivariable model. Of these, only age less than 60 years remained significantly associated with clinical improvement in multivariable analysis (odds ratio, 3.56; 95% CI, 1.02–12.34; $p = 0.045$).

Several factors were associated with mortality by univariable analysis (**Table S2**, Supplemental Digital Content, <http://links.lww.com/CCX/A368>). These included age, male gender, hypertension, smoking history, cancer history, lower absolute lymphocyte count at baseline, and higher Sequential Organ Failure Assessment score. Azithromycin administration was the only pharmacologic

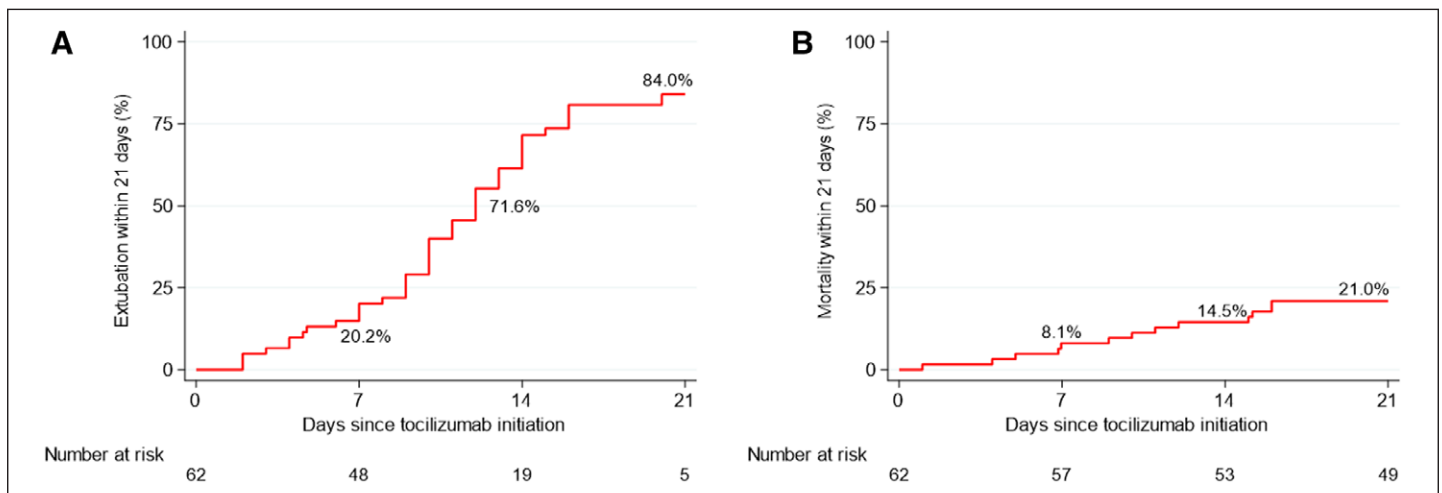


Figure 1. Kaplan-Meier curves assessing clinical improvement and mortality until day 21 after tocilizumab. Clinical improvement (extubation) (**A**) and mortality (**B**).

TABLE 3. Factors Associated With Clinical Improvement at Day 21 Post-Tocilizumab

Characteristics	Univariable		Multivariable (Area Under the Receiver Operating Characteristic Curve = 0.79)	
	OR (95% CI)	<i>p</i>	OR (95% CI)	<i>p</i>
Age < 60 (yr)	4.80 (1.60–14.45)	0.01	3.56 (1.02–12.34)	0.045
Male gender ^a	0.37 (0.12–1.09)	0.07		
Hypertension	0.24 (0.07–0.77)	0.02	0.49 (0.08–0.97)	0.29
Cancer history	0.16 (0.03–0.85)	0.03	0.20 (0.03–1.22)	0.08
Ribavirin	3.13 (0.96–10.17)	0.06	2.77 (0.72–10.14)	0.14

OR = odds ratio.

^aGender was evaluated in the initial model; however, it was not significant and had some confounding effect on age. Further evaluation between models with and without gender suggested no difference in the performance, which indicated by a nonsignificant *p* of the likelihood ratio test. Given the number of covariates needing to be kept at minimum, gender was not included in the final model.

agent associated with survival at 21 days. Due to the low number of deaths in the cohort, multivariable analysis was not performed. Interestingly, in patients receiving remdesivir (*n* = 11) in combination with tocilizumab, only one death occurred by day 21. Similarly, only one out of 11 patients who received convalescent plasma with tocilizumab died during the same period.

Changes in Inflammatory Markers and Respiratory Status

In all patients, IL-6 increased beginning on day 1 post-tocilizumab as expected and remained elevated throughout the first week (mean increase of 1,166 pg/mL; *p* = 0.054; **Fig. 2A**). CRP decreased by a mean of 50% (\pm 40) of the pre-tocilizumab value by day 2 and by 80% (\pm 20) by day 3 post-tocilizumab. Overall, CRP

decreased significantly in all patients from baseline to day 7 post-tocilizumab (mean decrease of 24.6 mg/dL; *p* < 0.001; **Fig. 2B**). Ferritin, LDH, and Pao₂/Fio₂ did not change significantly over the 7 days post-tocilizumab (**Fig. 2C–E**), whereas PEEP decreased slightly (mean decrease 1.7 cm H₂O; **Fig. 2F**).

Overall, there were no differences in inflammatory markers, Pao₂/Fio₂, or PEEP over the 7 days post-tocilizumab therapy based on clinical outcomes (**Figs. S1 and S2**, Supplemental Digital Content, <http://links.lww.com/CCX/A368>). However, slight improvements in Pao₂/Fio₂ and PEEP were seen at the end of the period in those with better outcomes.

Since CRS could lead to abnormalities in alveolar-capillary permeability and cause infiltrations on the chest radiograph, a RALE score was calculated to quantify trends in pulmonary edema in

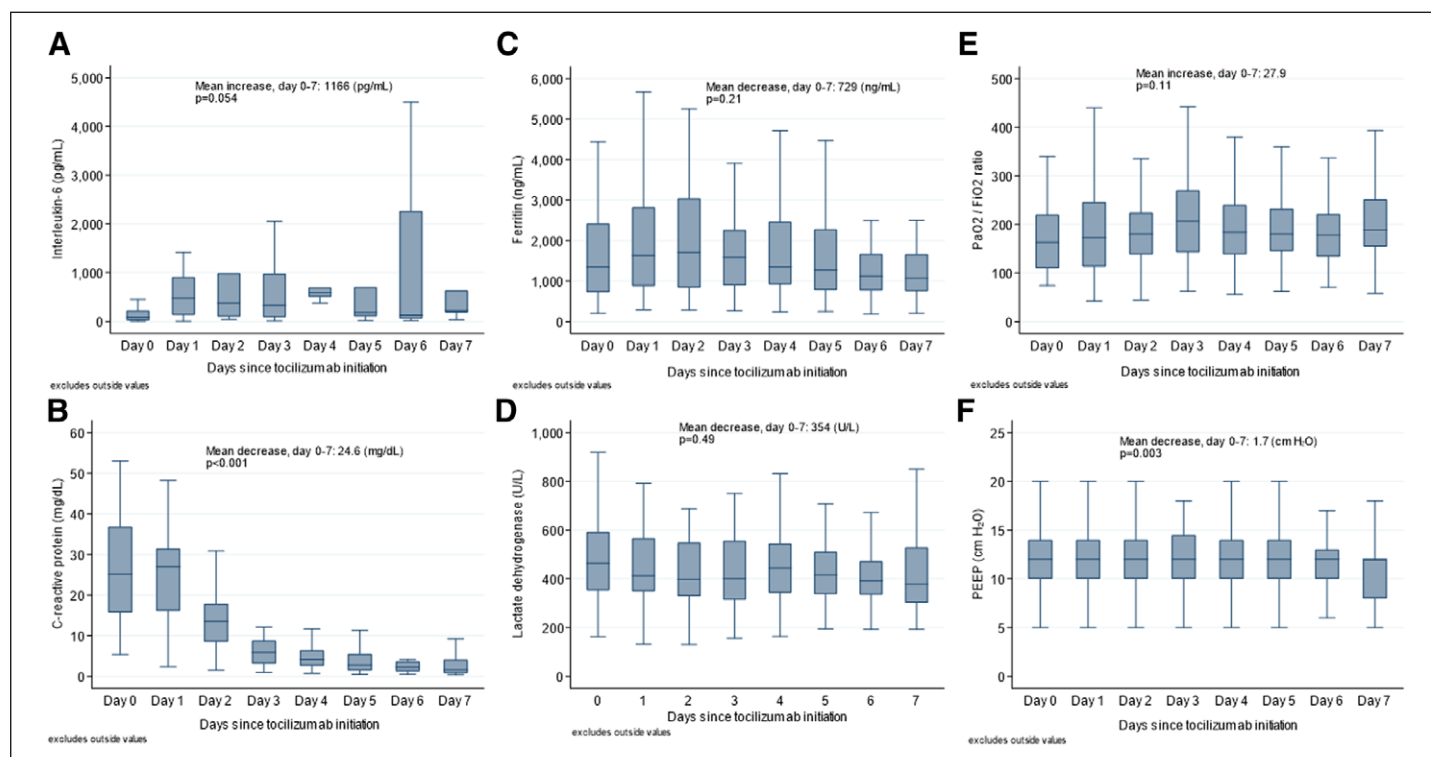


Figure 2. Box plots showing inflammatory markers, respiratory status, and oxygenation support for all patients. (A) Interleukin-6, (B) C-reactive protein, (C) ferritin, (D) lactate dehydrogenase, (E) Pao₂/Fio₂ ratio, and (F) positive end-expiratory pressure (PEEP).

days 0–7, then at days 10, 14, and 21 following tocilizumab administration. As shown in **Figure S3** (Supplemental Digital Content, <http://links.lww.com/CCX/A368>), the scores did not change significantly over the follow-up period, nor did they differ significantly based on 21-day clinical improvement status.

Safety

The most common adverse event following tocilizumab administration was new-onset elevation in transaminases to greater than three times the upper limit of normal, which occurred in 25 patients (40%). This was transient in 23 patients, while two patients had persistence/reoccurrence of transaminitis. Transaminase levels peaked at a mean of 6.2 ± 3.9 days post-tocilizumab. Five patients (8%) developed serious infections following tocilizumab administration, including two with bloodstream infections and three with bacterial pneumonia. No fungal or secondary viral infections were detected in the 21-day follow-up period. Four patients (6.5%) experienced severe thrombocytopenia ($< 50,000$ per mm^3). No patient experienced severe neutropenia (< 500 per mm^3) or gastrointestinal perforations.

One patient experienced an anaphylactic reaction with a probable association to tocilizumab. During the infusion, a 74-year-old male became hypotensive and required discontinuation of the infusion, vasopressor therapy, diphenhydramine, and hydrocortisone. The patient recovered from the anaphylactic reaction but continued to deteriorate clinically due to ongoing multiple organ dysfunction over the following 6 days and eventually succumbed to multiple organ system failure.

DISCUSSION

At nearly 800,000 deaths globally related to COVID-19 reported thus far and the lack of an effective treatment for critically ill patients, there remains an urgent need to evaluate both investigational and commercially available off-label therapies for the management of COVID-19. Based on descriptions of the role of CRS in the pathogenesis of COVID-19 pneumonia, as well as the devastating outcomes initially described in critically ill patients, our center adopted the use of tocilizumab to mitigate the hyperinflammatory response thought to contribute to ARDS and mortality. Patients with severe COVID-19 reviewed here were not only mechanically ventilated, but also had several risk factors for poor outcomes following COVID-19, including a high prevalence of patients with hypertension, diabetes, obesity, and smoking history. Our report of tocilizumab in patients exclusively receiving invasive mechanical ventilation demonstrates a 21-day mortality of 21% and clinical improvement at day 21 in 58% of patients with severe disease.

Mortality rates among critically ill patients with severe COVID-19 are difficult to ascertain due to geographic variation and differences in follow-up duration. Staggering mortality rates of 81–97% in mechanically ventilated patients were initially observed in Chinese cohorts (1, 2), whereas U.S. experiences describe rates of 24–67% (3–5). Reports on tocilizumab, specifically in critically ill populations, are limited. Some include patients of moderate to severe disease, with smaller numbers of patients requiring invasive ventilation (11–13). In a series from Qatar, of 21 patients who

required invasive ventilation prior to tocilizumab, seven remained on ventilation at 14 days post-tocilizumab administration (14). Another larger series from Italy found that among 43 patients requiring invasive ventilation, 77% improved and 24% died after 10 days after tocilizumab administration (15). In a cohort from Yale, 14-day survival among 42 mechanically ventilated patients with severe disease was 74% (16). Finally, a recent study of 78 patients receiving tocilizumab showed lower mortality when compared with 76 patients who did not receive tocilizumab (18% vs 36%) at 28 days (17). On the contrary, a news article cited tocilizumab as failing to reduce severe respiratory symptoms, ICU visits, and deaths compared with standard care in a nonrandomized trial (18), while release of phase III data noted tocilizumab did not meet its endpoints of improved clinical status or reduced mortality (19). Importantly, details of these studies, which also included patients at earlier stages of the disease and outcomes specifically in the most severe patients have not been described. Therefore, mortality and clinical improvement rates in our tocilizumab cohort appear to be at least comparable if not more favorable than those in similar populations previously reported.

Interestingly, mortality and clinical improvement in our cohort closely resemble those seen in mechanically ventilated patients from the compassionate use experience with remdesivir (20). In those patients, Grein et al (20) reported mortality of 18% and improvement in 56% with a median follow-up of 18 days. Preliminary data from the placebo-controlled trial of remdesivir, which subsequently led to its emergency use authorization by the FDA for treatment of severe COVID-19, do not demonstrate differences in recovery or mortality rates between the remdesivir and placebo groups among patients on invasive ventilation (21). Thus, it is still crucial to identify effective therapies, particularly in critically ill patients. It is noteworthy that in our cohort, mortality appeared to be lower in those who received either remdesivir or convalescent plasma with tocilizumab (9.1%) compared with tocilizumab without these therapies (23.5%). Hence, future studies may consider the use of combination therapies to combat COVID-19 in critically ill patients.

To identify early indicators of clinical improvement or mortality, we evaluated daily inflammatory markers as well as indicators of respiratory status and oxygenation support during the first 7 days post-tocilizumab. While CRP changed significantly over this time, no differences were seen in CRP, IL-6, ferritin, or LDH in relation to clinical improvement or survival status. Other studies that evaluated biomarkers later in the disease progression after 7 days have demonstrated reductions in inflammatory markers among recovering patients (22). Therefore, it is possible that monitoring of inflammatory markers immediately post-tocilizumab may not aid in identification of patients with poor prognosis, particularly among those who have already reached ARDS.

Information on radiographic scoring in the setting of COVID-19 is limited. A study using modified RALE scoring found that chest radiograph consolidation peaked at 10–12 days from symptom onset (23), which was consistent with the time from symptom onset to tocilizumab administration in our cohort. However, no significant change was seen in RALE scores during the 21-day period following tocilizumab administration. This could be attributed to

other confounders such as fluid balance, PEEP management, or radiographic lag time compared with clinical improvement.

Given the severity of illness and presence of concomitant diagnoses in this cohort, we limited our safety analysis to serious potential complications associated with tocilizumab. Tocilizumab had an acceptable safety profile for most patients, with transient transaminitis being the most common side effect and a low rate of new-onset infections. A probable case of anaphylaxis occurred, which has been reported in less than 1% of patients (24). Further study comparing tocilizumab use against a control group is vital to adequately evaluate the safety in this setting.

The primary limitations of this study are its retrospective nature, relatively small sample size, and lack of a control group, which prevents any assertion of the effectiveness of tocilizumab. The dosing of tocilizumab also varied among patients, with a flat dose used in most cases. Furthermore, in the setting of rapidly progressing respiratory distress and without known effective therapies against COVID-19, a myriad of off-label and experimental agents were used in this cohort, which may have confounded the true impact of tocilizumab. This includes the frequent use (69%) of corticosteroids, which has been shown in a large cohort of mechanically ventilated patients to reduce mortality (25). Finally, although our multivariate logistic regression model has a ratio of events per covariate slightly less than the ratio of 10 events per predictor as suggested by Harrell et al (26), there is a growing number of more recent publications recommended that the rule of “10 events for one covariate” can be relaxed. Specifically, in their large factorial simulation study, Vittinghoff and McCulloch (27) suggested that models with 5–9 events per covariate are usually comparable to those with 10–16 events per covariate (28). Several strengths of the current report should be noted as well. Our experience represents one of the largest series of tocilizumab-treated patients on invasive mechanical ventilation. The population is diverse, with nearly 30% of the cohort being African American or Hispanic/Latino. The data offer insights into early trends in inflammatory markers and respiratory status and is the first to evaluate RALE scores assessing changes in chest radiographs in a cohort of its kind. Finally, these results may inform certain plausible combinations of therapies, such as tocilizumab with remdesivir or convalescent plasma, for the management of critically ill COVID-19 patients. Since the release of preliminary phase III data, we have removed tocilizumab from the COVID-19 treatment algorithm, but continue to consider its use or the use of other immunomodulatory agents on a case-by-case basis pending further analyses.

CONCLUSIONS

In conclusion, mortality and clinical improvement rates reported here appear to be better than initial reports in similar critically ill cohorts, and comparable to reports on emerging treatment modalities. While recent reports cite tocilizumab as failing to improve clinical outcomes in COVID-19 positive patients, it is important to note that our cohort was focused on a high-risk cohort of patients already exhibiting severe respiratory distress and on invasive mechanical ventilation. Our experience, therefore, supports the need for continued evaluation of the IL-6 inhibitor tocilizumab

in a randomized controlled trial for treatment of COVID-19, particularly in invasively ventilated patients.

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