Tocilizumab in patients with severe COVID-19: A single-center observational analysis

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Abstract
Patients with coronavirus disease 2019 (COVID-19) may develop severe respiratory distress, thought to be mediated by cytokine release. Elevated proinflammatory markers have been associated with disease severity. Tocilizumab, an interleukin-6 receptor antagonist, may be beneficial for severe COVID-19, when cytokine storm is suspected. This is a retrospective single-center analysis of the records of patients diagnosed with COVID-19 who received tocilizumab. Outcomes, including clinical improvement, mortality and changes in oxygen-support at 24, 48, and 72 hours, and 7, 14, and 28 days post-tocilizumab, are reported. Patients were evaluated by baseline pre-tocilizumab oxygenation status and changes in proinflammatory markers within 7 days post-tocilizumab are reported. Sixty-six patients received tocilizumab at a mean dose of 724 mg (7.4 mg/kg), 3.7 days from admission. At baseline, 53% of patients were on ventilation support and all had elevated proinflammatory markers, including c-reactive protein (CRP). Common comorbidities were diabetes mellitus (43%) and hypertension (74%). Most patients received concomitant glucocorticoids and hydroxychloroquine. Seven days after tocilizumab, ten patients (15.2%) had clinical improvement in their oxygenation status, and there was a 95% decrease in CRP. Within 14 days of treatment, 29% of patients had clinical improvement, 20% had minimal or no improvement, 17% worsened, 27% died, and 7% were transferred to an outside hospital. Ultimately, 42% of all patients that received tocilizumab expired and 49% were discharged. This study found limited clinical improvement in patients that received tocilizumab in the setting of severe COVID-19. Clinical trials are ongoing to further evaluate tocilizumab's benefit in this patient population.

Keywords
COVID-19, cytokine release syndrome, cytokine storm, IL-6 antagonist, tocilizumab

INTRODUCTION

A novel coronavirus disease (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), which is now designated coronavirus disease 2019 (COVID-19) by the World Health Organization (WHO) has become a pandemic. As of 13 May 2020 there are 4,248,389 confirmed cases and 294,046 confirmed deaths throughout 216 countries. The first case in the United States was reported on 24 January 2020. The presentation of COVID-19 can range from asymptomatic infection to hypoxic respiratory failure. The more severe manifestations are thought to be caused by cytokine storm or cytokine release syndrome (CRS), an excessive production of inflammatory cytokines, including interleukin-6 (IL-6). Elevated proinflammatory markers, such as IL-6, lactate dehydrogenase (LDH), D-dimer, ferritin, and procalcitonin (PCT) have been associated with lung damage and death in patients with COVID-19 infection.
There are currently no Food and Drug Administration approved treatments for COVID-19 but there are numerous clinical trials evaluating pharmacologic agents, including antivirals and immunomodulators. Tocilizumab is an IL-6 receptor antagonist that is approved for rheumatoid arthritis and CRS in patients on CAR-T cell therapy. Tocilizumab has been used off-label in patients with COVID-19 infection with suspected cytokine storm. Current IDSA guidelines only recommend use of tocilizumab in the setting of a clinical trial. Current National Institutes of Health and Society of Critical Care Medicine guidelines for COVID-19 recommend that there is insufficient evidence for or against tocilizumab use. Current guidelines from China state that tocilizumab may be used for up to two doses in patients with severe COVID-19.

The earliest report of tocilizumab use in COVID-19 was published by Xu et al. They evaluated 21 patients and showed a decrease in CRP and oxygen intake, and most patients were discharged within 14 days post-tocilizumab. A study in 15 patients by Luo et al showed decreased CRP and IL-6 levels in patients who received tocilizumab. Alattar et al reported the results of 25 patients with a 14 day follow-up, showing a reduction in patients requiring invasive ventilation 14 days post-tocilizumab. A study in 100 patients by Toniati et al showed clinical improvement in 77% of patients, 10 days after tocilizumab. Although these reports have shown some clinical efficacy with tocilizumab use in patients with COVID-19 with presumed cytokine storm, others have reported a lack of benefit. A study by Colaneri et al found that tocilizumab did not significantly affect admission to the intensive care unit or 7-day mortality in a cohort of 21 patients. In a case study published by Radbel and colleagues, two patients with COVID-19, CRS, and secondary hemophagocytic lymphohistiocytosis had clinical decompensation, despite a decrease in IL-6 levels. This retrospective single-center study reports on the outcomes of patients with severe COVID-19 who received tocilizumab at a large, urban medical center in the United States.

2 METHODS

This was a retrospective observational evaluation conducted at Einstein Medical Center Philadelphia and Einstein Medical Center Elkins Park of all patients with confirmed SARS-CoV-2 infection who were administered tocilizumab for COVID-19 between 25 March and 24 April 2020. Tocilizumab was administered to patients who met criteria per hospital protocol: confirmed COVID-19, age ≥18 years, elevated D-dimer (>1.5 mg/L), and interstitial pneumonitis. Prescribing was limited to a small number of designated pulmonary and infectious diseases physicians. Tocilizumab was dosed at 8 mg/kg with a maximum of 800 mg per dose, rounded to the nearest 200 mg vial size. The treatment protocol originally allowed for a maximum of three doses of tocilizumab if patients had no clinical improvement at least 8 hours after the first dose. However, this was later modified to a maximum of one dose per patient due to limited availability, lack of supportive clinical data and high cost. Tocilizumab was reconstituted in 100 mL of 0.9% sodium chloride solution and administered intravenously over 60 minutes, according to package insert recommendations. Data was collected via chart review at a pre-tocilizumab baseline, and at 24 hours, 48 hours, 72 hours, 7 days, 14 days, and 28 days post-tocilizumab. Data was collected through 23 May 2020 to allow for a 30-day follow-up for all patients, and all patients were followed through hospitalization.

Study outcomes included clinical improvement and mortality 7 and 14 days after tocilizumab in the overall group, and between invasive ventilation and noninvasive ventilation groups. Clinical improvement was defined as discharge from the hospital, or a decrease of at least two oxygen-support categories on a modified ordinal scale as recommended by the WHO R&D Blueprint Group. The scale consisted of the following categories: invasive ventilation defined as patients requiring mechanical ventilation or extracorporeal membrane oxygenation (ECMO); noninvasive ventilation defined as patients requiring bilevel positive airway pressure (BiPAP), continuous positive airway pressure (CPAP), high-flow oxygen (O2), or mid-flow O2; low-flow O2 defined as patients requiring nasal cannula or a nonrebreather mask; and ambient air defined as patients requiring room air at the time of tocilizumab administration.

Other endpoints included overall clinical status 24 hours, 48 hours, 72 hours, 7 days, and 14 days post-tocilizumab, and overall disposition of tocilizumab treated patients. Median D-dimer, CRP, ferritin, and LDH levels were evaluated in patients that had documented values at baseline and 7 days post-tocilizumab. In a separate analysis, patients were evaluated by overall clinical outcomes to compare differences in baseline D-dimer, CRP, ferritin, and LDH.

Descriptive statistics were used to report variables expressed as median (interquartile range [IQR]), or number (%) ± standard deviation. Categorical variables were compared using Fisher’s exact tests, and non-parametric continuous variables were compared using Mann-Whitney U tests. Survival curves were calculated for overall 28-day survival and 28-day clinical improvement according to the Kaplan-Meier method and comparisons were made using the log rank test. Statistical analyses were made using GraphPad Prism version 8 software, and differences with two-sided P values of less than .05 were considered statistically significant.

3 RESULTS

A total of 66 patients received tocilizumab in this cohort. Of these, 18 (27.3%) were on mechanical ventilation at the time of their dose, and 48 (73.7%) were on noninvasive oxygen support or ambient air. Tocilizumab was given at a mean dose of 7.4 (±1.4) mg/kg (724 [±115] mg/dose), 3.7 (±2.9) days from admission. Seven patients in the noninvasive oxygen support group received two doses, and one patient in both groups received three doses. Age, weight, and sex distribution were comparable between groups. The majority of patients (77%) were black or African American with a median body mass index of 32.8 kg/m². Most patients (74.2%) had a past medical history of hypertension, 42.4% had diabetes, 16.7% had asthma.
or chronic obstructive pulmonary disease, and 9.1% were immunocompromised. Baseline inflammatory markers, including D-dimer, ferritin, CRP, and LDH were elevated in the majority of patients, with median values significantly higher than the upper limit of normal. At baseline, PCT and D-dimer levels were higher in the patients on invasive ventilation, but only the difference in PCT was statistically significant ($P = .030$ and $P = .064$, respectively). Two-thirds of patients received at least one dose of concomitant steroids, and the majority of patients received hydroxychloroquine. All baseline characteristics are summarized in Table 1.

Seven days after tocilizumab, 10 patients (15.2%) had clinical improvement as defined as discharge or improvement by two or more points on an ordinal scale; 40.9% had either no change or only a modest improvement in their oxygenation support (improvement by one point on an ordinal scale); 34.8% of patients required advancement of oxygen support; and 6% died. (Table 2) More patients in the invasive ventilation group had clinical improvement than in the noninvasive oxygen support group, but this was not statistically significant (22.2% vs 12.5%; $P = .442$). Patients who were receiving noninvasive ventilation pre-tocilizumab (ie, BiPAP, CPAP, high-flow oxygen, or mid-flow oxygen) had similar improvement (23.5%) as patients receiving invasive ventilation at baseline. Only 7.4% of patients in the low-flow oxygen subgroup had clinical improvement by 7 days, and no patients in the ambient air subgroup had clinical improvement. By day 7, 5.6% of patients in the invasive ventilation group died, compared with 6.3% in the noninvasive oxygen support group ($P = 1.00$).

By post-tocilizumab day 14, 28.8% of all patients had clinical improvement; 19.7% had either no change, or only a modest improvement in their oxygenation support; 16.7% required advancement of oxygen support; and 27% died. In the invasive ventilation group, 16.7% had clinical improvement, compared with 33.3% of patients in the noninvasive oxygen support group ($P = .233$). By day 14, 39% of patients in the invasive ventilation group died, compared with 22.9% in the noninvasive oxygen support group ($P = .224$). Mortality rates were similar by baseline oxygenation subgroup: noninvasive ventilation (24%), low-flow oxygen (22%), and ambient air (25%). Figure 1 depicts Kaplan-Meier curves for overall survival at (A) 28-days post-tocilizumab, and (B) cumulative incidence of clinical improvement at 28-days post-tocilizumab, between invasive and noninvasive groups. No statistically significant differences were observed between groups.

Clinical status by subgroup at all time points is summarized in Figure 2. Most patients in the invasive ventilation group had no change in clinical status through the first 7 days. Patients that had improvement in the invasive ventilation group improved within 48 hours of tocilizumab. In comparison, patients who were on noninvasive ventilation or low-flow oxygen at baseline did not demonstrate any clinical improvement until at least 72 hours post-tocilizumab. The majority of patients who were on low-flow oxygen at baseline and had disease progression, progressed rapidly within 24 hours post-tocilizumab. Of the four patients that were on ambient air at baseline, two progressed to mechanical ventilation rapidly within 24 hours, one progressed to noninvasive ventilation within 24 hours, and no improvement was observed by day 14 in any of these.

All patients were observed through the duration of their hospitalization. Overall, 42.4% of all patients who received tocilizumab expired at a median of 14.7 (IQR: 10.6, 22.0) days from admission and 9.9 (IQR: 7.6, 18.0) days from tocilizumab. The reported causes of death were acute hypoxic respiratory failure (n = 23), cardiopulmonary failure (n = 3), cardiogenic shock (n = 1), and refractory shock (n = 1). One mortality (cardiopulmonary failure) was not directly attributed to COVID-19. A total of 48.5% were discharged from the hospital at a median of 16.4 (IQR: 8.8, 23.0) days post-admission and 12.7 (IQR: 7.2, 18.6) days post-tocilizumab. Five patients (7.5%) were transferred to outside hospitals at a median of 5.8 (IQR: 5.0, 6.3) days post-admission and 4.1 (IQR: 3.0, 4.3) days post-tocilizumab (three to hospitals with lower patient volumes, one for specialized care at their transplant center, and one for increased level of care to continue ECMO). At the time of this analysis, one patient was still hospitalized, with a length of stay of 61 days post-admission, and 58 days post-tocilizumab.

Median values for D-dimer, CRP, ferritin, and LDH were available for 44 (67%), 29 (44%), 32 (48%), and 39 (59%) patients, respectively. (Figure 3) The median baseline CRP level was 179.1 mg/L (IQR: 94.4, 276.9) which decreased to a median of 9.8 mg/L (IQR: 4.6, 34.0) 7 days post-tocilizumab. Levels of D-dimer, ferritin, and LDH remained significantly elevated 7 days post-tocilizumab. In a separate analysis, patients were analyzed by overall clinical outcome 14 days post-tocilizumab. There did not seem to be a relationship between baseline D-dimer, CRP, ferritin, and LDH, with regard to clinical outcome. (Figure 4)

4 | DISCUSSION

This retrospective, observational study reports on the largest series to date of patients that received tocilizumab for COVID-19 in the United States. All patients in this study were on a ventilator, noninvasive oxygen support, or required oxygen support within 24 hours of receiving a dose of tocilizumab. While it is difficult to determine efficacy in a single-arm study, only 15% of patients had clinical improvement at 7 days and 29% had clinical improvement at 14 days post-tocilizumab. At 14 days post-tocilizumab, 39% of patients had either no change in oxygenation status, had only a modest improvement in oxygenation status, or required an increase in oxygen support needs. Overall, 42% of patients that received tocilizumab died during the observational period. These results call into question the benefit of tocilizumab for this indication.

At the time of this manuscript preparation, data supporting tocilizumab use was still limited to non-randomized studies. Xu et al evaluated outcomes in 21 patients with severe or critical COVID-19 infection. Unlike the population presented in the current study, only 15% of their patients were on either invasive or noninvasive ventilation at baseline, whereas 53% of the population of this study was. 11
They found that 75% of their patients had decreased oxygen intake within 5 days of receiving tocilizumab and they reported no deaths. Alattar et al reported on the results of 25 patients in the intensive care unit that were on mechanical or nonmechanical ventilation and found that the percentage of patients on invasive ventilation decreased by 67% within 14 days post-tocilizumab. They reported that 36% of their patients were discharged from the ICU within 14 days, and 12% died. Luo et al reported on 15 patients with COVID-19

### TABLE 1  Baseline characteristics

|                       | All patients (n = 66) | Invasive ventilation (n = 18) | Noninvasive oxygen support (n = 48) |
|-----------------------|-----------------------|-----------------------------|-----------------------------------|
| Age, median, y (IQR)  | 61 (54.5, 67)         | 59 (54.5, 68)               | 61 (55.5, 67)                     |
| Male sex, n (%)       | 41 (62.1)             | 11 (61.1)                   | 30 (62.5)                         |
| Race, n (%)           |                       |                             |                                   |
| Black                 | 51 (77.2)             | 14 (77.8)                   | 37 (77.1)                         |
| White                 | 6 (9.1)               | 4 (22.2)                    | 2 (4.2)                           |
| Hispanic              | 3 (4.5)               | ...                         | 3 (6.3)                           |
| Native American       | 2 (3.0)               | ...                         | 2 (4.2)                           |
| Asian                 | 1 (1.5)               | ...                         | 1 (2.1)                           |
| Not documented        | 3 (4.5)               | ...                         | 3 (6.3)                           |
| Weight, median, kg (IQR) | 98.2 (82.3, 115.0)  | 100.0 (74.7, 112.2)         | 98.2 (83.4, 115.5)                |
| BMI, median, kg/m² (IQR) | 32.8 (28.5, 39.0)  | 35.1 (24.1, 39.8)           | 32.5 (29.4, 38.3)                 |
| Oxygen support category, n (%) |   |                             |                                   |
| Ventilator            | 18 (27.3)             | 18 (100)                    | ...                               |
| BiPAP                 | 2 (3)                 | ...                         | 2 (4.2)                           |
| High-flow O₂          | 4 (6.1)               | ...                         | 4 (8.3)                           |
| Mid-flow O₂           | 11 (16.7)             | ...                         | 11 (2.9)                          |
| Nasal cannula         | 20 (30.3)             | ...                         | 20 (4.7)                          |
| Nonrebreather         | 7 (10.6)              | ...                         | 7 (1.6)                           |
| Ambient air           | 4 (6.1)               | ...                         | 4 (8.3)                           |
| Past medical history, n (%) |                     |                             |                                   |
| Hypertension          | 49 (74.2)             | 13 (72.2)                   | 36 (75)                           |
| Diabetes              | 28 (42.4)             | 7 (38.9)                    | 21 (43.8)                         |
| Asthma/COPD           | 11 (16.7)             | 3 (16.7)                    | 8 (16.7)                          |
| Immunocompromised     | 6 (9.1)               | 3 (16.7)                    | 3 (6.3)                           |
| Procalcitonin, ng/mL, median (IQR) |           |                             |                                   |
| Range                 | 0.38 (0.15, 1.29)     | 1.14 (0.43, 5.51)           | 0.31 (0.11, 1.19)                 |
| D-dimer, mg/L, median (IQR) |                 |                             |                                   |
| Range                 | 2.99 (1.52, 6.56)     | 5.03 (2.22, 17.29)          | 2.38 (1.15, 5.83)                 |
| CRP, mg/L, median (IQR) |               |                             |                                   |
| Range                 | 174.3 (94.4, 250.6)   | 156 (94.2, 329.6)           | 176.7 (99.5, 246.2)               |
| Ferritin, µg/L, median (IQR) |           |                             |                                   |
| Range                 | 1146 (753, 2422)      | 1153 (793, 1884)            | 1074 (661, 2470)                  |
| LDH, IU/L, median (IQR) |              |                             |                                   |
| Range                 | 607 (502, 765)        | 563 (382, 708)              | 611 (522, 805)                    |
| Tocilizumab dose, mean, mg (SD) |           |                             |                                   |
|                       | 724 (115)             | 700 (157)                   | 733 (95)                          |
| Tocilizumab dose, mean, mg/kg (SD) |         |                             |                                   |
|                       | 7.4 (1.4)             | 7.5 (1.7)                   | 7.4 (1.2)                         |
| Days from admission to dose, mean (SD) |     |                             |                                   |
|                       | 3.7 (2.9)             | 3.7 (3.2)                   | 3.8 (2.8)                         |
| Received glucocorticoids, n (%) |               |                             |                                   |
|                       | 44 (66.7)             | 10 (55.6)                   | 34 (70.1)                         |
| Received hydroxychloroquine, n (%) |       |                             |                                   |
|                       | 55 (83.3)             | 11 (61.1)                   | 44 (91.7)                         |

Abbreviations: BiPAP, bilevel positive airway pressure; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase.
with varying degrees of illness. Overall, 47% of their patients were critically ill, however they did not report on patients’ baseline oxygenation requirements. They reported outcomes 7 days post-tocilizumab. Of their patients, three died by day seven, two had disease aggravation, nine were clinically stable, and one had clinical improvement. Toniati et al reported on the outcomes of 100 patients with COVID-19 and hyperinflammatory syndrome. They reported that 77% of patients had improvement in the Brescia COVID-19 Respiratory Severity Scale (BCRSS) 10 days after tocilizumab. Baseline ventilation status was not reported, but patients had a relatively low average BCRSS score of 3. Colaneri et al reported on outcomes of 21 patients with COVID-19 and found that treatment with tocilizumab did not significantly affect admission to an intensive care unit or 7-day mortality when compared with standard of care treatment. The current study identified patients that worsened or died beyond 7 days, indicating that five or 7 days may be inadequate to assess for clinical outcome in COVID-19 as a result of tocilizumab. This study reports clinical outcomes and changes in oxygenation status at multiple time points up to 14 days post-tocilizumab, and mortality and clinical improvement through 28 days.

In all studies including this one, most patients received a single dose of tocilizumab. However, patients in each of the previously described reports could have received up to three doses if there was insufficient clinical response as determined by their prescriber. The protocol used in the patients of this study targeted a dose of 8 mg/kg, and the majority of patients received a dose of 800 mg. The mean time from admission to tocilizumab dose was 3.7 days. This is the same regimen used in the reports by Toniati et al and Colaneri et al. Toniati et al gave tocilizumab on average, 5 days after admission. Alattar et al used a median dose of 5.7 mg/kg/dose, and reported a median time of 1 day from intensive care unit (ICU) admission to tocilizumab dose, and 1 day from hospital admission to ICU admission. Luo et al used lower doses of tocilizumab (80-600 mg per dose), and Xu et al targeted a dose of four to eight mg/kg per dose. Neither Luo et al, Xu et al, or Colaneri et al reported on the timing from hospital admission to tocilizumab dose.

### TABLE 2 Clinical improvement 7 d post-tocilizumab by baseline oxygenation category

| Category on ordinal scale: | Invasive ventilation (n = 18) | Noninvasive oxygen support (n = 48) | Low-flow O₂ (n = 27) | Ambient air (n = 4) | All patients (n = 66) |
|---------------------------|-------------------------------|----------------------------------|---------------------|-------------------|----------------------|
| Death                     | 6                             | 1 (5.5)                          | ...                 | ...               | ...                  |
| Invasive                  | 5                             | 13 (72.2)                        | 4 (23.5)            | 9 (33.3)          | ...                  |
| Noninvasive               | 4                             | ...                              | 4 (23.5)            | 4 (14.8)          | ...                  |
| Low-flow O₂               | 3                             | 2 (11.1)                         | 2 (11.8)            | 7 (25.9)          | ...                  |
| Ambient Air               | 2                             | 1 (5.8)                          | 1 (37)              | ...               | ...                  |
| Discharged                | 1                             | 2 (11.1)                         | 3 (1.8)             | 2 (7.4)           | ...                  |
| Transferred               | ...                           | 3 (17.6)                         | 1 (3.7)             | 1 (25)            | ...                  |
| Clinical improvement      | 4 (22.2%)                     | 4 (23.5%)                        | 2 (7.4%)            | 0 (0%)            | 10 (15.2%)           |

Total for noninvasive group: 6 (12.5%)

Bold values significance $P = .442$ vs. invasive group.

![FIGURE 1](image-url) Kaplan-Meier curves for (A) 28-day survival and (B) 28-day clinical improvement
These varying dosage regimens make it difficult to compare these studies and to evaluate the impact of this treatment.

The cohort presented here had the highest mortality rate compared with the other published report. A greater proportion of patients in this study were on invasive ventilation at baseline, and there were high rates of hypertension and/or diabetes, known risk factors for mortality in adult patients with COVID-19. The patients in this study were largely of black race with a high incidence of obesity. Obesity has also been associated with increased COVID-19 disease severity and need for intensive care treatment.

![Comparison of clinical status over time by baseline oxygenation status](image1)

**FIGURE 2** Comparison of clinical status over time by baseline oxygenation status. Definitions: clinical improvement (decrease two or more points on the ordinal scale), improved oxygenation (decrease one point on the ordinal scale), worsened oxygenation (increase one or more points on the ordinal scale, excluding death)

![Changes in inflammatory markers from baseline to 7 days post-tocilizumab](image2)

**FIGURE 3** Changes in inflammatory markers from baseline to 7 days post-tocilizumab. Median, interquartile range, and range of inflammatory markers of patients that had evaluable levels at baseline and post-tocilizumab day-7. CRP, c-reactive protein; LDH, lactate dehydrogenase
hypothesis at baseline was 74% and the rate of diabetes was 42%. Patient populations in previous studies reported rates of hypertension ranging from 43% to 60% and rates of diabetes ranging from 24% to 48%.\(^{3,11-13}\) The median D-dimer level in the current cohort was greater than 1 mg/L, which has been associated with increased mortality in patients with COVID-19.\(^{10}\) Xu et al reported a baseline D-dimer of 0.8 mg/L and Toniati et al reported a baseline D-dimer of 0.5 mg/L, while Alattar et al, Luo et al, and Colaneri et al did not report baseline D-dimer levels.\(^{3,11-14}\)

Given the association of elevated IL-6 and inflammatory marker levels with COVID-19 disease severity, and the mechanism of tocilizumab as an IL-6 receptor antagonist, assessment of these laboratory values before and during therapy is reasonable. Luo et al\(^{11}\) found a reduction of IL-6 and CRP levels in their patients 7 days after treatment with tocilizumab. Xu et al did not find a reduction of IL-6 levels in the 5 days post dose.\(^{11}\) Alattar et al\(^{21}\) reported a decrease in CRP by day seven, but not did not report IL-6 levels. Ten days after tocilizumab administration, Toniati et al\(^{13}\) reported a decrease in CRP, fibrinogen and ferritin levels towards a normal range, however, D-dimer and IL-6 levels increased in both improved and worsened patients. This suggests that not all inflammatory markers may be reduced by IL-6 antagonism. This study observed a 95% reduction in CRP levels from baseline in the 29 patients that had evaluable levels at baseline and 7 days post-tocilizumab, but levels of D-dimer, ferritin and LDH seemed relatively unchanged. In an analysis by overall clinical outcome, patients had similarly elevated baseline D-dimer, ferritin, CRP, and LDH, regardless of their ultimate clinical status. IL-6 levels were not collected in this study due to the inability for the laboratory to measure these, and the turnaround time for results from an external laboratory would limit the result's utility in patient care.

The main limitation of this study was that it was an observational, retrospective study that lacked a randomized control group. Additional limitations include a small sample size, which make it difficult to draw clear conclusions regarding the efficacy of tocilizumab. Per the treatment protocol, inclusion criteria for administration of tocilizumab was very broad, and included patients with severe COVID-19 and elevated D-dimer levels. This may have contributed to a selection bias towards patients with severe or advanced illness. Approximately two-thirds of patients received glucocorticoids and 83.3% received hydroxychloroquine. While the benefit of these agents in COVID-19 is still a matter of debate, there is potential confounding from concomitant application of multiple interventions. Routine laboratory monitoring was not included in the treatment protocol. This led to inconsistencies in the timing of laboratory orders, making it difficult to determine what impact tocilizumab may have had on inflammatory markers. Emerging literature has shown an association with elevated D-dimer levels and thrombotic events in patients with COVID-19, however, this was not evaluated in this study.\(^{20}\) Lastly, this study did not assess for adverse drug reactions such as serious infections, which have been reported with tocilizumab use.\(^{3,15,21}\) A study by Campochiaro et al reported serious adverse events in 25% patients who received tocilizumab. Bacteremia was reported in 13% of patients in the tocilizumab group.\(^{15}\) A study in 51 patients by Morena et al\(^{21}\) reported adverse events that included an increase in hepatic enzymes of at least three times above the normal range (29%), thrombocytopenia (14%), and bacteremia (27%).

This study observed limited clinical improvement in patients that received tocilizumab in the setting of severe COVID-19. This study did not identify a difference in outcomes between patients who were on mechanical ventilation at baseline or noninvasive oxygen support. Given the paucity of supporting clinical evidence, tocilizumab may be best reserved for use in a randomized clinical trial, a recommendation supported by recently published practice guidelines.\(^{7-9}\)

ACKNOWLEDGMENTS
The authors thank Travis Reinaker, PharmD, BCPS, BCCCP, Jennifer Vidal, PharmD, BCPS, for their critical review of this manuscript.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.
AUTHOR CONTRIBUTIONS
SH contributed to literature search, study design, data collection, data analysis, data interpretation, and writing. CM contributed to literature search, data collection, data analysis, and writing. VC contributed to literature search, data collection, data analysis, statistical analysis, and writing. JK contributed to literature search, study design, data collection, data analysis, statistical analysis, data interpretation, and writing.

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How to cite this article: Knorr JP, Colomy V, Mauriello CM, Ha S. Tocilizumab in patients with severe COVID-19: A single-center observational analysis. J Med Virol. 2020;92:2813-2820. https://doi.org/10.1002/jmv.26191