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Tocilizumab in the treatment of critical COVID-19 pneumonia: A retrospective cohort study of mechanically ventilated patients

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ABSTRACT

Objectives: The purpose of this study is to evaluate clinical outcomes in patients with critical COVID-19 pneumonia requiring invasive mechanical ventilation who were treated with tocilizumab
Design: Single-center retrospective cohort study
Setting: Stony Brook University Hospital, a 600-bed academic tertiary medical center in Suffolk County, New York
Participants: Consecutive patients with COVID-19 confirmed by nasopharyngeal polymerase chain reaction (PCR) who were admitted to Stony Brook University Hospital between March 10 and April 2 2020 and required mechanical ventilation in any intensive care unit during their hospitalization
Exposure: Treatment with tocilizumab while intubated
Main Outcome: Overall mortality 30 days from the date of intubation
Results: Forty-five patients received tocilizumab compared to seventy controls. Baseline demographic characteristics, inflammatory markers, treatment with corticosteroids, and sequential organ failure assessment (SOFA) scores were similar between the two cohorts. Patients who received tocilizumab had significantly lower Charlson co-morbidity index (2.0 vs 3.0,P = 0.01) than controls. There was a trend towards younger mean age in the tocilizumab exposed group (56.2 vs 60.6; P = 0.09). In logistic regression analysis there was no reduction in mortality associated with receipt of tocilizumab (odds ratio (OR) 1.04; 95% CI, 0.27–3.75). There was no observed increased risk of secondary infection in patients given tocilizumab (28.9 vs 25.7; OR 1.17; 95% CI, 0.51–2.71).
Conclusion: When controlling for age, severity of illness, and co-morbidities, tocilizumab was not associated with reduction in mortality in this retrospective cohort study of mechanically ventilated patients with COVID-19 pneumonia. Further studies are needed to determine the role of tocilizumab in the treatment of COVID-19.

Introduction

The spectrum of disease manifested by COVID-19 ranges from asymptomatic infection to severe pneumonia leading to acute respiratory distress syndrome with a high mortality rate (Guan et al., 2020). While the pathophysiology of COVID-19 remains a subject of ongoing investigation, it has been apparent since the early stages of the pandemic that elevated levels of pro-inflammatory cytokines such as interleukin-6 contribute to the development of more severe disease and confer a worse prognosis (Ruan et al., 2020; Chen et al., 2020; Zhang et al., 2020). This has led to speculation about the potential role of immunomodulatory therapies, including those aimed at blocking the interleukin-6 signaling pathway, in patients with severe COVID-19 (Zhang et al., 2020; Ye et al., 2020; Xu et al., 2020; Gritti et al., 2020).

Tocilizumab is a monoclonal antibody that binds to the interleukin-6 receptor. It has been approved by the US Food and Drug Administration for the treatment of autoimmune diseases such as rheumatoid arthritis and for chimeric antigen receptor (CAR) T cell-induced severe or life threatening cytokine release syndrome. Although there have been emerging anecdotal reports and observational studies supporting the off-label use of tocilizumab in COVID-19 with positive results, the efficacy of such therapy remains an unsettled question demanding further

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evidence (Xu et al., 2020; Roumier et al., 2020; Somers et al., 2020; Biran et al., 2020; Sinha et al., 2020).

Methods

In this retrospective, single center observational study, consecutive patients with COVID-19 pneumonia confirmed by nasal swab PCR for SARS-CoV-2 who were admitted to Stony Brook University Hospital in Suffolk County, New York between March 10 and April 2 2020, and required invasive mechanical ventilation in any intensive care unit during their hospitalization were included for analysis. Patients who received tocilizumab while intubated were compared to a contemporaneous cohort of COVID-19 patients requiring invasive mechanical ventilation who received standard hospital protocol. The study was approved by the institutional review board at Stony Brook University.

According to our institution's COVID-19 treatment protocol, patients were eligible to receive a standardized 400 mg dose of tocilizumab if they required respiratory support in the form of high-flow nasal cannula or higher. The decision to administer tocilizumab was made by the primary healthcare provider in consultation with the infectious disease service, often in the context of evaluating signs and symptoms indicative of cytokine release syndrome such as high fever and elevation in inflammatory markers. Patients could have received a second dose after 24 h if there was a perceived lack of response to the initial dose. A total of 54 doses of tocilizumab were available to the hospital during the time period from March 10 to April 2 2020.

Patient data was extracted from the electronic medical record for analysis. Baseline characteristics including age, sex, race, body mass index (BMI), maximum temperature on day of intubation, baseline C-reactive protein (CRP) and ferritin on day of intubation, baseline interleukin-6 during hospitalization, sequential organ failure assessment (SOFA) score within 24 h of intubation, Charlson co-morbidity index (CCI), and treatment with corticosteroids, as well as clinical outcomes including patient mortality, date of extubation, discharge from hospital, and microbiologic culture data, were collected.

The primary outcome assessed was mortality within 30 days of intubation. A multivariate analysis including the independent variables age, sex, BMI, SOFA score, CCI, interleukin-6 level, CRP, ferritin, corticosteroid treatment, and tocilizumab treatment was performed for the dependent outcome of mortality within 30 days of intubation. Secondary outcomes assessed were extubation within 14 days of intubation, secondary infection within 14 days of intubation, and discharge from the hospital within 30 days of intubation. Secondary infection was defined as a positive culture for bacterial or fungal pathogen that was deemed by the primary provider to represent infection rather than colonization.

Statistical analysis was conducted in SAS v9.4 (SAS Institute, Inc., Cary, NC). Chi-square, Fisher Exact, Independent *t* test and Wilcoxon Rank sum tests were used to complete the descriptive analyses depending on normality. Binary logistic regression was used for multivariate analyses with dichotomous outcomes.

Results

A total of 115 patients admitted between March 10 and April 2 2020 required mechanical ventilation, during which time 45 patients received tocilizumab. The mean dose of tocilizumab administered was 4.8 mg/kg, including three patients for whom a second dose was given; mean time from intubation to treatment was 2.5 days.

Those who received tocilizumab had significantly lower median CCI (2.0 vs 3.0; $P = 0.01$) and higher mean temperature on the date of intubation (38.7 °C vs 38.2 °C; $P = 0.004$) than controls. There was a trend towards younger age (mean 56.2 vs 60.6; $P = 0.09$) of those treated. There were no significant differences in baseline interleukin-6 level, CRP, ferritin, or SOFA score within 24 h of intubation between the two groups (Table 1).

Treated patients experienced a 0.5 °C reduction in maximum temperature on average in the 24–72 hour period after receiving tocilizumab. CRP decreased by 88% from baseline within 7 days of treatment (Supplemental Table 1).

For the primary outcome, 13 out of 45 patients (29%) who received tocilizumab and 28 out 70 controls (40%) died within 30 days of intubation (OR 0.61; 95% CI, 0.27–1.36). The median time to death was 15 days for those receiving tocilizumab compared to 13 days for controls ($P = 0.84$). After controlling for age, sex, BMI, SOFA score, CCI, baseline interleukin-6, CRP, ferritin, and corticosteroid therapy, treatment with tocilizumab was not associated with lower mortality within 30 days of intubation (OR 1.04; 95% CI, 0.27–3.75).

In univariate analyses of the secondary outcomes, there was no difference in the proportion of patients extubated at fourteen days (44.4 vs 34.2; OR 1.53; 95% CI, 0.71–3.30). The median time to extubation in the tocilizumab group was 10 days compared to 10.5 days for controls ($P = 0.86$). There was no significant difference in hospital discharge at 30 days (44.4 vs 35.7; OR 1.44; 95% CI,

Table 1
Patient Demographics and Baseline Characteristics.

	Tocilizumab (n = 45)	Controls (n = 70)	P-value
Mean age – yr (SD)	56.2 (14.7)	60.6 (13.4)	0.09
Male – no (%)	29 (64.4)	51 (72.9)	0.34
Race – no (%) White non-Hispanic	19 (42.2)	33 (47.1)	0.44
Hispanic	20 (44.4)	27 (38.6)	
Black	3 (6.7)	3 (4.3)	
Asian	3 (6.7)	11 (15.7)	
Mean BMI – kg/m^2 (SD)	30.7 (5.3)	31.3 (6.9)	0.58
Tmax on day of intubation– degree C, mean (SD)	38.7 (0.82)	38.2 (0.89)	0.004
C-reactive protein on day of intubation – mg/dL, median (IQR)	19.5 (15.7)	17.6 (18.0)	0.81
Ferritin on day of intubation – ng/mL, median (IQR)	1507 (1518)	1462[a] (1435)	0.90
Interleukin-6 baseline – pg/mL, median (IQR)	81.6 (99.4)	92.3[b] (131.5)	0.66
Corticosteroid treatment – no (%)	33 (73.3)	55 (78.6)	0.52
Hydroxychloroquine treatment– no (%)	43 (95.6)	65 (92.9)	0.70
SOFA score within 24 h intubation, median (IQR)	6.0 (3.0)	6.0 (3.0)	0.36
Charlson Comorbidity Index, median (IQR)	2.0 (3.0)	3.0 (3.0)	0.01

[a] n = 68;
[b] n = 56.

Table 2
Primary and Secondary Outcomes.

	Tocilizumab (n = 45)	Controls (n = 70)	OR (95% CI)	P-value
Death within 30 days – no (%)	13 (28.9)	28 (40.0)	0.61 (0.27–1.36)	0.23
Extubation within 14 days – no (%)	20 (44.4)	24 (34.2)	1.53 (0.71–3.30)	0.28
Discharged within 30 days – no (%)	20 (44.4)	25 (35.7)	1.44 (0.67–3.09)	0.35
Secondary infection – no (%)	13 (28.9)	18 (25.7)	1.17 (0.51–2.71)	0.71

0.67–3.09). There was no observed increased risk of secondary infection within 14 days of treatment with tocilizumab (28.9 vs 25.7; OR 1.1736; 95% CI, 0.507–2.714) (Table 2).

Interleukin-6 levels were obtained in 101 out of 115 patients, of which 97 were obtained within 48 h of intubation. The median interleukin-6 level in the study population was 82.6 pg/mL, with a median level of 81.6 pg/mL in the tocilizumab exposed group and 92.3 pg/dL in the controls. In all study patients for whom an interleukin-6 was obtained, there was a significantly increased risk of death associated with interleukin-6 level greater than 90 pg/mL (relative risk 1.70; 95% CI, 1.16–2.49) (Supplemental Table 3). However, among the 49 patients with interleukin-6 greater than 90 pg/mL, there was no difference in 30-day mortality between those who received tocilizumab and controls (50.0 vs 48.3; P = 0.91), or in extubation within 14 days (25.0 vs 37.9; P = 0.34) or discharge from the hospital in 30 days (30.0 vs 27.5; P = 0.57) (Supplemental Table 2).

Discussion

In this retrospective study, tocilizumab was not associated with lower mortality in mechanically ventilated patients with COVID-19 pneumonia. Patients who were selected to receive tocilizumab were more likely to be younger, presented with higher fever on the day of intubation, and had significantly fewer comorbidities than controls. While the mortality rate was numerically lower in the tocilizumab group, this was not found to be significant in a multivariate analysis accounting for baseline differences in the study cohorts. Furthermore, while elevated interleukin-6 levels were associated with higher mortality risk, treatment with tocilizumab did not reduce mortality in this subset of patients. Further research is required to determine the optimal timing and patient population that will most benefit from this intervention.

As was first reported by Xu et al., patients in our study experienced a significant reduction in fever and inflammatory markers in the days following tocilizumab administration (Xu et al., 2020). However, this did not appear to translate to significant improvement in overall clinical outcomes when compared to controls.

Our findings contrast with those of two recently published retrospective studies by Somers et al. and Biran et al. suggesting decreased mortality associated with the use of tocilizumab in critical COVID-19. In their unadjusted cohorts, as in ours, patients who received tocilizumab differed significantly from their untreated counterparts in terms of younger age and lower frequency of co-morbidities. One important difference in our study is that a majority of patients, 77% overall, were concurrently treated with corticosteroids, which has been demonstrated to reduce mortality in severe and critical COVID-19 in a prospective, randomized controlled trial (RECOVERY Collaborative Group et al., 2020). By comparison, only 25% and 43% of patients in the aforementioned studies received steroids. It is possible that the high prevalence of corticosteroid use in our patient population may have obscured any further benefit derived from additional immunomodulatory therapy.

An important limitation of any retrospective study is the inherent inability to perfectly control for all known or unknown confounders. Our study is further limited by its relatively small size which was insufficiently powered to detect small differences in the primary and secondary outcomes. Nevertheless, given the still evolving body of evidence, our study is a valuable contribution to the scientific discussion regarding this therapy. Ongoing randomized controlled trials are needed to clarify the role of tocilizumab in the treatment of COVID-19.

Declaration of interest

The authors declare no conflicts of interest.

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Ethical approval

This study was approved by the Institutional Review Board of Stony Brook University.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2020.12.021.

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