Tocilizumab in the Treatment of Critical COVID-19 Pneumonia

Matthew Fisher MD, Luis Marcos Raymundo MD, Melinda Monteforte PharmD,
Erin Taub MPH, Roderick Go DO

Department of Internal Medicine, Division of Infectious Diseases Stony Brook University Hospital

Stony Brook Medicine

Background

- Patients with severe COVID-19 have been observed to have elevated levels of pro-inflammatory cytokines including interleukin-6. It has been postulated that these cytokines may contribute to the pathophysiology of severe COVID-19
- The anti-interleukin-6 receptor monoclonal antibody tocilizumab has been proposed as a treatment for severe COVID-19 pneumonia although the efficacy remains unknown
- 115 patients admitted to our hospital with COVID-19 between March 10th and April 2nd 2020 would ultimately require mechanical ventilation, of whom 45 received tocilizumab as an off-label use

Objective

- Evaluate clinical outcomes in patients with critical COVID-19 pneumonia requiring invasive mechanical ventilation who were treated with tocilizumab

Methods

- Patients with COVID-19 confirmed by nasal swab PCR for SARS-CoV-2 who were admitted to Stony Brook University Hospital in Suffolk County, New York between March 10th and April 2nd and underwent mechanical ventilation in any intensive care unit were retrospectively analyzed from data available in the electronic medical record
- Baseline characteristics and clinical outcomes were compared between those who received at least one 400mg dose of tocilizumab and controls. Median follow up was 28 days.
- A multivariate analysis including the independent variables age, sex, BMI, SOFA score, Charlson co-morbidity index, interleukin-6 level, corticosteroid treatment, and tocilizumab treatment was performed for the dependent outcome of mortality

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/African American	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 day of intubation – degree C, mean (SD)	38.7 (0.82)	38.2 (0.89)	0.004
C-reactive protein day of intubation – mg/dL, median (IQR)	19.5 (15.7)	17.6 (18.0)	0.81
Ferritin 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, median (IQR)	5.0 (3.0)	5.0 (5.0)	0.35
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% C.I.)	P-value
Extubation in 14 days – no (%)	20 (44.4)	24 (34.2)	1.53 (0.71-3.3)	0.28
Discharged – no (%)	23 (51.1)	28 (40.0)	1.57 (0.73-3.34)	0.24
Death – no (%)	14 (31.1)	29 (41.4)	0.64 (0.29-1.44)	0.27
Secondary infection – no (%)	13 (28.9)	18 (25.7)	1.17 (0.5-2.71)	0.71

References

1. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020 Jun;80(6):607-613.
2. Zhang C, Wu Z, Li J, Zhao H, Wang G. The cytokine release syndrome (CRS) of severe COVID-19 and Interleukin-6 receptor (IL-6R) antagonist Tocilizumab may be the key to reduce the mortality *Int J Antimicrob Agents*. 2020
3. Xu X, Han M, Li T, *et al*. Effective Treatment of Severe COVID-19 patients with Tocilizumab. Proc Natl Acad Sci U S A. Apr 29 2020.

Results

- Forty-five patients received tocilizumab compared to seventy controls
- Baseline demographic characteristics, inflammatory markers, interleukin-6 level, SOFA score, and corticosteroid treatment were similar between the two cohorts (Table 1)
- Patients who received tocilizumab had significantly *fewer* co-morbidities than controls (p = 0.01)
- There was no significant association between receipt of tocilizumab and the rate of extubation within fourteen days (44.4 percent versus 34.2 percent; OR = 1.53, 95% C.I. 0.71 – 3.3), discharge from hospital (51.1 percent versus 40.0 percent; OR = 1.57, 95% C.I. 0.73 – 3.34), or mortality (31.1 percent versus 41.4 percent; OR = 0.64, 95% C.I. 0.29 – 1.4) (Table 2)
- In multivariate analysis, there was no reduction in mortality associated with receipt of tocilizumab (OR 1.40, 95% C.I. 0.46 – 4.22)
- The median interleukin-6 level was 89.4 pg/mL. IL-6 level above 90 was significantly associated with increased risk of death (RR 1.7, 95% C.I. 1.2 – 2.3)
- Among 49 patients with interleukin-6 greater than 90 pg/mL, there was no difference in mortality between those who received tocilizumab and controls (55.0 percent versus 48.3 percent, p = 0.64)
- Patients administered tocilizumab within two days of intubation had increased likelihood of extubation within fourteen days compared to those who were treated later (OR = 3.50, 95% C.I. 1.01 – 12.18).

Conclusions

- Tocilizumab was not associated with reduced mortality in COVID-19 patients requiring mechanical ventilation, including those with elevated levels of interleukin-6
- Further studies are needed to determine whether earlier treatment may result in improved outcomes