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562. Tocilizumab for the Treatment of Severe COVID-19: A Retrospective, Multi-Center, Case-Matched Series

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Session: P-21. COVID-19 Treatment

Background: At the time of this writing, there is no FDA approved medication for the treatment of COVID-19. One medication currently under investigation for COVID-19 treatment is tocilizumab, an interleukin-6 (IL-6) inhibitor. It has been shown there are increased levels of cytokines including IL-6 in severe COVID-19 hospitalized patients attributed to cytokine release syndrome (CRS). Therefore, inhibition of IL-6 receptors may lead to a reduction in cytokines and prevent progression of CRS. The purpose of this retrospective study is to utilize a case-matched design to investigate clinical outcomes associated with the use of tocilizumab in severe COVID-19 hospitalized patients.

Methods: This was a retrospective, multi-center, case-matched series matched 1:1 on age, BMI, and days since symptom onset. Inclusion criteria included ≥ 18 years of age, laboratory confirmed positive SARS-CoV-2 result, admitted to a community hospital from March 1st – May 8th, 2020, and received tocilizumab while admitted. The primary outcome was in-hospital mortality. Secondary outcomes included hospital length of stay, total mechanical ventilation days, mechanical ventilation mortality, and incidence of secondary bacterial or fungal infections.

Results: The following results are presented as tocilizumab vs control respectively. The primary outcome of in-hospital mortality for tocilizumab (n=26) vs control (n=26) was 10 (38%) vs 11 (42%) patients, p=0.777. The median hospital length of stay for tocilizumab vs control was 14 vs 11 days, p=0.275. The median days of mechanical ventilation for tocilizumab (n=21) vs control (n=15) was 8 vs 7 days, p=0.139, and the mechanical ventilation mortality was 10 (48%) vs 9 (60%) patients, p=0.463. In the tocilizumab group, for those expired (n=10) vs alive (n=16), 10 (100%) vs 7 (50%) patients respectively had a peak ferritin > 600 ng/mL, and 6 (60%) vs 8 (50%) patients had a peak D-dimer > 2,000 ng/mL. The incidence of secondary bacterial or fungal infections within 7 days of tocilizumab administration occurred in 5 (19%) patients.

Conclusion: These findings suggest that tocilizumab may be a beneficial treatment modality for severe COVID-19 patients. Larger, prospective, placebo-controlled trials are needed to further validate results.

Disclosures: Christian Cheatham, PharmD, BCIDP, Antimicrobial Resistance Solutions (Shareholder)

563. Tocilizumab in the Treatment of Critical COVID-19 Pneumonia

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Session: P-21. COVID-19 Treatment

Background: The anti-interleukin-6 receptor monoclonal antibody tocilizumab has been proposed as a treatment for COVID-19 pneumonia although the efficacy remains unknown.

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 received tocilizumab while undergoing 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 to mechanically ventilated patients admitted during the same time period who received standard hospital protocol.

Results: Forty-five patients received tocilizumab compared to seventy controls. Mean dose of tocilizumab given was 4.8mg/kg and mean time to receipt from initial intubation was 2.5 days. Baseline demographic characteristics, inflammatory markers, treatment with corticosteroids, and SOFA scores were similar between the two cohorts (Table 1). Patients who received tocilizumab had significantly lower Charlson co-morbidity index (2.0 versus 3.0, p = 0.01) and higher temperature (38.7 C versus 38.2 C, p = 0.004) than controls. 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 – 3.30), discharge from hospital (51.1 percent versus 40.0 percent; OR = 1.568, 95% C.I. 0.737 – 3.337), or mortality (31.1 percent versus 41.4 percent; OR = 0.639, 95% C.I. 0.290 – 1.4407) (Table 2). Patients who were 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). There was no observed increased risk of secondary infection in patients given tocilizumab (28.9 versus 25.7, OR = 1.1736, 95% C.I. = 0.507 – 2.714).

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)	0.0935
Male – no (%)	29 (64.4)	51 (72.9)	0.3386
Race – no (%) White non-Hispanic	19 (42.2)	33 (47.1)	0.4416
Hispanic	20 (44.4)	27 (38.6)	
Black/AA	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)	0.5820
Tmax on ICU admission – degree C, mean (SD)	38.7 (0.82)	38.2 (0.89)	0.0042
C-reactive protein on ICU admission – mg/dL, median (IQR)	19.5 (15.7)	17.6 (18.0)	0.8120
Ferritin baseline – ng/mL, median (IQR)	1507 (1518)	1462[a] (1435)	0.8950
Interleukin-6 baseline – pg/mL, median (IQR)	81.6 (99.4)	92.3[b] (131.5)	0.6569
Corticosteroid treatment – no (%)	33 (73.3)	55 (78.6)	0.5178
Hydroxychloroquine treatment– no (%)	43 (95.6)	65 (92.9)	0.7030
SOFA score, median (IQR)	5.0 (3.0)	5.0 (5.0)	0.3539
Charlson Comorbidity Index, median (IQR)	2.0 (3.0)	3.0 (3.0)	0.0141

a) n = 68; b) n = 56

Table 2: Primary Outcomes

	Tocilizumab (n=45)	Controls (n=70)	OR (95% C.I.)	P-value
Extubation in 14 days – no (%)	20 (44.4)	24 (34.2)	1.533 (0.712-3.304)	0.2751
Discharged – no (%)	23 (51.1)	28 (40.0)	1.568 (0.737-3.337)	0.2429
Death – no (%)	14 (31.1)	29 (41.4)	0.639 (0.290-1.4407)	0.2658
Secondary infection – no (%)	13 (28.9)	18 (25.7)	1.1736 (0.507-2.714)	0.7081

Conclusion: Tocilizumab was not associated with a significant improvement in rate of extubation, hospital discharge, or reduction in mortality in this retrospective cohort study of mechanically ventilated patients with COVID-19 pneumonia. Further studies are needed to determine whether earlier treatment may result in improved outcomes.

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564. Tocilizumab Induces Rapid, Sustained Improvement of Inflammatory Markers in COVID-19.

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Session: P-21. COVID-19 Treatment

Background: Frequent observation of increasing fever and rising inflammatory markers late after onset of COVID-19 suggests Cytokine Release Syndrome (CRS, "Cytokine Storm") may contribute to pathophysiology. Tocilizumab (TCZ), a monoclonal antibody targeting the receptor for the pro-inflammatory cytokine, IL-6, is effective in suppressing pathological inflammation in several rheumatological diseases. After administering TCZ to COVID-19 patients with suspected CRS, we observed a sharp fall in inflammatory indices. We analyzed this effect using results from the first 19 COVID-19 patients receiving TCZ at our hospital.

Methods: Data for all patients with confirmed COVID-19 who received TCZ at our center, a 200 bed community hospital in New England, were extracted from the Electronic Medical Record, including demographics, body temperature, C-Reactive Protein (CRP), IL-6 levels, clinical severity on the Ordinal Scale for Clinical Improvement (OSCI), and clinical outcome (recovery/discharge home, partial recovery/discharge rehab, death). Results were tabulated and statistical significance of changes in indices pre- and post- TCZ assessed by Wilcoxon Signed-Rank Test.

Results: 19 patients received TCZ: 16 got 400mg x1, 2 got 400 mg x2, 1 got 660 mg x1. Median age was 64 years (range: 44–94), 68% male. Mean interval from symptom onset to receiving TCZ was 11.5 days. Mean IL-6 was 145 pg/mL. Demographics, OSCI

scores, and discharge status are shown in Table 1. Average daily peak temperatures (T_{max}) pre- and post- TCZ were 100.7 and 98.9°F, p< 0.001. Mean CRP pre- and post- were 234 and 84.6 mg/L, p=0.001 (Fig.1). Decrease in T_{max} and CRP was rapid and sustained (Fig. 2, 1st 8 patients shown for clarity.). 58% had improved clinical improvement by OSCI by day 7, 68% by day 14. 7 of 19 of patients were discharged home, 6 to rehab or acute care facility, and 6 died.

Table 1: Patient Demographics, Clinical Severity Score, and Discharge Status

			Ordinal Scale for Clinical Improvement			
Patient	**Age - Sex**	**PMHx**	**TCZ day 0**	**Day 7**	**Day 14**	**Discharge status**
1	70 M	HT,HL,DM,CD	7	7	4	Rehab* day 19
2	67 M	None	7	6	6	Deceased day 24
3	58 M	HL	7	6	4	Home day 26
4	51 M	HT,HL,OB	7	4	3	Home day 24
5	62 M	CAD	7	7	7	Rehab day 27
6	66 M	HT	4	4	-	Home day 11
7	64 M	CD,DM,HT	7	8	8	Deceased day 3
8	84 M	HT,PD	3	-	-	Home day 6
9	45 M	None	4	2	-	Rehab day 5
10	44 M	SM	7	4	3	Home day 15
11	64 M	HT,AS	4	4	-	Home day 11
12	79 F	KD	4	8	8	Deceased day 1
13	56 M	HT,HL,OB	7	8	8	Deceased day 6
14	91 F	HT, HF	4	8	8	Deceased day 5
15	58 F	CD	7	6	6	Rehab day 20
16	46 M	None	4	3	-	Home day 7
17	86 F	HT	7	4	8	Deceased day 10
18	94 F	HT,HL,DM	4	-	-	Rehab day 3
19	53 F	HT,DM,OB	6	4	3	Rehab day 13

*Rehab (includes Skilled Nursing Facility, or Long Term Acute Care). AS=Asthma, CA=Cancer, CD=Cardiovascular Disease, DM=Diabetes, HF=Heart Failure, HT=Hypertension, HL=Hyperlipidemia, KD=Kidney Disease, OB=Obesity, PD=COPD, SM=Smoking

Figure 1 CRP and Tmax pre- and post- Tocilizumab

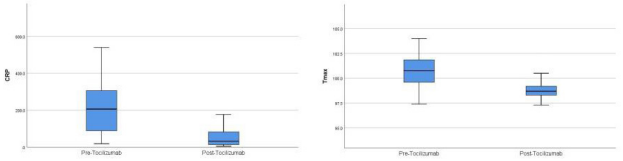
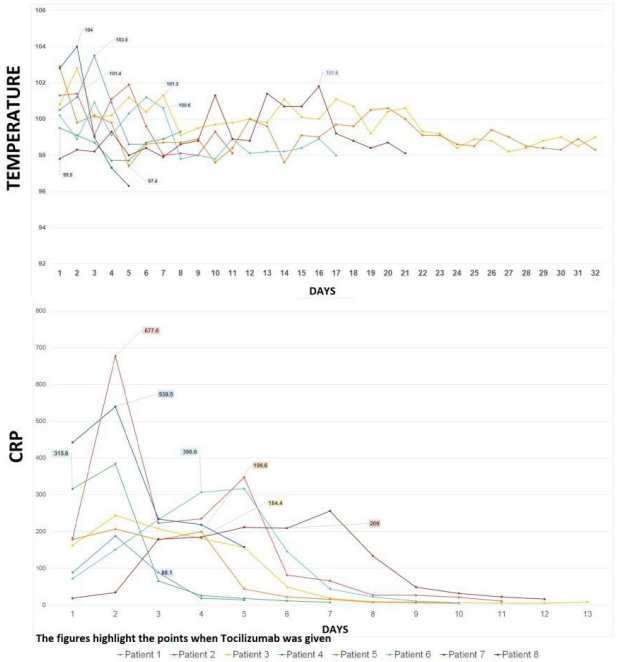


Figure 2: Time course of Temperature and CRP after Tocilizumab



Conclusion: In this cohort of patients with moderate-to-severe COVID-19 and evidence of Cytokine Release Syndrome, tocilizumab was associated with rapid resolution of fever and marked decline in CRP. Most patients showed improvement in clinical severity scores and no adverse reactions were noted. Tocilizumab may be useful in control of pathological inflammation in COVID-19. Controlled trials will be needed to assess overall clinical benefit.

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565. Tocilizumab Use in COVID-19: Act(emra) to Inhibit Intubation and Decompensation

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Session: P-21. COVID-19 Treatment

Background: Tocilizumab is an IL-6 receptor inhibitor that has been utilized for the prevention and treatment of the cytokine storm inflammatory reaction in COVID-19. The objectives of this analysis were to evaluate clinical outcomes of tocilizumab treatment in relation to respiratory status improvements and to analyze the association between initial inflammatory markers and treatment outcomes.

Methods: IRB approved retrospective chart review of adult patients with confirmed COVID-19 treated with tocilizumab from March- May 2020. Data collection focused on relevant past medical history, hematologic and inflammatory markers before and after tocilizumab administration, concomitant COVID-19 treatments, and disease outcomes such as mortality and discharge. Assessed baseline characteristics and treatment outcomes in patients who received tocilizumab prior to intubation versus after intubation, and evaluated for any significant markers of treatment success and failure.

Results: 84 patients were evaluated. Baseline characteristics did not vary between intubated and not intubated patients (Figure 1). Overall mortality in patients who received an IL-6 inhibitor was 43%. Mortality in patients who received IL-6 inhibitor when intubated (63%) compared to patients who were not intubated (26%) was significantly higher (p = 0.005). Patients with BMI's of 30 or above and patients with diabetes had a higher rate of treatment failure (p < 0.05) (Figure 2). Patients with IL-6 levels of 1000 or above had higher rates of treatment failure (p = 0.0001); however, given the small sample size larger studies are required for further analysis (Figure 3).

Baseline Characteristics by Respiratory Status Pre-Tocilizumab Administration

	Not Intubated (N=46)	Intubated (N=38)	P-value
Age (median)	59	55	0.26
Gender			
Male	70%	68%	0.91
Female	30%	32%	
Ethnicity			
Hispanic	65%	45%	0.06
Non-Hispanic	35%	55%	
Race			
Black	65%	61%	0.5
White	35%	39%	
Past medical history			
Hypertension	41%	44.7%	0.44
Diabetes	35%	34%	0.06
Asthma/COPD	19%	13%	0.79
BMI (kg/m²)	28.9	30.5	0.45
Baseline labs/vitals			
T-max (°F)	100.5	101.4	0.08
IL-6 (pg/mL)	116.5	233.5	0.08
CRP (mg/dL)	21.9	24.9	0.07