Early Clinical Outcomes with Tocilizumab for Covid-19: A Two-Center Retrospective Study

Steven Smoke, PharmD, BCPS, BCIDP[1]; Karan Raja, PharmD, BCPS, BCIDP[2]; Patrick Hilden, MS[1]; Nicole Daniel, PharmD[2]

1. Saint Barnabas Medical Center, Livingston, NJ; 2. Clara Maass Medical Center, Belleville, NJ

BACKGROUND

- Severe Covid-19 is associated with elevated inflammatory markers, consistent with cytokine release syndrome (CRS).
- Tocilizumab is an IL-6 inhibitor, effective in treating CRS secondary to CAR-T cell therapy.
- The efficacy of tocilizumab in treating Covid-19 is unknown.

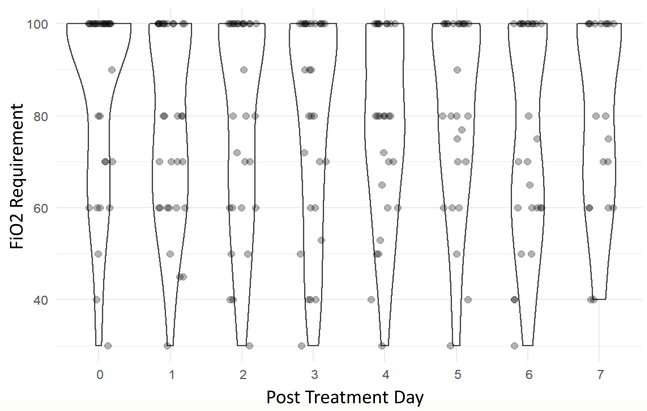
METHODOLOGY

- This was a retrospective cohort study conducted at two hospitals in northern New Jersey.
- All patients treated with tocilizumab for confirmed or suspected Covid-19 between the dates of 3/10/20 and 4/9/20 at the study sites were included.
- The primary endpoint was clinical improvement on day 7 after treatment as assessed by respiratory status.
- Univariate analysis compared data between those who improved and those who did not.

Table 1: Respiratory Status Assessment

Score	Respiratory Status
7	Death
6	Hospitalized, on invasive mechanical ventilation or ECMO
5	Hospitalized, on non-invasive ventilation or high flow oxygen devices
4	Hospitalized, requiring supplemental oxygen
3	Hospitalized, not requiring supplemental oxygen
2	Not hospitalized, limitation on activities
1	Not hospitalized, no limitations on activities

Figure 1: FiO2 Requirement by Post Treatment Day



RESULTS

- Forty five severe and critically ill patients treated with tocilizumab for Covid-19 were evaluated.
- Eleven (24%), 22 (49%) and 12 (27%) patients improved, had no change and worsened by day 7 after treatment, respectively.
- Lower WBC and LDH at the time of drug administration as well as shorter time from supplemental oxygen initiation to dose were significantly associated with clinical improvement in the univariate analysis.

Table 2: Pre-dose Characteristics

Variable (N[%], median [IQR])	Missing Data	Not Improved (n = 34)	Improved (n = 11)	p-value
No Vasopressor Use (pre-dose)		19 (70.4)	8 (29.6)	0.482
Vasopressor Use (pre-dose)		15 (83.3)	3 (16.7)	
Respiratory Rate (pre-dose, breaths per minute)		25.5 (22.0, 31.8)	25.0 (22.5, 29.5)	0.905
Heart Rate (pre-dose, beats per minute)		114.0 (104.2, 123.8)	107.0 (92.0, 115.5)	0.110
Temperature (pre-dose, F)		100.9 (100.0, 102.2)	100.7 (100.4, 102.2)	0.989
Neutrophils (admission, kcells/mm^3)		5.5 (4.4, 7.6)	7.4 (4.0, 9.8)	0.905
Lymphocytes (admission, kcells/mm^3)		0.8 (0.5, 1.2)	0.8 (0.5, 0.9)	0.730
Neutrophil to Lymphocyte Ratio (admission)		7.8 (5.0, 12.1)	8.2 (4.7, 14.5)	0.653
White Blood Cell (pre-dose, k/mm^3)		10.1 (8.3, 12.3)	8.1 (5.8, 9.4)	0.038
Platelets (pre-dose, k/mm^3)		249.0 (210.2, 358.5)	325.0 (207.0, 364.5)	0.812
Lymphocytes (pre-dose, k/mm^3)	5 (11.1)	0.8 (0.5, 1.4)	0.7 (0.6, 0.9)	0.696
Ferritin (pre-dose, mg/L)	18 (40)	1303.0 (684.6, 1777.0)	1397.0 (1066.8, 1922.8)	0.622
Creatinine (pre-dose, mg/dL)		1.0 (0.7, 2.3)	1.0 (0.9, 1.0)	0.682
Bilirubin (pre-dose, mg/dL)	5 (11.1)	0.6 (0.4, 1.1)	0.5 (0.4, 0.7)	0.549
Lactate Dehydrogenase (pre-dose, u/L)	21 (46.7)	599.0 (425.0, 684.5)	354.0 (320.0, 394.0)	0.015
C-reactive Protein (pre-dose, mg/dL)	21 (46.7)	20.3 (8.1, 27.5)	12.4 (10.7, 12.9)	0.251
Baseline Respiratory Status		6.0 (6.0, 6.0)	6.0 (4.5, 6.0)	0.136
Baseline Respiratory Status < 6		8 (61.5)	5 (38.5)	0.251
Baseline Respiratory Status = 6		26 (81.2)	6 (18.8)	
Time from Symptom Onset to Dose (days)		10.5 (7.0, 13.8)	13.0 (8.5, 15.5)	0.218
Time from Admission to Dose (hours)		116.4 (85.6, 170.8)	82.2 (38.5, 114.6)	0.055
Time from Admission to Intubation (hours)	10 (22.2)	87.8 (45.5, 121.9)	34.7 (23.4, 89.6)	0.146
Time from Initiation of Oxygen Supplementation to Dose (hours)	1 (2.2)	117.2 (88.4, 177.3)	80.7 (41.2, 115.4)	0.044
Time from initiation of High Flow Oxygen to Dose (hours)	6 (13.3)	93.8 (33.8, 113.2)	35.0 (28.9, 55.7)	0.123
Time from ARDS to Dose (hours)	14 (31.1)	87.3 (40.0, 107.6)	49.5 (32.3, 63.3)	0.091
Time from Intubation to Dose (hours)	16 (35.6)	60.0 (28.6, 93.8)	24.6 (11.7, 41.4)	0.114

Table 3: Baseline Characteristics

Variable (N[%], median [IQR])	Group	Not Improved (n = 34)	Improved (n = 11)	p-value
Site	Site 1	11 (78.6)	3 (21.4)	> 0.999
	Site 2	23 (74.2)	8 (25.8)	
Age (years)		57.0 (49.8, 63.8)	53.0 (44.5, 56.0)	0.149
Body Mass Index (kg/m^2)		29.5 (26.5, 36.1)	35.0 (28.6, 37.7)	0.457
Sex	F	15 (93.8)	1 (6.2)	0.067
	M	19 (65.5)	10 (34.5)	
End-Stage Renal Disease	No	33 (75.0)	11 (25.0)	> 0.999
	Yes	1 (100.0)	0	
Malignancy	No	32 (74.4)	11 (25.6)	> 0.999
	Yes	2 (100.0)	0	
Hypertension	No	14 (63.6)	8 (36.4)	0.141
	Yes	20 (87.0)	3 (13.0)	
Diabetes Mellitus	No	21 (67.7)	10 (32.3)	0.132
	Yes	13 (92.9)	1 (7.1)	
Heart Disease	No	30 (73.2)	11 (26.8)	0.558
	Yes	4 (100.0)	0	
Chronic Obstructive Pulmonary Disease	No	33 (75.0)	11 (25.0)	> 0.999
	Yes	1 (100.0)	0	
Asthma	No	33 (78.6)	9 (21.4)	0.143
	Yes	1 (33.3)	2 (66.7)	
Cumulative Tocilizumab Dose (mg/kg)		7.3 (6.2, 8.3)	7.1 (4.7, 7.8)	0.552
Redose	No	28 (75.7)	9 (24.3)	> 0.999
	Yes	6 (75.0)	2 (25.0)	
Corticosteroid Use	No	12 (66.7)	6 (33.3)	0.304
	Yes	22 (81.5)	5 (18.5)	

Discussion

- Without a comparator group, this cannot prove efficacy or lack thereof
- Note bias, any apparent differences between responders and non-responders may reflect severity of illness, not factors predictive of tocilizumab efficacy
- Lower predose WBC and LDH, as well as shorter time from supplemental O2 initiation to dose were significantly associated with clinical improvement in the univariate analysis
- Comorbidities, dose intensity, steroid use, vital signs and lab values prior to drug administration did not appear to predict response
- Note that high rates of missing data led to excluding fibrinogen, d-dimer, troponin, triglycerides, procalcitonin, and IL-6 levels from the analysis.
- Most timing variables trended towards lower values in those who responded (admit to dose, O2 to dose, high flow to dose, vent to dose), suggesting earlier administration may be more effective.

CONCLUSION

- Tocilizumab administration was associated with a low rate of clinical improvement within 7 days in this cohort of severe and critically ill patients with Covid-19.

Contact Information: Steven Smoke, PharmD; steven.smoke@rwjbh.org

Disclosures: The authors have no conflicts of interest to declare. There was no financial support for this project.