Real-world Experience Highlighting Tocilizumab Use in the Treatment of COVID-19

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Background

- The Food and Drug Administration issued an emergency use authorization for tocilizumab (TCZ) for treatment of COVID-19 in patients requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation in early 2021.[1]
- In January 2021, the University of Pennsylvania Health System (UPHS) COVID-19 Therapeutics Committee added TCZ to the treatment algorithm for COVID-19 given a favorable mortality benefit demonstrated in the REMAP-CAP trial.[2]
- Despite seeing positive results in other trials, there still remain unanswered questions surrounding the use of TCZ.[3]

Objectives

- The primary objective of this study is to characterize the efficacy and safety of TCZ for treatment of COVID-19 in a real world setting.
- Secondary objectives include providing detailed data regarding disposition status, adverse events, and steroid usage in TCZ patients.

Methods

- **Study Design:** retrospective, multicenter cohort study
- **Study Period**: January 29th, 2021 to June 30th, 2021
- **Population**: Any patient who received TCZ (8 mg/kg; max dose 800 mg once) for treatment of confirmed COVID-19 within five of the UPHS centers per UPHS COVID-19 Therapeutics guidance.

Figure 1: UPHS COVID-19 Therapeutics Guidance for TCZ Use

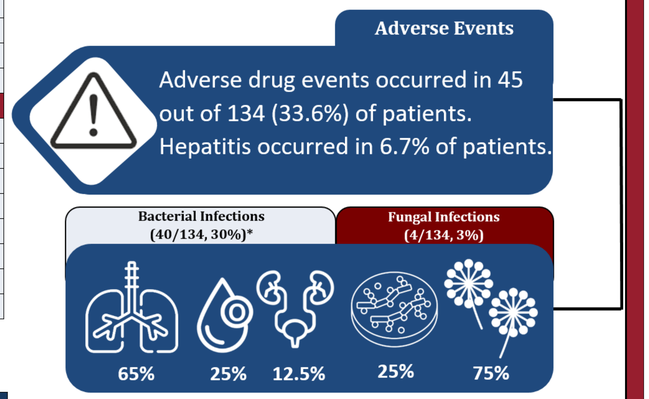
Inclusion Criteria	Exclusion Criteria
• <14 days of acute symptoms and <72 hours of hospitalization • Requiring high-flow nasal cannula with FiO2 ≥40%, non-invasive positive pressure ventilation, or mechanical ventilation • In intensive care unit (ICU), ICU eligible, and/or clinically deteriorating or high-risk of deterioration even if not in the ICU (as long as patient fits other inclusion criteria) • <24 hours of ICU/ICU eligible for severe respiratory failure due to COVID-19	• Platelets ≤50 • ALT and AST ≥3 times upper limit of normal

Results

Table 1: Baseline Characteristics	N=134
Male, n (%)	74 (55.2)
Age (years), mean (SD)	58.3 (15.5)
Body mass index (kg/m²), mean (SD)	33.9 (9.5)
TCZ	
Time from admission to order entry (hours), median (IQR)	22 (13.2 to 41.5)
Time from hospital admission to ICU admission (hours), median (IQR)	7.4 (4.3 to 23.3)
ICU at time of order entry, n (%)	102 (76.1)
WHO ordinal scale at time of TCZ order entry, n (%)	
5	117 (87.3)
6	7 (5.2)
7	10 (7.5)
Date of symptom onset documented, n (%)	100 (74.6)
Time from symptom onset to administration (days), mean (SD)	7.3 (2.7)
Vaccination status at time of TCZ order entry, n (%)	
Fully vaccinated	3 (2.2)
Partially vaccinated	12 (9)
Unvaccinated	104 (77.6)
Unknown	15 (11.2)
Comorbid conditions, n (%)	
Diabetes mellitus	46 (34.3)
Immunocompromised	19 (14.2)
Chronic kidney disease	18 (13.4)
Heart failure	18 (13.4)
Asthma	13 (9.7)
Chronic obstructive pulmonary disease	10 (7.5)
Cystic fibrosis	1 (1)
Liver cirrhosis	1 (1)

Table 3: Clinical Outcomes and Disposition	
Mortality within 30 days of TCZ, n/N (%)	28/134 (20.9)
WHO ordinal scale 5 at baseline, n/N (%)	23/117 (19.7)
WHO ordinal scale 6 & 7 at baseline, n/N (%)	5/17 (29.4)
Immunocompromised, n/N (%)	8/19 (42.1)
Days from TCZ to mortality, median (IQR)	12.5 (5 to 18.3)
Days from admission to mortality, median (IQR)	15 (6.8 to 20)
Discharged by day 30, n/N (%)	96/106 (90.6)
Home	68/96 (70.8)
Skilled nursing facility or rehabilitation	20/96 (20.8)
Long term acute care hospital	8/96 (8.3)
Mortality within 60 days of TCZ, n/N (%)	34/134 (25.4)
WHO ordinal scale 5 at baseline, n/N (%)	28/117 (23.9)
WHO ordinal scale 6 & 7 at baseline, n/N (%)	6/17 (35.3)

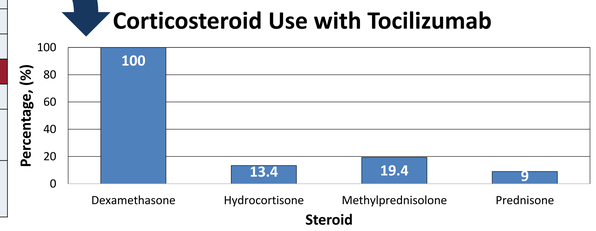
Figure 2: Adverse Events



*Other: intra-abdominal (5%), Other (17.5%)

Table 2: Concomitant Medications	
Medications received within 30 days of TCZ, n (%)	
Corticosteroids	134 (100)
Remdesivir	131 (97.8)
Monoclonal antibody	3 (2.2)
Convalescent plasma	2 (1.5)
Inhaled nitric oxide or prostacyclin	5 (3.7)
Corticosteroids, continued	
Total prednisone equivalents (mg), median (IQR)	400 (335.6 to 480)
Total corticosteroid length of therapy (days), median (IQR)	10 (9 to 12)
Average daily prednisone equivalent (mg), median (IQR)	40 (40 to 42.7)

Figure 3:



ALT: alanine transaminase
AST: aspartate transaminase
HFNC: high flow nasal cannula
NIV: non-invasive ventilation
MV: mechanical ventilation

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Discussion

- Use of TCZ in severe COVID-19 resulted in an observed 30 day mortality rate of 20.9%. An additional 6 patients expired at day 60 from TCZ administration (34/134, 25.4%).
- A small percentage of our cohort was immunocompromised (14.2%). These patients experienced higher mortality compared to the rest of our cohort (42.1%).
- For those alive at day 30, only 9.4% remained hospitalized at day 30. A majority of patients were discharged home (70.8%).
- All patients received corticosteroids. The median prednisone equivalents and days of therapy align with dexamethasone dosing and duration recommendations for severe COVID-19.
- Approximately one third of patients developed a bacterial infection while fungal infections represented less than 5% of patients.
- Our study has multiple limitations including lack of generalizability given hybrid inclusion and exclusion criteria when compared to landmark trials and retrospective design.

Conclusion

- A majority of deaths in patients receiving TCZ for severe COVID-19 occurred by day 30. Mortality at days 30 and 60 was higher among those with a higher ordinal scale at the time of TCZ dosing (29.4% and 35.3%, respectively).
- In a real world setting, adverse events were observed in approximately one-third of patients treated with TCZ for severe COVID-19.
- Our cohort had a small percentage of immunocompromised patients that experienced a higher mortality rate in comparison to the rest of the cohort. More data is needed regarding use of TCZ in an immunocompromised patient population.

References

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3. RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (Recovery): a randomised, controlled, open-label, platform trial. *The Lancet*. 2021;397(10285):1637-1645.