Clinical Impact of Tocilizumab Therapy in SARS-CoV-2 Respiratory Infections in ICU and non-ICU Patients

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Purpose

No therapy is approved for COVID-19 pneumonia. The aim of this study was to assess the clinical impact of tocilizumab (TCZ) in managing severe respiratory infections by SARS-CoV-2 in patients admitted to ICU and non-ICU.

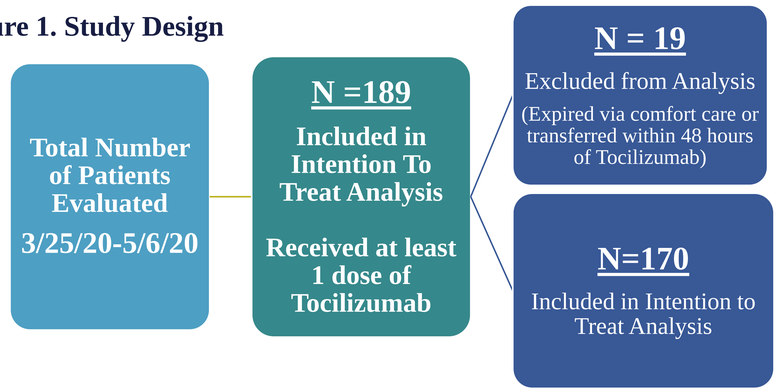
Background

- There has been a strong inverse correlation between the need of supplemental oxygenation and fatality rates with COVID-19 with recent review documenting mortality rate up to 57% in ICU patients.
- TCZ was used as an investigational medication for management of cytokine release syndrome (CRS) in respiratory infections caused by COVID-19 at our institution.
- Following institutional criteria was set for patients to receive TCZ in CRS:
  - COVID-19 positive
  - ClinicRapidly worsening respiratory gas exchange AND – $SpO_2 \leq 93\%$ on room air OR > 6 L/min O_2
  - At least three of the following laboratory findings:
    - Fever > 38° C
    - Elevated CRP (>10 mg/L) or > 50% increase with clinical worsening
    - Elevated D-dimer > 1 ug/dl
    - Ferritin > 500
- The dosing strategy was determined at 8 mg/kg x 1 dose with consideration of giving additional dose 24 hours after if clinically warranted (maximum 2 doses).

Methods

- TCZ was offered to patients if they met criteria for use in CRS after review by antimicrobial stewardship and infectious diseases service.
- Patients were included if they were ≥ 18 years old, admitted with SARS-CoV-2 respiratory infection in CRS and received at least one dose of TCZ.
- Patient were excluded if they expired or transferred within 48 hours of administration of TCZ.
- Primary endpoint of the study was to assess clinical improvement (CI) at the end of admission.
  - CI was defined by extubation, downgrade from ICU, discharged or improvement in Clinical Ordinal Scale (COS) by 2 during admission.
- Secondary endpoint of the study was to assess inpatient mortality (IM) and risk factors associated with IM.
  - Subgroup analysis included impact of early (< 96 hours) vs late (>=96 hours) therapy on IM.

Figure 1. Study Design



Results

Table 1: Baseline Demographics

	TCZ Non-ICU N=83	TCZ ICU N=87	P value
Age, mean years	63.6	63.6	NS
Sex, % male	67.5%	62%	NS
LOS, mean (Days)	9.2	16.5	0.0001
BMI, mean	28.4	32.5	0.001
Tocilizumab			
Dose 1, mean	575 mg	625 mg	
Mg/kg, mean	8 mg/kg	7.7 mg/kg	
Dose 2, mean	320 mg	360 mg	
Mg/kg, mean	4 mg/kg	4.4 mg/kg	
Received 2 doses, %	67.5%	82.7 %	0.001
Day from illness to hospitalization, mean	6.4	5.7	0.15
Day of admission to dose administered, mean	3	4	NS
Oxygenation at day of toci %			
HFNC / NC	78%	40%	0.03
Oxymizer	4%	11.5%	0.02
IPPV	2.5%	3.4%	NS
IMV	0%	45%	0.001
RA	11%	0%	0.01
Hydroxychloroquine, %	47%	73.5%	0.001
Corticosteroids, %	45.1%	51.7%	0.67

Table 2: Clinical Outcomes

	TCZ Non-ICU N=83	TCZ ICU N=87	P value
Clinical Improvement, %	85.5%	57.5%	0.002
% Inpatient Mortality	8.4%	28.7%	0.0014
Cause of death			
Cardiac Arrest	28.6%	52%	
Comfort Care	71.4%	48%	

Table 3: Subgroup Analysis

	TCZ Patients		P value
	Toci ≤ 96 hours	Toci > 96 hours	
Overall Mortality	17 %	25.7 %	0.24
ICU Mortality	26.9 %	35 %	0.58
Non-ICU Mortality	7.4 %	13.3 %	0.60
IMV Mortality	29 %	33.3 %	1.0
Non-IMV Mortality	13.6 %	23.1 %	0.24

Table 4: Risk Factor Association to IM

	Odds ratio	95 % Confidence interval
ICU Admission	6.17	[2.4, 15.9]
BMI	1.13	[1.02, 1.24]
AKI During Admission	4.22	[1.7, 10.2]

Table 5: COS analysis

	TCZ Non-ICU N=83	TCZ ICU N=87
COS, day 7		
COS – 1, %	4.8%	3.8%
COS – 2, %	2.4%	2.5%
COS – 3, %	14.3%	5%
COS – 4, %	33.7%	12.5%
COS – 5, %	0%	20%
COS – 6, %	0%	45.5%
COS – 7, %	4.8%	11.2%
COS @ End of Stay		
COS – 1, %	51.8%	26.7%
COS – 2, %	26.5%	19.8%
COS – 3, %	2.4%	3.5%
COS – 4, %	8.4%	7.0%
COS – 5, %	0%	2.3%
COS – 6, %	0%	10.5%
COS – 7, %	8.4%	28.7%

COS: Clinical Ordinal Scale
1 = discharge w/ resumption normal activity
2 = discharge w/out resumption normal activity
3 = non-ICU not requiring O2
4 = non-ICU requiring O2
5 = ICU not requiring IMV
6 = ICU requiring IMV
7 = Death

Discussion

- Of the patients who received TCZ, more patients in ICU were likely to be obese, receive 2 doses of it, requiring IMV and have longer length of stay.
- Overall CI was noted at 71%; however, as expected, non-ICU patients had much better clinical outcomes compared ICU.
- Risk factors of ICU admission, BMI > 30 kg/m2 and AKI during admission were associated with higher risk of mortality.
- No differences were observed in patients receiving early vs late TCZ therapy, however, there were trends towards better outcomes in early TCZ therapy.
- Patient on HFNC/NC or oxymizer responded much better than those who needed IMV.
- Patients receiving corticosteroids had lower mortality however there was no associated noted with respect to IM.
- Our criteria allowed for use of TCZ in patients requiring supplemental oxygen and impact was noted in CI of these patients. None of the patients received remdesivir concomitantly.
- We didn't evaluate the rates of super infections noted after TCZ therapy however, most common side effect of therapy was transaminitis seen in 21% of patients.
- Our study didn't have a comparison group since this was not a clinical trial and a study with a controlled comparison group would lead to data that would give us more insight into the most appropriate place in therapy for TCZ for COVID-19.
- There was co-administration of hydroxychloroquine and corticosteroids which may have impacted clinical outcomes.

Conclusions

- Overall TCZ therapy led to much better CI compared what has been published in literature for patients with severe SARS-CoV-2 respiratory infections.
- ICU admission, obesity and AKI were associated with high rates of IM.
- Early therapy with TCZ didn't show improvement in CI or IM.
- Larger randomized controlled trials are needed to determine the benefit of TCZ for COVID-19.

References

- NIH COVID-19 Guidelines. https://www.covid19treatmentguidelines.nih.gov/whats-new/
- ***Lancet Rheumatol* 2020; 2: e603–12** https://doi.org/10.1016/S2665-9913(20)30277-0