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

S.J. Norman[1], PharmD, BCPS; S.J. Jones[1], PharmD, BCPS (AQ-ID), BCIDP; D. Reeves[1,2], PharmD, BCOP; S.C. Cheatham[1], PharmD, BCIDP

[1]Franciscan Health Indianapolis, Indianapolis, IN [2]Butler University College of Pharmacy, Indianapolis, IN

Contact Information:
Sarah Norman, PharmD, BCPS
Sarah.J.Norman@medstar.net

REVISED ABSTRACT

Purpose: 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.

BACKGROUND

- At the time of this writing, there is no FDA approved medication for the treatment of COVID-19.
- One medication under investigation for COVID-19 treatment is tocilizumab, an interleukin-6 (IL-6) inhibitor.[1]
- It has been shown that there are increased levels of cytokines including IL-6 in severe COVID-19 hospitalized patients attributed to cytokine release syndrome (CRS).[2]
- Inhibition of IL-6 receptors may lead to a reduction in cytokines and prevent progression of CRS.
- There have been case reports and non-randomized reports with conflicting findings regarding tocilizumab in COVID-19. [3-6]
- There have been limited case-matched series investigating the use of tocilizumab in COVID-19.
- Current prospective, randomized tocilizumab trials and research for COVID-19 are ongoing and rapidly evolving.

OBJECTIVES

- To compare clinical outcomes in patients that received tocilizumab vs those that did not for the treatment of severe COVID-19
- Primary outcome
  - In-hospital mortality
- Secondary outcomes
  - Total mechanical ventilation days
  - Mechanical ventilation mortality
  - Hospital length of stay
  - Incidence of secondary bacterial or fungal infections

METHODS

- Design
  - Retrospective, multi-center, case-matched series
  - Matched 1:1
- Matching Criteria
  - Age
  - BMI
  - Days since symptom onset
- Eligibility Criteria
  - Inclusion
    - ≥18 years of age
    - Laboratory confirmed positive SARS-CoV-2 result
    - Admitted to Franciscan Health Indianapolis or Franciscan Health Mooresville from March 1st – May 9th, 2020
    - Received tocilizumab while admitted at Franciscan Health
  - Exclusion
    - <18 years of age
    - Received tocilizumab at outside hospital
- Data Collection
  - Admit and discharge date
  - In-hospital mortality
  - Age, admission height, weight, BMI
  - Co-morbidities
  - Approximate symptom onset date
  - Baseline respiratory status
  - Date of first COVID-19 positive result
  - Date/time of tocilizumab administration
  - Tocilizumab dose(s)
  - Concomitant investigational medications/therapies
  - Pressor requirements
  - Oxygen requirements
  - Total mechanical ventilation days
  - Respiratory status at time of tocilizumab and 7 days afterwards
  - Baseline labs and 7-day trend after tocilizumab: D-dimer, fibrinogen, ferritin, IL-6, LFTs, CK, LDH
  - Temperature prior to tocilizumab and within 48 hours after administration
  - High suspicion or confirmed secondary bacterial or fungal infection prior to tocilizumab and within 7 days after administration
- Approved by Franciscan Health IRB

RESULTS

Table 1: Baseline Characteristics

	Tocilizumab (n=26)	Control (n=26)	p-value
Age (years) Mean	58.2	61.7	0.336
BMI Mean	32.2	32.4	0.891
Days Since Symptom Onset Median	8	8	0.896

Figure 1: In-Hospital Mortality

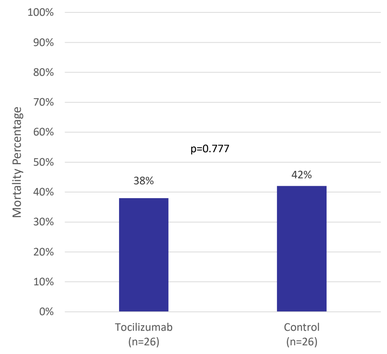


Figure 3: Total Vent Days

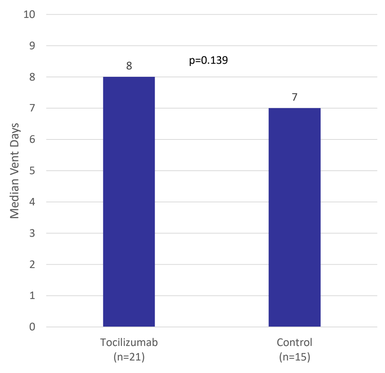


Table 2: Baseline Tocilizumab Labs

	Expired (n=10)	Alive (n=16)
D-Dimer (ng/mL) Median >2,000 ng/mL	18,810 6 (60%)	13,686 8 (50%)
Ferritin (ng/mL) Median >600 ng/mL	2,922 10 (100%)	828 7 (50%)*
Fibrinogen (ng/mL) Median	723	695
IL-6 (pg/mL) Median	42	76

*n=14

Figure 2: Hospital Length of Stay

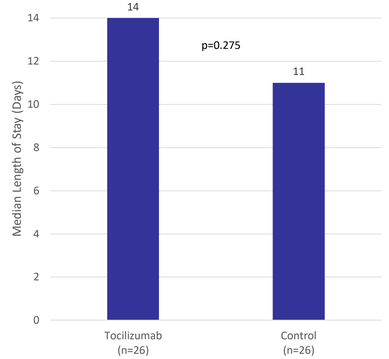
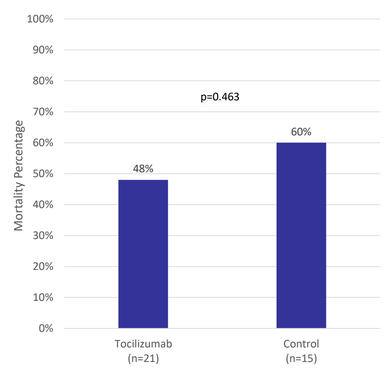


Figure 4: Vent Mortality



RESULTS

Table 3: Bacterial or Fungal Infection in Tocilizumab Group

Secondary Bacterial or Fungal Infection	Tocilizumab (n=26)
At time of Tocilizumab	2 (7.7%)
Within 7 days of Tocilizumab administration	5 (19.2%)

DISCUSSION

- In the tocilizumab group, most patients received either a maximum dose of 800 mg or an 8 mg/kg dose. 9 (35%) patients received a second dose of tocilizumab.
- There was a lower in-hospital mortality for tocilizumab (38%) vs control (42%), but it did not meet statistical significance.
- The tocilizumab group had a longer hospital length of stay, which may be contributed to patients staying alive longer in the tocilizumab group.
- Patients were matched by age, BMI, and days since symptom onset, but there was a lower number of patients requiring mechanical ventilation in the control group. This may represent a difference in disease severity at baseline with the tocilizumab group possibly presenting as more severe.
- The total vent days were similar between the two groups, but a 12% difference in vent mortality was noted, favoring the tocilizumab group.
- Adverse events of tocilizumab were monitored. 19% of patients developed a confirmed or highly suspicious secondary bacterial or fungal infection within 7 days of tocilizumab administration. There are other contributing factors to development of secondary infections, but infection rates should be carefully monitored.

CONCLUSION

- These findings suggest that tocilizumab may be a beneficial treatment modality for severe COVID-19 patients.
- There was a decreased overall trend in in-hospitality and mechanical ventilation mortality in the tocilizumab group. Though not statistically significant, this may be clinically significant.
- Larger, prospective, randomized, placebo-controlled trials are needed to further validate results.

DISCLOSURES

- The authors have the following disclosures:
  - SJ Norman, SJ Jones, D Reeves: Nothing to disclose
  - SC Cheatham: Antimicrobial Resistance Solutions

REFERENCES

1. Tocilizumab. Package Insert. Genentech, Inc., 2019.
2. Chen G, Wu D, Guo W, et al. Clinical and immunological features of severe and moderate coronavirus disease 2019. *J Clin Invest.* 2020;130(5): 2620-9.
3. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol.* 2020;2(8): e474-e84.
4. Campochiaro C, Della-Torre E, Cavalli G, et al. Efficacy and safety of tocilizumab in severe COVID-19 patients: a single-centre retrospective cohort study. *Eur J Intern Med.* 2020;76:43-9.
5. Kewan T, Covut F, Al-Jaghbeer MJ, et al. Tocilizumab for treatment of patients with severe COVID-19: A retrospective cohort study. *EClinicalMedicine.* 2020;24:100418.
6. De Rossi N, Scarpazza C, Filippini C, et al. Early use of low dose tocilizumab in patients with COVID-19: A retrospective cohort study with a complete follow-up. *EClinicalMedicine.* 2020;25:100459.