
Tocilizumab (TOC) is NOT recommended for management of COVID-19 outside of clinical trials (IDSA 2020, NIH 2020).1,2 Preliminary, unpublished data from a randomized, controlled trial failed to demonstrate benefit.2 Additional clinical trials are needed to inform research on the effectiveness of treatment with TOC for patients with COVID-19.1

COVACTA: The first available global, randomized, placebo-controlled trial (RCT) designed to evaluate the safety and efficacy of TOC in 438 hospitalized adults with severe COVID-19 pneumonia failed to demonstrate a benefit in survival or clinical status at 28 days compared to placebo. The primary endpoint, clinical status, was measured by a seven-point ordinal scale based on need for supplemental oxygen, ICU, and ventilator support. Mortality in the TOC group (19.7%) was similar to placebo (19.4%). Additional secondary outcomes require prospective evaluation - median time to discharge was 8 days shorter with TOC compared to placebo, and median duration of ICU stay was 5.8 days shorter compared to placebo. Use of steroids was more common with placebo (54.9%) than TOC (36%) but mortality was similar across treatment groups, irrespective of steroid use. Adverse effects were similar between treatment groups. Additional clinical trials ongoing. Uncontrolled reports – see below.

Summary: Tocilizumab cannot be recommended for management of severe COVID-pneumonia at this time. A multi-center RCT failed to demonstrate a benefit in mortality or clinical outcomes.3 Internal data suggests risk of bacterial infection and viral reactivation following TOC / steroid administration.4

**Decision to use TOC must meet the following criteria:**

- COVID-19 positive lab result.
- Progression of oxygen requirements by GREATER THAN 4L despite best available therapy (i.e. steroids, remdesivir).
- Evaluation of underlying infection risk.
- Critical Care (or pulmonary) AND Infectious Diseases agreement required for ALL patients – irrespective of patient location (ICU / non-ICU).
- At least two of the following biomarkers:
  - Ferritin > 1250 ng/mL; LDH > 400 unit/L; CRP > 5 mg/dL; D-dimer > 3 mg/L; Progressive lymphopenia (ALC ≤600)
  - Additional Required Labs Prior to Verification (Do not need to await results): IL-6 level, Quantiferon, Chronic hepatitis panel

**Dose:** Tocilizumab 400mg IV x 1. Doses greater than 400mg and repeat doses are not recommended and must be approved by one of the physicians listed below.

- Universal HSV prophylaxis is advised following TOC administration.4 Suggested dose: valacyclovir 500mg PO BID or acyclovir 400mg PO BID or 200mg IV daily. Suggested duration: 4 weeks.
- Use of tocilizumab with baricitinib is discouraged.
- Pharmacists will review all COVID-related TOC orders against criteria and notify physicians of additional requirements prior to order verification.

**Use outside of criteria above will be handled on a case by case basis with ID Medical Staff Leadership prior to drug release:**

- Wisconsin: MD Brummitt, MD (414-222-1438); J Meidl, MD (414-222-7753). Illinois: R Citronberg, MD (PerfectServe).

References – Guidelines / Controlled Data


References - Uncontrolled Reports:

2. Xu, X, Han, M, Li, T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. March 2020. In Press. Uncontrolled case series of 21 COVID positive patients treated at two Chinese hospitals with moderate to severe COVID infection. Younger population (mean age 56.8 years). Two of 21 patients were intubated. All patients received lopinavir, methylprednisolone and TOC 400mg, three patients received a second dose of TOC due to sustained fever at 12hours. Survival to discharge: 19/21 patients. Two of 21 patients remained intapatient at the time of publication. Mean LOS: 13.5days after TOC. No adverse effects reported
4. Roumier M, et al. Interleukin-6 blockade for severe COVID-19. In Press. https://doi.org/10.1101/2020.04.20.20061861. Prospective evaluation of TOC in 30 adults (23% in ICU) with weight comparison for age, gender and disease severity control group. IL-6 blockade reduced requirement for mechanical ventilation (OR 0.25 95% CI 0.05-0.95), p=0.04 and ICU admission. Mortality in TOC group at time of publication: 10% (3/30pts). Safety – LFT elevations (n=2) and VAP (n=1) reported.
5. Rosas, B, et al effect of tocilizumab in hospitalized patients with severe pneumonia COVID-19: a cohort study. medRxiv. 2020. Available at: preprint doi: https://doi.org/10.1101/2020.06.06.20122341. Single center (France), retrospective, case-controlled study of 246 adults treated with single dose TOC 400mg (n=106) or placebo in patients on >6L supplemental O2 for more six hours. Excluded patients in ICU or on mechanical ventilation. Primary outcome: composite of all-cause mortality and mechanical ventilation at 28 days. Propensity score matched 84 patient pairs. Steroid use more common in the TOC group (40.6%) compared to placebo (27.1%) p=0.27. In matched cohort, TOC was associated with fewer events (HR 0.49 [95% CI 0.31-0.81] p=0.005).