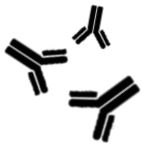
Tocilizumab

What is it?

- A recombinant, humanized monoclonal antibody that inhibits the binding of interleukin-6 (IL-6) to IL-6 receptors, preventing subsequent inflammatory signaling.
- IL-6 is proposed to play a role in propagating the hyper-inflammatory response implicated in lung and other organ dysfunction in severe COVID-19.



On October 13th, 2022, Health Canada authorized tocilizumab IV for the treatment of hospitalized adults with COVID-19 who are receiving systemic corticosteroids, and require supplemental oxygen, non-invasive or invasive mechanical ventilation or extracorporeal membrane oxygen, via a Notice of Compliance.

Additional Health Canada Indications:	Rheumatoid arthritis, giant cell arteritis, junior idiopathic arthritis, cytokine release syndrome in chimeric antigen receptor T-cell (CAR-T) therapy

Evidence:

- Early randomized trials of tocilizumab in hospitalized but primarily non-critically ill COVID-19 patients did not appear to impact mortality.[2-6] Many patients in these studies did not receive corticosteroids as part of their care.
- The **RECOVERY** randomized controlled trial[7] investigated tocilizumab in over 4000 hospitalized patients with COVID-19. This open-label study randomized patients with hypoxia (14% of whom were receiving mechanical ventilation, 41% non-invasive respiratory support and 45% receiving simple oxygen therapy) and evidence of systemic inflammation as indicated by an elevated CRP ≥ 75 mg/L to tocilizumab up to 800 mg IV x 1 along with usual care (could be repeated once) or usual care alone. 82% of these patients also received corticosteroid treatment. Key findings below.

RECOVERY: Tocilizumab substudy findings

- **Reduced 28-day mortality:** 31% (621/2022) of tocilizumab patients vs 35% (729/2094) of usual care patients died. RR 0.85 (95% CI 0.76-0.94), p = 0.0028.
- **In patients not previously ventilated, less progression to mechanical ventilation or death:** overall composite outcome occurred in 35% (619/1754) of tocilizumab vs 42% (754/1800) of usual care patients [RR 0.84 (95% CI 0.77-0.92), p = 0.0001]. Consistent reduction in each outcome independently: progression to mechanical ventilation in 15% (265/1754) of tocilizumab vs 19% (343/1800) usual care patients [RR 0.79 (95% CI (0.69-0.92), p = 0.0019)] and death in 28% (490/1754) tocilizumab vs 32% (580/1800) usual care patients [RR 0.87 (95% CI 0.78-0.96), p = 0.0055)].
- **No difference in reported serious adverse events**

Number needed to treat (NNT): For every 25 COVID-19 patients with hypoxia and elevated CRP who receive tocilizumab (plus dexamethasone), one death was prevented at 28 days versus usual care alone.

A large meta-analysis[8] reports similar findings for reduced mortality in a range of hospitalized COVID-19 patients, the majority of whom received corticosteroids in addition to tocilizumab [19 randomized trials with n = 8048; OR 0.83 (95% CI 0.74-0.92), p <0.001], but the effect in other systematic reviews with meta-analyses has not consistently reached statistical significance[9-11]. Bayesian re-analysis of only the subset of COVID-19 patients already receiving mechanical ventilation has suggested uncertain benefit in this population[12]. Early administration of tocilizumab (i.e., within 24 hours of ICU admission as implemented in the REMAP-CAP study[13]) for mechanically ventilated patients with COVID-19 has been suggested as a predictor of benefit[11].

Infectious Diseases Society of America (IDSA): conditionally recommends tocilizumab in addition to standard of care (i.e., steroids) in hospitalized adults with progressive severe or critical COVID-19 with elevated markers of systemic inflammation (updated Sept.14, 2021)[11]

Practical Considerations

- IV infusion runs over one hour.
- NS Health uses a dosing strategy of tocilizumab 8 mg/kg to a maximum of 800 mg as a single dose.
- Staff administering tocilizumab should be capable of managing anaphylaxis and infusion reactions.
- Half-life of tocilizumab is 13 days.
- The product monograph recommends against administering tocilizumab in patients with ALT/AST elevated about 10x the upper limit of normal. No dosage adjustment required in renal impairment.

Prepared by: COVID-19 Clinical Pharmacy Working Group
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References:

1. Actemra (tocilizumab) product monograph. Mississauga (ON): Hoffman-La Roche Limited. Revised October 13, 2022. Accessed 2022 October 27.
2. Salama C, Han J, Yau L, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2020. DOI: 10.1056/NEJMoa2030340
3. Rosas I, Bräu N, Waters M, et al. Tocilizumab in Hospitalized Patients With COVID-19 Pneumonia. medRxiv 2020:2020.08.27.20183442.
4. Stone JH, for the BACC Bay Tocilizumab Trial Investigators. N Engl J Med 2020;383:2333-44. DOI: 10.1056/NEJMoa2028836
5. Hermine O, Mariette X, Tharaux L. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia. JAMA Intern Med. 2021;181(1):32-40. doi:10.1001/jamainternmed.2020.6820
6. Salvarani C, Dolci G, Massari M. Effect of Tocilizumab vs Standard Care on Clinical Worsening in Patients Hospitalized With COVID-19 Pneumonia. JAMA Intern Med. 2021;181(1):24-31. DOI:10.1001/jamainternmed.2020.6615
7. Abani O, Abbas A, Abbas F, et al. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. The Lancet. 2021 May 1;397(10285):1637-45.
8. The WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT)Working Group. Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. Jama. 2021 Aug 10;326(6):499-518.
9. Tleyjeh IM, Kashour Z, Damlaj M, et al. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis. Clinical Microbiology and Infection. 2021 Feb 1;27(2):215-27.
10. Lin WT, Hung SH, Lai CC, et al. The effect of tocilizumab on COVID-19 patient mortality: a systematic review and meta-analysis of randomized controlled trials. International Immunopharmacology. 2021 Jul 1;96:107602.
11. Bhimraj A, Morgan RL, Shumaker AH, et al. Infectious diseases Society of America guidelines on the treatment and management of patients with COVID-19. Updated October 18, 2022: Available at: https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/ . Accessed 2022 November 2.
12. Albuquerque AM, Tramujas L, Sewanan LR, et al. Mortality Rates Among Hospitalized Patients With COVID-19 Infection Treated With Tocilizumab and Corticosteroids: A Bayesian Reanalysis of a Previous Meta-analysis. JAMA Netw Open. 2022 Feb 1;5(2):e220548. doi: 10.1001/jamanetworkopen.2022.0548. Erratum in: JAMA Netw Open. 2022 Mar 1;5(3):e225937.
13. The REMAP-CAP Investigators. Interleukin-6 receptor antagonists in critically ill patients with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2100433.