Background Summary

Tocilizumab for COVID-19

What is tocilizumab?

Tocilizumab (also known as atlizumab) is an immunosuppressive drug that targets the IL-6 receptor. Mainly used to treat rheumatoid arthritis, it also has the potential to combat cytokine storm in patients with life-threatening COVID-19. Brand name: Actemra [1]

New in this update (January 31, 2023)

Since the last background summary on tocilizumab was completed (November 22, 2022):

- The US FDA approved tocilizumab for use in certain hospitalized adult patients with COVID-19
- A prespecified secondary analysis of REMAP-CAP trial found that IL-6 receptor antagonists (tocilizumab or sarilumab) had >99.9% probability of improving 6-month survival

Drug approval

Canada

- Approved by Health Canada on October 13, 2022 to treat hospitalized adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation [2]
- Recommended by the BC COVID-19 Therapeutics Committee for patients on life support, at a dosage of 400 mg IV (single dose), administered within 24 hours of initiation of life support measures [3]
- Recommended by the Alberta COVID-19 Therapeutics Working Group for hospitalized patients that are critically ill and experiencing significant progressive respiratory failure, or severely ill and requiring supplemental oxygen or non-invasive ventilation [4]

US

- *New* Approved by the FDA on December 21, 2022 to treat hospitalized adult patients (aged 18+) who are receiving systemic corticosteroids and require supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation [5]
    - The emergency use authorization granted on June 24, 2021 for the same use is still in effect for hospitalized pediatric patients (aged 2–17) [6]
- Guidance from the National Institutes of Health:
    - Tocilizumab may be used in specific groups of hospitalized patients [7]
    - Tocilizumab and sarilumab should only be administered in combination with dexamethasone or an alternative corticosteroid; tocilizumab and sarilumab should also be used cautiously in populations that have not been well represented in clinical trials (e.g. the significantly immunosuppressed) [8]

UK and EU

- Now a licensed treatment per the UK Clinical Commissioning Policy for hospitalised adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation (additional exclusion criteria apply) [9]

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- Recommended by the European Medicines Agency on December 6, 2021 for use in adults with severe COVID-19 who are receiving systemic treatment with corticosteroids and require supplemental oxygen or mechanical ventilation [10]

Australia

- Granted provisional approval by the Therapeutic Goods Administration on December 1, 2021 to treat hospitalized adults aged 18+ who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation [11]

Evidence syntheses

WHO

Living guideline on drugs for COVID-19 (updated September 16, 2022) [12]:

- Treatment with IL-6 receptor blockers (tocilizumab or sarilumab) is strongly recommended for patients with severe or critical COVID-19
- Baricitinib, IL-6 receptor blockers (tocilizumab or sarilumab) and corticosteroids can now be combined in patients with severe or critical COVID-19

In support of their decision to recommend IL-6 antagonists, WHO published a meta-analysis in *JAMA* on July 6, 2021. It synthesizes data from 27 RCTs, and found that administration of IL-6 antagonists, compared with usual care or placebo, was associated with lower 28-day all-cause mortality in patients hospitalized for COVID-19 [13].

Other

JAMA published a bayesian reanalysis of a previous meta-analysis on February 28, 2022 to clarify tocilizumab's association with mortality benefit in hospitalized patients receiving corticosteroids; the results indicated that those receiving simple oxygen only or noninvasive ventilation were associated with a clinically meaningful mortality benefit whereas the benefit for those receiving invasive mechanical ventilation was uncertain [14].

Association between tocilizumab, sarilumab and all-cause mortality at 28 days in hospitalised patients with COVID-19: A network meta-analysis (Godolphin et al., PLoS ONE, July 8, 2022) [15]

- A network meta-analysis with the objective of estimating the pairwise associations between administration of tocilizumab, sarilumab and usual care or placebo and 28-day mortality
- Patient population of interest is COVID-19 patients receiving concomitant corticosteroids and ventilation
- Conclusions: "Administration of either tocilizumab or sarilumab was associated with lower 28-day all-cause mortality compared with usual care or placebo. The association is not dependent on the choice of interleukin-6 receptor antagonist."

Clinical trials

As of January 31, 2023, Epistemonikos lists 145 reports of RCTs on tocilizumab for COVID-19, of which 58 have reported data.

CORIMUNO-19

Tocilizumab plus dexamethasone versus dexamethasone in patients with moderate-to-severe COVID-19 pneumonia: A randomised clinical trial from the CORIMUNO-19 study group (Hermine et al., EClinicalMedicine, March 24, 2022) [16]

- A randomized, open-label, clinical trial investigating the efficacy and safety of dexamethasone and tocilizumab
- Participants received dexamethasone (10 mg/d 5 days tapering up to 10 days) alone or in combination with tocilizumab (8 mg/kg IV) at day 1, with a second dose (400 mg IV) at day 3 if needed

- Conclusions: "Mechanical ventilation need and mortality were not improved with TCZ+DEX compared with DEX alone. The safety of both treatments was similar. However, given the wide confidence intervals for the estimate of effect, definitive interpretation cannot be drawn."

RECOVERY

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a randomised, controlled, open-label, platform trial (RECOVERY Collaborative Group, The Lancet, May 1, 2021) [17]

- A randomized, controlled, open-label, platform trial assessing several possible treatments
- Participants in the tocilizumab comparison received standard of care alone or standard of care plus tocilizumab (400 mg–800 mg, depending on weight) intravenously, with a second dose 12–24 hours later if needed
- Conclusions: "In hospitalized COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes. These benefits were seen regardless of the level of respiratory support and were additional to the benefits of systemic corticosteroids."

REMAP-CAP

New **Long-term (180-Day) Outcomes in Critically Ill Patients With COVID-19 in the REMAP-CAP Randomized Clinical Trial** (Writing Committee for the REMAP-CAP Investigators, JAMA, December 16, 2022) [18]

- Prespecified secondary analysis of REMAP-CAP trial
- Main outcome was survival through day 180, analyzed using a Bayesian piecewise exponential model
- Conclusions: " Among critically ill patients with COVID-19 randomized to receive 1 or more therapeutic interventions, treatment with an IL-6 receptor antagonist had a greater than 99.9% probability of improved 180-day mortality compared with patients randomized to the control"

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 (The REMAP-CAP Investigators, New England Journal of Medicine, February 25, 2021) [19]

- International, multifactorial, adaptive platform trial evaluating tocilizumab and sarilumab
- Participants received tocilizumab (8 mg/kg of body weight, up to a max. 800 mg) intravenously, sarilumab (400 mg) intravenously, or standard care
- Conclusions: "In critically ill patients with Covid-19 receiving organ support in ICUs, treatment with the interleukin-6 receptor antagonists tocilizumab and sarilumab improved outcomes, including survival."

Other

Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia (Rosas et al., New England Journal of Medicine, February 25, 2021) [20]

- A phase 3 randomized, placebo-controlled, platform trial assessing single intravenous infusion of tocilizumab
- Participants received a single intravenous infusion of tocilizumab (8 mg/kg of body weight) or placebo, with approx. one quarter of participants receiving a second dose 8 to 24 hours after the first dose
- Conclusions: "In this randomized trial involving hospitalized patients with severe Covid-19 pneumonia, the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days."

Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial (Soin et al., The Lancet Respiratory Medicine, March 4, 2021) [21]

- A randomized, controlled, open-label, platform trial assessing the efficacy of tocilizumab
- Participants received tocilizumab (6 mg/kg) plus standard care or standard care alone
- Conclusions: "Routine use of tocilizumab in patients admitted to hospital with moderate to severe COVID-19 is not supported. However, post-hoc evidence from this study suggests tocilizumab might still be effective in patients with severe COVID-19 and so should be investigated further in future studies."

Tocilizumab, netakimab, and baricitinib in patients with mild-to-moderate COVID-19: An observational study (Bryushkova et al., PLoS ONE, August 24, 2022) [22]

- An observational cohort study assessing a combination of treatments including anti-IL-17A netakimab, anti-IL-6R tocilizumab, and JAK1/JAK2 inhibitor baricitinib to treat hospitalized adults
- Participants were divided into treatment groups: baricitinib (4 mg) 1 or 2 times a day for an average of 5 days; netakimab (120 mg) one dose; tocilizumab (400 mg) one dose; standard of care only
- Conclusions: "In hospitalized patients with mild-to-moderate COVID-19, the combination of SOC with anti-IL-17A or anti-IL-6R therapy were superior or comparable to the combination with JAK1/JAK2 inhibitor, and all three were superior to SOC alone. Our data suggest that such therapy could be a rational choice for mild-to-moderate disease, considering the generally high safety profile of IL-17A blockers."

Please note: This summary reflects evidence up to and including January 31, 2023 only.

Search Methods

Date searched: 2023-01-23

- Google for news items and clinical trials in progress
- Epistemonikos L-OVE on COVID-19 (manual search)
- Ovid MEDLINE search with built-in COVID-19 filter: (tocilizumab or atlizumab or actemra).ti,ab.

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