CCRC
OSLER COVID CLINICAL RESPONSE COMMITTEE

Use of Tocilizumab for COVID-19 Pneumonia in Critically Ill Patients **20 April 2021**

The Ontario COVID-19 Drugs and Biologics Clinical Practice Guideline Working Group recently recommended tocilizumab (an IL-6 inhibitor) for the treatment of moderately ill and critically ill patients with COVID-19 infection. This most recent update is to provide an interpretation of these recommendations for local practice.

The Ontario COVID Critical Care Command Table Guidance and practice direction will supersede this document in the event rationing is required.

The COVID Clinical Response Committee (CCRC) wishes to provide guidance on the local implementation of this therapy as it is currently a non-formulary indication, in conjunction with the full review of the Pharmacy and Therapeutics Committee.

1. Tocilizumab may benefit moderately (in-hospital, on oxygen) ill and critically ill patients with suspected or confirmed COVID-19 infection, including a possible signal indicating an increased number of days in which organ support is not required AND a possible signal indicating improved hospital and overall survival.
2. We recommend one fixed dose of 400 mg given intravenously be considered for patients who meet inclusion criteria for EITHER the REMAP-CAP or RECOVERY trials.
3. Given the limited supply of the drug, prior to the initiation of this process of evaluation and distribution, we suggest contacting the Pharmacist on call to establish the supply. If the drug is not available and you believe the patient requires the drug, the pharmacist can be asked to escalate a request for supply.
4. The COVID Critical Care Command Centre will assume responsibility for the distribution of tocilizumab provincially.
5. We recommend an informed discussion with patients who meet the following criteria:
    a. The patient should be in hospital for a total of fewer than 14 days or have acquired COVID-19 nosocomially less than 14 days ago.
    b. Meet ONE of the below criteria:
        i. Group 1: Critical Illness: require mechanical ventilation or high flow nasal cannula who require oxygen concentration FiO2 0.50 or greater or non-rebreather oxygen mask and/or who are on vasopressors or inotropes.
        ii. Group 2: Moderate illness: require supplemental oxygen (at least 40% by face mask), have evidence of systemic inflammation (CRP 75 mg/L or higher), and have evidence of disease progression (increasing oxygen requirement over the past 24-48 hours (or at least on day 2 of hospital stay)) despite dexamethasone therapy
    c. All patients should be receiving dexamethasone concomitantly but without other ongoing immunosuppression*.

6. We recommend the following as possible exclusion criteria:
    a. Condition or treatment resulting in ongoing immunosuppression* including neutropenia (ANC below 2)
    b. Platelet count below 50
    c. ALT or AST above five times the upper limit of normal
    d. Known hypersensitivity to tocilizumab
    e. Death is imminent.
7. We recommend dispensing this drug as ordered by Pharmacy unless we identify that less than 10 doses are available for dispensing or are at risk of supply outstripping demand based on allocation.
8. The following applies to local measures to fairly distribute the drug in the setting of a paucity of supply and assumes all other venues have been exhausted. All requests will be made of the pharmacist on call and assessed at 9 am and 3 pm. If simultaneous patients qualify and want the drug and the supply is limited, the following approach will be taken:
    a. Critically ill patients will be prioritized over moderately ill patients.
    b. If the supply is not sufficient, for even the critically ill patients, those patients will be listed in a random list selector and the drug given to those individuals at the top of that list.
    c. If the supply is sufficient for critically ill patients but insufficient for moderately ill patients, those individuals will also be prioritized using the same random list generator.
    d. If a patient does not receive a drug on the first day they are eligible, daily reassessment is required but if they remain a candidate for the drug the following day AND are felt to be equally likely to benefit others in their group, they will be randomized again.
    e. This process will be managed by the pharmacy leadership team but will often require multidisciplinary input from ID, CCRT, and MRPs.
9. A second dose will not be administered.
10. For patients who are critically ill (as per the REMAP-CAP trial), the opinion of an **intensivist or a specialist in infectious diseases is** required prior to the drug being requested for Group 1 patients.
11. For patients who are moderately ill (as per the RECOVERY trial), a consensus opinion of **the most responsible physician AND either an intensivist (usually the CCRT physician) OR a specialist in infectious diseases** is required prior to the drug being requested for Group 2 patients.
12. This is not an emergent therapy and if availability is limited, after-hours or off-hours administration can be delayed to the following morning.
13. It is our preference that we administer tocilizumab prior to transfer but as long as supply can be confirmed at the receiving hospital for eligible patients, this is not absolutely required.
14. A standardized form must be completed in advance and a record maintained in the chart. The completed form will be scanned to the pharmacy with the order.
15. As the drug is in limited supply at present (this may change), we recommend utilizing the therapy in the patient population most likely to receive the benefit.
16. We recommend a dictated note describing the informed consent discussion and the fact that the patient meets the criteria above.

This decision will be revisited as new data becomes available.

Rationale

1. The supply chain for tocilizumab is uncertain although, while on allocation, provincially a supply has been increased recently.
2. All but two studies have been negative for the use of tocilizumab.
3. The absolute mortality benefit expressed in REMAP-CAP was 8% whereas the absolute mortality benefit in RECOVERY (less sick paitents) was 4%. While there is reasonably low certainty around these point estimates, critically ill patients are felt to experience more absolute benefit than moderately ill patients and are thus prioritized. This may require revision as more data and analysis become available.
4. We will follow locally adapted advice from the Biologics and Therapeutics Subcommittee of the Science Table in interpreting the evidence at Osler.

*In patients who are otherwise immunosuppressed, the data is very limited. We recommend multidisciplinary expert consultation. Within REMAP-CAP (critically ill patients), this was a relevant exclusion criterion ("other immunosuppression") however within RECOVERY (less critically ill patients overall), this was not an exclusion criterion but there is no data available at this time describing whether these patients were included.
*Tocilizumab is routinely administered in pregnancy.

References

1. https://www.thebottomline.org.uk/summaries/remap-cap-il-6/
2. Interleukin-6 Receptor Antagonists in Critically Ill Patients with COVID-19 - Preliminary Report. medRxiv preprint
3. Ontario COVID-19 Drugs and Biologics Clinical Practice Guideline Working Group
4. British Columbia Centre for Disease Control COVID-19 Therapeutics Committee Recommendations
5. REMAP-CAP preprint
6. RECOVERY preprint

Additional Reviewers

Haghshenas, Ehsan (ASP Pharmacist)
Puri, Kavita (Drug Utilization Evaluation Pharmacist)
Goel, Rakhi (Critical Care Pharmacist)
Mosnia, Patricia (Director, Pharmacy)
Moltyaner, Yuri (Critical Care Physician)
Osler Antimicrobial Stewardship Program
Osler Division of Infectious Disease
Osler Division of Critical Care