**Introduction**: Tocilizumab (or Actemra) is a monoclonal antibody that binds to IL-6 receptor and inhibits IL-6 mediated cytokine storm. It is currently FDA approved for use in Rheumatoid arthritis, polyarticular juvenile idiopathic arthritis (JIA) and systemic JIA. It has been widely used by oncology for Chimeric Antigen Receptor Therapy (CAR-T) T cell-induced severe cytokine release syndrome (CRS).

**Mechanism of action**: Tocilizumab binds to both soluble and membrane-bound IL-6 receptors and inhibits IL-6 mediated signaling. IL-6 is a pro-inflammatory cytokine that is elevated in the CRS.

**What we know so far about use of IL-6-Receptor Blockers in COVID-19**: An open label, pre-print non-peer reviewed Chinese case series of 21 COVID-19 patients showed benefit of Tocilizumab in COVID-19 patients with reductions in lymphocytes, CRP, oxygen requirement, and lung lesion size and Roche has received approval from the Chinese government for the use of Tocilizumab in the treatment of COVID-19 pneumonia.

Currently here in the USA, the FDA has approved Phase III clinical studies of Tocilizumab in COVID-19 patients and clinical studies (TOCIVID-19) are ongoing.

The Society for Immunotherapy in Cancer has also put out a statement endorsing the use of Tocilizumab in select COVID-19 patients. View SITC statement here.

In the Chinese studies, all patients had IL-6 evaluated prior to use. Included patients were defined as severe or critical.

- The diagnosis of severe was defined if any of the following conditions were met: (1) respiratory rate ≥ 30 breaths/min; (2) SpO2 ≤ 93% while breathing room air; (3) PaO2/FiO2 ≤ 300 mmHg.
- The diagnosis of critical case was diagnosed if any of:
  - (1) respiratory failure which requiring mechanical ventilation
  - (2) shock
  - (3) combined with other organ failure,
  - Need to be admitted to ICU.

**What are other Facilities doing?**

**University of Michigan** was using a criteria of

- COVID-19 positive Plus
- Abnormal chest imaging consistent with COVID-19 plus
- Rapidly worsening gas exchange requiring >6 L/min O2, and an absence of systemic bacterial or fungal co-infection plus
- Laboratory parameters supportive of cytokine storm including:
  - Serum IL-6 at least 3 X ULN; OR
  - Ferritin >300 ug/L (or surrogate) with doubling within 24 hours; OR
  - Ferritin > 600 ug/L at presentation with LDH >250 U/L; OR
  - Elevated D-dimer (> 1 mg/L).
- Need for supplemental O2 to maintain sats >92% or PaO2/FiO2 <300 mmHg plus
- At least 2 abnormal labs
  - CRP >100 or >50 but doubled in past 48 hours
  - LDH >250
  - Ferritin >500
  - D-dimer > 1000 ng/mL or
  - lymphocyte count <0.6x10^9/L.

**The Italian guidelines** recommend tocilizumab administration should be guided by the presence ≥ 1 of the following criteria:
- PaO2/FiO2 ratio <300 mmHg,
- Rapid worsening of respiratory gas exchange with or without availability of non-invasive or invasive ventilation
- IL-6 levels >40 pg/mL (or if not available D-dimer >1000 ng/mL).

They recommend repeat D-dimer, CRP, fibrinogen, and ferritin levels (+/- IL-6) before each administration, 24 hours from the last administration, and 36 hours from the last infusion of tocilizumab.

They also recommend that steroids are mandatory if tocilizumab is used:
- Methylprednisolone 1 mg/kg daily IV for 5 days followed by 40 mg daily x 3 days, followed by 10 mg daily x 2 days OR
- Dexamethasone 20 mg IV daily for 5 days, followed by 10 mg daily for 3 days, followed by 5 mg daily for 2 days).

**Current Situation at VMC**
1. We have limited supplies of Tocilizumab.
2. IL-6 which was used to trigger dosing Tocilizumab is a send out lab with a 4 to 7-day turnaround time.
3. Need to define what severe disease constitutes.

**Potential Solution**
Correspondence by Mehta, et al specifically in regards to COVID-19 recommends identification and treatment of hyperinflammation using existing approved therapies with proven safety profiles to address the immediate need to reduce rising mortality.

They discuss secondary hemophagocytic lymphohistiocytosis (sHLH) including cardinal features of unremitting fever, cytopenia’s, and hyperferritinemia and note that a cytokine profile resembling sHLH is associated with COVID-19 disease severity.

They recommend that severe COVID-19 patients be screened for:
1. Hyperinflammation using laboratory trends (increasing ferritin, decreasing platelets, or ESR) and
2. The HScore to identify the subgroup of patients for whom immunosuppression could improve mortality (steroids, IVIG, selective cytokine blockade with anakinra or tocilizumab, or JAK inhibition). The HScore generates a probability for the presence of sHLH.
   a. HScores >169 are 93% sensitive and 86% specific for HLH.
   b. See table below to calculate HScore or use the online HScore calculator at [http://saintantoine.aphp.fr/score/](http://saintantoine.aphp.fr/score/)
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Number of Points</th>
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<tbody>
<tr>
<td><strong>Temperature</strong></td>
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<tr>
<td>&lt;38.4 C</td>
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<tr>
<td>38.4-39.4 C</td>
<td>33</td>
</tr>
<tr>
<td>&gt;39.4 C</td>
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<tr>
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<tr>
<td>Hepatomegaly or splenomegaly</td>
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<tr>
<td>Hepatomegaly and splenomegaly</td>
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<tr>
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<td>One lineage</td>
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<td><strong>Triglycerides (mg/dL)</strong></td>
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<td><strong>Known immunosuppression including HIV positive or receiving long-term</strong></td>
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<tr>
<td>immunosuppression therapy (glucocorticoids, cyclosporine, azathioprine, etc)</td>
<td>No 0</td>
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<tr>
<td></td>
<td>Yes 18</td>
</tr>
</tbody>
</table>
Proposed VMC Guidelines for Tocilizumab

Criteria (all criteria #1 to #8 must be present):

Tocilizumab will be considered after 4-days of confirmed COVID-19 diagnosis in the following circumstances:

1. COVID-19 positive
2. Bilateral pulmonary infiltrates
3. Evidence of prolonged severe hypoxic respiratory failure defined as the presence of:
   a. Ventilator Dependent Severe Hypoxic Respiratory failure and
   b. P/F ratio < 200 despite at least 16 hours of prone ventilation +/- Inhaled flolan
4. At least 72 hours of up trending and abnormal inflammatory markers (any 2 (two) of the markers below):
   a. CRP > 100 or > 50 but doubled in past 48 hours
   b. LDH > 250
   c. Ferritin > 500
   d. D-dimer > 1000 ng/mL
   e. Lymphocyte count < 0.6x10^9/L.
5. HScore > 134; (note that presence of LFTS > 2X ULN qualifies for Hepatosplenomegaly = score of 38)
6. Absence of bacterial super/co-infection defined as:
   a. Blood/Trach aspirate/Urine cultures negative x 5-days or
   b. Serial daily negative procalcitonin x 5 days
7. Ideally a negative Quantiferon-TB Gold Plus** (ordered on admission); decision will be on a case by case basis
8. Completed 5-day course of Chloroquine or Plaquenil per COVID-19 recommended dosing schedule
9. Completed the first 24-hours of steroid therapy given as:
   a. 0.5mg to 1mg/Kg methylprednisolone or equivalent dexamethasone dose (to a maximum of 20mg) given daily x 5 to 7-days or
   b. Dexamethasone 20 mg IV daily for 5 days, followed by 10 mg daily for 3 days, followed by 5 mg daily for 2 days) or
   c. Methylprednisolone 1 mg/kg daily IV for 5 days followed by 40 mg daily x 3 days, followed by 10 mg daily x 2 day
10. Patients receiving Tocilizumab must continue and complete concomitant steroid therapy

To Order Tocilizumab:
- If patient meets all the criteria above
- Contact ID for approval at phone number 252-814-4296

Monitoring:

All patients admitted to the ICU with COVID-19 Pneumonia should have the following admission and Follow labs.

Admission labs/Parameters:

I. HLH Score documented on admission HPI see online version
   A. Note that presence of LFTS > 2X ULN qualifies for Hepatospleno megaly = score of 38
II. Quantiferon-TB Gold Plus
III. Routine Labs - CBC with Diff, Chem7, LFTs
IV. Procalcitonin
V. Inflammatory Markers - CRP, LDH, Ferritin, D-dimer, Fibrinogen, Triglyceride
VI. Radiology - CXR
VII. Cultures - Blood, Urine, Tracheal/Respiratory culture

Daily AM Labs:
I. Routine Labs - CBC with Diff, Chem7, LFTs
II. Procalcitonin
III. Inflammatory Markers - CRP, LDH, Ferritin, D-dimer, Fibrinogen, Triglyceride

After patient receives Tocilizumab
- Repeat inflammatory markers at 12-hours and 24-hours

Consider re-dosing Tocilizumab in 24 hours if
- If CRP at 24 hours does not drop 50% or greater than baseline pre-dosing CRP level AND
- Patient has persistent respiratory failure with no improvement in the clinical parameters for which initial dose was given. These clinical parameters include:
  - P/F Ratio
  - Hemodynamics
  - Persistent fever

Dose Recommendations:
A: Johns Hopkins Guidelines_Tocilizumab dosing guidelines:
- $>30$ kg: 8mg/Kg IV x 1 dose (Maximum single dose is 800mg)
  - Dose can be repeated 8 to 12 hours after preceding dose 2 additional times for a total of 3 doses.
- $<30$ Kg: 12mg/Kg IV x 1 dose (Maximum single dose is 800mg)

B: Chinese study: Used a flat dose of 400 mg with no mention of patient weight

C: VMC Proposed Dosing (after discussions with ID, critical care, heme/onc, and pharmacy and based on limited supply):
4 mg/kg based on actual body weight (max dose 800 mg). Clinical assessment and laboratory assessment (including CRP) to guide need for repeat dosing, which can be done 24 hours after the initial dose. Repeat doses are based on same criteria for initial dosing. Max 3 doses. Round dose to nearest vial size (either 80 mg or 200 mg vials depending on availability)

Potential Adverse Effects
1. Risk of latent TB reactivation, so suggest Quantiferon-TB Gold Plus (but would not wait on result as it might take 3-4 days to return)
2. Initiation in patients with an absolute neutrophil count below 2000/mm(3), platelet count below 100,000/mm(3), or ALT or AST above 1.5 times ULN is not recommended, but consider risk versus benefit
in those with severe or life-threatening cytokine release syndrome and cytopenias or in the presence of elevated liver enzymes.

3. Other adverse effects can include cytopenias, GI perforation, hepatitis, infusion reaction, bacterial infection.

These guidelines may change as knowledge about the disease evolves and/or as tocilizumab availability at VMC changes.

References:

1. FDA Approves Phase III Clinical Trial of Tocilizumab for COVID-19 Pneumonia
4. National Health Commission & State Administration of Traditional Chinese Medicine, Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia [Trial Version 7], March 2020