Tocilizumab (Actemra®)

A Review of Pertinent Drug Information for SARS-CoV-2

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• Tocilizumab is a humanized monoclonal antibody against human IL-6 receptor (IL-6R)
• Binds to membrane-bound and soluble forms of IL-6R
• Competitively inhibits IL-6 to IL-6R thereby inhibiting signal transduction
“Cytokine storm” as an immune response in viral infection is not a new concept (excellent review: PMID 22390970)

Pathogenesis of previous coronaviruses (SARS, MERS) suggests a cytokine storm is involved.\textsuperscript{1,2}

A recent study suggest the same may be true in COVID-19 infections.\textsuperscript{3}

Figure 2. Percentage of GM-CSF+ or IL-6+ cells from CD4+ T cells isolated from peripheral blood in healthy controls, ICU and non-ICU patients of 2019-nCoV.
### Purpose
Retrospectively evaluate efficacy of tocilizumab in treating severe or critical COVID-19 patients (N = 21)

### Inclusion

**Severe**
Any of the following:
1. RR $\geq 30$ bpm
2. $\text{SpO}_2 \leq 93$
3. $\text{PaO}_2 / \text{FiO}_2 \leq 300$ mmHg

**Critical**
Any of the following required ICU admission:
1. Mechanical ventilation
2. Shock
3. Organ failure

### Methods

- **Tocilizumab Dose:**
  400 mg IV once*
- All patients received SOC** for at least 7 days prior to tocilizumab, but had sustained fever, hypoxemia, and CT worsening.
- IL-6 measured by electrochemical luminescence (reference range: < 7 pg/ml).

### Results

- 81% (17/21) severe
- 19 % (4/21) critical

Baseline elevations seen in CRP and mean IL-6 levels
- Body temperature normalized within 24h in all patients
- 15 (75%) patients lowered their $\text{O}_2$ intake
- 17 (90.5%) patients with CT scan lesion improvement

### Conclusion
Tocilizumab appeared to improve clinical symptoms in patients with severe/critical COVID-19

**Note:**
- *Three patients had one repeat 400 mg dose due to persistence of fever within 12 hours.
- **Included lopinavir, methylprednisolone, symptom relievers, and $\text{O}_2$ therapy.
- RR: respiratory rate; ICU: intensive care unit; SOC: standard-of-care; CRP: C-reactive protein; ADR: adverse drug reaction.

Xu X, Mingfeng H, Tiantian L, et al. 2020. [https://t.co/2LmKN34HjM?amp=1](https://t.co/2LmKN34HjM?amp=1)
Limitations of Available Data

Randomized controlled trial results are not available at this time.

We still do not understand the complex nature of the immune response.

Cytokine measurements in peripheral blood may not correlate with immune response in deep tissues.

Link between cytokine response to therapy and disease outcomes is not well understood.

Questions remain from retrospective study by Xu and colleagues.

Use of tocilizumab therapy is not without risks.
Dosing

- FDA expanded approval in 2017 for CAR-T cell therapy-induced cytokine release syndrome (CRS) after review of pooled data from 9 prospective clinical trials.¹
- Age: ≥ 2 years; Grade 3 or 4 CRS
- Median time to first dose: 4 days (0–18 days)
- Based on PK analysis: Repeating up to 4 doses, 8 hours apart, would maintain previously observed safe blood concentrations

< 30 kg: 12 mg/kg IV
≥ 30 kg: 8 mg/kg IV (maximum: 800 mg per dose)

- Xu and colleagues used a one-time 400 mg IV dose, with a single repeat dose for patients with persistent fever within 12 hours²
  - 86% received one dose
  - Mean weight not provided in study

400 mg IV once

Immune therapy: for patients with extensive and bilateral lung disease and severely ill patients with elevated IL-6 levels, treatment with tocilizumab may be attempted. The initial dose should be 4-8mg/kg, with the recommended dosage being 400mg. Dilute with 0.9% saline to 100ml and infuse over the course of more than 1 hour. Repeat once after 12 hours (same dosage) if the response to the first dose was poor. Maximum two cumulative doses. Single maximum dose is 800mg. Pay attention to allergic reactions. Prohibited in patients with active infections such as tuberculosis.
Safety

• Xu et al 2020: No adverse drug events reported

• CAR-T cell CRS clinical trials: No specific assessments for the safety of tocilizumab, however, no reports of adverse reactions

• RA Clinical Trials: Meta-analysis has shown significantly higher risk of infection for 8 mg/kg dose compared to controls (in combination with other DMARDs; OR = 1.30; 95% CI 1.07, 1.58)
  • No increased incidence of malignancy, tuberculosis reactivation, or hepatitis
  • Cases of TB in patients taking tocilizumab have been reported in Japan

RA: Rheumatoid Arthritis; DMARD: disease-modifying antirheumatic drugs

# Adverse Drug Reactions

## Infections
- Serious and potentially fatal infections reported
- Most at risk: patients on immunosuppressive therapy and the elderly
- Do not administer to patients with active infections

## Tuberculosis (TB)
- Both reactivation of latent infection and new infections reported
- Patients should be screened for latent TB prior to initiating therapy
- Consider TB therapy for those with latent or active TB who have not been fully treated

## Liver Injury
- Canadian Safety Alert May 2019:
  - Serious cases reported, including cases of acute liver failure requiring transplant
  - Not recommended for patients with baseline ALT or AST >1.5 × ULN

## Neutropenia
- Reported in clinical trials and initial dosing studies
- Lack of association between neutrophil levels and infection rates
- Thought to be a margination effect rather than myelosuppression

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Drug-Drug Interactions

Immunosuppressants
- Including other DMARDs and tacrolimus
- However, studied in combination with other DMARDs for RA; risk vs. benefit

CYP3A4 Substrates
- Tocilizumab may decrease the serum concentration of CYP3A4 substrates
- Blockade of IL-6 may enhance CYP function

Clinical Pearls

• Who?
  • Criteria for use in resource-limited settings
    • Identifying and categorizing CRS (i.e. CTCAE criteria, Lee or Penn Scales, H-Score)
    • $$$: CAR-T vs SARS-CoV-2
    • Availability and turn-around time of IL-6 levels >> CRP
  • Rule out latent TB – utility in critically ill patients
  • Monitor other drugs (i.e. tacrolimus)

• What?
  • Dosing: flat dose vs weight-based; repeat doses

• When?
  • Optimal timing of administration
1. A multicenter, randomized controlled trial for the efficacy and safety of tocilizumab in the treatment of new coronavirus pneumonia (COVID-19)

2. Tocilizumab vs CRRT in Management of Cytokine Release Syndrome (CRS) in COVID-19 (TACOS)
   • More information available at: https://clinicaltrials.gov/ct2/show/NCT04306705?term=tocilizumab&cond=covid-19&draw=2&rank=1
Tocilizumab is a humanized monoclonal antibody against human IL-6 receptor (IL-6R)

It is currently approved to treat cytokine release syndrome (CRS) from chimeric antigen receptor T-cell (CAR-T) therapy for hematologic malignancies.

Since CRS may be involved in the pathogenesis of SARS-CoV-2, tocilizumab is under investigation for this indication.

Available data is limited to a single-center observational retrospective cohort study of 21 patients.

Safety profile includes increased risk for infection and potential liver injury.

In the pipeline: sarilumab (Kevzara)