FAQ: Tocilizumab for COVID-19, does it help and how should it be used?

There appears to be two distinct clinicopathologic phases of COVID-19, with the first characterized by the viral infection itself followed by a host inflammatory response phase (Figure 1). While the latter stage does not occur in most patients, it is characterized by a cytokine storm or cytokine release syndrome (CRS) involving a considerable release of proinflammatory cytokines such as IL-6, TNF-α, IL-12, GM-CSF, and IFN-γ. Complications of this syndrome include acute respiratory distress syndrome (ARDS), shock, and cardiac failure. Several treatment options for patients with severe immune-mediated complications associated with COVID-19 are under investigation. This FAQ outlines the role of tocilizumab in the treatment of patients with severe COVID-19.

IL-6 is an inflammatory cytokine produced by inflammatory macrophages and pathogenic T-cells in patients infected with the SARS-CoV-2 and is important in the development of CRS in COVID-19. It is hypothesized that tocilizumab, an anti-soluble IL-6 receptor monoclonal antibody, reduces complications from the cytokine storm (e.g., ARDS and mortality). Tocilizumab is currently indicated, among others, for severe chimeric antigen receptor (CAR) T cell induced cytokine release syndrome in adults, and it is also used in other chronic inflammatory syndromes such as rheumatoid arthritis. Serious but rare complications associated with tocilizumab use include intestinal perforation and secondary bacterial infections. More frequent but less severe adverse effects include neutropenia, thrombocytopenia, hyperlipidemia, and abnormal ALT and AST.

At this time, robust clinical data are not available to inform a recommendation either for or against the use of tocilizumab for patients with COVID-19; similarly NIH guidelines state there is insufficient data to recommend or discourage use of IL-6 inhibitors for treatment of COVID-19. However, several peer-reviewed and preprint studies have been published that provide insight on the potential benefits and risks associated with tocilizumab use for COVID-19. While there are ongoing controlled clinical trials, results from these clinical trials have not yet been published in peer-reviewed journals (6/15/2020).

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There are several challenges related to administering and monitoring tocilizumab for COVID-19 that clinicians should consider:

- Due to its immunomodulatory effects, tocilizumab should be avoided in patients with underlying bacterial co-infection. However, it is difficult to distinguish true cytokine storm or CRS from underlying bacterial co-infection in patients with COVID-19 since they both have the potential to produce sepsis-like symptoms.

- The timing of tocilizumab administration within the clinical course of COVID-19 is important. For example, early administration might have a contradictory harmful effect by allowing viral replication to go unchecked without impacting the harmful immune response and simultaneously increase the risk for secondary bacterial infections, while late administration might not prevent irreversible damage caused by the host immune response. Future peer-reviewed studies are needed to help elucidate when in the course of illness tocilizumab administration is most effective.

- The dose of tocilizumab evaluated in clinical trials published to date has been variable, and treatment duration has also varied from one-time doses to regimens containing up to 6 consecutive doses. However, current large clinical trials such as COVACTA and RECOVERY are typically dosing tocilizumab based on weight, e.g., COVACTA protocol uses 8 mg/kg up to 800 mg x1 and RECOVERY protocol allows a second dose allowed 12-24 hours later based on assessment that the patient has not improved.

- Tocilizumab monitoring also presents challenges. While IL-6 concentrations have been used to determine whether or not tocilizumab administration might be beneficial in patients with CRS, laboratory testing of IL-6 concentration is not readily available at many hospitals. Other biomarkers, including CRP, ferritin, fibrinogen, and D-dimer, often correspond with worsening respiratory failure in patients with COVID-19, but it is unclear how these laboratory values should be used to guide tocilizumab initiation or subsequent doses. Further, these biomarkers are not specific to CRS and cannot be used to rule out bacterial co-infection in the absence of other clinical data. There are preprint, non-peer reviewed studies suggesting patients with higher CRP values at baseline (>150mg/L) may benefit more from tocilizumab, suggesting monitoring CRP values may be an alternative to measuring IL-6. (see Tocilizumab Reference Table)

- Tocilizumab is associated with significant side effects that must be considered prior to initiation. Although published data to date have not demonstrated an increase in overall mortality, several notable adverse events have been reported in clinical trials including one patient that developed a gastrointestinal perforation requiring surgery.

In conclusion, immunomodulatory agents, such as tocilizumab, might reduce mortality and improve clinical outcomes related to ARDS and CRS in patients with COVID-19. However, we do not yet have robust data to guide appropriate timing, dosing, and duration of tocilizumab or clinical scenarios in which the potential benefit outweighs the risks. While the studies available at this time provide an important foundation, more robust clinical trials are required to make definitive conclusions regarding the role of tocilizumab in COVID-19.

For more detailed information on current studies evaluating tocilizumab see our Tocilizumab Reference Table.

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References: