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Practical aspects of targeting IL-6 in COVID-19 disease

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ABSTRACT

Severe cases of COVID-19 are often attended by a syndrome that has been described as "cytokine storm," with some features shared with macrophage activation syndrome. A variety of experimental therapies targeting this hyperinflammatory state are now being applied in hospitals around the world. Among the most widely used treatments are monoclonal antibodies targeting interleukin-6 (IL-6) or the IL-6 receptor. Anti-IL-6 drugs are being widely used experimentally and as off-label therapy for patients with COVID-19 who are sick and deteriorating but have a reasonable chance of recovering, but they are still unproven and unapproved for this use. The pandemic has created major ethical and practical questions about patient selection and nonapproved use vs use in the context of a randomized clinical trial.

INTRODUCTION

COVID-19 is a mild to moderate, self-limiting disease in approximately 80% of cases, but more severe in the rest, with 5% or more of patients requiring intensive care and with a mortality rate of 1% to 2%.[1] In the most severe forms of the disease, the course is often attended by a syndrome that has been described as "cytokine storm," with some features shared with macrophage activation syndrome.[2] A variety of experimental therapies targeting this hyperinflammatory state are now being applied in hospitals around the world. Of note, however, the US Centers for Disease Control and Prevention[3] makes no recommendations for the use of any specific agent for treating COVID-19, since no agent has regulatory approval.

Among the most widely used treatments are monoclonal antibodies targeting interleukin-6 (IL-6) or the IL-6 receptor (**Table 1**). While these drugs have been widely used to treat a variety of immune-mediated diseases, including cytokine release syndrome secondary to chimeric antigen receptor T cell (CAR-T) therapy, they have not been frequently used in intensive care. Thus, this brief review is designed to provide practical information on their use and safety in treating COVID-19.

RATIONALE AND BACKGROUND FOR TARGETING IL-6

IL-6 is a cytokine with broad-ranging effects on both immune function and a host of nonimmune physiologic functions affecting the liver, kidneys, central nervous system, muscles, and bone as well as glucose and lipid metabolism.[4] More relevant to COVID-19 disease, however, is its central role as a driver of inflammation. C-reactive protein (CRP), a key acute-phase reactant, can be viewed as a downstream secondary messenger for IL-6 and thus is a reliable biomarker of its activity.[4]

The currently available anti-IL-6 drugs were first approved for autoimmune disorders, and in 2017 tocilizumab was also approved for treating cytokine release syndrome accompanying CAR-T therapy of cancer, a syndrome akin to the hyperinflammatory phase of COVID-19 disease.[5] Cytokine dysregulation has been studied in previous viral pneumonias, ie, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), and SARS has been associated with higher levels of proinflammatory cytokines that lead to T-cell depletion and pulmonary inflammation with extensive lung disease. IL-6 levels were noted be elevated in SARS and correlated with disease severity.[6] Several anticytokine therapies have been proposed for treating the hyperinflammatory phase of COVID-19, targeting IL-1 and most notably IL-6.[7]

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TABLE 1
Currently available IL-6 inhibitors

Agent	Mechanism of action	Current FDA-approved indications and dosing	Contraindications and cautions
Tocilizumab (Actemra)	Binds to soluble and membrane-bound IL-6 receptors and inhibits IL-6-mediated signaling	**Rheumatoid arthritis:** 4 mg/kg IV every 4 weeks (up to 8 mg/kg every 4 weeks); 162 mg SQ every other week (up to every week) **Giant cell arteritis:** 162 mg SQ once weekly or every other week **Polyarticular juvenile idiopathic arthritis:** 8 mg/kg IV every 4 weeks (10 mg/kg if < 30 kg); 162 mg SQ every other week (every 3 weeks if < 30 kg) **Systemic juvenile idiopathic arthritis:** 8 mg/kg IV every other week (12 mg/kg if < 30 kg); 162 mg SQ every week (every other week if < 30 kg) **Cytokine release syndrome** (due to CAR-T cell therapy): 8 mg/kg IV (10 mg/kg if < 30 kg)	**Avoid use** in patients with: • ANC < 2,000/mm^3 • Platelet count < 100,000/mm3 • ALT/AST > 1.5 x ULN • Tuberculosis or latent tuberculosis infection **Use with caution** in patients with: • Serious active infection • Increased risk of gastrointestinal perforation
Sarilumab (Kevzara)	Binds to soluble and membrane-bound IL-6 receptors and inhibits IL-6-mediated signaling	**Moderately to severely active rheumatoid arthritis:** 200 mg SQ every other week	**Avoid use** in patients with: • ANC < 2,000/mm^3 • Platelet count < 150,000/mm^3 • ALT/AST > 1.5 x ULN • Tuberculosis or latent tuberculosis infection **Use with caution** in patients with: • Serious active infection • Increased risk of gastrointestinal perforation
Siltuximab (Sylvant)	Binds to IL-6 and prevents binding of IL-6 to soluble and membrane-bound IL-6 receptors	**Multicentric Castleman disease:** 11 mg/kg IV over 1 hour every 3 weeks until treatment failure	**Use with caution** in patients with: • Serious active infection • Increased risk of gastrointestinal perforation

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; CAR-T = chimeric antigen receptor T cell; IV = intravenously; SQ = subcutaneously; ULN = upper limit of normal

Thus far, there are limited data on the results of IL-6-targeting in COVID-19 patients.[8] The studies so far have reported promising clinical results for patients with severe disease but need to be replicated in robust clinical trials. Two large international trials of tocilizumab (ClinicalTrials.gov Identifier NCT04320615) and sarilumab (ClinicalTrials.gov Identifier NCT04315298) are under way and promise to rapidly recruit patients to allow generation of data. In the meantime, IL-6 inhibitors are being used off-label in many centers. An analysis of patients with COVID-19 who have been treated with tocilizumab at Cleveland Clinic is also under way.

PRINCIPLES OF SAFETY

Targeting of IL-6 carries several warnings and safety concerns.

An increased risk of infections with long-term use is prominent among the concerns.[9] IL-6 inhibitors are associated with a rate of serious and opportunistic infections similar to that with other biologic agents, though these data are derived from chronic use, as opposed to the acute application in the current setting. Further, a body of data from studies in animals suggests that IL-6 plays an important role in defense against infections in general and in particular

against viral infections.[10] Most of these studies were in animals completely deficient in IL-6 signaling, which is different from partial neutralization over a few days. The infectious complications of IL-6 inhibition in the acute setting will not be known until a large number of patients is analyzed. Still, an active and uncontrolled secondary infection with bacteria, fungi, or mycobacteria would be a strong reason not to embark on a course of IL-6 inhibition.

Gastrointestinal perforations. IL-6 inhibitors are also associated with a higher incidence of gastrointestinal perforations (1 to 2 per 1,000 patient-years compared with tumor necrosis factor inhibitor use),[11] which may be relevant in acutely decompensating COVID-19 patients. Thus, vigilance is warranted. Patients who have had diverticulitis in the past are in theory at increased risk, but such a history by itself should not be a contraindication to single use of this therapy in severe COVID-19.

Laboratory abnormalities. Neutralization of IL-6 can be associated with leukopenia, thrombocytopenia, and aminotransferase elevations. Chronic use of anti-IL-6 agents is also associated with perturbations of serum lipids, though this is not a concern in the acute setting. Nevertheless, clinicians should be aware of these laboratory associations.

Safety in pregnancy or breastfeeding has not been established.

PATIENT SELECTION

For patients with COVID-19 pneumonia who are rapidly deteriorating with progression to acute respiratory distress syndrome (ARDS), there are limited data to direct the management of the hyperinflammatory state. An international task force led by the American Thoracic Society made no recommendations for or against IL-6 targeting.[12] Nevertheless, IL-6 targeting is actively being used at many centers.

At present, the ideal candidate for IL-6-directed therapy remains unknown. In general, reasonable candidates may be similar to those in a case series reported by Xu et al,[5] ie, patients with:

- Severe pneumonia, with hypoxemia while breathing room air (Spo_2 < 94%), tachypnea (respiratory rate > 30 breaths/min), or Pao_2/Fio_2 ratio < 300, or
- Critical pneumonia, defined as requiring mechanical ventilation, being in circulatory shock, or multiorgan failure requiring intensive care unit admission.

Given the similarities of COVID-19 to cytokine release syndrome, several biomarkers have been proposed to aid in identifying those likely to respond. These include marked and progressively rising elevations in serum CRP, ferritin, IL-6, and D-dimer and lymphopenia.[13,14] Of note, in most medical centers, IL-6 measurement is a "send-out" test that entails a delay in obtaining the results.

DOSING, ADMINISTRATION, AND RESPONSE

Most patients with COVID-19 who have been treated with an anti-IL-6 drug received tocilizumab, an IL-6 receptor antagonist that is currently approved for treatment of CAR-T therapy-induced cytokine release syndrome, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and rheumatoid arthritis. At the time of this writing, 2 case series have been published describing the use of tocilizumab in the setting of COVID-19.[5,15]

Xu et al[5] described 21 patients with COVID-19 who received tocilizumab in a single center in China. Tocilizumab was given as a single intravenous dose of 400 mg; 3 patients received a second 400-mg dose within 12 hours due to persistent fever. Of the patients, 81% were described as having severe illness, 19% were considered to have critical illness, and 10% required invasive ventilation. The mean white blood cell (WBC) count was 6.3×10^9/L before tocilizumab administration, 8.05 on day 1 after tocilizumab, 6.02 on day 3, and 5.25 on day 5. The corresponding lymphocyte percentages were 15.52%, 11.78%, 16.93%, and 22.62%, and the mean CRP levels were 75.06, 38.13, 10.61, and 2.72 mg/L. At the time of publication, 19 patients had been discharged and none had died.

Luo et al[15] described 15 patients who received tocilizumab at a single center in Wuhan, China. Tocilizumab was given at doses ranging from 80 to 600 mg per dose; most patients received a single dose, but 5 received multiple doses. Additionally, 8 patients received methylprednisolone concurrently. Most of patients were classified as being seriously or critically ill. After receiving tocilizumab, CRP levels trended down in all but one patient. Of note, after tocilizumab administration, serum IL-6 levels increased in 12 of the 15 patients, which is to be expected due to formation of tocilizumab-soluble IL-6 receptor complex.[16] At the time of publication, 3 of the 15 patients had died.

Although the authors of both studies concluded that tocilizumab was effective in this patient population, there were significant limitations including lack of a control group. We anxiously await the results of

more robust studies and clinical trials.

The appropriate dosing regimen of tocilizumab in this patient population is currently unknown, as no randomized clinical trials or dose-finding studies of tocilizumab in COVID-19 patients have yet been published. In the aforementioned case series, the dose was between 80 and 600 mg. In cytokine release syndrome due to CART therapy, the recommended dose is 8 mg/kg intravenously (for patients over 30 kg).[17] Currently, numerous clinical trials of tocilizumab are under way in patients with COVID-19, with doses ranging from 4 to 8 mg/kg, most with a maximum dose of either 400 or 800 mg and most recommending only 1 dose, but some allowing repeat administration after a specified period of time. Additionally, 1 study is evaluating the dosing of tocilizumab for COVID-19 and is randomizing noncritically ill patients to receive either 200 mg or 80 mg of tocilizumab.[18] Although there is no standardized regimen for this patient population, dosing regimens of 4 to 8 mg/kg intravenously appear reasonable at this time.

Regarding the number of doses to be administered, the best approach is unknown, but at this time, no clinical trial is evaluating more than 2 doses of tocilizumab, and thus it is reasonable to provide a single dose, and if fever and associated symptoms do not approve, a second dose is reasonable to administer 12 hours after the initial dose.

EXPECTED EFFECT ON BIOMARKERS

For now, the most important response to monitor this therapy is clinical, but there is a strong rationale to use appropriate biomarkers to aid in clinical decision-making, both for patient selection and for monitoring the response to therapy. As noted above and consistent with the known effects of toclizumab in other cytokine-release settings, a number of readily available clinical biomarkers that are abnormal at baseline[19] can be monitored, including CRP, ferritin, and D-dimer, though the optimal rate and degree of response is yet undefined.[5] As mentioned above, it is well documented that IL-6 levels will rise in the short term after administration of IL-6 receptor targeting agents, so it is not appropriate to monitor IL-6 levels when using tocilizumab. Results of the aforementioned multicenter trials currently under way will provide a rich assessment of clinical and laboratory biomarkers and are eagerly awaited.

CONCLUSIONS

Anti-IL-6 drugs are being widely used experimentally and as off-label therapy for patients with COVID-19 who are sick and deteriorating but have a reasonable chance of recovering, but they are still unproven and unapproved for this use. The pandemic has created major ethical and practical questions about patient selection and nonapproved use vs use in the context of a randomized clinical trial. Pandemics such as this one suggest that we cannot wait for perfect data from randomized trials when there are reasonable data available that suggest potential efficacy without demonstrated major safety concerns.

This review is an attempt to provide practical information as to why, how, and when to target IL-6, and how to do so safely. We eagerly await the ability to define the standard of care, which will ultimately only be determined by properly performed trials.

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