

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

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■ ABSTRACT

Interleukin 6 (IL-6) took center stage as a therapeutic target, given its role in the cytokine storm phase of COVID-19. While IL-6 inhibitors have been widely used to treat a variety of immune-mediated disease states, they have not been used often in the intensive care setting, and new data question their efficacy. This brief review provides practical information on their administration and safety.

■ CURRENT STATUS OF INTERLEUKIN 6-TARGETING

The natural history of COVID-19 is one of a mild-moderate, self-limiting disease in approximately 80% of patients, but a more severe disease in the remainder, requiring intensive care in 5% and carrying a mortality rate of 1% to 2%.¹ In patients with the most severe forms of the disease the course is frequently 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 are being applied in hospitals around the world targeting this hyperinflammatory state. Early on, interleukin 6 (IL-6) took center stage as a therapeutic target given its role in the cytokine storm phase of COVID-19,³ and numerous studies have investigated the efficacy of IL-6 inhibitors in this setting. New data have come

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to light questioning the efficacy of this class of targeted therapies, though they are still being utilized in ongoing trials and presumably are being used off-label in extreme circumstances. The currently available agents are listed in **Table 1**.

While these drugs have been widely used to treat a variety of immune mediated disease states, including cytokine release syndrome secondary to chimeric antigen receptor T-cell (CART) therapy, they have not been frequently used in the intensive care setting. In this review, we provide practical information on their administration and safety.

■ RATIONALE AND BACKGROUND FOR TARGETING IL-6

IL-6 is a cytokine with broad-ranging effects on immune function and on a host of nonimmune physiologic functions affecting liver, kidney, central nervous system, muscle, and bone, as well as on 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 for its activity.⁴

While currently available anti-IL-6 drugs were first approved for autoimmune disorders, tocilizumab was also approved for treatment of cytokine release syndrome accompanying CART therapy of cancer, a syndrome akin to the hyperinflammatory phase of COVID-19 disease. Cytokine dysregulation has been studied in previous viral pneumonias (severe acute respiratory syndrome coronavirus and Middle East respiratory syndrome) and has been associated with increased levels of pro-inflammatory cytokines that lead to T-cell depletion and pulmonary inflammation with extensive lung disease. IL-6 levels were noted to be elevated and correlated with disease severity.⁵ However, serum IL-6 levels are only modestly ele-

TABLE 1
Currently available interleukin 6 (IL-6) inhibitors

	Tocilizumab (Actemra)	Sarilumab (Kevzara)	Siltuximab (Sylvant)
Mechanism of action	Tocilizumab and sarilumab: Bind to soluble and membrane-bound IL-6 receptors and inhibit IL-6-mediated signaling		Binds to IL-6 and prevents binding of IL-6 to soluble and membrane-bound IL-6 receptors
Approved indications and dosing	<p>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)</p> <p>Giant cell arteritis: 162 mg SQ once weekly or every other week</p> <p>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)</p> <p>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)</p> <p>Cytokine release syndrome (due to chimeric antigen receptor T-cell therapy): 8 mg/kg IV (10 mg/kg if < 30 kg)</p>	Moderately to severely active rheumatoid arthritis: 200 mg SQ every other week	Multicentric Castleman disease: 11 mg/kg IV over 1 hour every 3 weeks until treatment failure
Contraindications	<p>Tocilizumab, sarilumab, and siltuximab:</p> <ul style="list-style-type: none"> Safety data are insufficient to recommend use of these agents during pregnancy or breastfeeding Use with caution in patients with serious active infection or increased risk of gastrointestinal perforation <p>Tocilizumab and sarilumab: avoid use in patients with</p> <ul style="list-style-type: none"> ANC < 2,000/mm³ Platelet count < 100,000/mm³ ALT/AST > 1.5 x ULN Tuberculosis or latent tuberculosis infection 		
COVID-19 dosing	4-8 mg/kg IV for one or two doses (doses given within 24 hours of each other) Maximum dose: 800 mg IV	200 mg SQ once 400 mg IV once	11 mg/kg IV once
Current COVID-19 clinical trials	NCT04317092, NCT04335071, NCT04320615, NCT04306705, NCT04310228, NCT04335305, NCT04333914, NCT04339712, NCT04330638, NCT04322773, NCT04331795, NCT04332094, NCT04332913, NCT04331808	NCT04341870, NCT04315298, NCT04327388, NCT04324073, NCT04321993, NCT04322773	NCT04329650, NCT04322188, NCT04330638

ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; IV = intravenously; SQ = subcutaneously; ULN = upper limit of normal

vated in COVID-19 compared with other conditions associated with acute respiratory distress syndrome (ARDS) and often considered under the umbrella of cytokine storm.⁶

■ RESULTS OF CLINICAL TRIALS

Over the past several months, numerous nonrandomized studies of IL-6 inhibition in patients with severe COVID-19 infection have been published, and the results have been generally positive.⁷ It should be emphasized, however, that many of these trials suffer from confounders, including inability to account for the progressive improvement in overall management of patients with severe COVID-19, variability in timing of therapy, and use of numerous and nonstandardized concomitant therapies. Similar criticisms have been made of the positive uncontrolled trials of hydroxychloroquine, an agent that has totally failed when put to the test in rigorous randomized controlled trials.⁸ Most importantly, larger, well-designed international randomized controlled trials for tocilizumab (COVACTA, [clinicaltrials.gov NCT04320615](https://clinicaltrials.gov/NCT04320615)) and for sarilumab ([clinicaltrials.gov NCT04315298](https://clinicaltrials.gov/NCT04315298)) were stopped early for futility. While results of these large clinical trials have not yet been published, their results question the efficacy of IL-6 for the treatment of COVID-19.

Reasons these studies may have failed include the timing of drug administration and the way patients were stratified into study groups. It is possible that post hoc subgroup analyses could show trends toward efficacy in different patient populations.

Large trials still under way include REMDACTA (NCT04409262), which is evaluating the efficacy and safety of remdesivir plus tocilizumab in patients with severe COVID-19 pneumonia, and the large tocilizumab arm of the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial (850 patients, and larger than COVACTA), and we anxiously await their results.

At this juncture, we believe there is still reason for the use of anti-IL-6 therapies in clinical trials, but we question its off-label use given the mounting evidence for modest effects and the positive results in the dexamethasone arm of the RECOVERY trial.⁹

■ PRINCIPLES OF SAFETY

Targeting IL-6 carries a series of warnings and safety concerns. Clearly prominent is the increased risk of infection, which attends its chronic use.¹⁰ IL-6 inhibitors are associated with rates of serious and opportunistic infections similar to those of other

biologic agents, though these data are derived from the chronic rather than the acute application in the current setting. Furthermore, a body of data from pre-clinical models suggests an important role of IL-6 in defense against infections in general, and in particular against viral infections.¹¹ Most of these models use 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 are analyzed. Still, an active and uncontrolled secondary bacterial, fungal, or mycobacterial infection would be a strong reason not to embark on a course of IL-6 inhibition.

IL-6 inhibitors are also associated with an increase in gastrointestinal perforations (1–2 per 100 patient-years compared with tumor necrosis factor inhibitor use),¹² which may be relevant in patients with acutely decompensating COVID-19; thus, vigilance is warranted. Patients with previous diverticulitis are theoretically at increased risk, but this should not be a contraindication to single use of this therapy in the extreme.

From a laboratory perspective, neutralization of IL-6 can be associated with leukopenia, thrombocytopenia, and elevations of hepatic transaminases, and considerations for discontinuation of the currently available agents are summarized broadly in **Table 1**. Chronic administration 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 using IL-6 inhibitors should be aware of these laboratory associations.

■ PATIENT SELECTION

For patients with COVID-19 pneumonia who are rapidly deteriorating with progression to ARDS, there are limited data to direct the management of the hyperinflammatory state. A guidance document by the international task force led by the American Thoracic Society makes no recommendations for or against IL-6 targeting (<https://www.thoracic.org/professionals/clinical-resources/disease-related-resources/covid-19-guidance.pdf>). Early on in the pandemic, many centers were actively using IL-6 inhibitors in the treatment of severe COVID-19; however, this has slowed since press releases of COVACTA and the sarilumab study were publicized.

At present, the ideal candidate for IL-6-directed therapy has not yet been defined. Potential candidates are patients with severe pneumonia—classi-

fied as hypoxemia on room air (peripheral oxygen saturation < 94%) and tachypnea (respiratory rate > 30 breaths per minute), with or without a partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 mm Hg—and patients with critical pneumonia, defined as requiring mechanical ventilation and involving circulatory shock, with or without multiorgan failure requiring intensive care.

Given the similarities to cytokine release syndrome, a series of biomarkers have been proposed to aid in identifying patients likely to respond and include marked and progressively rising elevations in serum CRP, ferritin, IL-6, and D-dimer, and lymphopenia.^{13,14} Note that IL-6 in most medical centers is a “send-out” test associated with a delay in obtaining results.

■ DOSING, ADMINISTRATION, AND RESPONSE

The majority of patients with COVID-19 treated with anti-IL-6 therapy have received tocilizumab, which is currently labeled for the treatment of CART therapy-induced cytokine release syndrome, giant cell arteritis, polyarticular juvenile idiopathic arthritis, systemic juvenile idiopathic arthritis, and rheumatoid arthritis.

The appropriate dosing regimen of tocilizumab in COVID-19 is currently unknown. A nonrandomized trial by Somers et al, in which 78 COVID-19 patients on mechanical ventilation received tocilizumab, utilized the standard 8-mg/kg intravenous (IV) dose (maximum 800 mg).⁷ In cytokine release syndrome due to CART therapy, the recommended IV tocilizumab dose is 8 mg/kg for patients over 30 kg (www.gene.com/download/pdf/actemra_prescribing.pdf).

A number of trials of tocilizumab in patients with COVID-19 are under way, with doses ranging from 4 to 8 mg/kg, most with a maximum dose of 400 or 800 mg, and most recommending only one dose, but some allowing repeat administration after a specified period of time. Clearly, there is no standardized regimen for this patient population, but dosing regimens of 4 to 8 mg/kg IV appear reasonable at this time.

■ EXPECTED EFFECT ON BIOMARKERS

For now, the most important response to monitor this therapy is clinical, but there is a strong rationale for using appropriate biomarkers to aid in clinical decision-making, both for patient selection and for monitoring response to therapy. As noted above and consistent with known effects of tocilizumab in other cytokine release settings, a number of readily

available clinical biomarkers that are abnormal at baseline¹⁵ can be monitored, including CRP, ferritin, and D-dimer, though the optimal rate and degree of response are yet undefined.

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.

■ CONCLUSIONS

IL-6 targeting has been widely utilized experimentally and also off-label in selected patients with COVID-19 who are sick and deteriorating. Yet it is currently an unproven and unapproved for therapy of COVID-19, and its place in treatment is less than certain. We continue to eagerly await the ability to define the standard of care, which will ultimately only be determined by properly performed trials.

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