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# Role for Anti-Cytokine Therapies in Severe Coronavirus Disease 2019

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**Objectives:** The causative agent for coronavirus disease 2019, severe acute respiratory syndrome coronavirus 2, appears exceptional in its virulence and immunopathology. In some patients, the resulting hyperinflammation resembles a cytokine release syndrome. Our knowledge of the immunopathogenesis of coronavirus disease 2019 is evolving and anti-cytokine therapies are under active investigation. This narrative review summarizes existing knowledge of the immune response to coronavirus infection and highlights the current and potential future roles of therapeutic strategies to combat the hyperinflammatory response of patients with coronavirus disease 2019.

**Data Sources:** Relevant and up-to-date literature, media reports, and author experiences were included from Medline, national newspapers, and public clinical trial databases.

**Study Selection:** The authors selected studies for inclusion by consensus.

**Data Extraction:** The authors reviewed each study and selected appropriate data for inclusion through consensus.

**Data Synthesis:** Hyperinflammation, reminiscent of cytokine release syndromes such as macrophage activation syndrome and hemophagocytic lymphohistiocytosis, appears to drive outcomes among

adults with severe coronavirus disease 2019. Cytokines, particularly interleukin-1 and interleukin-6, appear to contribute importantly to such systemic hyperinflammation. Ongoing clinical trials will determine the efficacy and safety of anti-cytokine therapies in coronavirus disease 2019. In the interim, anti-cytokine therapies may provide a treatment option for adults with severe coronavirus disease 2019 unresponsive to standard critical care management, including ventilation.

**Conclusions:** This review provides an overview of the current understanding of the immunopathogenesis of coronavirus disease 2019 in adults and proposes treatment considerations for anti-cytokine therapy use in adults with severe disease.

**Key Words:** coronavirus; inflammation; interleukin-1; interleukin-6; pneumonia, viral; sepsis

The coronavirus disease 2019 (COVID-19) pandemic has brought the manifold consequences of inflammation into sharp focus for the medical and lay communities (1). While our understanding of the pathobiology of COVID-19 remains incomplete, one hypothesis proposes that the most severe complications of infection with this virulent virus arise from overzealous innate immune responses, akin to other viral sepsis syndromes (2, 3). Although we have just begun to approach rigorous and data-driven understanding of this complex disease, clinical management decisions depend on the most recent published evidence, despite its incomplete and nascent nature. This review lays out the current state of knowledge regarding the role of cytokine biology in COVID-19 and how this background informs the potential use of anti-cytokine therapies to combat complications of severe COVID-19.

## IMMUNOPATHOLOGY OF SEVERE ACUTE RESPIRATORY SYNDROME CORONAVIRUS 2

The causative agent of COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), enters the upper respiratory tract primarily through airborne droplets (4, 5). Ubiquitous

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expression of angiotensin-converting enzyme 2 (ACE2), the cellular receptor for SARS-CoV-2, provides a fertile cellular environment for SARS-CoV-2 replication in the nose, throat, and lungs (6–8). The receptor-binding domain of the SARS-CoV-2 spike protein possesses greater affinity for ACE2 than that of SARS-CoV-1, the causative agent of the 2002–2003 SARS pandemic (9, 10).

After approximately 1 week of mild fever, cough, fatigue, anorexia, and myalgia, a subset of infected individuals develops dyspnea and hypoxemia that herald progression to severe COVID-19 with potential for rapid decompensation and acute respiratory distress syndrome (ARDS). This complication, particularly when it requires mechanical ventilation, often proves fatal (11–14). Other tissues that express ACE2, such as the heart (15, 16), have proven vulnerable to SARS-CoV-2 and SARS-CoV-1 (17–20).

Progression to severe COVID-19 coincides with increasing levels of inflammatory biomarkers (Fig. 1). Anecdotal experience suggests that patients decompensate more suddenly and rapidly than expected based upon experience with other viral pneumonias. In comparison to other coronaviruses and respiratory viruses, SARS-CoV-2 induces a weak type I, II, and III interferon response and strong activation of the interleukin (IL)–1/IL-6 pathway (21–24). SARS-CoV-1 and Middle East respiratory syndrome coronavirus produce interferon antagonist proteins that may explain the impaired interferon response observed in SARS-CoV-2 (25). SARS-CoV-2 may activate directly pro-inflammatory pathways through tumor necrosis factor  $\alpha$ -converting enzyme (TACE or a disintegrin and metalloproteinase 17, ADAM17) and loss of ACE2's counter-regulatory function (26, 27).

The exuberant IL-1/IL-6 response to SARS-CoV-2 appears to contribute importantly to patient symptomology and outcomes (Fig. 2). In the lung, coronavirus infection of type II alveolar epithelial cells activates the inflammasome, a multiprotein complex that produces mature IL-1 $\beta$  (28), as well as mature IL-18 (another

pro-inflammatory cytokine) and N-terminal gasdermin-D (the pore-forming protein that permits release of IL-1 $\beta$  from cells) (29–31). After maturation, IL-1 $\beta$  induces chemokine secretion and adhesion molecule expression (32, 33). IL-1 $\beta$  amplifies the inflammatory response by inducing endothelial cell and vascular smooth muscle cell secretion of IL-6, which can activate a broad array of cell types (34, 35). An auto-induction amplification loop whereby IL-1 $\beta$  induces IL-1 $\beta$  secretion perpetuates these actions (36–38).

IL-1 $\beta$  expression and activity in patients with COVID-19 exceed that of healthy controls (39, 40). IL-6 and C-reactive protein, both downstream of IL-1 $\beta$ , can serve as biomarkers of IL-1 activity. Patients with severe COVID-19 exhibit greater elevations in IL-6 and C-reactive protein than those with moderate COVID-19 (41, 42). Higher IL-6 levels predict both ARDS occurrence and death in adults with COVID-19 (43). While IL-6 concentrations begin to rise approximately 2 weeks after illness onset in COVID-19 nonsurvivors, they remain stable in COVID-19 survivors (44). This innate immune response has been compared to chimeric antigen receptor T cell-induced cytokine release syndrome, secondary hemophagocytic lymphohistiocytosis, and macrophage activation syndrome (45).

An intriguing finding among patients with COVID-19 is early depletion and late functional exhaustion of CD4+ T cells (40, 44, 46–48), potentially due to direct viral infection via CD147 (49–51) or migration of T cells to the lungs. Since CD4+ T cells regulate the innate immune response, their depletion may promote a second wave of cytokine release and pulmonary immune cell infiltration (52). Indeed, lower lymphocyte and interferon- $\gamma$  expressing CD4+ T cell counts portend worse outcomes in COVID-19 (44, 48). Helper (CD3+CD4+), suppressor (CD3+CD8+), and regulatory (CD3+CD4+CD25+CD127low+) T cell counts may be lower in severe COVID-19 cases than in moderate cases (39, 42). Concentrations of IL-10, an anti-inflammatory cytokine, also are higher in severe COVID-19

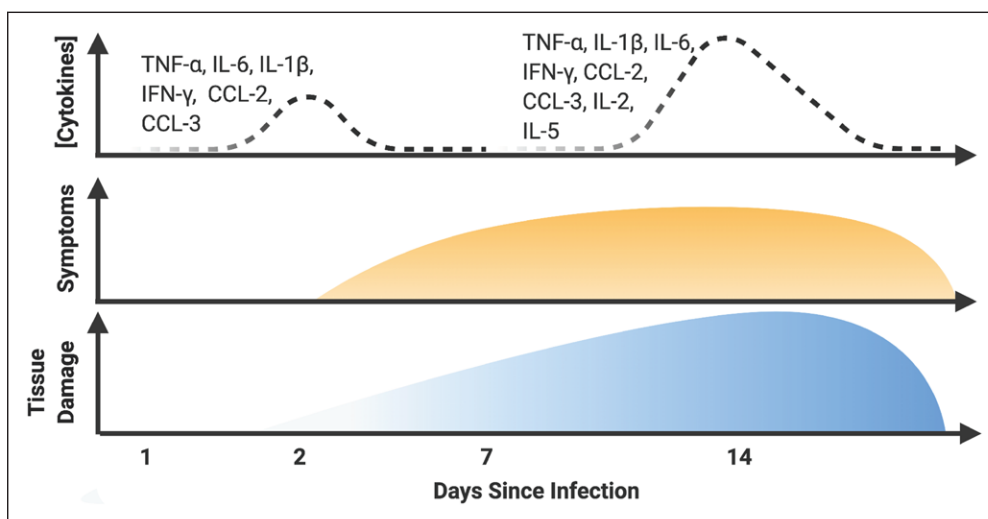
cases, likely representing a counter-regulatory response (39). The mechanisms of inflammation resolution in COVID-19 warrant further research (53).

## IL-1 BLOCKERS IN COVID-19

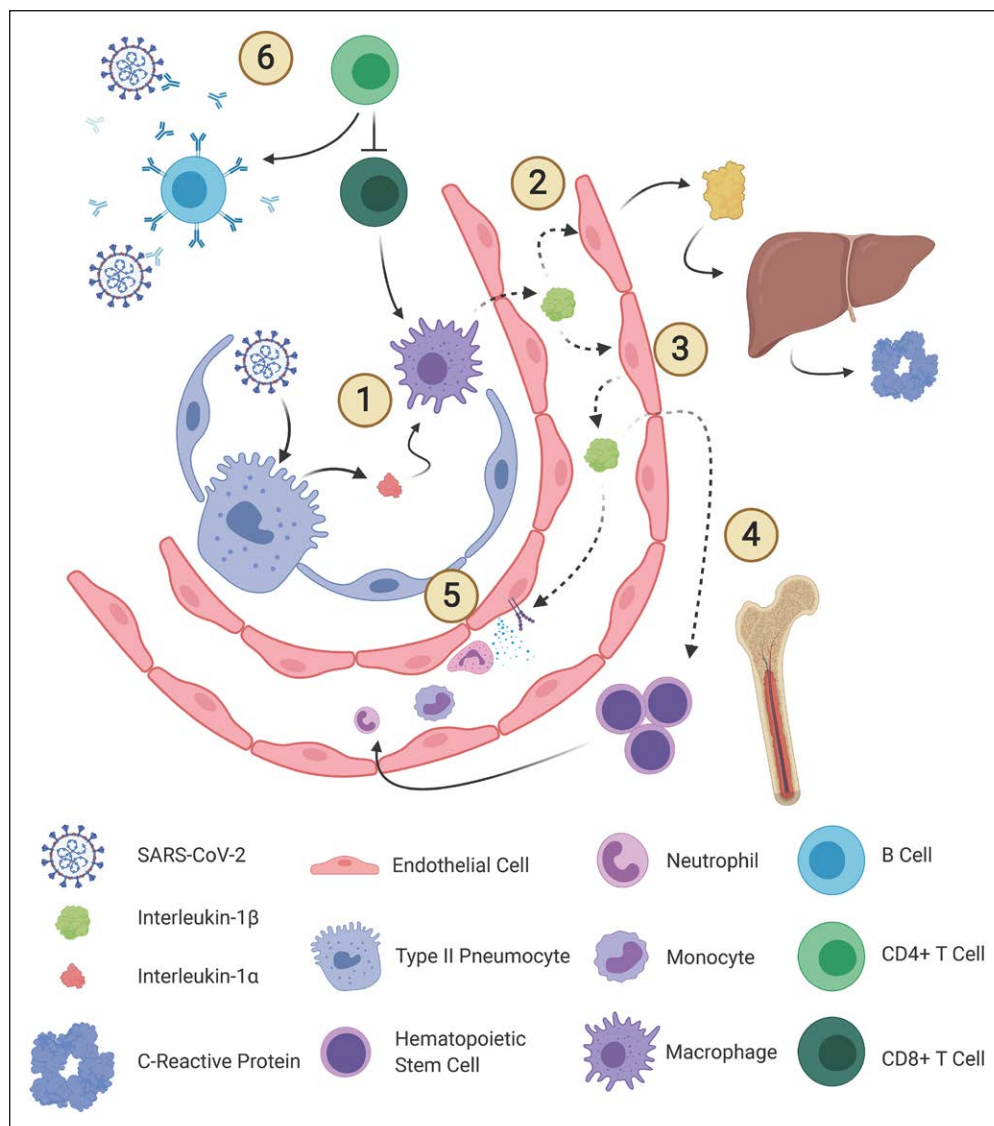
### Pharmacology of IL-1 Blockers

Three distinct pharmacologic options can interrupt IL-1 activity (Fig. 3) (54).

Although anakinra, canakinumab, and rilonacept are approved for subcutaneous administration (Table 1; and Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCX/A262>), the IV route may be preferred in critically ill patients based upon experience with anakinra in patients with severe sepsis and hemophagocytic lymphohistiocytosis syndrome (55). Canakinumab and rilonacept have longer half-lives that allow for



**Figure 1.** Infiltration of key immune cells and activity of key cytokines in coronavirus disease 2019 (COVID-19). This hypothetical diagram portrays how the second wave of inflammatory activity may be a major determinant of outcome in COVID-19. This second wave features both innate and adaptive cytokines. This diffuse cytokine release syndrome damages not only the lungs but also the heart, kidneys, and other organs. Identification of patients at risk for a cytokine release syndrome and prompt treatment with direct and selective inhibitors of the inflammasome, interleukin (IL)–6, or IL-1 ( $\beta$  or  $\alpha$ ) may prevent severe organ damage. IFN- $\gamma$  = interferon gamma, TNF- $\alpha$  = tumor necrosis factor- $\alpha$ .



**Figure 2.** Roles of interleukin (IL)-1 $\beta$  in coronavirus disease 2019. IL-1 $\beta$  is a primordial pro-inflammatory cytokine that plays multiple roles in innate immunity (1). After detecting damage-associated molecular patterns released from type 2 pneumocytes, sentinel immune cells, such as alveolar macrophages, activate IL-1 $\beta$  through the inflammasome (1). IL-1 $\beta$  then exerts pleiotropic paracrine and endocrine effects. IL-1 $\beta$  promotes secretion of IL-6 (2) as well as IL-1 $\beta$  (3) from endothelial cells. IL-6 initiates hepatic production of acute phase reactants, among many inflammatory actions. IL-1 $\beta$  initiates hematopoietic progenitor cell proliferation (4) and facilitates infiltration of neutrophils and monocytes by upregulating adhesion molecule expression and chemokine secretion (5). Exhausted CD4+ T cells can fail to execute antibody-mediated viral clearance, which allows a second, more powerful, and destructive wave of cytokine activity (6). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immune evasion tactics also impair the immune response. CCL = chemokine ligand.

expanded dosing intervals, but the shorter half-life of anakinra allows for more rapid clearance of the drug upon discontinuation (56, 57).

Organ dysfunction occurs commonly in critically ill adults with COVID-19. Anakinra and riloncept have been used in patients with end-stage renal disease on hemodialysis in patients without COVID-19 (58, 59). Renal dysfunction has minimal effects on the pharmacokinetics of monoclonal antibodies such as canakinumab (60). Dose adjustments are not recommended for anakinra, riloncept, or canakinumab in patients with hepatic dysfunction. None of the IL-1 blockers appear to cause hepatic toxicity.

## Efficacy and Safety of IL-1 Blockade

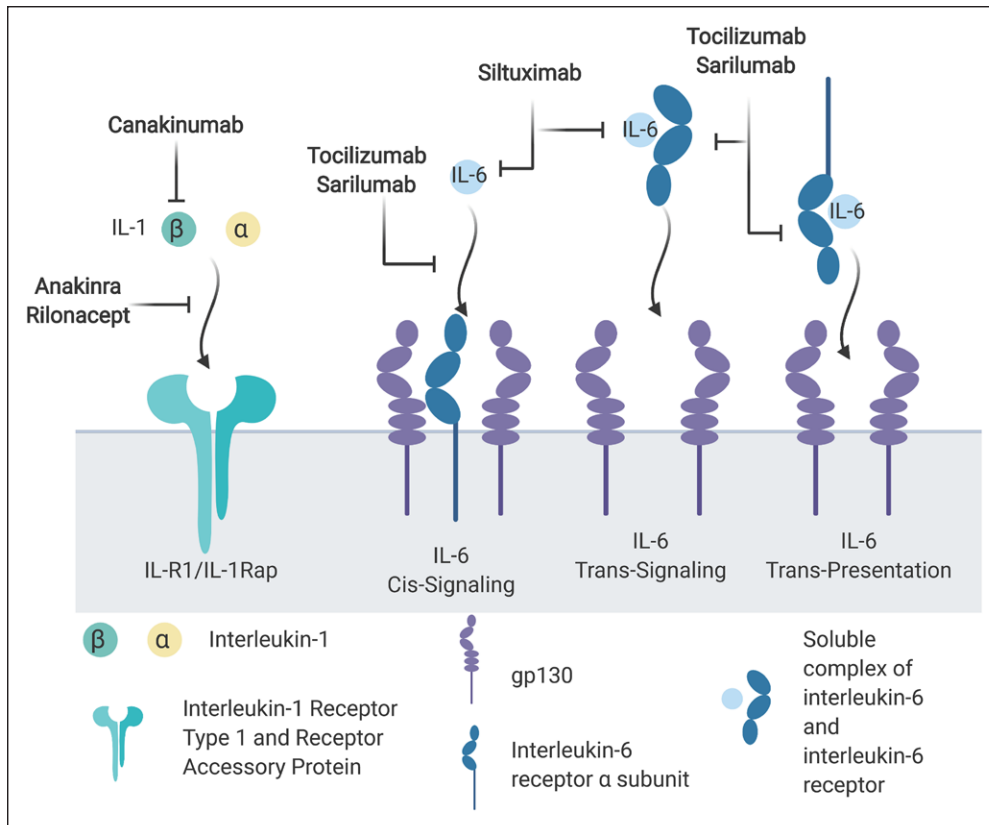
Evidence to support the efficacy of IL-1 blockade in COVID-19 includes two case series and extrapolation of human and experimental studies of other cytokine release syndromes, including notable data from severe sepsis clinical trials. Several randomized clinical trials with anakinra and canakinumab are underway (Table 1; and Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCX/A262>).

Cavalli et al (61) reported that 21 of 29 patients (72%) with COVID-19 who received IV anakinra (5 mg/kg bid for a median of 9 d) experienced clinical improvement, defined as a 75% or greater reduction in serum C-reactive protein concentration and a  $\text{PaO}_2:\text{FiO}_2$  ratio of greater than 200 mm Hg for 48 hours and 26 of the 29 survived (90%) through day 21 (only 56% of a historical control group survived to day 21). A series of eight patients who received IV anakinra (200 mg every 8 hr for 7 d or 300 mg daily for 7 d followed by 100 mg once daily), showed no significant changes in C-reactive protein concentration, but the  $\text{PaO}_2:\text{FiO}_2$  ratio increased (62). At the end of follow-up, three patients were dead, four remained on mechanical ventilation, and one patient who did not require ICU admission was discharged alive. Similarly, a case series of five patients with COVID-19 reported that C-reactive protein and temperature declined while  $\text{PaO}_2:\text{FiO}_2$  ratio increased after anakinra 100 mg IV every 8 hours and a retrospective analysis of 10 patients who received

canakinumab 300 mg subcutaneously demonstrated a more rapid reduction in C-reactive protein levels and a faster improvement in  $\text{PaO}_2:\text{FiO}_2$  ratio when compared to a historical control group (63, 64).

A separate case series reported the efficacy and safety of anakinra 100 mg bid for 72 hours followed by 100 mg daily for 7 days (100 mg daily for 72 hr followed by 100 mg every other day for 7 d if creatinine clearance < 30 mL/min or on dialysis) in patients hospitalized with COVID-19 who did not require ICU admission compared to a historical control group (65). After multivariate adjustment, anakinra-treated patients had a significantly lower risk of death or mechanical ventilation than usual care historical





**Figure 3.** Pharmacologic interleukin (IL)-1 and IL-6 inhibitors. IL-1 $\beta$  and IL-1 $\alpha$  initiate intracellular signaling by binding the IL-1 receptor (IL-1R) type 1, which recruits the IL-1 receptor accessory protein (IL-1Rap). IL-6 binds to the IL-6 receptor  $\alpha$  as well as two glycoprotein (gp) 130 receptors. Three possible scenarios lead to IL-6 signaling. IL-6 binds cell surface IL-6 receptor and gp130 in cis signaling. Trans signaling occurs when soluble IL-6/IL-6 receptor complex binds membrane-associated gp130. Last, plasmacytoid dendritic cells can present IL-6/IL-6 receptor to gp130 on T helper cell (Th) 17 cells.

controls (hazard ratio, 0.22; 95% CI, 0.10–0.49). Anakinra significantly reduced C-reactive protein within 48–72 hours.

Two landmark clinical trials investigated the efficacy and safety of anakinra in patients with severe sepsis not due to SARS-CoV-2 (66–68). The isolated organisms were most frequently bacteria and fungi. All participants received background antimicrobial therapy. While anakinra did not reduce mortality in these studies, this short-term (up to 72 hr), high-dose anakinra regimens did not increase the risk of bacterial superinfection, a concern in patients with COVID-19. A post hoc analysis found that anakinra reduced mortality in the subgroup of patients with hepatobiliary dysfunction and disseminated intravascular coagulation, two features consistent with macrophage activation syndrome (69). Anakinra appears effective in patients with hemophagocytic lymphohistiocytosis syndrome and in animals with chimeric antigen receptor T cell-induced cytokine release syndrome (55, 70, 71). Anakinra also demonstrates safety and efficacy in a range of acute inflammatory cardiovascular conditions (72).

## IL-6 BLOCKERS IN COVID-19

### Pharmacology of IL-6 Blockers

IL-6's three distinct signaling pathways render targeting its activity complex (Fig. 3) and thus the three approved IL-6 monoclonal

antibodies differ in their pharmacological effects on the IL-6 pathway (Table 1; and Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCX/A262>) (35, 73, 74).

Tocilizumab should be given IV, as the cytokine release syndrome appears to accelerate tocilizumab clearance (75). Sarilumab and siltuximab have delayed onset of action when administered subcutaneously (76, 77). Renal impairment dose adjustments are not required for any of the IL-6 blockers. The prescribing information for tocilizumab, sarilumab, and siltuximab recommend treatment interruptions or discontinuations for elevated hepatic transaminase concentrations or decreases in neutrophil or platelet counts.

Potential serious adverse effects of tocilizumab and sarilumab include elevations of hepatic transaminases, increases in serum cholesterol and triglyceride concentrations, and opportunistic infection. Tocilizumab increased low-density lipoprotein cholesterol levels by 11% and triglyceride levels by 14% at 4 weeks in adults with rheumatoid arthritis (78). Two case reports illustrate the potential for tocilizumab to contribute to acute pancreatitis (79). The long half-life of these agents (30–40 hr and 8–10 d for IV tocilizumab and subcutaneous sarilumab, respectively) may constitute a disadvantage if adverse effects do occur. IL-6 blockade restores cytochrome P450 activity; therefore, doses of concomitant therapies with narrow therapeutic windows metabolized by cytochrome P450 substrates require close monitoring. Because IL-6 concentrations increase after tocilizumab treatment due to circulation of the cytokine-antibody complex, IL-6 cannot serve as a treatment response biomarker (80).

### Efficacy and Safety of IL-6 Blockade

There are several ongoing studies with the different IL-6 receptor blockers in patients with COVID-19 (Table 1; and Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCX/A262>). Two trials have reported preliminary or interim results. One announcement reported that tocilizumab met its primary outcome of death or need for mechanical ventilation in a randomized trial of 129 patients with moderate-severe COVID-19. Detailed results of this clinical trial remain unreported (81). A press release indicates that an ongoing sarilumab adaptive clinical trial will proceed with enrollment of only severe or critical patients with COVID-19 based upon analysis of initial results (81). Tocilizumab has an approved indication for chimeric antigen

**TABLE 1. Potential Anti-Cytokine Therapies for Coronavirus Disease 2019**

Characteristic	Anakinra	Canakinumab	Tocilizumab	Sarilumab	Adalimumab
Type	Recombinant human receptor antagonist	Human monoclonal antibody	Humanized monoclonal antibody	Human monoclonal antibody	Human monoclonal antibody
Target	Interleukin-1 receptor	Interleukin-1 $\beta$	Interleukin-6 receptor	Interleukin-6 receptor	Tumor necrosis factor- $\alpha$
Approved indication(s)	RA, CAPS	CAPS, TRAPS, HIDS/MKD, FMF, and SJIA	RA, giant cell arteritis, polyarticular juvenile idiopathic arthritis, SJIA, chimeric antigen receptor T cell-induced cytokine release syndrome	RA	Crohn's disease, ulcerative colitis, ankylosing spondylitis, RA, SJIA, SJPA, plaque psoriasis, hidradenitis suppurativa, uveitis
Black box warnings	None	None	Increased risk of serious infection	Increased risk of serious infection	Increased risk of serious infection and malignancy
Usual subcutaneous dose regimen	100 mg once daily subcutaneously	30 to 150 mg every 4–8 wk (depending on indication/body weight) may titrate to clinical response in CAPS, TRAPS, HIDS/MKD, and FMF	162 mg weekly or every other week depending upon body weight and clinical response	200 mg every 2 wk	10–160 mg every other week depending upon age, indication, and body weight; loading dose required for certain indications
Usual or studied IV dose regimen	Studied as 100 mg loading dose followed by 2 mg/kg/hr for 72 hr	Studied as 0.3, 1, 3, or 10 mg/kg on day 1 and day 15	Approved as 4–12 mg/kg every 2–4 wk depending upon indication and body weight	NA	NA
COVID-19 clinical trial dose regimen	–10 mg/kg bid until 75% C-reactive protein reduction and Pao <sub>2</sub> :Fio <sub>2</sub> $\geq$ 200 mm Hg for 2 d –100 mg IV every 4 hr dose for 15 d –200 mg IV every 8 hr –100 mg subcutaneous daily for 28 d	–450 to 750 mg IV once based on patient weight –300 or 600 mg IV once	4–8 mg/kg or 400 mg once (maximum 800 mg/dose), may repeat	200–400 mg once; may repeat in 48–72 hr	Unknown
Select COVID-19 clinical trials <sup>a</sup>	NCT04324021 NCT04339712 NCT04330638	NCT0436281 NCT04365153	NCT04320615 NCT04317092 NCT04346355 NCT04315480	NCT04315298 NCT04327388 2020-001162-12	ChiCTR2000030089

CAPS = cryopyrin-associated periodic syndrome, ChiCTR = Chinese Clinical Trial Registry, COVID-19 = coronavirus disease 2019, FMF = familial Mediterranean fever, HIDS/MKD = hyperimmunoglobulin D syndrome/mevalonate kinase deficiency, NA = not available, NCT = National Clinical Trial, RA = rheumatoid arthritis, SJIA = systemic juvenile idiopathic arthritis, TRAPS = tumor necrosis factor receptor associated periodic syndrome.

<sup>a</sup>NCT accessed at [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov); ChiCTR accessed at <http://www.chictr.org.cn/abouten.aspx>.

receptor T cell-induced cytokine release syndrome (75). There are no studies of IL-6 blockers in patients with severe sepsis due to non-COVID-19 causes.

Observational studies suggest that tocilizumab rapidly decreases fever, reduces systemic inflammation over 5–7 days and associates with improved indices of oxygenation within 48–72 hours, and decreased risk of intubation or mortality (80,

82–87). For example, a case series of 20 patients who received tocilizumab for COVID-19 reported that C-reactive protein concentration decreased to less than 2 mg/L within 5 days, oxygen requirements decreased, and all patients survived to hospital discharge (82). Additionally, variation in background antiviral and immunosuppressive therapies across studies and across patients within studies further argues for cautious

interpretation of these results. Nevertheless, clinicians must make treatment decisions using clinical judgment and these limited data until completion and full reporting of COVID-19 clinical trials.

## POTENTIAL ROLE OF OTHER ANTI-CYTOKINE THERAPIES IN COVID-19

SARS-CoV-1, and presumably SARS-CoV-2, activate TACE/ADAM17 during the process of gaining host cell entry and can increase circulating tumor necrosis factor- $\alpha$  levels (26, 27, 88). The commercially available tumor necrosis factor- $\alpha$  inhibitors include adalimumab (human monoclonal antibody), etanercept (fusion protein), infliximab (chimeric monoclonal antibody), golimumab (human monoclonal antibody), and certolizumab pegol (humanized fragment antigen binding fragment) (Table 1). Like IL-1 blockade, tumor necrosis factor- $\alpha$  antagonism does not appear to increase the risk of secondary infection in patients with sepsis receiving background antimicrobial therapy (89, 90). One ongoing clinical trial is investigating tumor necrosis factor blockade and others have called for research on this therapeutic in COVID-19 (91). Biosimilar tumor necrosis factor- $\alpha$  blockers have become available (Supplemental Table 1, Supplemental Digital Content 1, <http://links.lww.com/CCX/A262>).

Glucocorticoids, given their broad-spectrum immune-suppressing effects, have seen wide use in patients with severe COVID-19 for the treatment of cytokine release syndrome and ARDS. Although the Surviving Sepsis Campaign suggests use of short courses of glucocorticoids for moderate-severe ARDS related to COVID-19, evidence supporting their benefit is lacking in this population and concerns that their use may prolong viral shedding persist (92, 93). Preliminary results from the Randomised Evaluation of COVID-19 Therapy trial reported that dexamethasone 6 mg daily for up to 10 days significantly reduced all-cause mortality in patients hospitalized for COVID-19. Subgroup analysis suggested significantly greater reductions in mortality for dexamethasone in patients receiving invasive mechanical ventilation (29.0% vs 40.7%;  $p < 0.001$ ) and those receiving oxygen without invasive mechanical ventilation (21.5% vs 25.0%;  $p = 0.002$ ). All-cause mortality rates for dexamethasone in patients not receiving invasive mechanical ventilation or oxygen was 17.0% versus 13.2% for usual care.

## SECONDARY AND OPPORTUNISTIC INFECTIONS IN COVID-19

In the advanced stages of COVID-19 disease, immune exhaustion and inhibition of usual defense mechanisms such as ciliary clearance can favor bacterial superinfection as in other severe viral pneumonitides. Anti-cytokine treatments may impair further host defenses and/or delay the recognition of infection. The absolute risk associated with short-term treatment may be acceptable in patients with life-threatening cytokine release syndrome.

IL-1 blockade has a favorable safety profile as demonstrated by the minimal increase in risk of fatal and lack of opportunistic infection associated with long-term canakinumab treatment (94). Chronic IL-6 and tumor necrosis factor- $\alpha$  blockade predispose

to opportunistic infection, and all IL-6 and tumor necrosis factor blockers carry a black box warning for serious infection. In patients with bacterial or fungal severe sepsis on background antimicrobial therapy, short-term use of IL-1 or tumor necrosis factor- $\alpha$  blockers does not increase the risk of infection. Clinicians should consider testing for latent tuberculosis, hepatitis B, and hepatitis C during hospital admission in patients who receive an IL-6 or tumor necrosis factor- $\alpha$  blocker.

## THERAPEUTIC CONSIDERATIONS FOR ANTI-CYTOKINE THERAPIES IN COVID-19

Current treatment for severe COVID-19 includes supportive respiratory and hemodynamic care. No agent has received approval from the U.S. Food and Drug Administration for the treatment of severe COVID-19, but randomized trials of many therapeutic candidates are ongoing (95). While the optimal COVID-19 treatment would be an effective antiviral intervention, the high mortality of hospitalized patients with COVID-19 complications mandate adjunctive therapies as well (96).

Important unanswered questions include the target population for use (including the severity of COVID-19, age, comorbidities, the underlying immunologic profile [i.e., chemokine concentrations, immune cell function, inflammation resolution, and anti-inflammatory mediators], the presence of chronic or acute organ dysfunction), the optimal time to initiate therapy (asymptomatic, mild, or severe), the optimal dose and duration (related to the disease severity), the optimal biomarkers and clinical indicators of response, the use of concomitant agents (some of which may have immunomodulating effects), and the prevalence and risk factors for safety concerns. The heterogeneity of the sepsis syndrome poses a further barrier to implementation of anti-cytokine therapies in COVID-19 (97).

Indeed, improving outcomes in the heterogeneous population of adults with severe sepsis remains a challenge (98, 99). The specific risks and benefits of each anti-cytokine agent must be thoughtfully considered within the context of particular patients and diverse populations. Furthermore, clinicians and investigators should continue to explore strategies beyond cytokine blockade, such as immune stimulation with checkpoint inhibitors to promote viral clearance given the profound lymphopenia prevalent among patients with severe COVID-19, although these agents have their own toxicities.

Both the National Institutes of Health and the Surviving Sepsis Campaign concluded that current evidence is insufficient to issue recommendations related to the use of anti-cytokine therapies in COVID-19 (92, 100). Several institutions have made their own treatment protocols available publicly (101–104). Research is needed to identify patient subgroups with differential therapeutic responses to anti-cytokine therapies (69, 97).

Anti-cytokine therapies may offer an important treatment option in COVID-19. Of considerable concern, SARS-CoV-2 may cycle through the population, and we must prepare for recurring waves of involvement. Such resurgence may well occur before the development and testing of a vaccine. Furthermore, even if a vaccine were available, one cannot assume that COVID-19 will not

mutate rendering a vaccination approach incompletely protective. Last, the elderly and those with cardiometabolic risk factors who have high susceptibility to severe COVID-19 generally mount weaker responses to vaccination than younger individuals.

## CONCLUSIONS

Our understanding of the immunopathogenesis of COVID-19 in adults has evolved rapidly. For COVID-19 adults with a cytokine release syndrome clinical picture, clinicians must currently rely on anecdotes and observational studies to guide treatment decisions regarding anti-cytokine therapies. Prospective randomized trials evaluating a number of different anti-cytokine therapies in adults with COVID-19 are underway. New evidence will continue to inform clinicians about the role for anti-cytokine therapy in critically ill adults with COVID-19.

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