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Immunomodulatory Therapeutic Proteins in COVID-19: Current Clinical Development and Clinical Pharmacology Considerations

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic caused by infection with SARS-CoV-2 has led to more than 600 000 deaths worldwide. Patients with severe disease often experience acute respiratory distress characterized by upregulation of multiple cytokines. Immunomodulatory biological therapies are being evaluated in clinical trials for the management of the systemic inflammatory response and pulmonary complications in patients with advanced stages of COVID-19. In this review, we summarize the clinical pharmacology considerations in the development of immunomodulatory therapeutic proteins for mitigating the heightened inflammatory response identified in COVID-19.

Keywords

biologics, clinical pharmacology, COVID-19, immunomodulatory, review

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by newly emergent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It belongs to the beta-coronavirus family and is phylogenetically close to the severe acute respiratory syndrome (SARS) virus.[1] As of August 1, 2020, SARS-CoV-2 infection has been confirmed in more than 17 million people worldwide and has caused 680,894 deaths, as reported on the World Health Organization website. About 5% to 10% of COVID-19 patients developed lung injury and respiratory distress that progressed to acute respiratory distress syndrome (ARDS).[2]

According to statistics emerging from around the world, different demographics may have different susceptibilities to COVID-19. Patients who are male, elderly, or with preexisting medical conditions are facing worse outcomes with higher death rates in this pandemic.[3] Other potential risk factors that have been identified to date include race/ethnicity, background comedications, and poverty and crowding, among others.[4] At this time, no drugs or other therapeutics have been approved by the U.S. Food and Drug Administration (FDA) to prevent or treat COVID-19.[5] In May 2020, the FDA issued an emergency use authorization for the drug remdesivir, authorizing its emergency use by licensed health care providers to treat adults and children hospitalized with severe COVID-19.[6,7] Current clinical management includes secondary infection prevention, symptom control, and supportive care, such as supplemental oxygen and mechanical ventilatory support when indicated.[4]

Although most drug development programs take years before an effective drug can reach the market, drug development programs and regulatory review of potential COVID-19 therapies consider the urgent need for treatment and prevention options while adhering to the FDA's robust standards for demonstrating the safety and effectiveness of drug products. Clinical pharmacology is playing an increasingly crucial role in assessing drug activity, efficacy, and safety during development and regulatory review. Although COVID-19 presents a significant challenge from both drug development and regulatory review standpoints, it offers

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a unique opportunity for the clinical pharmacology community to facilitate the clinical development of therapies.[8] In this review, we summarize the role of clinical pharmacology during the COVID-19 pandemic, focusing on immunomodulatory therapeutic proteins.

Rationale for Immunomodulatory Therapeutic Proteins in COVID-19

Currently, no drugs, biologics, or other therapeutics have been approved by the FDA to prevent or treat COVID-19. Because clinical information about the optimal management of COVID-19 is evolving quickly, recommendations by the COVID-19 Treatment Guidelines Panel on the use of any agents for pre- or post-exposure prophylaxis against SARS-CoV-2 in patients with COVID-19 outside the clinical trial setting are updated frequently as published data and other authoritative information become available.[9] In the clinical trial setting, consideration of clinical manifestation is critical to any antiviral or immunomodulatory treatment strategy. Patients infected with SARS-CoV-2 can experience a range of clinical manifestations, from no symptoms to critical illness.[10] The symptomatic phases include: (1) mild illness, with such signs and symptoms as fever, cough, sore throat, malaise, headache, muscle pain without shortness of breath or abnormal imaging; (2) moderate illness, with evidence of lower respiratory disease; (3) severe illness, with dyspnea, hypoxia, or evidence of greater than 50% lung involvement on imaging tests; and (4) critical illness, with respiratory failure, septic shock, and/or multiple organ dysfunction. The Chinese Center for Disease Control and Prevention reported that of 44 500 confirmed infections, most infected patients (80%) experienced mild or moderate forms of the illness, 14% developed severe illness, and 5% developed critical illness.[11]

The 4 clinical manifestations seem to be controlled by the underlying 2 distinct but overlapping pathologic subsets: viral pathogenicity and host inflammatory response, based on which Siddiqui et al proposed a staging system to characterize the disease course of COVID-19.[12] During the first week of infection, the innate immunity reaction is involved, followed by the adaptive immunity reaction starting jn about the second week, including antigen-specific T cells and antibodies that are produced for more efficient viral clearance and blocking. In the initial stage of the illness, most patients experience mild to moderate forms of illness and recover on their own with minimal intervention. A minority of COVID-19 patients will transition to the severe and critical stages of the illness, which manifest as an extrapulmonary systemic hyperinflammation syndrome. The aggravation of symptoms often is associated with increased levels of acute-phase reactants (erythrocyte sedimentation rate, C-reactive protein [CRP], ferritin), coagulopathy (elevated titers of D-dimers, disseminated intravascular coagulation), and cell lysis (serum creatine kinase, lactate dehydrogenase).[13,14] These clinical and laboratory parameters are correlated with increased levels of proinflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α.[15-17] Massive and rapid release of these detrimental proinflammatory mediators, identified as a so-called cytokine storm, is associated with ARDS and multiple organ failure.[18] As such, the potential of immunomodulatory therapeutic proteins in blocking the inflammatory pathway has been hypothesized to prevent or mitigate disease progression of COVID-19. These also likely provide additional benefits in conjunction with the standard of care and with other potential treatments such as high doses of polyvalent immunoglobulins or convalescent serum.[15] These hypotheses of immunomodulatory therapeutic proteins in COVID-19 are being evaluated in various clinical settings and are elaborated below.

Current Status of Clinical Development of Immunomodulatory Therapeutic Proteins for COVID-19

In this review, we classify immunomodulatory therapeutic proteins in 2 categories: (1) FDA-approved drug products, and (2) drug products that have not been FDA-approved but are currently under investigation for illnesses other than COVID-19 (Table 1). Both categories involve repurposed drugs being evaluated for their ability to control the underlying hyperinflammatory syndrome in advanced stages of COVID-19. The available nonclinical and clinical experience is helpful for scientists in selecting candidate therapeutic proteins. For therapeutic proteins already approved for other indications, the known or anticipated benefits and risks for the approved indication(s), as well as reasonably anticipated adverse events, can be used to aid the benefit/risk assessment in COVID-19-related clinical trials. For novel investigational therapeutic proteins still in the early development stages, information on benefits and risks mostly is obtained from limited early clinical data and nonclinical assessment; therefore, they likely involve a higher degree of uncertainty than do the repurposed approved therapeutic proteins. At this writing, more than 110 COVID-19-related clinical studies evaluating immunomodulatory therapeutic proteins have been registered in clinicaltrials.gov (Supplemental Table). We categorize these registered clinical studies by the corresponding immunomodulatory targets (Figure 1) and summarize them below.

Table 1. List of Immunomodulatory Therapeutic Proteins in Interventional COVID-19 Trials

Repurposed Therapeutic Proteins			
Mechanism of Action	Therapeutic Proteins	Approved Dosing[a]	Evaluated Dosing in COVID-19[b]
IL-6 inhibitor	Actemra (tocilizumab)	RA: 4 mg/kg IV every 4 weeks followed by an increase to 8 mg/kg IV every 4 weeks based on clinical response; 162 mg SC every 2 weeks followed by an increase to every week based on clinical response (<100 kg) or 162 mg SC every week (>100 kg). GCA: 162 mg SC every week or every 2 weeks based on clinical considerations. PJIA: 10 mg/kg IV every 4 weeks (<30 kg), 8 mg/kg IV every 4 weeks (≥30 kg); 162 mg SC every 3 weeks (<30 kg), 162 mg SC every 2 weeks (≥30 kg). SJIA: 12 mg/kg IV every 2 weeks (<30 kg), 8 mg/kg IV every 2 weeks (≥30 kg); 162 mg SC every 2 weeks (<30 kg), 162 mg SC every week (>30 kg). CRS: 12 mg/kg IV (<30 kg), 8 mg/kg IV (≥30 kg), up to 3 additional doses with at least 8 hours apart may be needed.	8 mg/kg IV up to maximum of 800 mg, up to 1 additional dose may be given (multiple trials). 162 mg SC × 2 doses + tocilizumab 162 mg SC × 2 doses at 12 hours on day 1 (NCT04332094). 200 or 800 mg IV up to 2 doses (NCT04331795).
IL-6 inhibitor	Kevzara (sarilumab)	RA: 200 mg SC every 2 weeks.	400 mg IV (NCT02735707, NCT04341870). 400 mg SC (NCT04359901). 200 mg SC × 2 (NCT04357808). 200 or 400 mg SC (NCT04357860).
IL-6 inhibitor	Sylvant (siltuximab)	MCD: 11 mg/kg IV every 3 weeks.	5 mg/kg IV (NCT04380961). 11 mg/kg IV (NCT04329650).
IL-1 inhibitor	Kineret (anakinra)	RA: 100 mg/day SC. CAPS: starting dose of 1-2 mg/kg SC daily, titrated up to 8 mg/kg SC daily.	100 mg once daily SC for 28 days or until discharge (NCT04330638). 400 mg/day IV on days 1-3. 200 mg/day IV on days 4-10 (NCT04364009). 300 mg/day IV for 5 days then tapering (NCT04366232). 200 mg IV 3 times a day for 7 days (NCT04339712).
IL-1 inhibitor	Ilaris (canakinumab)	TRAPS, HIDS/MKD, FMF: 2 mg/kg SC, can be increased to 4 mg/kg SC every 4 weeks (≤40 kg); 150 mg SC, can be increased to 300 mg SC every 4 weeks (>40 kg). CAPS: 150 mg SC every 8 weeks (>40 kg); 2 mg/kg SC, can be increased to 3 mg/kg (15-40 kg). Still's disease: 4 mg/kg (maximum 300 mg) SC every 4 weeks (>7.5 kg).	150 mg/mL SC (NCT04348448). 300 or 600 mg IV (NCT04365153). 450 mg IV (40 to <60 kg). 600 mg IV (60-80 kg). 750 mg IV (>80 kg). (NCT04362813)
IFN-γ inhibitor	Gamifant (emapalumab-lzsg)	HLH: 1 mg/kg IV twice per week.	IV infusion every third day for a total of 5 infusions. Day 1: 6 mg/kg. Days 4, 7, 10, and 13: 3 mg/kg (NCT04324021).
TNF-α inhibitor	Remicade (infliximab)	RA: 3 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks. AS: 5 mg/kg IV at 0, 2, and 6 weeks, then every 6 weeks. CD, UC, Ps, PsA: 5 mg/kg IV at 0, 2, and 6 weeks, then every 8 weeks.	5 mg/kg IV (NCT04425538).
VEGF inhibitor	Avastin (bevacizumab)	Various metastatic cancers: weight-based dosing up to 15 mg/kg IV every 2 or 3 weeks.	7.5 mg/kg IV (NCT04344782, NCT04305106). 500 mg IV (NCT04275414).
C5 inhibitor	Soliris (eculizumab)	PNH, aHUS, NMOSD: weight-based dosing IV with loading once every week and every 2 weeks thereafter.	1200 mg IV on days 1, 4, 8, then 1200 or 900 mg on day 12 depending on the monitoring of plasma level and CH5O and sC5B9 and maintenance doses of 900 mg on days 15, 18, and 22 (NCT04346797).

Table 1. Continued

Repurposed Therapeutic Proteins			
Mechanism of Action	Therapeutic Proteins	Approved Dosing[a]	Evaluated Dosing in COVID-19[b]
C5 inhibitor	Ultomiris (ravulizumab-cwvz)	PNH, aHUS: weight-based dosing up to 3600 mg IV every 4 or 8 weeks.	Weight-based IV dosing on days 1, 5, 10, and 15 (NCT04369469).
PD-1 inhibitor	Opdivo (nivolumab)	Various metastatic cancers: 40 mg IV every 2 weeks or 480 mg IV every 4 weeks or weight-based dosing.	240 mg IV (NCT04413838).
PD-1 inhibitor	Keytruda (pembrolizumab)	Various metastatic cancers: 200 mg every 3 weeks or 400 mg every 6 weeks.	200 mg IV (NCT04335305).
Kallikrein inhibitor	Takhzyro (lanadelumab-flyo)	HAE: 300 mg every 2 weeks, dosing every 4 weeks may be considered in some patients.	300 mg on day 1 and 300 mg IV on day 4 if needed (NCT04422509). 300 mg IV or 300 mg on day 1 and day 4 (NCT04460105).
P-selectin inhibitor	Adakveo (crizanlizumab-tmca)	Sickle cell disease: 5 mg/kg IV in week 0, week 2, and every 4 weeks thereafter.	5 mg/kg IV (NCT04435184).
IL-17 inhibitor	Cosentyx (secukinumab)	PS, PsA, AS, nonradiographic Axial AS: 150 or 300 mg SC every 4 weeks with or without loading dose.	300 mg SC on day 1 and then 150 mg twice a day SC for 10 days (NCT04403243).
IL-2	Proleukin (aldesleukin, ILT101)	Metastatic RCC and melanoma: two 5-day treatment cycles at 0.037 mg/kg IV every 8 hours for a maximum of 14 doses separated by 9 days.	SC once daily for 10 days (NCT04357444).[c]
GM-CSF	Leukine (sargramostim)	Infection-related outcomes after allogeneic and autologous BMT and improves survival after delayed or failed engraftment: 250 $\mu g/m^2$/day IV over 2, 4, or 24 hours or SC injection once or once daily depending on indication.	125 μg/m2/day IV over a 4-hour period for up to 5 days (NCT04400929).
Therapeutic Proteins in Clinical Development			
Mechanism of Action	Therapeutic Proteins	Evaluated Dosing in Selected Diseases[b]	Evaluated Dosing in COVID-19[b]
CCR5 inhibitor	Leronlimab	Breast cancer: 350, 525, 700, MTD mg SC per week (NCT03838367).	700 mg IV (NCT04343651, NCT04347239).
C5aR inhibitor	Avdoralimab	NA	IV (NCT04371367).[c]
CD147 inhibitor	Meplazumab	Malaria: IV single dose (NCT04327310).	10 mg IV once daily for 2 days (NCT04275245).
GM-CSF inhibitor	Gimsilumab	AS: SC single or repeat once weekly for 4 weeks (NCT04205851).	High dose IV on day 1 followed with low dose IV on day 8 (NCT04351243).
GM-CSF inhibitor	Lenzilumab	Myelomonocytic leukemia: 200, 400 or 600 mg IV once monthly for a 28-day dosing cycle with extra dose on day 15 during cycle (NCT02546284).	IV (NCT04351152).[c]
GM-CSF inhibitor	Mavrilimumab	GCA: 150 mg SC every other week (NCT03827018). RA: 30, 100 and 150 mg SC every other weeks (NCT01706926).	6 or 10 mg/kg IV (NCT04447469). IV (NCT04399980, NCT04463004, NCT04397497).
GM-CSF inhibitor	Otilimab	RA: 90 or 150 mg SC weekly (NCT04333147).	IV (NCT04376684).[c]
GM-CSF inhibitor	TJ003234	RA: single dose (0.3, 1, 3, 10 mg/kg) or multiple doses (1, 3, 6 mg/kg, once every week for 8 weeks) IV (NCT04457856).	3 and 6 mg/kg IV (NCT04341116).
IL-6 inhibitor	Clazakizumab	Transplant: 25 mg SC monthly $\times$ 6 doses or maximum of 12 doses (NCT03380377). RA: SC (NCT02015520).	25 mg IV (NCT04348500, NCT04363502). 12.5 or 25 mg IV (NCT04343989).
IL-6 inhibitor	Olokizumab	RA: 60, 120, 240 mg SC every 2 weeks (NCT01463059).	64 mg SC (NCT04380519).
IL-6 inhibitor	Levilimab	RA: 162 mg SC once a week (NCT04227366). RA: 162 mg SC once a week or once every 2 weeks (NCT03455842).	324 mg SC (NCT04397562).
IL-8 inhibitor	BMS-986253	HCC: 1200 mg IV every 2 weeks (NCT04050462).	2400 mg IV, potential additional dose at 2 and 4 weeks (NCT04347226).
CD24 inhibitor	CD24Fc	Acute GVHD prophylaxis: 240 or 480 mg IV (NCT02663622).	NCT04317040.[c]
TNF-α inhibitor	XPro1595	Alzheimer: 0.3, 1, 3 mg/kg SC once a week for 12 weeks (NCT03943264).	1 mg/kg SC once a week up to 2 doses (NCT04370236).

Table 1. Continued

Therapeutic Proteins in Clinical Development			
Mechanism of Action	Therapeutic Proteins	Evaluated Dosing in Selected Diseases[b]	Evaluated Dosing in COVID-19[b]
Ang2 inhibitor	LY3127804	Advanced solid tumors: dose escalation IV every 2 weeks for a 28-day cycle (NCT02597036).	IV (NCT04342897).[c]
C5a inhibitor	IFX-1	Septic organ dysfunction (NCT02246595).	NCT04333420.[c]
CD6 inhibitor	Itolizumab	SLE: SC, dose not specified (NCT04128579).	1.6 mg/kg IV (NCT04475588).
CSF-1R inhibitor	Axatilimab (SNDX-6352)	Intrahepatic cholangiocarcinoma: 3 mg/kg IV on days 1 and 15 of each 28-day cycle (every 2 weeks), starting with cycle 2 (NCT04301778).	IV on days 1 and 15 (NCT04415073).[c]
CTGF inhibitor	Pamrevlumab	DMD: 35 mg/kg IV every 2 weeks (NCT04371666).	35 mg/kg IV on days 1, 7, 14, and 28 (NCT04432298).
CD73 inhibitor	CPI-006	Cancer: IV escalating dose until MTD once every 21 days (NCT03454451).	0.3, 1.0, 3.0, or 5.0 mg/kg, IV (NCT04464395).
FXIIa inhibitor	Garadacimab	PICC-associated thrombosis: IV dosing (NCT04281524, withdrawn).	IV (NCT04409509).[c]
IL-33 inhibitor	MSTT1041A	Asthma: 70, 210, 490 mg SC every 4 weeks (NCT02918019).	IV (NCT04386616).[c]
LIGHT inhibitor	CERC-002	—	16 mg/kg SC up to a maximum of 1200 mg (NCT04412057).
TIM-3 inhibitor	MAS825	—	IV (NCT04382651).[c]
IL-7	CTY107	Sepsis: 10 μg/kg IV twice a week for 3 weeks (NCT03821038).	3 μg/kg IM followed, after 48 hours of observation, by 10 μg/kg IM twice a week for 2 weeks (NCT04407689).
TLR agonist	BDB-001	Advanced solid tumors: dose escalation until MTD (NCT04196530).	NCT04449588.[c]
IL-15 agonist	N-803	NSCLC: 15 μg/kg SC every 3 weeks (NCT03520686).	NCT04385849.[c]

aHUS, atypical hemolytic uremic syndrome; AS, ankylosing spondylitis; C5, complement component 5; C5a, complement component C5a; C5aR, complement component fragment 5a receptor; CAPS, cryopyrin-associated periodic syndromes; CCR5, C-C chemokine receptor type 5; CD, Crohn"s disease; CD147, cluster of differentiation 147; CD24, cluster of differentiation 24; CD6, cluster of differentiation 6; CD73, cluster of differentiation 73; CRS, cytokine release syndrome; CSF-1R, colony-stimulating factor 1 receptor; CTGF, connective tissue growth factor; DMD, Duchenne muscular dystrophy; FMF, familial Mediterranean fever; FXIIa, factor XIIa; GCA, giant cell arteritis; GM-CSF, granulocyte-macrophage colony-stimulating factor; GVHD, graft-versus-host disease; HAE, hereditary angioedema; HCC, hepatocellular carcinoma; HIDS, hyperimmunoglobulin D syndrome; HLH, hemophagocytic lymphohistiocytosis; HS, hidradenitis suppurativa; IFN-γ, interferon gamma; IL-1, interleukin-1; IL-15, interleukin-15; IL-17, interleukin-17; IL-2, interleukin-2; IL-33, interleukin-33; IL-6, interleukin-6; IL-7, interleukin-7; IL-8, interleukin-8; IV, intravenous; MCD, multicentric Castleman's disease; MKD, mevalonate kinase deficiency; MTD, maximum tolerated dose; NMOSD, neuromyelitis optica spectrum disorder; NSCLC, non-small cell lung cancer; PD-1, programmed death receptor-1; PJIA, polyarticular juvenile idiopathic arthritis; PNH, paroxysmal nocturnal hemoglobinuria; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RCC, renal cell carcinoma; SC, subcutaneous; SJIA, systemic juvenile idiopathic arthritis; SLE, systemic lupus erythematosus; TIM-3, T-cell immunoglobulin and mucin domain 3; TLR, ioll-like receptor; TNF-α, tumor necrosis factor α; TRAPS, tumor necrosis factor receptor-associated periodic syndrome; UC, ulcerative colitis; VEGF, vascular endothelial growth factor.

[a] Information obtained from drugs@fda.

[b] Information obtained from clinicaltrials.gov (as of July 15, 2020; see full list in the Supplemental Table).

[c] Dose or dosing regimen not specified in the clinicaltrials.gov.

IL-6 Pathway Inhibitors

IL-6 is considered a key driver of the uncontrolled hyperinflammatory response/cytokine release storm (CRS) that accompanied ARDS in some COVID-19 patients.[19] A recent retrospective analysis that evaluated 201 patients with confirmed COVID-19 showed that the level of IL-6 was significantly higher (2.9-fold) in patients with ARDS compared with patients without ARDS.[11] As such, targeting the IL-6 pathway is one of the approaches that has gained substantial attention for the potential treatment of COVID-19-associated ARDS. Currently, IL-6 pathway inhibitors evaluated in 1 or more clinical trials for COVID-19 include the anti-IL-6 receptor monoclonal antibodies tocilizumab, sarilumab, and levilimab and the anti-IL-6 monoclonal antibodies clazakizumab, olokizumab, and siltuximab. Target-mediated clearance can be observed at low drug concentrations for the 3 anti-IL-6 receptor antibodies, but not for the 3 anti-IL-6 antibodies.

Tocilizumab has been evaluated in multiple clinical trials, either alone or in combination with other drugs in patients with COVID-19. Although the studied population overall fit in the moderate-critical criterion level, individual studies varied slightly in their patient enrollment criteria, for example, patients with at least moderate pneumonia, patients with severe pneumonia, patients hospitalized in intensive care, patients hospitalized with high risk of progression, and patients with confirmed infection and with evidence of systemic inflammation. The approved dosing regimen of

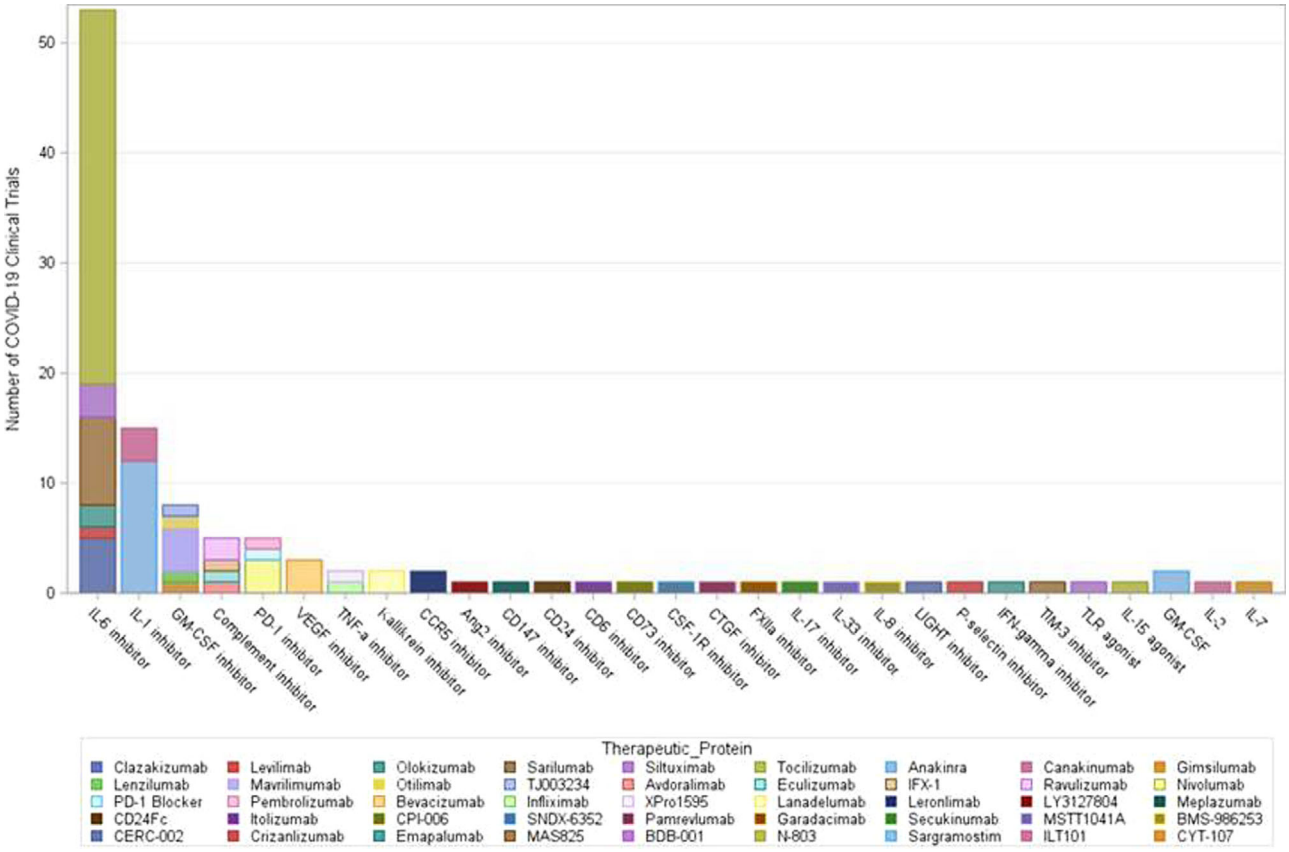

Figure 1. Number of COVID-19 clinical trials categorized by mechanism of action for immunomodulatory therapeutic proteins (data source: clinicaltrials.gov as of July 15, 2020).

tocilizumab for RA is 4 mg/kg intravenously every 4 weeks with an option of increasing to 8 mg/kg intravenously based on the clinical situation. In some COVID-19 trials, the tocilizumab dose selected was 8 mg/kg, with an option of 1 additional dose more than 8 hours later, which is consistent with the dose of tocilizumab approved for the treatment of CRS. Higher total tocilizumab doses than those for autoimmune diseases such as RA evaluated in these clinical trials are likely because of concern about increased clearance under hyperinflammation in advanced stages of COVID-19. Other than the intravenous route, subcutaneous dosing of tocilizumab also is being explored for the treatment effect in hospitalized patients with SARS-CoV-2 infection. Tocilizumab also is being evaluated in numerous smaller clinical trials to decipher COVID-19 and explore its mechanism of action such as the role of IL-6 and IL-6 receptor as predictors of efficacy in patients with severe COVID-19, the role of anti-IL-6 in calming the virus-induced cytokine storm, and so forth.

The use of the subcutaneous route of administration of sarilumab, the approved dosing route in RA, is planned in patients with moderate to severe COVID-19 and moderate COVID-19. The intravenous dosing regimen of sarilumab, although not approved, is considered to achieve peak concentration faster and hence has been evaluated in several COVID-19 trials. The dose for siltuximab of 11 mg/kg intravenously evaluated in patients with severe or critical COVID-19 is consistent with that approved for multicentric Castleman's disease. Levilimab is currently under development for the treatment of RA; single subcutaneous administration of levilimab at a dose of 324 mg is being evaluated for its efficacy and safety in patients with severe COVID-19. The subcutaneous dosing of olokizumab, also under development for the treatment of RA, is being evaluated in patients with severe COVID-19 to assess the proportion of those responding to therapy. For clazakizumab, the subcutaneous route is being evaluated in RA and transplant patients. However, the intravenous route of 25 or 12.5 mg is being assessed in multiple clinical trials for its treatment effect in patients with COVID-19.

In addition to some preliminary studies,[20-23] results from randomized, well-controlled trials for tocilizumab and sarilumab also are available. The first global randomized, double-blind, placebo-controlled phase 3 trial

investigating tocilizumab 8 mg/kg intravenously did not meet its primary end point of improved clinical status in adult patients hospitalized with severe COVID-19-associated pneumonia using a 7-category ordinal scale in week 4 (odds ratio, 1.19; 95%CI, 0.81-1.76; $P = .36$).[24] The trial did not meet its key secondary end point of reduced patient mortality (difference, 0.3%; 95%CI, −7.6% to 8.2%; $P = .941$); however, there was a positive trend in time to hospital discharge in patients treated with tocilizumab (median, 20.0 vs 28.0; 95%CI, 17.0-27.0 vs NE; $P = .0370$). No new safety signals were identified in the trial. The phase 3 trial of sarilumab 400-mg single intravenous dose in COVID-19 patients requiring mechanical ventilation did not meet its primary end point of the percentage of patients achieving at least a 1-point change from baseline on a 7-point ordinal scale; only minor trends were observed.[25] In this trial, sarilumab was added to best supportive care and compared with best supportive care alone (placebo). A higher number of adverse events occurred in the drug-treated group than in the placebo group (80%-77%) within the primary analysis population. It remains to be seen what the results will be in other trials, including in combination with antiviral therapy.

IL-1 Pathway Inhibitors

IL-1 production is induced in response to inflammatory stimuli and mediates various physiologic responses, including inflammatory and immunological responses. Patients with ARDS secondary to influenza and SARS have shown evidence of cytophagocytosis on histopathological examination.[26] Cytophagocytosis is a hallmark of macrophage activation syndrome (MAS), which is an inflammasome/IL-1-mediated disease.[27] Its levels have been elevated in COVID-19 patients with severe illness. IL-1 has been suspected to exert a negative impact on cardiac function, which may be the link to the myocardial injury in many COVID-19 patients.[28,29] IL-1 inhibitors canakinumab and anakinra are being evaluated in multiple clinical studies of COVID-19.

Canakinumab was approved for the treatment of periodic fever syndromes and active systemic juvenile idiopathic arthritis (SJIA) with a body weight-based subcutaneous dosing algorithm of up to 300 mg every 4 or 8 weeks. At this writing, 3 clinical studies investigating canakinumab for COVID-19 treatment have been registered in clinicaltrials.gov, with 1 study using subcutaneous dosing and 2 studies using intravenous dosing. Weight-based dosing of canakinumab (450 mg intravenously for body weight of 40 to <60 kg, 600 mg for 60-80 kg, or 750 mg for >80 kg) is being assessed in 1 phase 3 multicenter randomized, double-blind, placebo-controlled study designed to assess the efficacy and safety of canakinumab in patients with COVID-19-induced pneumonia and cytokine release syndrome. Its primary outcome is the rate of survival without ever requiring invasive mechanical ventilation between days 3 and 29. Pharmacodynamic (PD) assessments such as CRP, serum ferritin, and D-dimer are among the many secondary outcome assessments. Canakinumab 300 or 600 mg intravenously is being evaluated in a study testing the proof of concept that early treatment prevents progressive heart and respiratory failure in patients with COVID-19 infection. Subcutaneous dosing of 150 mg canakinumab is being assessed in COVID-19 pneumonia patients.

Anakinra was approved for the treatment of RA at a daily dose of 100 mg subcutaneously and for cryopyrin-associated periodic syndromes at a daily dose of 1-2 mg/kg subcutaneously. It is being evaluated in multiple clinical trials for COVID-19, either alone or jointly with other drug(s). Because of its short half-life of 4 to 6 hours, it is administered once daily or more frequently than daily. In a retrospective cohort study of patients with COVID-19 and ARDS managed with noninvasive ventilation outside the intensive care unit (ICU), treatment with high-dose anakinra of 5 mg/kg twice daily intravenously was safe and associated with clinical improvement in 72% of patients.[30] Another study on the off-label use of anakinra in 52 patients who were admitted to the hospital for severe forms of COVID-19 with symptoms indicative of worsening respiratory function showed that anakinra reduced both need for invasive mechanical ventilation in the ICU and mortality, without serious side effects.[31] Randomized, controlled trials are being conducted in patients with moderate to critical pneumonia associated with COVID-19 at intravenous doses up to 400 mg daily. Subcutaneous anakinra is being evaluated at 100 mg once daily or every 6 to 16 hours in patients with COVID-19.

IFN-γ Inhibitor

Interferons (IFNs) are a group of cytokines that communicate between cells against pathogens. They play a critical role in the immune system, such as activating natural killer cells and macrophages, as well as inducing flu-like symptoms of various diseases.[32] Because of their in vitro and in vivo antiviral properties, type I (IFN-α, -β, -ε, -κ, and -ω) and type II (IFN-γ) interferons are being evaluated extensively for their efficacy in patients with uncomplicated COVID-19 disease.

The hyperproduction of proinflammatory IFN-γ during the later stages may be responsible for COVID-19-associated acute lung injury. Therefore, the removal of this cytokine by anti-IFN-γ antibodies during the late stage of the disease is believed to block this pathologic pathway and provide therapeutic benefit.[33] Emapalumab, a monoclonal antibody directed against

IFN-γ and approved for the treatment of hemophagocytic lymphohistiocytosis (HLH), is being evaluated in a phase 2/3 randomized trial in COVID-19 patients experiencing hyperinflammation and respiratory distress. The dosing regimen being investigated is intravenous 6 mg/kg on day 1 followed by 3 mg/kg on days 4, 7, 10, and 13, which is borrowed from the approved dosing regimen for HLH. The primary outcome measure of the trial is the proportion of patients not requiring invasive mechanical ventilation or extracorporeal membrane oxygenation.

Low-Dose IL-2

IL-2, a pleiotropic cytokine, plays a key role in the development and function of regulatory T cells (Tregs).[34] Low-dose IL-2 has been shown to control autoimmune and inflammatory disorders by enhancing Tregs.[35] As such, aldesleukin (ILT-101), a human recombinant IL-2, was repurposed for COVID-19 to investigate its therapeutic benefit as a Treg inducer for controlling SARS-CoV-2-related ARDS. ILT-101 was given as a once-daily subcutaneous administration for 10 consecutive days, which differs from the approved intravenous dosing of every 8 hours in 1 cycle of 14 doses in metastatic melanoma and metastatic renal cell carcinoma.

IL-8 Inhibitor

IL-8, also known as CXCL8, is a proinflammatory cytokine orchestrating the recruitment of neutrophils in tissue injuries.[36] It was reported to be positively correlated with disease severity of COVID-19, with severe cases having the highest IL-8 levels.[37,38] Zhang et al showed that the adverse outcome of COVID-19 was associated with depletion of $CD3^+$ T lymphocytes (LTs), which is tightly linked to bursts of cytokines such as IL-6 and IL-8. BMS-986253, an anti-IL-8 monoclonal antibody, is being investigated for the treatment of inflammatory diseases and as cancer immunotherapy at a dose of up to 2400 mg intravenously. The 2400-mg intravenous single dose currently is adopted to evaluate the effect of BMS-986253 in patients with COVID-19.

IL-17 Inhibitor

IL-17 expression was reported to be elevated in patients with COVID-19, and its level was correlated with severity of lung injury.[39] This indicates that IL-17 may serve both as a biomarker of disease severity and as a potential target of therapy to mitigate the damage of SARS-CoV-2, particularly to the lung. Secukinumab, a human IgG1κ monoclonal antibody that binds to IL-17A, is being repurposed for COVID-19 in an small prospective open-label, randomized trial with a subcutaneous 300-mg first dose and then 150 mg twice a day subcutaneously for 10 days. This dosing regimen is more frequent than the approved dosing regimens (150 or 300 mg once every week for the loading dose or once every 4 weeks) for the treatment of psoriasis, ankylosing spondylitis, and psoriatic arthritis.

TNF-α Inhibitors

TNF-α is produced during inflammation and is important in the coordination and development of the inflammatory response. Blockade of TNF-α alleviates inflammation and suppresses the production of other proinflammatory cytokines. The TNF-α level is upregulated in patients with COVID-19, especially in those with severe disease in the ICU.[40] Duret et al reported a patient with spondyloarthritis recovered from COVID-19 after treatment with etanercept, a TNF-α inhibitor, at a weekly dose of 50 mg subcutaneously.[41] As such, Feldmann et al encouraged conducting more clinical trials of anti-TNF-α therapy for COVID-19.[42] Currently, anti-TNF-α monoclonal antibodies such as adalimumab, infliximab, and XPro1595 are being evaluated in COVID-19 studies.

A randomized, open-label, controlled trial for the efficacy and safety of adalimumab in patients with elevated TNF-α levels in the critical stages of severe COVID-19 is ongoing in Shanghai, China, with the main outcome of time to clinical improvement.[43] The dosing of adalimumab is not reported. A phase 2 trial of the efficacy and safety of infliximab was initiated to evaluate whether early institution of TNF-α inhibitor therapy in patients with severe COVID-19 infections could prevent further clinical deterioration and reduce the need for advanced cardiorespiratory support and early mortality at a 5 mg/kg intravenous single dose. XPro1595, an investigational anti-TNF-α antibody, is being evaluated for prevention of disease progression in patients $\geq$ 65 years who have a diagnosed COVID-19 infection with pulmonary complications. This is a high-risk group of patients whose condition can deteriorate rapidly, requiring intensive care beds and increased respiratory support. The dose of 1 mg/kg subcutaneously once a week up to 2 doses in the COVID-19 trial is within the dosing range for XPro1595 evaluated in patients with Alzheimer's disease.

Complement System Inhibitors

The complement system, which is involved in both innate and adaptive immunity, is considered an essential defense system against invading pathogens. An overactivated complement system has been reported to be associated with microvascular injuries and multiorgan failures in patients with COVID-19, and blocking complement overactivation may attenuate the proinflammatory sequelae of SARS-CoV-2 infection.[44] Mastaglio et al reported a favorable course in a patient

with COVID-19 severe pneumonia with systemic hyperinflammation after treatment with the Compstatin-based C3 inhibitor AMY-101.[45] Preliminary data on anticomplement C5 therapy with eculizumab as an off-label agent in 4 COVID-19 patients admitted to the ICU showed that all 4 patients recovered with reduction of serum CRP levels.[46] These 4 patients received eculizumab 900 mg intravenously for 2 doses. Eculizumab is being evaluated in a randomized, controlled clinical trial at a dosing regimen of 1200 mg intravenously on days 1, 4, and 8, then at 1200 or 900 mg on day 12 in patients with COVID-19 infection to assess its efficacy and safety. Ravulizumab, an approved anti-C5 monoclonal antibody, also is being repurposed to evaluate its potential for treatment of COVID-19 disease. The approved dosing for ravulizumab in paroxysmal nocturnal hemoglobinuria and in atypical hemolytic uremic syndrome is being used in the COVID-19 patients. Furthermore, the safety and efficacy assessment of avdoralimab (anti-C5aR) and IFX-1 (anti-C5a) in patients with severe COVID-19-induced pneumonia is underway.

Immunostimulants: TLR Agonist, IL-15 Agonist, PD-1 Inhibitor, and TIM-3 Inhibitor

Programmed cell death protein-1 (PD-1) is a lymphoid cell surface protein of the immunoglobin superfamily and a member of the extended CD28/CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) family of T-cell regulators. It is known to act as a mature T-cell checkpoint for the modulation of apoptosis. PD-1 interaction with either of its ligands constitutes significant negative immune checkpoints in the pathway responsible for blunting cell-mediated immune responses, specifically CD8+ responses, and for upregulating resulting pathologies (eg, COVID-19) and malignancies.[47-50] T-lymphocyte counts are decreased in patients with COVID-19, which is responsible for host anergy toward viral infection, leading to increased risk of severe forms of COVID-19. It has been shown that healing from COVID-19 is associated with LT PD-1 expression normalization.[51] Nivolumab, a PD-1 blocker, was approved for metastatic melanoma at 3 mg/kg given intravenously once every 2 weeks. It is being evaluated for the efficacy and safety in nivolumab in hospitalized COVID-19 patients at 3 mg/kg intravenously and in a pilot study of adult patients with COVID-19 to evaluate the efficacy of anti-PD-1 antibody in relation to viral clearance and its safety at the low dose of 0.3 mg/kg intravenously.

T-cell immunoglobulin and mucin domain 3 (TIM-3) is an immune-inhibitory factor on a T-cell surface as a checkpoint because of exhaustion during prolonged infection. According to Chiappelli et al, the overexpression of TIM-3 appears to parallel that of other cytokines and mediate apoptotic T cytopenia in COVID-19 patients.[50] MAS825, an investigational anti-human TIM-3 monoclonal antibody in the early clinical development phase, is being evaluated after intravenous dosing in a phase 2 randomized, placebo-controlled, participant- and investigator-blinded multicenter study to assess efficacy and safety for the treatment of SARS-CoV-2-infected patients with COVID-19 pneumonia and impaired respiratory function.

Toll-like receptors in innate immunity participate in the first line of defense against invading pathogens and play a significant role in inflammation, immune cell regulation, survival, and proliferation.[52] BDB-001, a TLR agonist with potential immune-stimulating and antineoplastic activities, is being assessed in COVID-19 patients with severe pneumonia or acute lung injury/ARDS. IL-15 is a pleiotropic cytokine that plays a key role in immunotherapy.[53] Its overexpression promotes innate immune responses via the induction of natural killer, $CD8^+$ T, and Treg cells that may suppress the induced T-helper type 2-related cytokines. This results in decreased levels of IL-4, IL-5, and IL-13, thus mitigating SARS-CoV-2-induced inflammation and fibrosis via IFN-γ and IL-10, which inhibit viral replication and reduce viral load.[54] IL-15 agonist N-803, a fusion protein, is being evaluated in a phase 1b randomized, blinded, placebo-controlled study in adult subjects with COVID-19 to assess its safety and immunostimulatory activity, such as changes in lymphocyte counts.

Hematopoietic Cytokines: IL-7 and GM-CSF

IL-7 is important for differentiation of hematopoietic stem cells into lymphoid progenitor cells and activation of cytotoxic T-lymphocyte responses. Paradoxically, its expression is reported to be depleted during certain viral infections.[55] As such, IL-7-based therapies also are proposed to restore the lymphopenic status in patients with COVID-19. Indeed, treatment with CYT107 in lymphopenic COVID-19 patients improved the absolute lymphocyte count from randomization to day 30 when administered intramuscularly at 10 μg/kg twice a week for 2 weeks. In another trial, administration of IL-7 was reported not to affect the plasma concentrations of TNF-α, IL-1β, and IL-12p70 in 12 COVID-19 patients.[56]

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is used as a medication to stimulate the production of white blood cells following chemotherapy. This strategy may prove useful for stabilizing alveolar macrophage and epithelial cell function, increasing SARS-CoV-2 clearance, protecting against secondary infection, and contributing to lung repair mechanisms.[57] Currently, 2 randomized, controlled trials are ongoing to assess inhaled and/or intravenously

administered sargramostim, a recombinant human GM-CSF, in patients with acute hypoxic respiratory failure because of COVID-19. The repurposed dose in the COVID-19 studies coincides with that in the approved indications for sargramostim.

Other Immunomodulatory Therapies

Many other immunomodulatory therapeutic proteins also are currently under investigation for COVID-19 including but not limited to leronlimab (anti-CCR5), meplazumab (anti-CD147), MSTT1041A (anti-IL-33), axatilimab (anti-CSF-1R), CD24Fc (anti-CD24), LY3127804 (anti-Ang2), itolizumab (anti-CD6), pamrevlumab (anti-CTGF), CERC-002 (anti-LIGHT), bevacizumab (anti-VEGF), and lanadelumab (anti-kallikrein).

C-C chemokine receptor type 5 (CCR5) plays a central role in modulating immune cell trafficking to sites of inflammation, inhibition of which may suppress the hyperactive immune response observed in COVID-19 patients.[58] Leronlimab, a CCR5 antagonist, is being evaluated in patients who experience respiratory illness as a result of COVID-19 at a single dose of 700 mg intravenously, consistent with the dose used in the ongoing breast cancer trial. CD147, a receptor on host cells, is considered a novel route for SARS-CoV-2 invasion, and it is hypothesized that there exists an inhibitory potential for drugs interfering with CD147 on SARS-CoV-2 invasion.[59] Meplazumab, a humanized anti-CD147 monoclonal antibody, is in the early clinical development stage for the potential to mediate both treatment and prophylaxis of falciparum malaria. It is known to inhibit both T-cell chemotaxis and virus cell entry. In an open-label study in patients with COVID-19 pneumonia, the time to virus eradication in the meplazumab group given 2 doses of 10 mg intravenous once daily was significantly shorter than in the control group.[60] IL-33, an inflammatory cytokine, has been identified as an endogenous alarm signal to alert various types of immune cells in reaction to trauma.[61] The population of IL-33-producing cells was found to increase with disease severity of COVID-19.[62] Subcutaneous MSTT1041A, an IL-33 inhibitor, is being evaluated in asthma indications; the intravenous route is being assessed in a phase 2 randomized, double-blind, placebo-controlled multicenter study in patients hospitalized with COVID-19 pneumonia.

Colony-stimulating factor (CSF) supports survival, clonal expansion, and differentiation of hematopoietic progenitor cells. CSF-1R plays a key role in the differentiation, recruitment, and activation of tissue-associated macrophages, which has been associated with survival in classic Hodgkin's lymphoma and other lymphoma types.[63] Axatilimab (SNDX-6352), a high-affinity antibody targeting CSF-1R, is being evaluated in a randomized, double-blind, placebo-controlled 29-day study to assess its efficacy and safety in patients with respiratory signs and symptoms secondary to COVID-19 after intravenous dosing on days 1 and 15. It also is being evaluated in patients with intrahepatic cholangiocarcinoma at the same dosing route and frequency as in COVID-19 patients.

CD24 is an innate checkpoint against the inflammatory response to tissue injuries or danger-associated molecular patterns.[64] CD24Fc, a fusion protein that regulates host inflammatory response to tissue injuries, is in the phase 2/3 clinical development stage. A single dose of CD24Fc 480 mg intravenously is being evaluated in hospitalized subjects with severe COVID-19. Angiopoietin 2 (Ang2) levels were increased in ARDS patients.[65] LY3127804, an investigational selective monoclonal antibody against Ang2, is being evaluated in pneumonia patients hospitalized with COVID-19 who are at a higher risk of progressing to ARDS. In this trial, LY3127804 is given intravenously with the same dosing route as in the study of LY3127804 in patients with advanced solid tumors. CD6 is central to modulating the activity and trafficking of T cells involved in numerous immunoinflammatory diseases.[66] Diaz et al reported that the use of itolizumab, an anti-CD6 monoclonal antibody, in combination with other antiviral and anticoagulant therapies, is associated with a reduction in COVID-19 disease worsening and mortality in elderly patients with moderate COVID-19 in an expanded access clinical trial.[67] In this trial, patients received a single intravenous dose of 200 mg. Some patients received a second dose of 200 mg, depending on their clinical evolution and the physician criteria. In an ongoing clinical trial, an intravenous dose of 1.6 mg/kg of itolizumab, is being assessed in patients with COVID-19 complications for its efficacy and safety.

Cnnective tissue growth factor (CTGF) is involved in fibrotic and proliferative diseases and may promote vascular leakage and lead to pulmonary edema.[68] Pamrevlumab, an anti-CTGF monoclonal antibody, may mitigate or reverse this edema and thus improve oxygenation in patients with COVID-19-induced pneumonia. It is being evaluated in hospitalized patients with acute COVID-19 disease at a dosing regimen of 35 mg/kg intravenously on days 1, 7, 14, and 28. The levels of LIGHT, a cytokine in the TNF superfamily that can drive inflammation and induce many other cytokines, have been shown to be elevated in COVID-19-infected patients.[69] The efficacy and safety of CERC-002 are being studied in patients with severe COVID-19 over a 28-day period as a single dose on top of standard of care at 16 mg/kg subcutaneously to a maximum dose of 1200 mg.

Vascular endothelial growth factor (VEGF) plays an essential role in vascular endothelial homeostasis and

endothelial cell activation.[70] Significantly higher VEGF concentrations were observed in COVID-19 patients compared with healthy controls, and it was shown as an important indicator related to the severity of COVID-19.[71] Bevacizumab, an anti-VEGF monoclonal antibody, is being evaluated in hospitalized COVID-19 patients at the dose level consistent with the approved doses in oncology indications for bevacizumab. The kallikrein-kinin system is a zymogen system that is known to lead to the release of the nonapeptide bradykinin after activation. Binding of bradykinin to the B2R on endothelial cells can lead to capillary leakage, which causess angioedema.[72] Van de Veerdonk proposed that kallikrein-kinin blockade may have the potential to prevent ARDS in patients with COVID-19. Lanadelumab, a human monoclonal antibody targeting plasma kallikrein, was approved to prevent angioedema in patients with hereditary angioedema. It is being repurposed to evaluate its safety, pharmacokinetics (PK), and PD in adults hospitalized with COVID-19 pneumonia at a dose consistent with the approved one.

Further, garadacimab (anti-FXIIa), CPI-006 (anti-CD73), and nod-like receptor family, pyrin domain-containing 3 (NLRP3) inflammasome pathway[73] are gaining attention. Although not in the scope of discussion in this review, convalescent plasma, immunoglobin, and cell-based biologics also are being evaluated as the immunomodulatory therapies in COVID-19.

Trial Design

A recently published FDA guidance, "COVID-19: Developing Drugs and Biological Products for Treatment or Prevention," provides an overview of considerations for designing COVID-19 clinical trials.[74] The guidance recommends randomized, placebo-controlled, double-blind clinical trials using a superiority design for drugs to treat or prevent COVID-19. It notes that high-risk patients such as the elderly or those with cardiovascular or respiratory disease, chronic kidney disease, diabetes, or other comorbidities and immunosuppressed patients (eg, transplant, cancer, or HIV-infected) should be included in COVID-19 clinical trials. The guidance also encourages enrolling specific populations such as hepatic and renally impaired patients (provided data are available to guide dose adjustment) and ensuring racial and ethnic minorities are represented. The FDA also encourages enrolling pregnant and lactating individuals in phase 3 trials, if appropriate.

The guidance further acknowledges that decentralized, or platform, trials may be appropriate under certain circumstances and encourages sponsors to discuss such approaches with the FDA. Platform trials, in which multiple treatments are evaluated simultaneously, have been proposed before for the purpose of expediting late-stage drug development through trial designs that test multiple cancer drugs and/or multiple cancer subpopulations.[75] Master protocol, umbrella, basket, and platform trials are terms often used to describe the design of trials that investigate multiple therapies and/or multiple diseases under a common infrastructure. The FDA, the National Institutes of Health, and other stakeholders including industry are working together to facilitate the implementation of "master protocols" that enable the study of multiple promising drugs at one time to expedite drug development for COVID-19.[76]

In general, a master protocol is designed to evaluate more than 1 investigational drug at a time, enabling comparison of individual drug candidates to a single control group. Few platform trials are ongoing, as referenced on clinicaltrials.gov. For example, trial NCT02735707 is evaluating the effect of a range of interventions for improving outcomes of patients admitted to the ICU with community-acquired pneumonia.[77] The trial has implemented a subplatform to assess multiple interventions or treatments for COVID-19. NCT04354428 is another randomized platform trial, with 4 drugs planned in the protocol for severe SARS-CoV-2 infection in high-risk adults not requiring hospital admission.[78] Additional information on these trials is available at clinicaltrials.gov.

Clinical Pharmacology Considerations in Investigating Immunomodulatory Therapeutic Proteins for COVID-19 Treatment

The treatment goal of immunomodulatory therapeutic proteins in hyperinflammation management of COVID-19, as with most clinical therapeutics, is to achieve the desired benefit with minimal adverse effects. The contribution of clinical pharmacology to benefit/risk assessment largely resides in dosing regimen selection through the assessment of pharmacology, PK, PD, and intrinsic and extrinsic factors (Table 2). PK characterizes the dose-concentration relationship, whereas PD describes the concentration-effect relationship. Intrinsic (eg, weight, comorbidity, and age) and extrinsic (eg, concomitant medications) factors might potentially alter drug concentrations that require adjustment in dose or dosing regimen.

Dose Selection

The dose selection in clinical trials of COVID-19 treatments mostly leverages previous nonclinical and clinical experience, including the pharmacology, PK, PD, intrinsic and extrinsic factors, safety, and efficacy data. The dosing regimen that has been approved or

Table 2. Clinical Pharmacology Considerations for Immunomodulatory Therapeutic Proteins in COVID-19 Clinical Development and Therapies

Dosing Regimen	PK/PD	Intrinsic Factors (Specific Populations, Immunogenicity, and Comorbidity)	Extrinsic Factors (Concomitant Medications)	Clinical Pharmacology Considerations
Treatment window		x		Patient selection to maximize benefit.
Dose	x	x	x	Optimize dose selection through comprehensive assessment.
Route of administration	x			Intravenous treatment is likely desirable, because of maximum concentration being rapidly reached after intravenous dosing and of the acute nature of moderate and severe COVID-19.
Dosing frequency	x			Single dose is generally enough for monoclonal antibodies, which have a half-life of 2-3 weeks; possible 1 or 2 additional doses within 1 week of initial dose depending on the clinical situation. Multiple doses are needed for biologics with a short half-life.
Treatment duration	x			Consider longer follow-up to assess safety such as infection.
Dose adjustment	x	x	x	Evaluate the need and propose dose adjustment, if needed, for enrolled specific populations such as renal or hepatic impairment patients, pregnant and lactating individuals, racial and ethnic minority persons, geriatric population, and patients with high risk of complications in clinical trials, etc. These specific populations are encouraged in the COVID-19 trials. Clinical pharmacology strategies for real-time knowledge management to inform trial decision-making if there is limited information to support the potential for efficacy. Inform decision-making on dose adjustment to mitigate the impact of the treatment interruption. PK-based decision to mitigate interaction potential.

evaluated in clinical trials for other indications might be considered an appropriate starting point in clinical trials of COVID-19 patients. However, different indications may have different benefit/risk profiles, the assessment of which is necessary for dose selection. The effective dose for treating COVID-19 patients may be different from those for approved indications. For example, an acceptable benefit/risk ratio for certain oncology indications may not necessarily translate into the same favorable benefit/risk ratio for COVID-19. For therapeutic proteins with limited clinical experience, adaptive clinical trial design may be an option. In this case, dose selection could be aided by real-time PK assessment.

Treatment Duration

The median length of hospitalization among COVID-19 survivors has been reported as 10 to 13 days.[11,79] Immunomodulatory monoclonal antibodies generally have a half-life of 2 to 3 weeks, which is expected to provide adequate treatment duration to suppress elevated cytokine levels for the symptomatic phase of COVID-19 infection. Therefore, a single dose is likely to be adequate. However, for other therapeutic proteins with shorter half-lives (eg, anakinra), multiple doses may be needed. Occasionally, if no clinical improvement occurs after the first dose per clinical assessment, additional dose(s) are administered in the trial (eg, with tocilizumab). The number of additional doses and the interval between consecutive doses can be designed based on a modeling and simulation approach.

Given that the treatment duration for COVID-19 usually is a few weeks for hospitalized patients, adverse events associated with chronic treatment with certain biologics indicated for a disease lasting at least 3 months may not be relevant to COVID-19. More importantly, drug exposure may not be the same between different disease states. This needs to be considered in COVID-19 trials to safely achieve the desired PD responses. Although limited data are available regarding follow-up of COVID-19 patients, Wang et al emphasized the importance of long-term follow-up to monitor residual inflammation, especially in those patients with severe clinical manifestations or intense acute inflammatory responses.[80] Spagnolo et al also warned that pulmonary fibrosis in the survivor population as a result of long-term pulmonary consequences of COVID-19 is likely, although it still remains speculative and should be confirmed with an appropriate prospective study.[81]

Route of Administration

As described earlier, the immunomodulatory therapeutic proteins currently in clinical trials for the treatment of COVID-19 mostly are directed toward patients with moderate and severe stages of the disease. Given the acute severity of the disease,[82] especially in the advanced disease stage, rapid onset of drug action is necessary to neutralize the elevated cytokines and

rebalance the immune response. Intravenous dosing has the advantage of providing rapid onset of maximum concentration, which often is achieved at the end of the infusion, just minutes to a few hours following treatment initiation. The maximum concentration after subcutaneous dosing often is reached after a few days to a week, and the peak drug level often is significantly less than that after intravenous dosing. In this regard, subcutaneous dosing may not provide an advantage. For therapeutic proteins approved only for the subcutaneous route of administration to be repurposed for intravenous administration in COVID-19 patients, selection of a potential intravenous dose and the availability of a relevant clinical formulation could be potential challenges. PK/PD modeling and simulation can be useful in guiding dose selection. In this situation, considering the possibly limited clinical experience with intravenous dosing, close safety monitoring and early stopping rules should be put in place to ensure the safety of COVID-19 patients in clinical trials.

Some researchers have hypothesized that COVID-19 patients also may benefit from certain therapeutic protein treatment earlier in the disease course—before progressing to severe respiratory decompensation—through early cytokine inhibition, thus preventing disease progression to the severe or critical stages. As such, subcutaneous dosing likely fits in this scenario, as a week or so may be needed for the biologic to reach the maximum concentration. Although this hypothesis appears plausible, the timing chosen should not compromise a patient's innate immune response, which is necessary for fighting off the virus and avoiding the risk of infection.[83]

Comorbidity

The presence of underlying comorbidities is an important risk factor for SARS-CoV-2 infection, and the fatality rate of patients with comorbidities was reported to be much higher than that of patients without comorbidities.[84] Treatment decisions related to these comorbidities are further complicated with the potential risks of clinical therapies for COVID-19, such as those posed by immunomodulatory therapeutic proteins for autoimmune diseases. It is well known that immunomodulatory therapeutic proteins are associated with increased risk of serious bacterial or opportunistic infection; however, information on their association with the risk of viral infection is limited.

Nevertheless, in various academic societies, concern about the potential increased risks of immunomodulatory biological therapies for COVID-19 remains. The American College of Rheumatology recommended temporarily holding or stopping all non-IL-6 biologics in the context of documented or presumptive COVID-19, as well as in COVID-19 following known SARS-CoV-2 exposure.[85] Similarly, the American Academy of Dermatology recommended that patients discontinue or postpone biologic therapy until they recover from COVID-19.[86] The academy also recommended benefit/risk assessment for patients currently considered candidates for biologic therapy. This highlights the importance of the treatment window in biologic therapies for COVID-19.

These recommendations, however, have been debated. Data from a U.S. biologics registry showed that the rates of severe COVID-19 or complications were lower in patients prescribed ustekinumab and that there appeared to be little difference in mild cases between patients prescribed IL-17 and IL-23 antagonists and those in the corresponding placebo groups.[87,88] As with other diseases, treatment interruption may have a profound impact as well. The treatment decision recommendation balances benefits and risks of ongoing cancer therapy during the COVID-19 pandemic.[89] Collectively, although no general rule on the treatment decision recommendation exists, caution should be taken, and the impact of treatment interruption should be evaluated carefully. In this situation, modeling and simulation could potentially be useful, as it considers such factors as covariates and facilitates decision-making.[90]

Critically ill COVID-19 patients are likely to be susceptible to secondary infections and may have an increased risk of comorbid chronic infections, such as hepatitis B and tuberculosis.[91,92] In these cases, the treatment goal is to prevent or attenuate life-threatening inflammation while minimizing the potential for secondary infection.[93] For this reason, immunomodulatory treatments should be used cautiously. The use of prophylactic antibiotics may be indicated, and bacteriologic and fungal assessments are of great importance.

As discussed above, many therapeutic biologics already approved for other applications are being studied in COVID-19 patients. Many of these have FDA box warnings or other labeled safety warnings regarding use in subjects with a history of chronic infections such as latent tuberculosis and hepatitis B/hepatitis C. Although it is not known whether the acute dosing (7-14 days) of biologics with immunosuppressive properties may result in the same risk as chronic dosing of the labeled product, subjects with known chronic infections generally are excluded from studies of biologics with established safety warnings regarding chronic infections.

Pediatrics

Most COVID-19 patients have been adults. Although some children and infants have been infected with COVID-19, they generally experience mild, cold-like symptoms, such as fever, runny nose, and cough.[94]

However, severe outcomes have been reported in infants under 1 year, and children with underlying medical conditions such as chronic lung disease, moderate to severe asthma, serious heart conditions, or weak immune systems might be at higher risk of serious illness from COVID-19 than are other children.[21] The Centers for Disease Control and Prevention (CDC) and its partners also are investigating reports of multisystem inflammatory syndrome in children that is associated with COVID-19 and includes features similar to those of Kawasaki disease.[95-99]

Some ongoing clinical trials investigating immunotherapies in pediatric patients are registered at clinicaltrials.gov, and off-label use of biologics in pediatric patients has been reported.[100] The clinical management of COVID-19 complications with immunomodulatory therapeutic proteins in pediatric patients often takes body weight into consideration, because weight-based dosing regimens generally are used in these patients. It is noteworthy that as immunomodulatory therapeutic proteins often are used in many patients with more severe forms of asthma or allergies, concern exists that the treatments may compromise these patients' immune systems. Regarding treatment of severe allergic diseases with therapeutic proteins, a recent expert opinion article published by the European Academy of Allergy and Clinical Immunology suggested continuing them in otherwise healthy patients during the COVID-19 pandemic but pausing them in SARS -CoV-2-positive patients until they have recovered.[101]

Geriatric

According to the CDC, the risk for severe illness from COVID-19 increases with age; the greatest risk for severe illness is among those aged 85 years or older.[102] More research is needed to understand the higher risk to the elderly in general, whereas some seniors survive the infection. To enrich trial assessment in this regard, some clinical trials limited enrollment to the elderly, whereas others specified an age cap. For example, patients $\geq$ 65 years with pulmonary complications because of COVID-19 infection were enrolled in clinical trial NCT04370236 evaluating the efficacy and safety of XPro1595; patients with COVID-19 pneumonia between 18 and 80 years of age were enrolled in clinical trial NCT04335305 to evaluate the efficacy of tocilizumab plus pembrolizumab. In general, aging does not affect the elimination of monoclonal antibodies. A trend toward lower clearance with increasing age for adalimumab in patients 40 to >75 years of age with RA has been noted. For therapeutic proteins known to be substantially excreted by the kidney (eg, anakinra), caution should be taken, as increased risk of toxic reactions may be greater in patients with impaired renal function.

Pregnancy and Lactation

According to the CDC, pregnant women are at greater risk of illness from other respiratory viruses than are nonpregnant people.[4] Predose examinations in current COVID-19 clinical trials generally exclude pregnant patients, as well as those with positive pregnancy tests or who are breastfeeding. Yu et al reported that no SARS-CoV-2 was detected in mid-pregnancy amniotic fluid, but also warned that the possibility of vertical transmission in early and middle pregnancy could not be ruled out.[103] SARS-CoV-2 RNA has been shown to be much less stable than DNA in amniotic fluid.[104] A review on the transfer of monoclonal antibodies in the breast milk of women receiving treatment for neurologic and nonneurologic diseases noted low drug concentrations detected in breast milk, but longer-term effects on infant immunity and childhood development were unknown.[105] Because of ethical concerns and the feasibility of conducting efficacy studies in pregnant patients during COVID-19 and future outbreaks, without strategic prospective planning dosing recommendations are not likely to be available for these specific populations. As such, a modeling and simulation approach such as physiologically based pharmacokinetics can be used to simulate exposures and predict relevant doses in pregnant women.[106,107]

Concomitant Medications

In clinical trials, the treatment strategy for COVID-19 often combines an investigational drug with the standard of care (eg, acetaminophen for fever reduction). Investigators manage patient care with supportive therapies as clinically indicated and per local standard practice. A theoretical concern exists regarding the potential modulation of CYP enzyme expression by cytokine levels in COVID-19. The expression of CYP450 enzymes has been shown to be suppressed by increased levels of cytokines (eg, IL-6) in some chronic diseases.[108] Therefore, for biologics that antagonize cytokine activity, such as tocilizumab, it is expected that the expression of CYP450 enzymes could be increased to normal levels. Accordingly, RA patients treated with tocilizumab may exhibit restoration of CYP450 activities to higher levels than those in patients not treated with tocilizumab, leading to increased metabolism of certain drugs. The potential clinical meaning of drug interactions via the IL-6 pathway in COVID-19 needs to be further elucidated.

Ongoing COVID-19 clinical trials often exclude patients enrolled in other concurrent clinical interventional studies, as well as those on other investigational drugs or who are on chronic immunomodulatory therapy. The exclusions are in place mostly to avoid interfering with the study objectives from both safety and efficacy perspectives. Safety may be a concern if

patients are on 2 immunomodulators at the same time. Also, allowing another immunomodulator in the study would complicate the interpretation of efficacy data. Thus, excluding patients on other biological treatments for 2 weeks before inclusion in a study may not be long enough because of the relatively long half-lives of monoclonal antibodies. Knowledge of an individual drug's half-life is useful when determining the window between 2 treatments.

Pharmacokinetics

Serum concentrations often are measured to determine the PK properties of immunomodulatory therapeutic proteins in the COVID-19 trials. Real-time PK analysis is useful to inform dose selection in clinical trials, especially in situations in which there is limited clinical information.

COVID-19 has been associated with damages to lungs, heart, brain, kidneys, and other organs,[109,110] and elevated serum cytokine levels have been the suspected cause.[111] As such, multiple immunomodulatory therapeutic proteins are being investigated in COVID-19 patients with multiorgan impairment. In this situation, biodistribution of therapeutic proteins to tissues likely is needed for neutralization of cytokines or their downstream effect. Extravascular distribution for therapeutic proteins is generally limited because of large molecular size. However, it is unknown whether tissue distribution changes in COVID-19 patients with organ impairment because of the damage/impairment of the vascular endothelial system.

Hepatic and renal damage has been reported to be associated with SARS-CoV-2 infection. Alan Kliger reported that 14% to 30% of COVID-19 patients in New York, New York, and Wuhan, China, ICUs lost renal function and later required dialysis.[112] Similarly, Hu et al found that 9 of 26 people who died of COVID-19 in Wuhan had acute kidney injury, and 7 had SARS-CoV-2 detected in their kidneys.[113] More than one-third of patients admitted to the hospital with SARS-CoV-2 infection had abnormal liver function associated with longer hospital stays.[114] Although there are concerns about positive feedback — when increasing the systemic exposure to certain small-molecule drugs known to be associated with deteriorating liver and kidney function reduces their elimination, exposure to monoclonal antibodies is not likely to be elevated because of hepatic and/or renal impairment. That said, although no direct evidence exists yet, the likelihood of lower exposure of monoclonal antibodies cannot be ruled out in COVID-19 patients because of proteinuria.

Variation in cytokine levels or other disease manifestations may affect PK depending on the elimination mechanism. For example, tocilizumab exposure in CRS patients was about 41% lower than that in SJIA patients, possibly as a result of target-mediated clearance.[115] It remains to be seen whether the same trend would appear in COVID-19 patients. In addition, the impact of other intrinsic factors such as body weight on PK should not be ignored.

Pharmacodynamics

The measurement of various blood biomarkers such as cytokines and the exploratory analysis of their relationship with PK, safety, efficacy, disease progression, and severity are being widely studied in COVID-19 trials. The panel of cytokine testing potentially could include but not be limited to IL-2, IL-19, IL-4, IL-10, IL-8, G-CSF, GM-CSF, MCP-1, MIP1α, IL-7, IL-13, IL-31, IL-15, IL-6, IFN-α, IFN-γ, TNF-α, sIL-6R, CRP, and ferritin, among others. Assessment of actual values and relative changes from baseline for different biomarkers is generally descriptive. A model-based approach is useful in evaluating their association with PK, safety, and efficacy. Given a quick readout of disease outcome measures as a result of the rapid disease course, COVID-19 provides a unique opportunity to assess the utility of biomarkers and evaluate their association with clinical outcome measures. Of note is that CRP has been used as either a primary outcome measure or one of the major secondary outcome measures in some phase 2 COVID-19 trials. In a small COVID-19 study in China, CRP decreased significantly and returned to normal in 84.2% of patients (16 of 19) following tocilizumab treatment.[21] CRP also is being explored as a potential simple CRP measurement to inform decision-making for which patients are to be hospitalized because of risk of developing more severe infections.[116]

Immunogenicity

The immune response in COVID-19 patients includes the host immune reaction to the SARS-CoV-2 virus, administered therapeutic proteins, and future vaccine inoculation. Immunogenicity of therapeutic proteins is being assessed in some clinical trials of COVID-19. Given the acute inflammatory nature of COVID-19, especially in advanced stages of the disease, immunogenicity of therapeutic proteins in COVID-19 may be different from that in other autoimmune conditions.

Additional Considerations for Data Analysis

The usefulness of model-informed drug development approaches in quantifying PK/PD and in optimizing dosing in clinical trials and therapeutic use is well known. Pharmacometrics also enables tailored drug development. For drug development in COVID-19, scientists are under unprecedented pressure to learn about the disease and to conquer it in a short period amid the global pandemic environment. In a relatively short

time, the current paradigm of clinical drug evaluation in COVID-19 has prompted the generation of a large patient database with data from studies emulating close to real-world scenarios. With the help of electronic health records on patient demographics, treatment history, and outcome data, these meaningful data in general and special populations may be very helpful if their use becomes a part of regular medical practice.[117]

Furthermore, the use of real-world data sources for surveillance and adverse event reporting systems around the world presents an opportunity for clinical pharmacologists to study the relationships between dose and reported outcomes of potential therapies. Using real-world data sources that are fit for purpose may contribute to our understanding of disease risk factors and identification of potential treatment options.

Summary

We still are in the midst of this pandemic, and it is a rapidly evolving situation. Clinical trials assessing the safe and effective use of these immunomodulatory therapeutic proteins in the management of ARDS and CRS in COVID-19, which remains to be proven, are ongoing. As clinical pharmacologists, we are facing the prospect of an unprecedented timeline for COVID-19 drug development; namely, optimizing dose and dosing regimens for repurposed drug products to be evaluated in clinical trials. These optimizations involve potential changes in dosing route, identification of target cytokine levels, special considerations in various specific populations and mitigation of the potential for drug-drug interactions. Clinical pharmacologists also consider the impact of treatment interruption and comorbidities, if present. In the long term, we also must take a deliberative approach and think proactively and strategically to prepare for future challenges facing the discipline. Although we remain focused on dose regimen selection in the traditional randomized, controlled trial setting, we also must embrace the potential advantages of platform trial designs, real-world data analysis, and the potential to integrate this knowledge into a new paradigm.

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Conflicts of Interest

The authors have declared no conflicts of interest for this article.

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References

1. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733.
2. World Health Organization. Q&A: Influenza and COVID-19 - similarities and differences. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/question-and-answers-hub/q-a-detail/q-a-similarities-and-differences-covid-19-and-influenza?gclid=EAIaIQobChMIhM_os4W86QIVbAiICR1bXAuxEAAYASAAEgKp5fD_BwE. Accessed June 5, 2020.
3. Age, Sex, Existing Conditions of COVID-19 Cases and Deaths. https://www.worldometers.info/coronavirus/coronavirus-age-sex-demographics/. Accessed May 13, 2020.
4. Coronavirus Disease 2019 (COVID-19). Centers for Disease Control and Prevention. https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/assessing-risk-factors.html. Accessed June 22, 2020.
5. Coronavirus Disease 2019 (COVID-19). Centers for Disease and Control. https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html. Accessed May 13, 2020.
6. Food and Drug Administration. https://www.fda.gov/media/137564/download. Accessed June 5, 2020.
7. Coronavirus (COVID-19) Update: FDA issues emergency use authorization for potential covid-19 treatment. https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment. Accessed May 1, 2020.
8. Van der Graaf PH, Giacomini KM. COVID-19: a defining moment for clinical pharmacology? *J Clin Pharm Ther*. 2020;108(1):11-15.
9. NIH guideline. https://files.covid19treatmentguidelines.nih.gov/guidelines/covid19treatmentguidelines.pdf. Accessed May 1, 2020.
10. Wang Y, Wang Y, Chen Y, Qin Q. Unique epidemiological and clinical features of the emerging 2019 novel coronavirus pneumonia (COVID-19) implicate special control measures. *J Med Virol*. 2020;92(6):568-576.
11. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943.
12. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical–therapeutic staging proposal. *J Heart Lung Transpl*. 2020;39(5):405-407.
13. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
14. Zhang J-J, Dong X, Cao Y-Y, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. *Allergy*. 2020;75(7):1730–1741.
15. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet*. 2020;395(10229):1033-1034.
16. McGonagle D, Sharif K, O'Regan A, et al. The role of cytokines including interleukin-6 in covid-19 induced pneumonia

and macrophage activation syndrome-like disease. *Autoimmun Rev*. 2020;19(6):102537.
17. Chen G, Wu D, Guo W, et al. Clinical and immunologic features in severe and moderate coronavirus disease 2019. *J Clin Invest*. 2020;130(5):2620-2629.
18. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the 'Cytokine Storm' in COVID-19. *J Infect*. 2020;80(6):607-613.
19. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndrome and immunosuppression. *Lancet*. 2020;395(10229):1033-1034.
20. Guaraldi G, Meschiari M, Cozzi-Lepri A, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(8):e474-e484.
21. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci U S A*. 2020;117(20):10970-10975.
22. Gritti G, Raimondi F, Ripamonti D. IL-6 signalling pathway inactivation with siltuximab in patients with COVID-19 respiratory failure: an observational cohort study. *medRxiv*. 2020. https://doi.org/10.1101/2020.04.01.20048561.
23. Vaidya G, Czer LSC, Kobashigawa J, et al. Successful Treatment of severe COVID-19 pneumonia with clazakizumab in a heart transplant recipient: a case report. *Transplant Proc*. 2020. https://doi.org/10.1016/j.transproceed.2020.06.003.
24. Roche provides an update on the phase III COVACTA trial of Actemra/RoActemra in hospitalised patients with severe COVID-19 associated pneumonia. https://www.roche.com/investors/updates/inv-update-2020-07-29.htm. Accessed August 3, 2020.
25. Sanofi and Regeneron provide update on Kevzara® (sarilumab) Phase 3 U.S. trial in COVID-19 patients. https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00. Accessed July 5, 2020.
26. Harms PW, Schmidt LA, Smith LB, et al. Autopsy findings in eight patients with fatal H1N1 influenza. *Am J Clin Pathol*, 2010;134(1):27-35.
27. Grom AA, Horne A, De Benedetti F. Macrophage activation syndrome in the era of biologic therapy. *Nat Rev Rheumatol*. 2016;12(5):259-268.
28. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091.
29. Zheng Y, Ma Y, Zhang J, et al. COVID-19 and the cardiovascular system. *Nat Rev Cardiol*. 2020;17(5):259-260.
30. Cavalli G, De Luca G, Campochiaro C, et al. Interleukin-1 blockade with high-dose anakinra in patients with COVID-19, acute respiratory distress syndrome, and hyperinflammation: a retrospective cohort study. *Lancet Rheumatol*. 2020;2(6):e325-e331.
31. Huet T, Beaussier H, Voisin O, et al. Anakinra for severe forms of COVID-19: a cohort study. *Lancet Rheumatol*. 2020;2:e393-400.
32. Shahabi nezhad F, Mosaddeghi P, Negahdaripour M, et al. Therapeutic approaches for COVID-19 based on the dynamics of interferon-mediated immune responses. 2020. https://doi.org/10.20944/preprints202003.0206.v1.
33. Zhang W, Zhao Y, Zhang F, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): the perspectives of clinical immunologists from China. *Clin Immunol*. 2020. https://doi.org/10.1016/j.clim.2020.108393.
34. Tahvildari M, Dana R. Low-dose IL-2 therapy in transplantation, autoimmunity, and inflammatory diseases. *J Immunol*. 2019;203(11):2749-2755.
35. Ye C, Brand D, Zheng SG. Targeting IL-2: an unexpected effect in treating immunological diseases. *Sig Transduct Target Ther*. 2020. https://doi.org/10.1038/s41392-017-0002-5.
36. Zhang X, Tan Y, Ling Y, et al. Viral and host factors related to the clinical outcome of COVID-19. *Nature*. 2020;583(7816):437-440.
37. Chen L, Liu HG, Liu W, et al. Analysis of clinical features of 29 patients with 2019 novel coronavirus pneumonia. *Zhonghua Jie He He Hu Xi Za Zhi*. 2020;43(3):E005.
38. Gong J, Dong, H., Xia, S, et al. Correlation analysis between disease severity and inflammation-related parameters in patients with COVID-19 pneumonia. *medRxiv*. 2020. https://doi.org/10.1101/2020.02.25.20025643.
39. Pacha O, Sallman MA, Evans SE. COVID-19: a case for inhibiting IL-17? *Nat Rev Immunol*. 2020;20(6):345-346.
40. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;95(10223):497-506.
41. Duret P, Sebbag E, Mallick A, et al. Recovery from COVID-19 in a patient with spondyloarthritis treated with TNF-alpha inhibitor etanercept. *Ann Rheum Dis*. 2020. https://doi.org/10.1136/annrheumdis-2020-217362.
42. Feldmann M, Maini RN, Woody JN, et al. Trials of anti-tumour necrosis factor therapy for COVID-19 are urgently needed. *Lancet*. 2020;395(10234):1407-1409.
43. A clinical study for the efficacy and safety of Adalimumab Injection in the treatment of patients with severe novel coronavirus pneumonia (COVID-19). Chinese Clinical Trial Registry, Registration number: ChiCTR2000030089. http://www.chictr.org.cn/showprojen.aspx?proj=49889. Accessed July 15, 2020.
44. Magro C, Mulvey JJ, Berlin D, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res*. 2020;220:1-13.
45. Mastaglio S, Ruggeri A, Risitano AM, et al. The first case of COVID-19 treated with the complement C3 inhibitor AMY-101. *Clin Immunol*. 2020. https://doi.org/10.1016/j.clim.2020.108450.
46. Diurno F, Numis FG, Porta G, et al. Eculizumab treatment in patients with COVID-19: preliminary results from real life ASL Napoli 2 Nord experience. *Eur Rev Med Pharmacol Sci* 2020;24(7):4040-4047.
47. Winkler F, Bengsch B. Use of mass cytometry to profile human T cell exhaustion. *Front Immunol*. 2020. https://doi.org/10.3389/fimmu.2019.03039.
48. Lin X, Lu X, Luo G, et al. Progress in PD-1/PD-L1 pathway inhibitors: From biomacromolecules to small molecules. *Eur J Med Chem*. 2020. https://doi.org/10.1016/j.ejmech.2019.111876.
49. David P, Megger DA, Kaiser T, et al. The PD-1/PD-L1 pathway affects the expansion and function of cytotoxic CD8+ T cells during an acute retroviral infection. *Front Immunol*. 2019;10:54.
50. Chiappelli F, Khakshooy A, Greenberg G. CoViD-19 Immunopathology & Immunotherapy. *Bioinformation*. 2020;16(3):219-222.
51. Luo J, Rizvi H, Egger JV, et al. Impact of PD-1 blockade on severity of COVID-19 in patients with lung cancers. *Cancer Discov*. 2020;10(8):1121-1128.
52. Medzhitov, R. Toll-like receptors and innate immunity. *Nat Rev Immunol*. 2001;1(2):135-145.
53. Patidar M, Yadav N, Dalai SK. Interleukin 15: A key cytokine for immunotherapy. *Cytokine Growth Factor Rev*. 2016;31:49-59.

54. Kandikattu H, Venkateshaiah S, Kumar S, Mishra A. IL-15 immunotherapy is a viable strategy for COVID-19. *Cytokine Growth Factor Rev.* 2020. https://doi.org/10.1016/j.cytogfr.2020.06.008.
55. Pathangey LB, McCurry DB, Gendler SJ, et al. Surrogate in vitro activation of innate immunity synergizes with interleukin-7 to unleash rapid antigen-driven outgrowth of CD4C and CD8C human peripheral blood Tcells naturally recognizing MUC1, HER2/neu and other tumor-associated antigens. *Oncotarget*. 2017;8(7):10785-10808.
56. Laterre PF, François B, Collienne C, et al. Association of Interleukin 7 immunotherapy with lymphocyte counts among patients with severe coronavirus disease 2019 (COVID-19). *JAMA Network Open*. 2020;3(7):e2016485.
57. Lang FM, Lee KM, Teijaro JR et al. GM-CSF-based treatments in COVID-19: reconciling opposing therapeutic approaches. *Nat Rev Immunol* 2020;20(8):507-514.
58. Chua RL, Lukassen S, Trump S, et al. COVID-19 severity correlates with airway epithelium–immune cell interactions identified by single-cell analysis. *Nat Biotechnol*. 2020;38(8):970-979.
59. Ulrich H, Pillat MM. CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. *Stem Cell Rev Rep*. 2020;16(3):434-440.
60. Bian H, Zheng Z, Wei D, et al. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.21.2004069.
61. Erenler AK, Baydin A. Interleukin-33 (IL-33) as a diagnostic and prognostic factor in traumatic brain injury. *Emerg Med Int*. 2020. https://doi.org/10.1155/2020/1832345.
62. Stanczak MA, Sanin DE, Apostolova P, IL-33 expression in response to SARS-CoV-2 correlates with seropositivity in COVID-19 convalescent individuals. *medRxiv*. 2020. https://doi.org/10.1101/2020.07.09.2014805.
63. Martín-Moreno AM, Roncador G, Maestre L, et al. CSF1R protein expression in reactive lymphoid tissues and lymphoma: its relevance in classical Hodgkin lymphoma. *PLoS One*. 2015;10(6):e0125203.
64. Liu Y, Chen GY, Zheng P. CD24-Siglec G/10 discriminates danger- from pathogen-associated molecular patterns. *Trends Immunol*. 2009;30(12):557-561.
65. Tsangaris I, Tsantes A, Vrigkou E, et al. Angiopoietin-2 levels as predictors of outcome in mechanically ventilated patients with acute respiratory distress syndrome. *Dis Markers*. 2017. https://doi.org/10.1155/2017/6758721.
66. Nair P, Melarkode R, Rajkumar D, Montero E. CD6 synergistic co-stimulation promoting proinflammatory response is modulated without interfering with the activated leucocyte cell adhesion molecule interaction. *Clin Exp Immunol*. 2010;162(1):116-130.
67. Ramos-Suzarte M, Diaz Y, Martin Y. Use of a humanized anti-CD6 monoclonal antibody (itolizumab) in elderly patients with moderate COVID-19. *medRxiv*. 2020. https://doi.org/10.1101/2020.07.24.20153833.
68. Ma T, Dong LJ, Du XL, et al. Research progress on the role of connective tissue growth factor in fibrosis of diabetic retinopathy. *Int J Ophthalmol*. 2018;11(9):1550-1554.
69. Perlin DS, Zafir-Lavie I, Roadcap L, et al. Levels of the TNF related cytokine, LIGHT increase in hospitalized COVID-19 patients with Cytokine Release Syndrome and ARDS. *medRxiv*. 2020. https://doi.org/10.1101/2020.07.27.20152892.
70. E G, Cao Y, Bhattacharya S, Dutta S, Wang E, Mukhopadhyay D. Endogenous vascular endothelial growth factor-A (VEGF-A) maintains endothelial cell homeostasis by regulating VEGF receptor-2 transcription. *J Biol Chem*. 2012;287(5):3029-3041.
71. Kong Y, Han J, Wu X, et al. VEGF-D: a novel biomarker for detection of COVID-19 progression. *Crit Care*. 2020. https://doi.org/10.1186/s13054-020-03079-y.
72. Van de Veerdonk FL, Netea MG, van Deuren M, et al. Kallikrein-kinin blockade in patients with COVID-19 to prevent acute respiratory distress syndrome. *Elife*. 2020;9:e57555.
73. Vellingiri B, Jayaramayya K, Iyer M, et al. COVID-19: a promising cure for the global panic. *Sci Total Environ.* 2020. https://doi.org/10.1016/j.scitotenv.2020.138277.
74. FDA guidance for industry. COVID-19: Developing Drugs and Biological Products for Treatment or Prevention https://www.fda.gov/media/137926/download. Accessed June 20, 2020.
75. FDA guidance for industry. Efficient clinical trial design strategies to expedite development of oncology drugs and biologics. https://www.fda.gov/media/120721/download. Accessed June 20, 2020.
76. FDA Commissioner Says Agency Wants to Develop Master Protocol Trials to Test Multiple COVID-19 Drug and Vaccine Candidates at Once. https://www.centerwatch.com/articles/24655-fda-commissioner-says-agency-wants-to-develop-master-protocol-trials-to-test-multiple-covid-19-drug-and-vaccine-candidates-at-once. Accessed April 20, 2020.
77. Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia (REMAP-CAP). https://clinicaltrials.gov/ct2/show/NCT02735707. Accessed May 22, 2020.
78. Treatment for COVID-19 in High-Risk Adult Outpatients. https://clinicaltrials.gov/ct2/show/NCT04354428. Accessed June 20, 2020.
79. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720.
80. Wang L, Zhang Y, Zhang S. Cardiovascular impairment in COVID-19: learning from current options for cardiovascular anti-inflammatory therapy. *Front Cardiovasc Med*. 2020. https://doi.org/10.3389/fcvm.2020.00078.
81. Spagnolo P, Balestro E, Aliberti S, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? *Lancet Respir Med*. 2020;8(8):750–752.
82. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China. *Lancet Respir Med*. 2020;8(5):475-481.
83. Ferro F, Elefante E, Baldini C, et al. COVID-19: the new challenge for rheumatologists. *Clin Exp Rheumatol*. 2020;38(2):175-180.
84. Epidemiology Working Group for NCIP Epidemic Response, Chinese Center for Disease Control and Prevention. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19) in China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2020;41(2):145-151.
85. Mikuls TR, Johnson SR, Fraenkel L, et al. American College of Rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: version 1. *Arthritis Rheumatol*. 2020. https://doi.org/10.1002/art.41301.
86. American academy of dermatology. Guidance on the use of biologic agents during COVID-19 outbreak. https://assets.ctfassets.net/1ny4yoiyrqia/PicgNuD0IpYd9MSOwab47/023ce3cf6eb82cb304b4ad4a8ef50d56/Biologics_and_COVID-19.pdf. Accessed June 22, 2020.
87. Tucker R. View: should patients with psoriasis stop their biologics because of COVID-19? https://hospitalhealthcare.com/covid-19/view-should-patients-with-psoriasis-stop-their-biologics-because-of-covid-19/. Accessed April 20, 2020.

88. Bashyam AM, Feldman SR. Should patients stop their biologic treatment during the COVID-19 pandemic. *J Derm Treat*. 2020;31(4):317-318.
89. Cancer patient management during the covid-19 pandemic. https://www.esmo.org/guidelines/cancer-patient-management-during-the-covid-19-pandemic. Accessed May 23, 2020.
90. Venkatakrishnan K, Yalkinoglu O, Dong J, et al. Challenges in drug development posed by the COVID-19 pandemic: an opportunity for clinical pharmacology. *Clin Pharmacol Ther*. 2020. https://doi.org/10.1002/cpt.1879.
91. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481.
92. Ogawa E, Wei MT, Nguyen MH. Hepatitis B virus reactivation potentiated by biologics. *Infect Dis Clin N Am*. 2020;34(2):341-358.
93. Liu B, Li M, Zhou Z, et al. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? *J Autoimmun*. 2020. https://doi.org/10.1016/j.jaut.2020.102452.
94. Centers for Disease Control and Prevention. Pregnancy & breastfeeding. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/pregnancy-breastfeeding.html. Accessed June 5, 2020.
95. Jones VG, Mills M, Suarez D, et al. COVID-19 and Kawasaki disease: novel virus and novel case. *Hosp Pediatr*. 2020;10(6):537-540.
96. Rivera-Figueroa EI, Santos R, Simpson S, Garg P. Incomplete kawasaki disease in a child with COVID-19. *Indian Pediatr*. 2020;57(7):680-681.
97. Riphagen S, Gomez X, Gonzalez-Martinez C, et al. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet*. 2020;395(10237):1607-1608.
98. Centers for Disease Control and Prevention Health Advisory. Emergency Preparedness and Response. https://emergency.cdc.gov/han/2020/han00432.asp. Accessed May 20, 2020.
99. Royal college of paediatrics and child health guidance: paediatric multisystem inflammatory syndrome temporally associated with COVID-19. https://www.rcpch.ac.uk/sites/default/files/2020-05/COVID-19-Paediatric-multisystem-%20inflammatory%20syndrome-20200501.pdf. Accessed July 15, 2020.
100. Shekerdemian L, Mahmood N, Wolfe K, et al. Characteristics and outcomes of children with coronavirus disease 2019 (COVID-19) infection admitted to US and Canadian pediatric intensive care units. *JAMA Pediatr*. 2020. https://doi.org/10.1001/jamapediatrics.2020.1948.
101. Vultaggio A. Considerations on biologicals for patients with allergic disease in times of the COVID-19 pandemic. *Allergy*. 2020. https://doi.org/10.1111/all.14407.
102. Coronavirus Disease 2019 (COVID-19). https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/older-adults.html. Accessed July 15, 2020.
103. Yu N, Li W, Kang Q, et al. No SARS-CoV-2 detected in amniotic fluid in mid-pregnancy. *Lancet Infect Dis*. 2020. https://doi.org/10.1016/S1473-3099(20)30320-0.
104. Schaub B, Vouga M, Najioullah F, et al. Analysis of blood from Zika virus-infected fetuses: a prospective case series. *Lancet Infect Dis*. 2017;17(5):520-527.
105. LaHue SC, Anderson A, Krysko KM. Transfer of monoclonal antibodies into breastmilk in neurologic and non-neurologic diseases. *Neurol Neuroimmunol Neuroinflamm.* 2020;7(4):e769.
106. Dallmann A, Pfister M, van den Anker J, et al. Physiologically based pharmacokinetic modeling in pregnancy: a systematic review of published models. *Clin Pharmacol Ther*. 2018;104(6):1110-1124.
107. Templeton IE, Jones NS, Musib L. Pediatric dose selection and utility of PBPK in determining dose. *AAPS J*. 2018: 20(2):31.
108. Kenny JR, Liu MM, Chow AT, et al. Therapeutic protein drug–drug interactions: navigating the knowledge gaps–highlights from the 2012 AAPS NBC roundtable and IQ Consortium/FDA Workshop. *AAPS J*. 2013;15(4): 933–940.
109. Diao B, Wang C, Wang R, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. *medRxiv*. 2020. https://doi.org/10.1101/2020.03.04.20031120.
110. Bigica A. Neurologic manifestations of COVID-19 common, report shows. Neurology Times. https://www.neurologytimes.com/covid-19/neurologic-manifestations-covid-19-common-report-shows. Accessed April 21, 2020.
111. Costela-Ruiz VJ, Illescas-Montes R, Puerta-Puerta JM, et al. SARS-CoV-2 infection: The role of cytokines in COVID-19 disease. *Cytokine Growth Factor Rev*. 2020. https://doi.org/10.1016/j.cytogfr.2020.06.001
112. Kliger AS, Silberzweig J. Mitigating risk of COVID-19 in Dialysis Facilities. *Clin J Am Soc Nephrol*. 2020;15(5):707-709.
113. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int*. 2020;98(1):219-227.
114. Fan Z, Chen L, Li J, et al. Clinical features of COVID-19-related liver damage. *Clin Gastroenterol Hepatol*. 2020;18(7):1561-1566.
115. BLA multidisciplinary review and evaluation. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/125276Orig1s114MultidisciplineR.pdf. Accessed June 16, 2020.
116. C-reactive protein levels among individuals with COVID-19. https://clinicaltrials.gov/ct2/show/NCT04373798. Accessed May 4, 2020.
117. Karlin-Smith S. COVID-19 shakes up real-world data studies. https://pink.pharmaintelligence.informa.com/PS142088/COVID19-Shakes-Up-RealWorld-Data-Studies. Accessed April 27, 2020.

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