Severe acute respiratory syndrome coronavirus 2 is associated with higher concentrations of proinflammatory cytokines that lead to lung damage, respiratory failure, and resultant increased mortality. Immunomodulatory therapy has the potential to inhibit cytokines and quell the immune dysregulation. Controversial data found improved oxygenation after treatment with tocilizumab, an interleukin-6 inhibitor, sparking a wave of interest and resultant clinical trials evaluating immunomodulatory therapies. The purpose of this article is to assess potential proinflammatory targets and review the safety and efficacy of immunomodulatory therapies in managing patients with acute respiratory distress syndrome associated with coronavirus disease 2019.

**Keywords.** ARDS; COVID-19; cytokine storm; SARS-CoV-2; tocilizumab.
METHODS
A systematic literature search using PubMed, iSearch COVID-19 portfolio, World Health Organization (WHO) database of publications on COVID-19, Google Scholar, WHO International Clinical Trials Registry Platform (ICTRP), and clinicaltrials.gov was performed from December 21, 2019 to May 11, 2020. Key search terms included SARS-CoV-2 or COVID-19 and cytokine storm, ALI, ARDS, IL-1, IL-1RA, IL-6, JAK, AAK1, GAK, TH17 cells, VEGF, CD147, CD24Fc, and TNF-α. We included multiple spellings, truncated nomenclatures, and abbreviations in the search. Articles were screened by title and abstract for possible inclusion, and references within articles of interest were scanned to capture additional sources.

RESULTS AND DISCUSSION
Interleukin-6
Interleukin-6, a pleiotropic cytokine released by T-cells, endothelial cells, fibroblasts, macrophages, and monocytes during acute and chronic inflammatory disease, regulates the immune system through 2 pathways: classic and trans [16, 17]. In the classic pathway, IL-6 binds to membrane-bound IL-6 receptors (mIL-6R) on hepatocytes leading to the induction of the hepatic acute phase response and the release of CRP, hepcidin, a regulator of iron metabolism, and fibrinogen. This pathway is also associated with anti-inflammatory properties, such as intestinal epithelial cell proliferation and inhibition of epithelial cell apoptosis. In the trans pathway, IL-6 binds to soluble IL-6 receptor (sIL-6R) to form hyper-IL-6, a vastly more potent activator of gp130 receptors found on all nucleated mammalian cells. This binding activates the signal transducer and activator of transcription (STAT) 3, a transcription factor associated with cellular transformation, proliferation, and angiogenesis [18]. This leads to widespread hematopoiesis resulting in recruitment of mononuclear cells, inhibition of T-cell apoptosis, and inhibition of regulatory T-cell differentiation. In theory, hyper-IL-6 can activate all cells within the body, which explains its central role in cytokine storm.

Currently, there are 3 monoclonal antibodies capable of inhibiting IL-6 signaling: tocilizumab, sarilumab, and siltuximab (Table 1, Figure 1) [19–21]. Tocilizumab and sarilumab share an identical mechanism of action by inhibiting both the mIL-6R and sIL-6R, thereby preventing IL-6R activation and hyper-IL-6 formation. The mechanism of action for siltuximab differs in that it binds to IL-6 directly, resulting in the inhibition of IL-6R activation and hyper-IL-6 formation. However, all 3 lead to IL-6 signal inhibition.

These acute phase reactants may have a role in the manifestations of COVID-19, such as elevated ferritin and COVID-19-associated coagulopathy [22]. Elevated serum concentrations of IL-6 were found in patients with MERS-CoV, SARS-CoV, and SARS-CoV-2 [9, 23–25]. In those with SARS-CoV-2, postmortem biopsies showed significant elevations of IL-6 in the lungs. Interleukin-6 knockout mice had a profound defect mounting an antiviral T-cell response against influenza [26]. This was associated with enhanced infiltration of inflammatory monocytes into the lung, severe lung damage, extensive vascular leakage, and death. Based on these findings, blocking IL-6 seems counterintuitive for viral pneumonias.

During COVID-19 infection, serum IL-6 concentrations are increased above that of healthy controls, ranging from 13.3 pg/mL in nonsevere cases to 239 pg/mL in severe cases with ARDS [9, 14, 15, 27–29]. However, experimental administration of large doses of IL-6 to healthy volunteers did not cause ALI or ARDS [30]. In this experiment, subjects reached up to 4050 pg/mL of IL-6 without ALI, which is a 16 times more than that observed during in severe COVID-19 [9, 12, 30]. It remains unclear whether increased IL-6 concentrations represent a marker and/or mediator of disease.

The initial study prompting the enthusiastic exploration of the effects of IL-6 inhibition in COVID-19 was a case series from China that included 21 severe or critically ill patients with COVID-19 treated with tocilizumab, plus standard of care (SOC), for cytokine storm (Table 2) [14, 15]. Oxygen requirements decreased in most patients, whereas body temperature normalized in all within 1 day after receipt of tocilizumab. C-reactive protein and lymphocytes returned to normal values. Chest computed tomography scans showed resolution of pulmonary lesions in almost all patients within 1 week. Posttreatment serum IL-6 concentrations remained elevated through day 5. As a result of these findings, tocilizumab was added to the Chinese treatment guidelines for COVID-19 [31]. Since then, multiple studies have been published describing clinical outcomes and effects on laboratory values of patients with COVID-19 after treatment with tocilizumab (Table 2) [28, 29, 32–35]. In addition, a press release from the open-label CORIMUNO-TOCI trial in France suggested significantly lower mortality and need for ventilator support in patients treated with tocilizumab with moderate to severe disease compared with placebo (data are unavailable) [36]. Analysis of preliminary results from the phase 2 portion of an ongoing phase 2/3 randomized study comparing low-dose (200 mg) and high-dose sarilumab (400 mg) to placebo in severe or critically ill patients with COVID-19 revealed no benefit in clinical outcomes or mortality when the severe and critical groups were compared with placebo (limited data available) [37]. Compared with placebo, negative trends were observed in the severe group, whereas a slight trend toward improved outcomes was observed in the critical group. As a result, the Independent Data Monitoring Committee amended the study going forward to only include critically ill patients to receive high-dose sarilumab or placebo. Interim analysis of the SISCO (siltuximab in serious COVID-19) study reported lower oxygen requirements (Table 2) [38]. Of 21 patients
| Generic Name (Brand Name) | Dose | Dose Adjustment | Contraindications/Adverse Effects (Listed in Alphabetic Order) | Potential Drug Interactions |
|---------------------------|------|----------------|---------------------------------------------------------------|-----------------------------|
| **IL-6 Inhibitors**       |      |                |                                                               |                             |
| Tocilizumab (Actemra)     |      |                |                                                               |                             |
| IL-6 Inhibitors           |      |                |                                                               |                             |
| Tocilizumab               |      |                |                                                               |                             |
| (Actemra)                 |      |                |                                                               |                             |
| Cytokine Release Syndrome |      |                |                                                               |                             |
| ≤30 kg–12 mg/kg IV        |      |                |                                                               |                             |
| ≥30 kg–12 mg/kg IV        |      |                |                                                               |                             |
| (maximum 800 mg per IV infusion. Up to 3 additional doses 8 hours apart.) | | | | |
| Giant cell arteritis/RA   |      |                |                                                               |                             |
| 162 mg SQ every 7 to 14 days |      |                |                                                               |                             |
| Optimal dosage for COVID-19 unknown but doses of 4-8 mg/kg IV (maximum 800 mg/dose) that may be repeated in patients with suboptimal response are being studied in clinical trials | | | | |
| No dose adjustments recommended in renal dysfunction | | | | |
| Hepatic dysfunction: | | | | |
| ALT or AST >1–5× ULN: 4 mg/kg | | | | |
| ALT or AST >3–5× ULN: dose every other week | | | | |
| ALT or AST >5× ULN: discontinue | | | | |
| GI perforation | | | | |
| Hepatotoxicity | | | | |
| Hypersensitivity | | | | |
| Increased risk of infections including TB, IFI, opportunistic infections, and reactivation of HBV or VZV | | | | |
| Major adverse cardiovascular events | | | | |
| Neutropenia | | | | |
| Thrombocytopenia | | | | |
| Transaminitis | | | | |
| Sarilumab (Kevzara)       |      |                |                                                               |                             |
| RA                        |      |                |                                                               |                             |
| 200 mg SQ every 2 weeks   |      |                |                                                               |                             |
| Optimal dosage for COVID-19 unknown but doses of 200 mg SQ and alternative IV dosing regimens are being studied in clinical trials | | | | |
| No dose adjustments recommended in renal dysfunction | | | | |
| Hepatic dysfunction: | | | | |
| ALT >3–5× ULN: interrupt therapy, may result once ALT <3× ULN | | | | |
| ALT >5× ULN: discontinue | | | | |
| Neutropenia: | | | | |
| ANC 500–1000 cells/mm³: interrupt therapy, may resume once ANC >1000 cells/mm³ | | | | |
| ANC <500 cells/mm³: discontinue | | | | |
| Platelets 50 000–100 000 cells/mm³: interrupt therapy, may resume once platelets >100 000 cells/mm³ | | | | |
| Platelets <50 000 cells/mm³: discontinue | | | | |
| No dose adjustments recommended in renal dysfunction | | | | |
| Hepatic dysfunction: | | | | |
| ALT >3–5× ULN: interrupt therapy, may result once ALT <3× ULN | | | | |
| ALT >5× ULN: discontinue | | | | |
| Neutropenia: | | | | |
| ANC <1000 cells/mm³: interrupt therapy, may resume once ANC >1000 cells/mm³ | | | | |
| ANC <500 cells/mm³: discontinue | | | | |
| GI perforation | | | | |
| Hepatotoxicity | | | | |
| Hyperlipidemia | | | | |
| Hypersensitivity | | | | |
| Increased risk of infections including TB, IFI, opportunistic infections, and reactivation of HBV or VZV | | | | |
| Neutropenia | | | | |
| Thrombocytopenia | | | | |
| Transaminitis | | | | |
| Siltuximab (Sylvant)      |      |                |                                                               |                             |
| Castleman Disease         |      |                |                                                               |                             |
| 11 mg/kg IV every 3 weeks |      |                |                                                               |                             |
| Optimal dosage for COVID-19 unknown but doses of 11 mg/kg per day are being studied in clinical trials | | | | |
| No dose adjustments recommended in renal or hepatic dysfunction | | | | |
| Therapy should be delayed in patients with the following: | | | | |
| ANC <1000 cells/mm³ | | | | |
| Platelets <50 000 cells/mm³ | | | | |
| Hemoglobin ≥17 g/dL | | | | |
| GI perforation | | | | |
| Hepatotoxicity | | | | |
| Hypersensitivity | | | | |
| Increased hemoglobin | | | | |
| Increased risk of infections including TB, IFI, opportunistic infections, and reactivation of HBV or VZV | | | | |
| Neutropenia | | | | |
| Thrombocytopenia | | | | |
| Transaminitis | | | | |
| JAK Inhibitors            |      |                |                                                               |                             |
| Sunitinib (Sutent)        |      |                |                                                               |                             |
| GI stromal tumor, pancreatic neuroendocrine tumor, renal cell carcinoma |      |                |                                                               |                             |
| 37.5–50 mg PO every 24 hours, 4 weeks on, 2 weeks off |      |                |                                                               |                             |
| Optimal dosage for COVID-19 unknown | | | | |
| No dose adjustments recommended in renal or hepatic dysfunction | | | | |
| Therapy should be modified or discontinued in patients with the following: | | | | |
| EF >50% but <50% below baseline without signs of HF | | | | |
| Signs or symptoms of HF | | | | |
| Severe hypertension | | | | |
| Dermatologic toxicities | | | | |
| Grade 3 or 4 hepatotoxicity | | | | |
| Thrombotic microangiopathy | | | | |
| Reversible posterior leukoencephalopathy syndrome | | | | |
| Nephrotic syndrome | | | | |
| Proteinuria (≥3 g/day) | | | | |
| Cardiotoxicity (including HR, cardiomyopathy, myocardial ischemia, and MI) | | | | |
| Embryo-fetal toxicity | | | | |
| Erythema multiforme | | | | |
| Hand-foot skin reaction | | | | |
| Hemorrhage | | | | |
| Hepatotoxicity | | | | |
| Hypertension | | | | |
| Necrotizing fasciitis | | | | |
| Neutropenia | | | | |
| Osteonecrosis of the jaw | | | | |
| Proteinuria/nephrotic syndrome | | | | |
| QTc prolongation | | | | |
| Stevens-Johnson syndrome (SJS) | | | | |
| Thrombotic microangiopathy | | | | |
| Toxic epidermal necrolysis (TEN) | | | | |
| Strong CYP3A4 inhibitors may increase sunitinib plasma concentration | | | | |

**Table 1. Drug Information for FDA-Approved Therapies Under Consideration for Patients With COVID-19**
| Generic Name (Brand Name) | Dose | Dose Adjustment | Contraindications/Adverse Effects (Listed in Alphabetic Order) | Potential Drug Interactions |
|--------------------------|------|----------------|---------------------------------------------------------------|-----------------------------|
| **Erlotinib** (Tarceva)  |      |                | *Bullous and exfoliative skin disorders*                     | CYP3A4 and CYP1A2 inhibitors increase erlotinib plasma concentrations |
|                          |      | No dose adjustments recommended in renal or hepatic dysfunction | *Cardiovascular events (including cerebrovascular accidents, myocardial ischemia, and MI)* | CYP3A4 inhibitors decrease erlotinib plasma concentrations |
|                          |      | Therapy should be delayed in patients with grade 3 or 4 renal toxicity or renal failure associated with hepatorenal syndrome or dehydration | *Gl perforation* | Acid suppressive therapy |
|                          |      | Concomitant administration with CYP3A4 inducers: increase by 50 mg | *Hepatotoxicity* | |
|                          |      | Concomitant administration with CYP3A4 inhibitors: decrease by 50 mg | *Intestinal lung disease* | |
|                          |      | *Microangiopathic hemolytic anemia* | *Ocular toxicity* | |
|                          |      | *Renal dysfunction and/or failure* | *Embryo-fetal toxicity* | |
|                          |      | *Embryo-fetal toxicity* | Strong CYP3A4 inhibitors, flucloxacillin | |
| **Ruxolitinib** (Jakafi) |      | Therapy should be modified or discontinued in patients with the following: | | |
|                          |      | *Bleeding* | | |
|                          |      | *CrCl <60 mL/min and platelets <150 000 cells/mm²* | | |
|                          |      | *Hepatic impairment (Child-Pugh class A, B, C) and platelets <150 000 cells/mm²* | | |
| **Fedratinib** (Inrebic) |      | Renal dysfunction: | | |
|                          |      | *CrCl 15–29 mL/min: decrease dose to 200 mg every 24 hours* | | |
|                          |      | *Hepatic dysfunction:* | | |
|                          |      | *Total bilirubin >3× ULN and any AST value: avoid use* | | |
| **Baricitinib** (Olumiant) |      | Renal dysfunction: | | |
|                          |      | *CrCl 30–60 mL/min: decrease dose to 1 mg every 24 hours* | | |
|                          |      | *CrCl <30 mL/min: discontinue* | | |
|                          |      | No dose adjustments recommended in hepatic dysfunction | | |
| **Anakinra** (Kineret) |      | Renal dysfunction: | | |
|                          |      | *CrCl <30 mL/min or ESRD: administer every 48 hours* | | |
|                          |      | No dose adjustments recommended in hepatic dysfunction | | |
| **IL-1 Receptor Antagonists** | | Renal dysfunction: | | |
|                          |      | *Cross-sensitivity to Escherichia coli-derived proteins* | | |
|                          |      | *Hypersensitivity reactions including anaphylaxis* | | |
|                          |      | *Increased risk of infections including TB, IFI, opportunistic infections, and reactivation of HBV or VZV* | | |
|                          |      | *Injection site reactions* | | |
|                          |      | *Malignancy* | | |
|                          |      | *Neutropenia* | | |
|                          |      | *Thrombolysis* | | |

**Table 1. Continued**
treated with siltuximab, one third were weaned off continuous positive airway pressure and noninvasive ventilation, 43% remained in stable condition, whereas 24% clinically deteriorated requiring MV. C-reactive protein and IL-6 serum concentrations were elevated in all patients with available baseline values. After treatment with siltuximab, CRP normalized by day 5, but posttreatment serum IL-6 concentrations were not reported. Although most studies reported CRP normalized after treatment, posttreatment IL-6 serum concentrations remained above the upper limit of normal. In patients treated with CAR-T therapy, tocilizumab inhibition of IL-6Rs led to higher serum IL-6 concentrations, despite normalizing inflammatory markers [39–41]. Greater reductions in serum IL-6 concentrations may be observed because siltuximab binds directly to IL-6, but the clinical benefits (eg, need for MV, intensive care unit length of stay, mortality, etc) are unknown. Data addressing these uncertainties will hopefully be provided in the multiple clinical trials assessing the efficacy of IL-6 inhibitors in patients with COVID-19 (Table 3) [42–57].

Tocilizumab is effective in treating CRS secondary to CAR-T therapy, along with many other autoimmune diseases, including rheumatoid arthritis (RA) and Crohn’s disease, but it is associated with cardiovascular injury and increased risk of infections (Table 1). In 2 case reports, tocilizumab was successful in treating CRS secondary to CAR-T therapy and sHLH secondary to blinatumomab-associated CRS. After treatment, both patients were weaned off vasopressors and MV [58, 59]. Compared with tumor necrosis factor alpha (TNF-α) inhibitors in RA, tocilizumab had a higher risk for skin and soft tissue infections and diverticulitis [60]. Randomized control trials and real-world data suggest no clinically significant difference in cardiovascular risk between TNF-α inhibitors and tocilizumab in patients treated for RA [17]. In comparison to tocilizumab, sarilumab has a higher affinity for IL-6R and was more potent

### Table 1. Continued

| VEGF Inhibitors | Bevacizumab (Avastin) [127] | Metastatic Colorectal Cancer | 5–75 mg/kg IV every 2 to 3 weeks | No dose adjustments recommended in renal or hepatic dysfunction | Delayed wound healing |
|-----------------|--------------------------|-----------------------------|--------------------------------|-------------------------------------------------------------------------------------------------|----------------------|
|                 | Nonsmall Cell Lung Cancer | 15 mg/kg IV every 3 weeks Renal Cell Carcinoma | 10 mg/kg IV every 2 weeks Cervical Cancer | Therapy should be modified or discontinued in patients with the following: | Fetal toxicity |
|                 | Plaque psoriasis, uveitis | 80 mg SQ on day 1, then 1 week later, 40 mg SQ every 2 weeks Crohn disease, ulcerative colitis, hidradenitis suppurativa | 180 mg SQ × 1, then 2 weeks later, 80 mg SQ × 1, then 2 weeks later, 40 mg SQ every 2 weeks | Nephrotic syndrome | Fistula formation |
|                 | Fistula formation involving any internal organ | | | Proteinuria (≥2 g/day) | GI perforation (any grade) |
|                 | Glomerular filtration rate | | | Grade 3 or 4 hemorrhage | Hypertensive crisis |
|                 | | | | Hypertensive encephalopathy | Infusion reaction |
|                 | | | | Posterior reversible encephalopathy syndrome | Thromboembolic events |
|                 | | | | Wound healing complications | |

### TNF-α Inhibitors

| Adalimumab (Humira) [106] | RA, psoriatic arthritis, ankylosing spondylitis | 40 mg SQ every 2 weeks Plaque psoriasis, uveitis | 80 mg SQ on day 1, then 1 week later, 40 mg SQ every 2 weeks Crohn disease, ulcerative colitis, hidradenitis suppurativa | No dose adjustments recommended in renal or hepatic dysfunction | Demyelinating disease |
|--------------------------|---------------------------------|-----------------|--------------------------|-------------------------------------------------------------------------------------------------|----------------------|
|                         | Fistula formation involving any internal organ | | | Proteinuria/nephrotic syndrome | Hypersensitivity |
|                         | Glomerular filtration rate | | | HF | Increased risk of infections including TB, IFI, opportunistic infections, and reactivation of HBV or VZV |
|                         | | | | Thromboembolic events | Malignancy |
|                         | | | | Posterior reversible encephalopathy syndrome | Neurologic reactions |
|                         | | | | Wound healing complications | Pancytopenia |

**Potential Drug Interactions**: Use with TNF-α inhibitors may increase risk of serious infections. Live vaccines should be avoided.

### Abbreviations:

- ALT: alanine aminotransferase
- ANC: absolute neutrophil count
- AST: aspartate aminotransferase
- COVID-19: coronavirus disease 2019
- CrCl: creatinine clearance
- CYP: cytochrome P450
- EF: ejection fraction
- ESRD: end-stage renal disease
- FDA: US Food and Drug Administration
- GI: gastrointestinal
- HBV: hepatitis B virus
- HF: heart failure
- IFI: invasive fungal infections
- JAK: Janus kinase
- MI: myocardial infarction
- OI: opportunistic infections
- PO: by mouth
- RA: rheumatoid arthritis
- SQ: subcutaneous
- TB: tuberculosis
- TNF: tumor necrosis factor
- ULN: upper limit of normal
- VEGF: vascular endothelial growth factor
- VZV: varicella zoster virus

---
Figure 1. Figure compares healthy alveolus (left) to injured alveolus (right) from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced proinflammatory host response and proposed targets of immunomodulatory therapy in coronavirus disease 2019 (COVID-19)-related acute lung injury/acute respiratory distress syndrome. Vascular endothelial growth factor inhibitor (VEGF) inhibitors (green text box) bind to and neutralize VEGF to inhibit pulmonary edema caused by VEGF overexpression. Interleukin-6 receptor (IL-6R) inhibitors (purple text box) inhibit both membrane-bound IL-6R and soluble IL-6R leading to inhibition of IL-6R activation and hyper-IL-6 formation, whereas silteximab also binds directly to IL-6. Janus kinase (JAK) inhibitors (red text box) inhibit the activity JAK enzymes thereby interfering with the JAK/signal transducer and activator of transcription pathway responsible for inflammatory cytokine signaling. CD24Fc (pink text box) interacts with danger-associated molecular patterns (DAMPs) and sialic acid-binding Ig-like lectins (Siglecs) to inhibit nuclear factor-kappa B activation and release of inflammatory cytokines. Anti-CD147 antibodies (yellow text box) inhibit CD147, which may lead to decreased SARS-CoV-2 replication. Tumor necrosis factor (TNF)-α inhibitors (black text box) bind to TNF-α to prevent binding to TNF-α receptor (TNFR) sites and subsequent release of inflammatory cytokines. Interleukin-1R antagonists (blue text box) block activity of IL-1β by competitively inhibiting binding to IL-1R. RBC, red blood cell; TLR, Toll-like receptor. Created with BioRender.com.

in inhibiting IL-6R activation and IL-6-induced cell proliferation [61]. The most common adverse effects of sarilumab were injection site reactions, neutropenia, and transaminitis [62]. Two studies comparing sarilumab against tocilizumab showed no clinically significant difference in incidence of treatment-emergent adverse events [63]. The incidence of neutropenia was numerically higher with sarilumab than with tocilizumab. However, neutropenia occurred more frequently with sarilumab compared with TNF-α inhibitors [64]. Due to the protective effects associated with the IL-6 classic signaling pathway, caution should be used in patients with intestinal perforation or diverticulitis. Bacterial, fungal, and viral infections should be ruled out before starting IL-6 inhibitors given the increased risk of infections and/or reactivation of latent infections.

Interleukin-6 inhibitors could potentially be effective treatment options for patients with COVID-19 with early signs of inflammatory dysregulation, but blocking one of many diverse cytokines may prove insufficient to quell the proinflammatory response. Furthermore, both short- and long-term safety data with IL-6 inhibitors in this patient population are unknown. Given the cardiovascular risk with both COVID-19 (reported in 29% of patients with COVID-19) and tocilizumab, patients should be monitored closely for cardiovascular injury [11]. Additional data are needed to establish the dosing, timing, and
| Reference         | Study Design (Location) | Patient Population | Intervention | Outcome(s) | Limitations/Critique |
|-------------------|-------------------------|--------------------|--------------|------------|----------------------|
| **Tocilizumab**   |                         |                    |              |            |                      |
| Xu et al (2020)   | Retrospective (Hefei, China) | Demographic data (n = 21)  | Tocilizumab 4-8 mg/kg (recommended dose 400 mg IV once + SOC) | Normalized body temperature within 24 hours: 100%  
Decreased O₂ requirements: 75%  
Improvement in chest CT: 90.5%  
No reports of adverse effects, pulmonary infections, clinical deterioration, or death  
IL-6 concentration post-tocilizumab, mean (±SD)  
◦ Day 1: 129.18 (131.79) pg/mL  
◦ Day 3: 300.98 (341.90) pg/mL  
◦ Day 5: 274.90 (414.08) pg/mL  
CRP concentration post-tocilizumab, mean (±SD)  
◦ Day 1: 38.13 (54.21) mg/L  
◦ Day 3: 10.61 (13.79) mg/L  
◦ Day 5: 2.72 (3.60) mg/L | Small sample size  
Nonrandomized  
Limited description of methods and results  
Time to tocilizumab administration unknown  
3 patients received a second dose of tocilizumab 400 mg IV within 12 hours due to sustained fever |
| Luo et al (2020)  | Retrospective (Wuhan, China) | Demographic data (n = 15)  | Tocilizumab IV on study day 0 | Clinical improvement: 7%  
Clinical stabilization: 60%  
Death: 20%  
IL-6 concentrations post-tocilizumab, mean (±SD)  
◦ Day 1: 338.3 (383.4) pg/mL  
◦ Day 3: 314.5 (317.3) pg/mL  
◦ Day 5: 3196.8 (2191.4) pg/mL  
◦ Day 7: 739.8 (1290.0) pg/mL  
CRP concentration post-tocilizumab, mean (±SD)  
◦ Day 1: 74.44 (30.24) mg/L  
◦ Day 3: 21.61 (16.81) mg/L  
◦ Day 5: 28.02 (22.18) mg/L  
◦ Day 7: 14.15 (32.13) mg/L | Small sample size  
Nonrandomized  
Limited description of methods and results  
Suboptimal reporting of safety profile  
Initial tocilizumab doses included 80 mg (n = 2), 100 mg (n = 1), 240 mg (n = 1), 320 mg (n = 1), 400 mg (n = 3), 480 mg (n = 6), and 600 mg (n = 1)  
8 patients received tocilizumab in combination with methylprednisolone 20 mg to 80 mg IV every 12 to 24 hours  
5 patients received 2 or more doses of tocilizumab |
| Klopfenstein et al (2020) | Retrospective, case-control comparing tocilizumab vs SOC (Trévenans, France) | Demographic data (tocilizumab group [n = 20] vs SOC group [n = 25])  
Age >70 years: 75% vs 44%, P = .036  
Charlson comorbidity index, mean (± SD): 5.3 (2.4) vs 3.4 (2.6), P = .014  
CRP concentration: 158 mg/L vs 105 mg/L, P = .017  
Composite endpoint of death and/or ICU admission: 25% vs 72%, P = .002  
Deaths: 25% vs 48%, P = .066  
Receipt of invasive MV: 0% vs 32%, P = .006 | Small sample size  
Nonrandomized  
Scant demographic data available  
Limited description of methods and results  
Suboptimal reporting of safety profile  
On average, tocilizumab administered 13 days after symptom onset, 7 days after admission, and after failure of SOC  
Tocilizumab dosing regimen not defined |
| Reference | Study Design (Location) | Patient Population | Intervention | Outcome(s) | Limitations/Critique |
|-----------|-------------------------|--------------------|--------------|-------------|---------------------|
| Toniati et al 2020 [28] | Case series (Brescia, Italy) | Demographic data (n = 100)  • Age, median (IQR): 62 (57–71) years  • Male: 88%  • Hypertension: 46%  • Diabetes mellitus: 17%  • COPD: 9%  • IL-6 concentration, median (IQR): 41 (10–102) pg/mL  • CRP concentration, median (IQR): 113 (45–169) mg/L  • BCRSS score, median (IQR): 3 (3–7)  • Requirement of MV: 33.3% vs 55.2%, P = .089  • Unadjusted analysis  • Requirement of MV: 33.3% vs 55.2%, P = .089  • CRP concentration post-tocilizumab, median (IQR): 0.63 (0.45) mg/L vs 6.07 (16.42) mg/L | Tocilizumab 8 mg/kg (maximum dose 800 mg) IV × 2 doses, 12 hours apart + SOC | Clinical and respiratory improvement: 58%  • Clinical stabilization: 37%  • Clinical worsening: 5% (of which 80%) died  • Clinical and respiratory improvement or stabilization: 77%  • Clinical worsening: 23% (of which 87%) died  • IL-6 concentration, median (IQR): 41 (10–102) pg/mL  • CRP concentration, median (IQR): 113 (45–169) mg/L  • BCRSS score, median = 3 (IQR, 1–4) | Nonrandomized  • Limited description of methods and results  • Suboptimal reporting of safety profile  • Time to tocilizumab administration was 12 (9–14) days  • Median (IQR) time from admission to tocilizumab administration was 12 (9–14) days  • 13 patients received a third dose of tocilizumab 24 hours after the second based on clinical response  • No adverse events were noted during the 10-day follow-up: 2 fatal cases of septic shock, 1 nonfatal case of gastrointestinal perforation  • No peer-reviewed publication  • Limited description of methods and results  • Scant data on control group available  • Suboptimal reporting of safety profile  • Mean time from symptom onset to receipt of tocilizumab was 14.1 days  • Patients could receive a second dose of tocilizumab if insufficient response, but number of patients who received second dose is unknown  • 2 patients treated with tocilizumab received HCQ 200 mg every 8 hours and azithromycin 250 mg every 12 hours on day 1, then every 6 hours thereafter  • No moderate or severe adverse events were observed |
| Roumier et al 2020 [33] | Retrospective, case-control comparing patients treated with tocilizumab vs patients not treated with tocilizumab (Suresnes, France) | Demographic data (tocilizumab group [n = 30] vs control group [n = 29])  • Age, mean (±SD): 58.8 (12.4) vs 71.2 (15.4) years, P = .001  • Male: 80% vs 62.1%, P = .008  • Hyperinflammation and hypercoagulable, defined as at least 3 of the following:  • CRP > 10× ULN  • Ferritin > 1000 mg/mL  • D-Dimer > 10× ULN  • LDH > 10× ULN | Tocilizumab 8 mg/kg IV × 1 dose | Death: 17.2% vs 18.7%, P = .837  • BCRSS score, mean = 2 (IQR, 1–4) | Nonrandomized  • Limited description of methods and results  • Suboptimal reporting of safety profile  • Small sample size  • No adverse effects were reported |
| Sciascia et al 2020 [34] | Prospective open, single-arm multicenter (Torino, Italy) | Demographic data (n = 63)  • Age, mean (±SD): 62.6 (12.5) years  • Male: 88%  • Hypertension: 38%  • Diabetes mellitus: 9.5%  • COPD: 4.7%  • SARS-CoV-2 PCR-confirmed COVID-19 infection  • Pulmonary involvement defined as SpO2 < 93% on R or PaO2/FiO2 < 300 mmHg  • Hyperinflammation and hypercoagulable, defined as at least 3 of the following:  • CRP > 10× ULN  • Ferritin > 1000 mg/mL  • D-Dimer > 10× ULN  • LDH > 10× ULN | Tocilizumab 8 mg/kg IV (n = 34)  • Tocilizumab + SOCd  • Tocilizumab + SOCd (n = 91) | Mortality at 14 days: 11%  • CRP concentration, median (IQR): 21.38 (13.40) mg/L vs 167.4 (106.8) mg/L, P = .426  • Requirement of MV: 33.3% vs 55.2%, P = .089  • Death: 17.2% vs 18.7%, P = .837 | Nonrandomized  • Limited description of methods and results  • Suboptimal reporting of safety profile  • Small sample size  • No adverse effects were reported |
| Colaneri et al 2020 [35] | Retrospective case-control comparing patients treated with tocilizumab vs patients not treated with tocilizumab (Pavia, Italy) | Demographic data (tocilizumab group [n = 21] vs control group [n = 29])  • Age, median (IQR): 62.33 (18.68) vs 63.74 (16.32) years  • Male: 90% vs 69%  • Hypertension: 38% vs 22%  • Diabetes mellitus: 10% vs 9%  • CRP concentration, median (IQR): 21.38 (13.40) mg/L vs 14.88 (14.41) mg/L | Tocilizumab 8 mg/kg IV (n = 34)  • Tocilizumab 324 mg SQ (n = 29) | Mortality: OR = 0.78 (95% CI, 0.06–9.34)  • CRP concentration post-tocilizumab, median (IQR): 0.63 (0.45) mg/L vs 6.07 (16.42) mg/L | Nonrandomized  • Limited description of methods and results  • Suboptimal reporting of safety profile  • Tocilizumab dosing regimen not defined  • Time to tocilizumab administration unknown  • Severity of illness poorly described  • No adverse effects were reported |
| Reference            | Study Design (Location) | Patient Population                                                                 | Intervention                                                                 | Outcome(s)                                                                 | Limitations/Critique                                                                 |
|----------------------|-------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------|----------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| Siltuximab           | Retrospective (Bergamo, Italy) | Demographic data (n = 21) • Age, median: 64 years • Male: 86% • Hypertension: 43% • Diabetes mellitus: 24% • Cerebrovascular disease: 5% • IL-6 concentration, median (range): 139.5 (113–239) pg/mL • CRP concentration, median (range): 23.4 (9.3–43.1) mg/L | Siltuximab 11 mg/kg per day IV within 2 days of CPAP or NIV | • Clinical condition improved: 33% • Clinical condition unchanged: 43% • Clinical condition worsened: 24% | • Non-peer reviewed publication • Small sample size • Nonrandomized • Limited description of methods and results • Suboptimal reporting of safety profile • Median initial siltuximab dose was 900 mg (range 700–1200 mg) • 5 patients received a second dose of siltuximab at physician’s discretion, as part of a compassionate-use program approved by the hospital ethics board |
| Gritti et al (2020)  | [38]                    |                                                                                     |                                                                              |                                                                            |                                                                                     |
| Anakinra             | Retrospective case series (France) | Demographic data (n = 9) • Age, median (range): 55 (46–84) years • Male: 89% • Hypertension: 33% • Diabetes mellitus: 11% • CRP concentration, median (range): 177 (83–282) mg/L | Anakinra 100 mg SQ every 12 hours × 3 days, then 100 mg SQ every 24 hours × 7 days | CRP concentration post-anakinra, median (range): Day 6: 19.5 (11–65) mg/L Day 11: 4.5 (1–16) mg/L All patients were alive at last follow-up | • Small sample size • Nonrandomized • Limited description of methods and results • Follow-up period unknown • Severity of illness poorly described • Suboptimal reporting of safety profile • Median (range) time from symptom onset to anakinra administration was 8 (4–12) days • Treatment was discontinued in one patient who developed acute respiratory failure after the first dose |
| Aouba et al (2020)   | [85]                    |                                                                                     |                                                                              |                                                                            |                                                                                     |
| Cavalli et al (2020) | Retrospective cohort study comparing low-dose anakinra vs high-dose anakinra vs SOC (Milan, Italy) | Demographic data (low-dose anakinra [n = 167], high-dose [n = 29], SOC [n = 16]) • Age, median (IQR): 68 (51–73) vs 62 (55–71) vs 70 (64–78) years • Male: 71% vs 83% vs 88% • Hypertension: 43% vs 52% vs 50% • Diabetes mellitus: 29% vs 21% vs 19% • COPD: 14% vs 3% vs 13% • CRP concentration, median (IQR): 139 (109–172) vs 164 (105–227) vs 188 (130–246) mg/L | Low-dose anakinra 21 days post-anakinra (high-dose anakinra vs 100 mg SQ every 12 hours) + SOC | Discharged from the hospital: 45% vs 44% High-dose anakinra (5 mg/kg IV every 12 hours + SOC) Survival: 90% vs 56% (HR = 0.20 [95% CI, 0.04–0.63], P = .009) MV-free survival: 72% vs 50% (HR = 0.5 [95% CI, 0.16–1.30], P = .15) | • Nonrandomized • Limited description of methods and results • Selection of treatment regimens unclear • Low-dose anakinra did not improve clinical status or CRP concentrations and was abandoned in favor of high-dose Treatment continued until sustained clinical benefit, defined as 75% decrease in CRP, respiratory improvement for at least 2 days, or until death, bacteremia, adverse effects which equated to median (IQR) 9 (7–11) days with high-dose anakinra • Patients treated with high-dose who sustained clinical benefit were transitioned to anakinra 100 mg SQ every 12 hours × 3 days to prevent relapse • 7 patients discontinued high-dose anakinra due to adverse events after median (IQR) 9 (8–10) days of treatment • 3 patients discontinued high-dose anakinra due to increases in transaminases >3× ULN • 4 patients receiving high-dose anakinra developed Staphylococcus epidermidis bacteremia • 3 patients who did not improve after receiving high-dose anakinra were noted to have pulmonary emboli • All patients were treated with concomitant LPV/r and HCQ |
|                      |                         |                                                                                     |                                                                              |                                                                            |                                                                                     |

Table 2. Continued
| Reference (Year) | Study Design (Location) | Patient Population | Intervention | Outcome(s) | Limitations/Critique |
|------------------|-------------------------|--------------------|--------------|------------|---------------------|
| Meplazumab       | Prospective, single center, open-label case-control comparing patients treated with meplazumab vs patients not treated with meplazumab (Xi’an, China) | Demographic data (meplazumab group [n = 17] vs control group [n = 11]) | Meplazumab 10 mg IV x 1 dose on days 1, 2, and 5 + SOC | Virologic Clearance Rate | Non-peer reviewed publication |

- Day 7: 76.5% vs 27.3% (P = .019)
- Day 14: 94.1% vs 54.4% (P = .022)
- Median: 3 days vs 13 days, P = .014 (HR = 0.37 [95% CI, 0.155–0.833])

Clinical improvement defined as normalized vital signs:
- Day 7: 17.6% vs 0%
- Day 14: 47.1% vs 27.3%
- Day 21: 82.4% vs 54.5%
- Day 28: 94.1% vs 81.8%

- Non-peer reviewed publication
- Small sample size
- Limited description of methods and results
- All patients in both groups were treated with concomitant LPV/r and recombinant INFα-2b
- 94.1% and 63.6% (P = .062) received concomitant systemic corticosteroids, respectively
- 100% and 90.9% (P = .393) received concomitant antibiotics, respectively
- Increased ALT and AST ≥2× ULN occurred in 2 patients receiving meplazumab

**Abbreviations:** ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; BCRSS, Brescia COVID-19 respiratory severity scale; CI, confidence interval; COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CPAP, continuous positive airway pressure; CRP, C-reactive protein; CT, computed tomography; DRV/c, darunavir/cobicistat; FiO2, percentage of inspired oxygen; HCQ, hydroxychloroquine; ICU, intensive care unit; IL, interleukin; INE interferon; IQR, interquartile range; LPV/r, lopinavir/ritonavir; MV, mechanical ventilation; NIV, noninvasive ventilation; OP, odds ratio; PaO2, partial pressure of arterial oxygen; PCR, polymerase chain reaction; PMH, past medical history; RR, respiratory rate; SARSCoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SOC, standard of care; SpO2, peripheral oxygen saturation; SQ, subcutaneous; ULN, upper limit of normal.

*aSOC included LPV/r 200/50 mg/tablet, 2 tablets PO every 12 hours x 10 days, INFα 5 million units via inhalation every 12 hours, ribavirin 500 mg IV every 8 to 12 hours x 10 days, symptomatic therapy, ± methylprednisolone 1–2 mg/kg per day x 3–5 days in patients with rapid progression in respiratory dysfunction and/or imaging and excessive inflammatory response.

*bSOC included HCQ or LPV/r ± systemic corticosteroids (doses and frequencies undefined).

*cSOC included antiviral therapy (LPV/r 200/50 mg/tablet, 2 tablets PO every 12 hours or remdesivir 100 mg IV every 24 hours), antibacterial prophylaxis (azithromycin, ceftriaxone, or PTZ), HCQ 400 mg every 24 hours, and dexamethasone 20 mg every 24 hours. SOC included HCQ 200 mg PO every 12 hours + methylprednisolone 1–2 mg/kg per day x 3–5 days.**

*dSOC was undefined.

*eSOC included HCQ 200 mg PO every 12 hours, LPV/r 200/50 mg/tablet, 2 tablets PO every 12 hours.
| Target | Proposed Mechanism vs SARS-CoV-2 or COVID-19 | Drug | Study Identifier (Location) | Study Type | Patient Population | Intervention | Comparator(s) | Primary Outcome | Estimated Date of Completion |
|--------|---------------------------------------------|------|----------------------------|------------|---------------------|--------------|---------------|----------------|---------------------------|
| IL-6   | Diminish inflammatory dysregulation         | Tocilizumab | NCT04317092 [42] (USA)     | Prospective, observational, single arm (hospitalized, noncritically and critically ill) | Tocilizumab 8 mg/kg IV × 2 doses, 12 hours apart | – | Complete recovery (afebrile, normal SpO₂) | March 31, 2021 |
|        |                                             |      | NCT04331795 [43] (USA)     | Interventional, single arm (hospitalized, noncritically) | Tocilizumab 200 mg IV × 1 dose (high dose) | – | Clinical and biochemical response | December 2020 |
|        |                                             |      | NCT04332094 [44] (Spain)   | Randomized, multicenter, open-label, parallel assignment (hospitalized, noncritically and critically ill) | Tocilizumab 162 mg SQ × 2 doses, 12 hours apart + HCQ 400 mg PO every 12 hours × 2 doses, then 200 mg every 12 hours × 6 days + azithromycin 500 mg PO every 24 hours × 3 days | HCQ 400 mg PO every 12 hours × 2 doses, then 200 mg every 12 hours × 6 days + azithromycin 500 mg PO every 24 hours × 3 days | In-hospital mortality and need for MV in ICU | October 2020 |
|        |                                             |      | NCT04320615 [45] (USA)     | Randomized, double-blind, multicenter, parallel assignment (hospitalized, noncritically and critically ill) | Tocilizumab 8 mg/kg IV (up to 800 mg/dose) × 1 dose (an additional dose may be administered if symptoms worsen or no improvement) | Placebo | Clinical status | September 30, 2021 |
|        |                                             |      | NCT04332913 [46] (Italy)   | Prospective, observational cohort (hospitalized, noncritically and critically ill) | Tocilizumab³ | – | Complete recovery (afebrile, normal SpO₂) | March 31, 2021 |
|        |                                             |      | NCT04306705 [47] (China)   | Retrospective cohort (3 study arms) (hospitalized, noncritically and critically ill) | Tocilizumab 8 mg/kg IV × 1 dose | CRRT | Complete recovery (afebrile, normal SpO₂) | June 20, 2020 |
|        |                                             |      | NCT04310228 [48] (China)   | Randomized, multicenter, open-label, parallel assignment (3 study arms) (hospitalized, noncritically and critically ill) | Tocilizumab 4–8 mg/kg (recommended dose 400 mg) IV × 1 dose (an additional dose may be administered if patient remains febrile within 24 hours after first dose) + favipiravir 1600 mg PO every 12 hours on day 1, then 600 mg PO every 12 hours on days 2 through 7 | Tocilizumab 4–8 mg/kg (recommended dose 400 mg) IV × 1 dose (an additional dose may be administered if patient remains febrile within 24 hours after first dose) + favipiravir 1600 mg PO every 12 hours on day 1, then 600 mg PO every 12 hours on days 2 through 7 | Clinical cure (negative respiratory viral load) | May 2020 |
|        |                                             |      | NCT04333914 [49] (France)  | Prospective, randomized, multicenter, parallel assignment (patients with advanced or metastatic hematological or solid tumor) | Tocilizumab 400 mg IV × 1 dose | Chloroquine analog (GS6851) 200 mg PO every 12 hours × 2 doses, then 200 mg PO every 24 hours × 14 days + Nivolumab 0.3 mg/kg IV × 1 dose + SOC | 28-day survival | August 2020 |
| Target | Proposed Mechanism vs SARS-CoV-2 or COVID-19 | Drug | Study Identifier (Location) | Study Type (Patient Population) | Intervention | Comparator(s) | Primary Outcome | Estimated Date of Completion |
|--------|-------------------------------------------|------|-----------------------------|--------------------------------|--------------|--------------|----------------|--------------------------|
|        |                                            | Sarilumab | NCT04322773 [53] (Denmark) | Randomized, open label, sequential assignment (4 arms) (hospitalized, noncritically and critically ill) | Sarilumab 200 mg SQ x 1 dose | Tocilizumab 400 mg IV x 1 dose | Time to independence from supplemental oxygen therapy | June 1, 2020 |
|        |                                            | Sarilumab | NCT04315298 [54] (USA) | Randomized, double-blind, placebo-controlled, parallel assignment (3 study arms) (hospitalized, critically ill) | Sarilumab high dose<int>  
Sarilumab low dose<sup>a</sup> | Placebo | Time to clinical improvement, percent change in CRP | April 1, 2021 |
|        |                                            | Sarilumab | NCT04327388 [55] (USA) | Randomized, double-blind, placebo-controlled, parallel assignment (hospitalized, critically ill) | Sarilumab<sup>a</sup> | Placebo | Time to resolution of fever for at least 48 hours (phase II) Clinical severity (phase III) | June 2021 |
|        |                                            | Sarilumab | NCT04324073 [56] (France) | Randomized, multicenter, open-label cohort (hospitalized, noncritically and critically ill) | Sarilumab 400 mg IV x 1 dose | SOC | 14-day survival without need for MV | December 31, 2020 |
| Target | Proposed Mechanism vs SARS-CoV-2 or COVID-19 | Drug | Study Identifier (Location) | Study Type (Patient Population) | Intervention | Comparator(s) | Primary Outcome | Estimated Date of Completion |
|--------|-----------------------------------------------|------|----------------------------|--------------------------------|--------------|---------------|-----------------|-----------------------------|
| JAK, AAK1, and GAK<sup>a</sup> (baricitinib only) | Diminish inflammatory dysregulation, and inhibit receptor-mediated endocytosis<sup>a</sup> (baricitinib only) | Baricitinib, Ruxolitinib | NCT0432 1993 [57] (Canada) | Interventional, nonrandomized, open-label (hospitalized, noncritically and critically ill) | Baricitinib 2 mg PO every 24 hours x 10 days | LPV/r 200/50 mg/tablet, 2 tablets PO every 12 hours x 10 days, HCO 200 mg PO every 12 hours x 10 days | Clinical status | July 2021 |
| | | | NCT0432 2077 [36] (Italy) | Interventional, nonrandomized, open-label, crossover assignment (hospitalized, noncritically and critically ill) | Baricitinib 4 mg PO every 24 hours + LPV/r 200/50 mg/tablet, 1 tablet PO every 12 hours x 14 days | – | ICU transfer | April 30, 2020 |
| | | | ChiCTR2000029580 [77] (China) | Prospective, randomized, single blind, parallel assignment (hospitalized, noncritically and critically ill) | Ruxolitinib<sup>a</sup> + mesenchymal stem cells | SOC | Clinical improvement at 7 days and 1 month | December 31, 2020 |
| | | | NCT0433 1665 [78] (Canada) | Interventional, open-label, single arm (hospitalized, noncritically and critically ill) | Ruxolitinib 10 mg PO every 12 hours x 14 days, then 5 mg PO every 12 hours x 2 days, then 5 mg PO every 24 hours x 1 day | – | Clinical deterioration | January 31, 2021 |
| IL1RA | Diminish inflammatory dysregulation | Anakinra | NCT0433 4021 [86] (Italy) | Randomized, multicenter, open-label, parallel assignment (3 study arms) (hospitalized, noncritically) | Anakinra 100 mg IV every 6 hours x 15 days | Emapalumab 6 mg/kg IV on day 1, then 3 mg/kg IV on days 4, 7, 10, and 13, SOC | Treatment success, defined as proportion of patients not requiring MV or ECMO | September 2020 |
| VEGF | Decrease vascular permeability and pulmonary edema | Bevacizumab | NCT0430 5106 [93] (China) | Randomized, multicenter, parallel assignment (hospitalized, critically ill) | Bevacizumab 75 mg/kg IV x 1 dose | Placebo | Time to clinical improvement | July 31, 2020 |
| | | | NCT0427 5414 [94] (China) | Interventional, single arm (hospitalized, noncritically and critically ill) | Bevacizumab 500 mg IV x 1 dose + SOC | – | PaO<sub>2</sub>/FiO<sub>2</sub> ratio | May 2020 |
| CD147 | Block SARS-CoV-2 invasion of host cells | Meplazumab<sup>b</sup> | NCT0427 5245 [100] (China) | Interventional, single arm (hospitalized, noncritically and critically ill) | Meplazumab 10 mg IV every 24 hours x 2 days | – | Virologic clearance rate | December 31, 2020 |
| CD24Fc | Inhibit activation of NFκB and release of inflammatory cytokines | CD24Fc | NCT0431 7040 [102] (USA) | Randomized, multicenter, double-blind, placebo-controlled, parallel assignment (hospitalized, critically ill) | CD24Fc 480 mg IV x 1 dose | Placebo | Time to clinical improvement | May 2022 |
Janus Kinase (JAK) mediates the release of proinflammatory cytokines leading to increased inflammatory processes [30]. JAKs are a family of nonreceptor protein tyrosine kinases that play critical roles in regulating receptor-mediated endocytosis and cytokine signaling, thereby downregulating immune responses related to SARS-CoV-2 (Table 1) [67-72]. SARS-CoV-2 is known to enter cells via endocytosis, and by inhibiting AAK1 and GAK, virus entry may become impaired. Ruxolitinib and fedratinib have lower affinity for AAK1 and GAK and therefore require greater than currently tolerated therapeutic doses [66]. This suggests that ruxolitinib and fedratinib would be unlikely to inhibit receptor-mediated endocytosis of SARS-CoV-2 [66]. In addition, fedratinib decreases the expression of IL-17 by murine TH17 cells as well as IL-22 [74]. Other cytokine signaling, such as G-CSF, may block the JAK2 pathway so it is thought that fedratinib would not inhibit cytokine signaling, thereby downregulating immune responses related to SARS-CoV-2 [Figure 1] [65, 66]. In addition, cytokine signaling is a unique target different from the other JAK inhibitors. Sunitinib also acts as a vascular-endothelial growth factor (VEGF) receptor inhibitor [73]. Sunitinib also acts as a vascular-endothelial growth factor (VEGF) receptor inhibitor [73]. Sunitinib also acts as a vascular-endothelial growth factor (VEGF) receptor inhibitor [73]. Sunitinib also acts as a vascular-endothelial growth factor (VEGF) receptor inhibitor [73]. Sunitinib also acts as a vascular-endothelial growth factor (VEGF) receptor inhibitor [73]. Sunitinib also acts as a vascular-endothelial growth factor (VEGF) receptor inhibitor [73].
bacterial, fungal, and viral infections should be completed before initiation.

Currently, baricitinib and ruxolitinib are the only JAK inhibitors being studied for use in COVID-19 patients (Table 3) [76–78]. There are 2 clinical trials underway comparing baricitinib with SOC, as well as other potential immunomodulatory therapies [76, 77]. In addition, there is an ongoing study exploring the use of ruxolitinib in combination with mesenchymal stem cells [78]. Understanding the potential adverse effects of these drugs is key, and weighing the risks versus benefits should be completed before consideration of use. Further evidence is needed to define the role of JAK inhibitors for patients with COVID-19 given the paucity of safety and efficacy data.

Interleukin-1

Interleukin-1 family comprises 11 cytokines and 10 receptors, which, compared with other cytokine families, are more associated with nonspecific, damaging inflammation [79]. Of these, IL-1α and IL-1β are responsible for direct and indirect host response. In addition, IL-1β is detectable in bronchoalveolar lavage fluid in patients with ARDS [80]. Conversely, the IL-1 receptor antagonist (IL-1RA) serves as a naturally occurring anti-inflammatory by inhibiting IL-1α and IL-1β [79]. Anakinra, a recombinant, nonglycosylated IL-1RA, has been evaluated as a method to counteract the cytokine storm observed in severe sepsis and septic shock (Table 1) [81]. Initial phase III trials failed to demonstrate decreased mortality [82, 83], but post hoc analysis found a significant 28-day survival benefit in patients with sepsis with multiorgan dysfunction syndrome and/or shock with concurrent DIC and hepatobiliary dysfunction [84].

Because IL-1β serum concentrations were significantly increased in patients with COVID-19 compared with healthy controls, it is thought that anakinra may block the activity of IL-1β in these patients (Figure 1) [12]. A small retrospective case series from France found lower CRP concentrations on day 6 after administration of a tapered regimen of subcutaneous anakinra over 3 days to 9 patients with moderate to severe COVID-19 (Table 2) [85]. The authors noted that CRP concentrations continued to trend down but remained elevated, and all patients were alive through day 11 of follow-up. A retrospective cohort study comparing low-dose anakinra and high-dose anakinra to SOC found higher survival rates but similar rates of MV-free survival at 21 days with high-dose anakinra (Table 2) [27]. Low-dose anakinra was not associated with improved clinical status or CRP concentrations and was abandoned. An open-label study comparing SOC with or without anakinra is expected to begin soon in Italy (Table 3) [86].

Although anakinra is well tolerated at standard doses, these lower doses did not prove beneficial. Limited data are available describing the tolerability and toxicity of high-dose anakinra. Additional data are needed to determine the dosing, timing, and subsequent monitoring of anakinra in patients with COVID-19.

Vascular Endothelial Growth Factor

Vascular endothelial growth factor is a potent vascular permeability inducer whose precise role in the lung remains unknown [87]. Higher concentrations of VEGF may promote increased vascular permeability and pleural effusions with resultant ALI [88]. In early ARDS, intrapulmonary VEGF concentrations are decreased whereas serum concentrations are increased [89], which is associated with poor prognosis [90]. As ARDS resolves, intrapulmonary and serum VEGF concentrations normalize [89]. Bevacizumab, a recombinant monoclonal antibody that binds to and neutralizes VEGF, was found to inhibit pulmonary edema in a VEGF overexpression model (Table 1, Figure 1) [91]. A study comparing bevacizumab to placebo in reducing incidence of ARDS in patients with severe sepsis was withdrawn due to lack of funding [92]. In comparison to healthy controls, VEGF serum concentrations were significantly increased in patients with COVID-19 [12]. Two clinical trials in China are currently recruiting participants to assess the efficacy of bevacizumab in patients with severe COVID-19 (Table 2) [93, 94]. The advantages of blocking VEGF in patients with COVID-19 must be weighed against the potential benefits of increased VEGF in respiratory distress [95, 96]. In addition, considerations as they pertain to the risk of serious adverse effects, including myocardial ischemia, cerebral thrombosis, and gastrointestinal perforation, are important in determining whether targeting VEGF is a viable option [97].

Emerging Options

CD147 is a transmembrane glycoprotein expressed in various tumors, inflamed tissues, and infected cells [98]. Previous data suggest that CD147 facilitates invasion of SARS-CoV into host cells, and therefore blocking CD147 may prevent viral invasion. Based on these findings, Wang et al [99] conducted an in vitro study to describe the interaction between SARS-CoV-2 and CD147 because of purported similarities between SARS-CoV and SARS-CoV-2. The authors noted that SARS-CoV-2 spike protein facilitated the invasion of host cells via CD147, and they observed decreases in viral replication when inhibiting CD147 with meplazumab, an anti-CD147 antibody (Figure 1). On the contrary, SARS-CoV N protein was found to bind to CD147 and not spike protein [98]. Nevertheless, a small prospective, single-center, open-label case-control study found faster virologic clearance in patients with COVID-19 treated with meplazumab (data not peer reviewed) (Table 2) [72]. Another clinical trial evaluating the effects of meplazumab on rate of viral clearance is currently recruiting in China (Table 3) [100]. More data are needed to determine the safety and efficacy of meplazumab in patients with COVID-19.
CD24Fc is a recombinant fusion protein consisting of the nonpolymorphic regions of CD24 attached to the Fc domain of human immunoglobulin (Ig)G1 [101]. Acting as an immunomodulator, CD24Fc may decrease inflammation associated with tissue injury by interacting with danger-associated molecular patterns and sialic acid-binding Ig-like lectins (Siglecs) thereby inhibiting nuclear factor-kappa B activation and release of inflammatory cytokines (Figure 1). Indeed, decreased CD8+ T cells, leukocyte infiltration, and IL-6 were observed after systemic administration to SIVmac239-infected macaques, but effects were more focused in the intestinal tract. The reasons for focused activity of CD24Fc in the gut remain

| Immunotherapy discussed? (specific therapy named) | Guideline | Specific patient criteria |
|---------------------------------------------------|-----------|--------------------------|
| Yes (Tocilizumab)                                 | SSC, SCCM ESICM [114] Belgium [116] | None provided<br>Patients with critical disease<br>- Persistent inflammation (e.g., elevated IL-6, CRP, D-Dimer, ferritin) and ARDS requiring mechanical ventilation without evidence of bacterial superinfection/sepsis<br>- Severe cases of COVID-19 with suspicion of cytokine activation syndrome<br>- Use caution if secondary infection is clinically suspected<br>- Patients with extensive lung lesions and severe disease with elevated IL-6 concentration<br>- Patients with critical disease and ARDS<br>- Patients with severe disease with clinical deterioration despite other treatments<br>- Persistent fever with temperature ≥38°C and one of the following<br>  - Impending respiratory failure with increasing oxygen requirements or ARDS with a PaO2/FiO2 < 200 mm Hg<br>  - New nonischemic cardiomyopathy requiring inotropic support and/or hypotension that requires on or more vasopressors<br>  - Serum IL-6 concentration greater than 5x the upper limit<br>- Consider in critically ill patients with suspected cytokine storm<br>- Patients who clinically worsen despite other therapies<br>- Patients with evidence of cytokine release syndrome |
| Yes (Tocilizumab & Sarilumab)                    | University of Michigan [117] Yale New Haven Health System [121] | Patients who cannot receive in a timely fashion or are not candidates for sarilumab trial<br>Requirements:<br>- Positive COVID-19 test<br>- Abnormal chest imaging consistent with COVID-19<br>- Rapidly worsening gas exchange requiring >6 L/min O2<br>- Absence of systemic bacterial or fungal coinfection<br>Exclusion Criteria:<br>- Anticipated immediate death (≤ 24 hours) regardless of critical care support<br>- Cardiac: NYHA Class IV heart failure; Severe, inoperable multi-vessel coronary artery disease Cardiac arrest; Recurrent arrests in the current presentation, or unresponsive to defibrillation of pacing, or unwitnessed out-of-hospital cardiac arrest with poor prognosis<br>- Hepatic: Cirrhosis with MELD-Na score ≥ 25 (in patient who are not transplant candidate), alcoholic hepatitis with MELD-NA ≥ 30, advanced liver cancer<br>- Neurologic: Severe dementia leading to dependence in multiple ADLs; Rapidly progressive end-stage neuromuscular disease<br>- Oncologic: Advanced malignancy or high-grade primary brain tumors receiving only palliative treatment with estimated 3 or fewer months prognosis.<br>- Pulmonary: Severe, chronic lung disease with baseline oxygen requirement of ≥ 60% FiO2; Primary pulmonary hypertension with NYHA Class III or IV heart failure (and patient refractory to/nor a candidate for pulmonary vasodilators)<br>- Trauma: Severe trauma; severe burns: age 60 years and 50% of total body surface area affected<br>- Functional Status: dependent on all ADLs due to a progressive chronic comorbid condition |
| Yes (Tocilizumab, Baricitinib, Ruxolitinib)      | Penn Medicine [118] | None provided |
| Yes (Tocilizumab)                                | Mount Sinai Health System [123] | Patients with severe disease with respiratory failure with no other end organ damage |
| None                                             | NICE [110] John Hopkins [119] American Thoracic Society [113] | None provided None provided None provided |

ADLs, activities of dialing living; ARDS, acute respiratory distress syndrome; CRP, C-reactive protein; ESICM, European Society of Intensive Care Medicine; FiO2, percentage of inspired oxygen; IL, interleukin; NICE, National Institute for Health and Care Excellence; NYHA, New York Heart Association; PaO2, partial pressure of arterial oxygen; SCCM, Society of Critical Care Medicine; SSC, Surviving Sepsis Campaign
unknown. A trial aimed at evaluating time to clinical improvement in patients with severe COVID-19 after administration of CD24Fc is anticipated to start soon in the United States (Table 3) [102].

TNF-α is a proinflammatory cytokine primarily produced by monocytes and macrophages. One of its many functions is to induce the production of other cytokines and promote inflammation [103]. Increased TNF-α concentrations in blood and tissue have been observed in some, but not all, patients with severe COVID-19 [104]. If inhibited, this may result in diminished inflammation (Figure 1). Currently, there are 2 clinical trials recruiting in China evaluating the use of TNF-α inhibitors (Table 1) [105] in COVID-19 patients (Table 2) [106, 107]. The first is a phase IV trial evaluating time to clinical improvement in patients who received either SOC or adalimumab (unavailable in United States, but considered a biosimilar to adalimumab), tozumab (unavailable in United States, but considered a biosimilar to tocilizumab [108]), and SOC. This trial will be evaluating chest imaging, nucleic acid detection of virus, TNF-α, IL-6, and IL-10 in severe and critical COVID-19 patients [107].

Current Guideline Recommendations
As quickly as this situation is evolving, information available to guide treatment decisions is growing just as fast. Despite minimal evidence due to the short time frame there has been to develop it, there are varying recommendations pertaining to the use of immunomodulatory therapy in patients infected with SARS-CoV-2. Due to the evolving nature of this situation and limited number of guideline recommendations available, a general query web-search through Google was conducted on May 11, 2020 with the previously mentioned search terms. Institutional guidelines were screened by title for possible inclusion, and those focusing on special population of specific associated diagnosis were excluded. Of the varying immunomodulatory therapies discussed within this article, only the following are specifically named across a series of institutional, governmental, and societal guideline recommendations: tocilizumab, sarilumab, baricitinib, and ruxolitinib (Table 4) [31, 109–126].

Overall, there is varying guidance ranging from no mentions at all to supporting the use of immunotherapy under certain circumstances. The National Institute for Health and Care Excellence makes no mention of the use of immunomodulatory therapy among their available COVID-19 guidelines [110]. The American Thoracic Society makes no suggestion for or against the use of tocilizumab in hospitalized patients with COVID-19 [113]. Likewise, John Hopkins plans to provide recommendations specifically for the use of tocilizumab but has none at the time of writing [119].

Several recommendations exist supporting the use of immunomodulatory therapy in critically ill patients meeting specific criteria (Table 4) [31, 109, 111, 112, 115–117, 120–124]. Internationally, clinical guidance from China [31], Belgium [116], and Italy [115] recommends tocilizumab in specific patients. Stateside, the University of Michigan [117], University of Washington [111], Brigham and Women’s Hospital [109], Massachusetts General Hospital [120], Vanderbilt University [112], Yale New Haven Health System (YNHHS) [121], University of Mississippi Medical Center [122], Mount Sinai Health System [123], and Amita Health [124] provide specific recommendations for use of immunomodulatory therapy. Of the mentioned institutions, University of Michigan, YNHHS, and Mount Sinai Health System are involved with ongoing clinical trials with immunomodulatory therapy (eg, sarilumab) [117, 121, 123].

Recommendations against immunomodulatory therapy altogether are limited. The Society of Critical Care Medicine and European Society of Intensive Care Medicine jointly recommend against the use of tocilizumab due to insufficient evidence to issue a recommendation in critically ill adults [114]. Nebraska Medicine does not recommend the use of tocilizumab because of the unfavorable risk/benefit ratio [126]. Finally, Penn Medicine and University of Iowa Health Care discourage routine use of immunomodulatory therapy, highlighting lack of evidence [118, 125].

CONCLUSIONS
Severe acute respiratory syndrome coronavirus 2 leads to ALI and ARDS with increased mortality. Immunomodulatory therapies have the potential to inhibit cytokines, but the role of elevated cytokines with lung pathology is unclear. The overall lack of evidence and recommendations has forced practitioners to use their own judgment regarding use of immunomodulatory therapy. We are hopeful that as clinical trial data become available, their role in managing patients with COVID-19 will emerge. For now, available evidence suggests that these treatment options should be reserved for use in critically ill COVID-19 patients enrolled in clinical trials. Due to the potential adverse effects, risks and benefits must be weighed and proper screening must be completed before administration.

Acknowledgments
Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

References
1. Zhu N, Zhang D, Wang W, et al.; China Novel Coronavirus Investigating and Research Team. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382:727–33.
2. Perlman S. Another decade, another coronavirus. N Engl J Med 2020; 382:760–2.
3. Wu Z. CROI Special Session on COVID-19: 15-minute live video update from China. 2020. Available at: https://special.croi.capitalreach.com/. Accessed 6 April 2020.
4. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis 2020; 20:533–4.
10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China: a retrospective cohort study. Lancet Respir Med 2020; 8:475–81.

11. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with COVID-19 in Wuhan, China: a single-centered, retrospective, observational study. Lancet Resp Med 2020; 8:475–81.

12. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China: a retrospective cohort study. Lancet 2020; 395:1054–62.

13. Zhang C, Wu Z, Li JW, et al. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab. Proc Natl Acad Sci U S A. 2020; 117(20):10970–10975. doi: 10.1073/pnas.2005651117.

14. Aggarwal BB, Kunnumakkara AB, Harikumar KB, et al. Signal transducer and activator of transcription-3, inflammation, and cancer. Ann N Y Acad Sci 2009; 1171:59–76.

15. Acterena (Tocilizumab) [prescribing information]. South San Francisco, CA: Genentech Inc; 2019.

16. Kevzara (Sarilumab) [prescribing information]. Bridgewater, NJ: Sanofi-Aventis; 2020.

17. Zhang C, Wu Z, Li JW, et al. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab. Proc Natl Acad Sci U S A. 2020; 117(20):10970–10975. doi: 10.1073/pnas.2005651117.

18. Rose-John S. The soluble interleukin 6 receptor: advanced therapeutic options in inflammation. Clin Pharmacol Ther 2017; 102:591–9.

19. Xu X, Han M, Li T. Effective treatment of severe COVID-19 patients with tocilizumab. ChinaXiv [Preprint]. 2020;202003.00026. Available at: http://www.chinaxvr.org/abs/202003.00026. Accessed 6 April 2020.

20. 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. doi: 10.1073/pnas.2005651117.

21. Sybvant (Siltuximab) [prescribing information]. Hemel Hempstead, Hertfordshire, United Kingdom: EUSA Pharma (UK); 2019.

22. Tang N, Bai H, Chen X, et al. Anti-coagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. J Thromb Haemost 2020; 18:1094–99.

23. Castilletti C, Bordi L, Lalle E, et al. Coordinate induction of IFN-alpha and gamma by SARS-CoV also in the absence of virus replication. Virology 2005; 341:163–9.

24. Shi SQ, Peng JP, Li YC, et al. The expression of membrane protein augments the specific responses induced by SARS-CoV nucleocapsid DNA immunization. Mol Immunol 2006; 43:1791–8.

25. Tseng CT, Perrone LA, Zhu H, et al. Severe acute respiratory syndrome and the innate immune responses: modulation of effector cell function without productive infection. J Immunol 2005; 174:7977–85.

26. SAEF-KO Coronavirus (SARS) [clinical trial]. United States: EUSA Pharma (UK); 2020.

27. Castilletti C, Bordi L, Lalle E, et al. Coordinate induction of IFN-alpha and gamma by SARS-CoV also in the absence of virus replication. Virology 2005; 341:163–9.

28. 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 Rheumatology 2020; 2:E325–31.

29. Tonias P, Piva S, Cattalin M, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: a single center study of 100 patients in Brescia, Italy. Autonom Rev 2020; 19:102568.

30. Luoz L, Liu Y, Qiu L, et al. Tocilizumab treatment in COVID-19: a single center experience. J Med Virol 2020; doi: 10.1002/jmv.25801.

31. Tsigos C, Papanicolaou DA, Kyrou I, et al. Dose-dependent effects of recombi- nant human interleukin-6 on glucose regulation. J Clin Endocrinol Metab 1997; 82:4167–70.

32. Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment. 7th ed. China National Health Commission; 2020. Available at: http://kjfy. meetingchina.org/msite/news/show/cn/3337.html. Accessed 27 April 2020.
coronavirus pneumonia (COVID-19). Available at: http://www.chictr.org.cn/showprojen.aspx?proj=50693. Accessed 11 May 2020.

108. Ying W, Qian Y, Kun Z. Drugs supply and pharmaceutical care management practices at a designated hospital during the COVID-19 epidemic. [published online ahead of print April 6, 2020] Res Social Adm Pharm 2020; S1551-7411(20):30325–9. doi:10.1016/j.sapharm.2020.04.001.

109. Brigham and Women’s Hospital COVID-19 critical care clinical guidelines. Available at: https://www.covidprotocols.org/. Accessed 31 March 2020.

110. NICE. National Institute for Health and Care Excellence. Coronavirus (COVID-19). Available at: https://www.nice.org.uk/covid-19. Accessed 31 March 2020.

111. UW Medicine. UW Medicine COVID-19 resource site - UW ID treatment guidelines. Available at: https://covid-19.uwmedicine.org/Pages/default.aspx. Accessed 31 March 2020.

112. VUMC. Vanderbilt University Medical Center clinical recommendatoin for treatment of COVID-19 adult patients. Available at: https://www.vumc.org/coronavirus/sites/default/files/COVID%20Documents/Weekly%20COVID%20Clinical%20Guidelines%20Update%20Summary%20-%203.22.2020-%20FINAL.pdf. Accessed 1 April 2020.

113. Wilson KC, Chotirmall SH, Bai C, Rello J. On behalf of the International Task Force on COVID-19. COVID-19: Interim Guidance on Management Pending Empirical Evidence. From an American Thoracic Society-led International Task Force. Available at: https://www.thoracic.org/covid/covid-19-guidance.pdf. Accessed 11 May 2020.

114. Alhazzani W, Møller MH, Belley-Cote E, Citerio G. Intensive care medicine rapid practice guidelines (ICM-RPG): paving the road of the future. Intensive Care Med 2019; 45:1639–41.

115. Italian Society of Infectious and Tropical Diseases: Handbook for the Care of People with Disease-COVI 19. 2nd ed. Available at: http://www.simit.org/IT/simit/sezioni-regionali.xhtml/sezione/112-lombardia/comunicazioni/1. Accessed 31 March 2020.

116. Van Ierssel S, Dauby N, Bottieau E, et al. Interim clinical guidance for adults with suspect or confirmed COVID-19 in Belgium. Available at: https://epidemiowiv.isp.be/ID/Documents/Covid19/COVID-19_InterimGuidelines_Treatment_ENG.pdf. Accessed 31 March 2020.

117. University of Michigan: Michigan Medicine University of Michigan inpatient guideline for treatment of COVID-19 in adults and children. Available at: http://www.med.umich.edu/asp/pdf/adult_guidelines/COVID-19-treatment.pdf. Accessed 31 March 2020.

118. University of Pennsylvania Health System - Penn Medicine treatment guidelines for SARS-CoV-2 infection - treatment of adult patients with confirmed SARS-CoV-2 (COVID-19) infection. Available at: http://www.uphs.upenn.edu/antibiotics/COVID19.html. Accessed 31 March 2020.

119. Auwaerter PG. John Hopkins ABX guide Coronavirus Covid-19 (SARS-CoV-2). Available at: https://www.hopkinsguides.com/hopkins/view/Johns_Hopkins_ABX_Guide/540747ľa/Coronavirus_COVID_19_SARS_CoV_2_. Accessed 1 April 2020.

120. Massachusetts General Hospital COVID-19 treatment guidance. Available at: https://www.massgeneral.org/assets/IGH/pdf/news/coronavirus/IGH%20ID%20COVID19%20Here%20and%20Now%20Treatment%20Guidance%20V1.351%2003272020.pdf. Accessed 1 April 2020.

121. Yale New Haven Health System initial treatment algorithm for patients with COVID-19. Available at: https://files-profile.medicine.yale.edu/documents/e91b4e5c-ae56-4bf1-8d5f-e674b6450847. Accessed 11 May 2020.

122. University of Mississippi Medical Center. University of Mississippi Medical Center Management of patients with suspected SARS-CoV-2 (COVID-19). Available at: https://www.cumc.edu/CoronaVirus/Mississippi-Health-Care-Professionals/Clinical-Resources/Patient%20Treatment%20Guidelines/Management%20of%20Patients.html. Accessed 11 May 2020.

123. Mount Sinai Health System treatment guidelines for SARS-CoV-2 infection (COVID-19). Available at: https://www.mountsinai.org/files/MSHealth/Assets/HS/About/Coronavirus/MSHS-Treatment-Guidelines-COVID.pdf. Accessed 11 May 2020.

124. AMITA Health COVID-19 treatment guidelines. Available at: https://www.amitahealth.org/assets/documents/covid-19-playbook/amita-health-covid-19-treatment-guidelines-4-11-2020.pdf. Accessed 11 May 2020.

125. University of Iowa Health Care COVID-19 clinical information. Available at: https://medcom.uiowa.edu/theloop/covid-19-clinical-information#covid-19-treatment-guide. Accessed 11 May 2020.

126. Alexander B, Van Schooneveld T, Stohs E, et al. Nebraska Medicine Covid-19 antiviral and pharmacotherapy information. Available at: https://www.nebraskamed.com/sites/default/files/documents/covid-19/antiviral-and-pharmacotherapy-information.pdf?date=03242020. Accessed 1 April 2020.

127. Avastin (Bevacizumab) [prescribing information]. South San Francisco, CA: Genentech; 2019.

128. Bian H, Zheng Z-H, Wei D, et al. Meplazumab treats COVID-19 pneumonia: an open-labelled, concurrent controlled add-on clinical trial. 2020;2020.2004.20040691. doi:10.1101/2020.03.21.20040691.