Therapeutic Approach to Coronavirus Disease

Caroline Der-Nigoghossian, Alana Ciolek, and Taylor Chuich

5.1 Introduction to COVID-19 Therapeutics

The global pandemic of coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China, in December 2019. The viral genome was rapidly identified in order to develop diagnostic testing and therapeutic options. SARS-CoV-2 is a single-stranded RNA-enveloped virus that uses its surface spike (S) protein to bind host cell’s angiotensin converting enzyme 2 (ACE2) receptor in the presence of host cell protease TMRSS2, a cofactor for virus entry [1]. The virus uses RNA-dependent RNA polymerase to synthesize RNA leading to viral assembly and exocytosis [2].

Drug therapies that could target one or several of the phases of the viral entry and replication processes have been evaluated as potential therapeutics for the treatment of coronavirus disease 2019 (COVID-19). The COVID-19 pandemic has led the scientific community to repurpose different drugs that were previously used for other viral infections such as Middle East respiratory syndrome coronavirus (MERS-CoV) and severe acute respiratory syndrome coronavirus (SARS-CoV). In addition, dysregulation of the immune system and consequent cytokine release syndrome have been identified as the main pathophysiological processes associated with COVID-19 [3]. This has led to the evaluation of different immunomodulatory agents to target the inflammatory cascade.
As of July 2020, 2764 studies are registered on clinicaltrials.gov for COVID-19. In this chapter, we discuss the evidence regarding the use of different therapeutics. Due to the evolving nature of the evidence, we have included drugs that have at least five published and/or undergoing clinical trials evaluating their use in COVID-19. In addition, we summarize the recommendations provided by multiple societies including the Infectious Disease Society of America (IDSA), Society of Critical Care Medicine (SCCM), and the National Institute of Health (NIH) [4–8].

In the following sections, Fig. 5.1 depicts the mechanism of action of therapeutics discussed in this chapter.

Table 5.1 summarizes general information regarding investigational treatments for COVID-19 including dosing, common adverse effects, and pharmacotherapy pearls. Table 5.2 summarizes the recommendations from national guidelines and societies. Finally, due to the rapidly evolving volume of literature, Table 5.3 only summarizes randomized controlled trials of the therapeutic options discussed within the text.

## 5.2 Antiviral Agents

### 5.2.1 Favipiravir

Favipiravir is a competitive inhibitor of RNA-dependent RNA polymerase and is approved in Japan for the treatment of influenza (Table 5.1) [9]. It was also shown to decrease mortality in patients with Ebola virus and was effective at preventing Ebola virus infection. An in vitro study showed its effectiveness at inhibiting SARS-CoV2 growth; however, due to the higher EC50 (half maximal effective concentration) compared to influenza, higher than standard doses have been recommended for its use for the treatment of SARS-CoV2 [29].

Two studies have evaluated the efficacy and safety of favipiravir in patients with COVID-19. One was a before-after observational cohort study comparing favipiravir to lopinavir/ritonavir both in combination with inhaled interferon-α1b in patients with mild-moderate disease [30]. Treatment was continued until viral clearance, for up to 14 days. The study showed shorter time to clearance and more improvement in chest imaging in the favipiravir group. The second study was a randomized controlled trial from China of 240 patients who received favipiravir or umifenovir (Table 5.3) [17]. There was no difference between both treatments in the clinical recovery at 7 days. A post hoc analysis showed that patients with moderate disease had a higher clinical recovery at day 7 in the favipiravir group (71.4% vs. 55.9%, p = 0.0199). More hyperuricemia occurred in the favipiravir group: 13.79% vs. 2.5% (p = 0.0014).

The current evidence does not support the use of favipiravir for the treatment of COVID-19 patients. The observational study is hypothesis generating, and the randomized controlled trial is only available as a peer-print in MedRxiv since May 2020 and has not been peer reviewed yet. Future randomized controlled trials are needed to evaluate its efficacy and safety in this patient population (Table 5.2).
**Fig. 5.1** Viral cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) and target of therapeutic agents. ‘Corticosteroids posses anti-inflammatory and immunosuppressive effects through multiple mechanisms including indirect effects on gene expression, post-translational modification of the glucocorticoid receptor, and inhibition of inflammatory proteins. ’’Colchicine possesses multiple anti-inflammatory properties including inhibition of neutrophil recruitment, neutrophil adhesion and activation as well as the release of pro-inflammatory cytokines.
| Drug                     | MOA                                                                 | Dosing                                                                 | Pharmacotherapy pearls                                                                 | Monitoring and adverse events                                                                 |
|--------------------------|---------------------------------------------------------------------|-----------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|
| Favipiravir (Famvir®)    | Competitively inhibits RNA-dependent RNA polymerase                 | Variable dosing based on indication                                   | CYP2C8 and aldehyde oxidase inhibitor                                                   | Acute renal failure in patients with baseline renal dysfunction, hyperuricemia, hepatic transaminitis Common ADRs: Headache and nausea Limited data for ADRs at higher doses |
|                          |                                                                     | 1600 mg PO BID On day 1 followed by 600 mg twice daily on days 2–14     |                                                                                        |                                                                                          |
|                          |                                                                     |                                                                       |                                                                                        |                                                                                          |
| Remdesivir               | Prodrug nucleotide-analog inhibitor of RNA-dependent RNA polymerases | 200 mg IV once on day 1 followed by 100 mg IV daily for 4–9 days        | No significant effect on CYP enzymes                                                   | Hepatic transaminitis, acute kidney injury                                                  |
|                          |                                                                     |                                                                       |                                                                                        |                                                                                          |
| Lopinavir/ritonavir (LPV/r) (Kaletra®) | Lopinavir: Inhibits the enzyme 3-chymotrypsin-like protease (3CL\textsuperscript{pro}), disrupting the cleaving and processing of polyproteins translated from the viral RNA Ritonavir: Inhibits CYP3A4 metabolism of lopinavir, leading to increased plasma concentrations | LPV/r 400/100 mg PO twice daily for no more than 10 days | Can be taken with or without food Do not crush (increases systemic exposure)—must use solution in patients who cannot swallow tablets whole Significant drug-drug interactions possible—ritonavir is a strong CYP3A4 inhibitor | GI: Primarily gastrointestinal (diarrhea, nausea, vomiting) Liver: Hepatotoxicity: Hepatic panel Cardiac: Increased serum triglycerides, hyperlipidemia: Lipid panel |
### Chloroquine Hydroxychloroquine (Plaquenil®) +/- Azithromycin (Zithromax®)

| Action                                                                 | Dosing                                                                 | Monitoring                                                                 |
|-----------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Increases the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membrane | Chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor | Avoid concomitant medications that prolong the QTc interval |
|                                                                       | Azithromycin: Induction of IFN-stimulated genes, attenuating viral replication, enhanced neutrophil activation, attenuation of inflammatory cytokines (IL-6 and IL-8) in epithelial cells and inhibition of fibroblast growth factor in airway smooth muscle cells [NIH] | Inhibitor of CYP2D6 and P-glycoprotein |
|                                                                       |                                                                       | Cardiac: QTc prolongation, TDP, ventricular arrhythmia: EKGs, serum creatinine, electrolytes (potassium and magnesium) |
|                                                                       |                                                                       | GI: Nausea, vomiting, diarrhea, hepatitis: Hepatic panel |
|                                                                       |                                                                       | Endocrine: Hypoglycemia: Blood glucose |
|                                                                       |                                                                       | Heme: Hemolysis: CBC |
|                                                                       |                                                                       | CV: Cholesterol: May increase total cholesterol, LDL and/or HDL: Lipid panel 4–8 weeks after initiation |
|                                                                       |                                                                       | ID: Increased risk of infection: Monitor for infectious symptoms. Hepatitis B reactivation possible |
|                                                                       |                                                                       | Hepatic: Hepatic injury, hepatic transaminitis: Monitor LFTs |
|                                                                       |                                                                       | GI: Monitor for evidence of GI perforation |
|                                                                       |                                                                       | Heme: Neutropenia and thrombocytopenia may occur: Monitor CBC |

### Interleukin 6 inhibitors

| Monoclonal antibodies that inhibit the IL-6 receptor: May potentially mitigate cytokine release syndrome symptoms in severely ill patients |
|--------------------------------------------------------------------------------------------------------------------------------|
| Clinical trial dosing: Tocilizumab 4–8 mg/kg IV once or in divided doses (max 800 mg) Sarilumab 200–400 mg SQ or IV once or in divided doses Siltuximab 11 mg/kg IV once Olokizumab 64 mg SQ once Clazakizumab 12.5–50 mg IV |
| Elevated IL-6 may downregulate CYP enzymes. Use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates |
| CV: Cholesterol: May increase total cholesterol, LDL and/or HDL: Lipid panel 4–8 weeks after initiation |
| ID: Increased risk of infection: Monitor for infectious symptoms. Hepatitis B reactivation possible |
| Hepatic: Hepatic injury, hepatic transaminitis: Monitor LFTs |
| GI: Monitor for evidence of GI perforation |
| Heme: Neutropenia and thrombocytopenia may occur: Monitor CBC |

(continued)
| Drug               | MOA                                                                                       | Dosing                                                                 | Pharmacotherapy pearls                                                                 | Monitoring and adverse events |
|--------------------|-------------------------------------------------------------------------------------------|------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-------------------------------|
| Corticosteroids    | Anti-inflammatory effects of corticosteroids could have a beneficial effect in suppressing the cytokine-related lung injury | Clinical trial dosing: Dexamethasone 6 mg daily for up to 10 days       | Moderate cytochrome 3A4 inducer, which may reduce the concentration and potential efficacy of concomitant medications that are CYP3A4 substrates | Neuro: May cause psychiatric disturbances, including insomnia and euphoria Endo: Hyperglycemia ID: Increased risk of infection. Monitor for infectious symptoms |
|                    |                                                                                          | Methylprednisolone dosing varies widely: 40 mg every 12 h for 3 days followed by 20 mg every 12 h for 3 days |                                                                                       |                               |
| Anakinra (Kineret®) | Recombinant human interleukin-1 receptor antagonist, inhibiting the activity of proinflammatory cytokines IL-1α and IL-1β | 100 mg SQ every 6 h, other reports of 5 mg/kg twice daily Duration variable (7–21 days) based on patient response | Administered subcutaneously Test patients for latent TB prior to initiation | Generally well tolerated Common ADRs include: Headache, nausea, vomiting Serious ADRs: Hypersensitivity reactions/injection site reactions, infections, neutropenia, reactivation of TB |
| Colchicine (Colcrys®) | Multiple anti-inflammatory properties including: Inhibits neutrophil recruitment by inhibiting chemotactic factor release Inhibits neutrophil adhesion via inhibiting expression of E-selectin Inhibits neutrophil activation and release on proinflammatory cytokines (IL-1, IL-8, superoxide) Promotes activation of dendritic cells to become antigen presenting cells | Variable based on indication, typically 1–1.5 mg load, then 0.3–0.6 mg PO once to twice daily | Must adjust dose for renal or hepatic dysfunction Hazardous drug—must be handled accordingly Potential for significant drug interactions—P-glycoprotein substrate and metabolized by CYP3A4 | GI symptoms, most commonly diarrhea, nausea, vomiting Bone marrow suppression (leukopenia, thrombocytopenia, pancytopenia, aplastic anemia) |
| Vitamins | Prevent inflammatory cascade by anti-inflammatory and antioxidant activity  
Fundamental for the structural organization of the epithelial and endothelial barriers; fundamental for phagocytosis and chemotaxis; protection from reactive oxygen species injury  
Regulation of NK-κB activity | Dosing is not available in the COVID-19 patient population | Zinc: Run drug interaction report to see if concomitant medication administration requires staggered time schedules  
No significant interactions exist for ascorbic acid or vitamin D | Zinc: Nausea, vomiting, changes in taste  
Ascorbic acid: Possible nephrolithiasis with large doses  
Vitamin D: Toxicity can manifest as nausea, vomiting, loss of appetite, weakness, and fatigue |
| Therapies/ guideline recommendations | Remdesivir | Favipiravir | Lopinavir/ritonavir | Hydroxychloroquine/chloroquine | Hydroxychloroquine / chloroquine ± - azithromycin | Convalescent plasma | interleukin-6 inhibitors | Colchicine | Corticosteroids | interleukin -1 inhibitors | Vitamin C | Vitamin D | Zinc |
|--------------------------------------|------------|------------|--------------------|-----------------------------|-----------------------------|-----------------|------------------------|-----------|----------------|-------------------------|----------|-----------|------|
| Infectious Disease Society of America | Severe disease | Yellow | Yellow | Red | Yellow | Yellow | Orange | Red | Yellow | Yellow | Orange | Orange | Orange |
| National Institute of Health         | Supplemental oxygen but not HFO, MV, or ECMO | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red |
| Society of Critical Care Medicine    | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red | Red |
| Italian Society of Infectious and Tropical Diseases | Severe disease | Yellow | Yellow | Yellow | Yellow | Yellow | Yellow | Yellow | Yellow | Yellow | Yellow | Yellow | Yellow |

*Green recommended, Yellow recommended in the setting of clinical trial, Orange not mentioned OR insufficient data to provide recommendation*

*Red recommended against except in the setting of a clinical trial*

Severe disease defined as SaO₂ < 94% on room air, supplemental oxygen, mechanical ventilation, or ECMO
| Trial title and design                                                                 | Patient population                                                                 | Dosing and duration                                                                 | Results                                                                                                                                                                                                 |
|--------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| **Favipiravir**                                                                       |                                                                                     |                                                                                     |                                                                                                                                                                                                         |
| Favipiravir vs. Arbidol for COVID-19: A Randomized Clinical Trial [17]                | 18 years or older with COVID-19 pneumonia, symptom onset within 12 days             | 1:1 randomization to umifenovir 200 mg PO TID for 7 days or favipiravir 1600 mg PO BID on day 1 followed by 600 mg PO BID for 10 days | • No difference between both groups in clinical recovery at 7 days (rate ratio: 0.0954; 95% CI –0.0305, 0.2213), use of auxiliary oxygen therapy or noninvasive mechanical ventilation  
  • Favipiravir group had a shorter time to relief of pyrexia (difference 1.7 days, \( p < 0.0001 \)) and cough (difference 1.75 days, \( p < 0.0001 \))  
  • More hyperuricemia in favipiravir group: 13.79% vs. 2.5% (\( p = 0.0014 \)) |
| **Remdesivir**                                                                        |                                                                                     |                                                                                     |                                                                                                                                                                                                         |
| Remdesivir in Adults with Severe COVID-19: A Randomised, Double-Blind, Placebo-Controlled Multicentre Trial [18] | Hospitalized patients with SARS-CoV-2 infection, \( \text{SaO}_2 \leq 94\% \) on room air, symptom onset within 12 days | 2:1 randomization to remdesivir or placebo Remdesivir 200 mg IV once on day 1 followed by 100 mg IV once daily for 9 days | • No difference in time to clinical improvement (HR 1.23, 95% CI 0.87–1.75)  
  • ADRs in 66% of remdesivir group vs. 78% of placebo group  
  • Median time to recovery shorter in remdesivir group: 11 (95% CI; 9–12) vs. 15 (95%CI; 13–19) days (\( p < 0.001 \))  
  • Mortality at 14 days not different between both groups: 7.1% vs. 11.9%, HR 0.70; (95% CI; 0.47–1.04)  
  • Mortality by 14 days not different between both groups; HR 0.70; (95% CI; 0.47–1.04)  
  • Serious ADRs 21.1% vs. 27.0% |
| Remdesivir for the treatment of COVID-19—Preliminary Report [19]                      | Adult patients with SARS-CoV-2 infection, \( \text{SaO}_2 \leq 94\% \) on room air or radiologic evidence of PNA or requiring MV or supplemental oxygen | 1:1 randomization to remdesivir or placebo Remdesivir 200 mg IV once on day 1 followed by 100 mg IV once daily for 9 days |                                                                                                                                                                                                         |
Table 5.3 (continued)

| Trial title and design | Patient population | Dosing and duration | Results |
|------------------------|--------------------|---------------------|---------|
| Remdesivir for 5 or 10 days in Patients with Severe COVID-19 [20] *Open-label, randomized controlled phase 3 trial* | $N = 397$ Hospitalized patients with SARS-CoV-2 infection, $\text{SaO}_2 \leq 94\%$ on room air and radiologic evidence of PNA | Remdesivir 200 mg IV once on day 1 followed by 100 mg IV once daily 1:1 randomization to 5 or 10 days of therapy | • Patients in the 10-day group had worse clinical status at baseline than patients in the 5 day group  
• Day 14 clinical improvement: 64% (5-day) vs. 54% (10-day); baseline-adjusted different $-6.5\%$ (95% CI, $-15.7$ to $2.8$)  
• Most common ADRs included nausea (9%), worsening respiratory failure (8%), elevated alanine transferase level (7%) and constipation (7%) |
| Lopinavir/ritonavir | *A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19 [21] Open-label, randomized controlled trial* | $N = 199$ Severe disease ($\text{SaO}_2 \leq 94\%$ on room air or $\text{PaO}_2/\text{FiO}_2 < 300 \text{ mmHg}$) 1:1 randomization: LPV/r 400/100 mg PO every 12 h for 14 days + SOC vs. SOC | • LPV/r not associated with faster time to clinical improvement compared to SOC (HR 1.31; 95% CI 0.95–1.80)  
• No difference in % of patients with detectable viral RNA at various time points  
• Modified intention to treat: LPV/r lead to a median time to clinical improvement that was shorter by 1 day vs. SOC  
• GI ADRs more common with LPV/r vs. SOC |
| Study Title                                                                 | Participants                                                                 | Intervention                                                                 | Outcomes                                                                                     |
|---------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Efficacy and Safety of Lopinavir/Ritonavir or Arbidol in Adult Patients with Mild/Moderate COVID-19: An Exploratory Randomized Controlled Trial [22] | - N = 86<br>- Mild/moderate disease (mild = mild clinical symptoms with no signs of PNA on imaging; moderate = fever, respiratory symptoms, or PNA on imaging) | LPV/r vs. umifenovir vs. SOC:  
  - Rate of conversion from positive to negative COVID-19 pharyngeal swab from first day of treatment to day 21: 9.0 ± 5.0 vs. 9.1 ± 4.4 vs. 9.3 ± 5.2 (p = 0.981)  
  - Rate of conversion at day 14, rate of antipyresis, rate of cough alleviation, improvement rate of chest computed tomography scan at days 7 and 14, deterioration rate of clinical status from mild/moderate to severe/critical: No difference between groups for any of the outcomes  
  - Adverse effects higher in LPV/r group compared to umifenovir and SOC: 35.5% vs. 14.3% vs. 0% | 2:2:1 randomization: LPV/r 400/100 mg PO every 12 h for 7–14 days vs. umifenovir 200 mg PO every 8 h for 7–14 days vs. SOC |
| Hydroxychloroquine Effect of High vs. Low Doses of Chloroquine Diphosphate as Adjunctive Therapy for Patients Hospitalized with SARS-COV-2 Infection: A Randomized Clinical Trial [23] | - N = 81<br>- Hospitalized patients with clinical suspicion of COVID-19  
  - Aged 18 years or older at the time of inclusion  
  - RR > 24 rpm and/or HR > 125 bpm (in the absence of fever), and/or peripheral oxygen saturation < 90% and/or shock | High dose vs. low dose CQ:  
  - Viral RNA detection: 77.5% vs. 75.6%  
  - Lethality until day 13: 15% vs. 39% (p = 0.03)  
  - QTc interval > 500 ms: 11.1% vs. 18.9% | Randomized, double-blind, Phase 2b trial  
  - High dose: CQ 600 mg BID for 10 days  
  - Low dose: 450 mg BID for 1 day then 450 mg daily for 4 days  
  - Hospital protocol: Ceftriaxone 1 g BID for 7 days + azithromycin 500 mg QD for 5 days  
  - If influenza suspected, oseltamivir 75 mg BID for 5 days |

(continued)
| Trial title and design                                                                 | Patient population                                                                                           | Dosing and duration                                                                                     | Results                                                                                       |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|
| Hydroxychloroquine in Patients with Mainly Mild to Moderate Coronavirus Disease 2019: Open Label, Randomized Controlled Trial [24] Multicenter, open label, randomized controlled trial | \( N = 150 \) 18 years or older with ongoing SARS-CoV-2 infection confirmed in upper or lower respiratory tract specimens with RT-PCR | Hydroxychloroquine 1200 mg QD for 3 days followed by 800 mg QD  
- Total treatment duration: 2 or 3 weeks for patients with mild to moderate or severe disease, respectively  
- SOC: Antiviral agents, glucocorticoids and antibiotics | SOC plus hydroxychloroquine vs. SOC  
- Probability of negative conversion by 28 days: 85.4% vs. 81.3% |
| Corticosteroids                                                                      |                                                                                                             |                                                                                                        |                                                                                            |
| Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report [25] Randomized, controlled, open-label, adaptive platform trial | \( N = 6425 \) Clinically suspected or laboratory confirmed SARS-CoV-2 infection | Dexamethasone 6 mg QD for 10 days vs. SOC | Dexamethasone vs. SOC  
- 28 day mortality: 21.6% vs. 24.6% (RR 0.83; 95% CI 0.74–0.92; \( p < 0.001 \))  
- Discharged from hospital within 28 days: 64.6% vs. 61.1% (RR 1.11; 95% CI 1.04–1.19; \( p = 0.002 \)) |
| GLUCOCOVID: A Controlled Trial of Methylprednisolone in Adults Hospitalized with COVID-19 Pneumonia [26] Partially randomized preference, open-label, controlled, two-arm, parallel-group trial | \( N = 85 \) Over 18 years of age with a laboratory confirmed diagnosis of SARS-CoV-2 infection  
Additional inclusion criteria:  
- Symptom duration of at least 7 days  
- Radiological evidence of lung disease in chest X-ray or CT-scan  
- Moderate-to-severe disease with abnormal gas exchange  
- Laboratory parameters indicative of hyper-inflammatory state (CRP > 15 mg/dL, D-dimer >800 mg/dL, ferritin >1000 mg/dL, or IL-6 levels >20 pg/mL) | Methylprednisolone 40 mg every 12 h for 3 days then 20 mg every 12 h for 3 days + SOC vs. SOC  
SOC treatment could include the following: Antibiotics for co-infections, azithromycin, hydroxychloroquine, and/or lopinavir plus ritonavir | Composite endpoint including in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required non-invasive ventilation:  
- Intention-to-treat, age stratified analysis (RR 0.55 95% CI 0.33–0.91; \( p = 0.024 \))  
- Per protocol analysis:  
  - Patients aged 72 or less: RR 0.11 (95% CI; 0.01–0.83)  
  - Patients age greater than 72: RR 0.61 (95% CI; 0.32–1.17)  
  - All patients: RR 0.50 (95% CI; 0.27–0.94) |
### Colchicine

**Effect of Colchicine vs. Standard of Care on Cardiac and Inflammatory Biomarkers and Clinical Outcomes in Patients Hospitalized with Coronavirus Disease 2019: the GRECCO-19 Randomized Clinical Trial** [27]

*Open-label randomized controlled trial*

| Control vs. colchicine |
|------------------------|
| • Biochemical (maximum hs cTn, time for CRP to reach more than three times the upper reference limit): No difference in hs cTn level between groups or CRP |
| • Clinical (time to deterioration by 2 points on a 7-grade clinical status scale): 14.0% vs. 1.8%, OR 0.11 (95% CI 0.01–0.96) |
| • Cumulative event-free 10-day survival: 83% vs. 97% ($p = 0.03$) |
| • Diarrhea: 45.5% vs. 18.0% ($p = 0.003$) |

| N = 105 |
| Mild to moderate disease (temperature 37.5 °C or more plus 2 or more of the following: Sustained cough, sore throat, anosmia and/or ageusia, fatigue and/or tiredness, and SaO₂ < 95% on room air) |

| SOC only vs. colchicine 1–1.5 mg loading dose PO (1 mg if on concomitant azithromycin) then 0.5 mg PO twice daily (once daily if body weight < 60 kg) until hospital discharge up to a maximum of 21 days |

**Convalescent plasma**

**Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients with Severe and Life-Threatening COVID-19: A Randomized Clinical Trial** [28]

*Open-label, multicenter, randomized controlled trial*

| Convalescent plasma (n = 52) vs. SOC (n = 51) |
| No difference in clinical improvement within 28 days: 51.9% (CP) vs. 43.1% (SOC), HR 1.40 [95% CI, 0.79–2.49] |
| – Benefit seen in subgroup of patients with severe disease: 91.3% (CP) vs. 68.2% (SOC), HR 2.15 [95% CI; 1.07–4.32] |
| No difference in 28-day mortality: 15.7% (CP) vs. 24.0% (SOC) ($p = 0.30$) |
| No difference in time from randomization to discharge: 51.0% (CP) vs. 36.0% (SOC) ($p = 0.12$) |
| Negative conversion rate of viral PCR at 72 h: 87.2% (CP) vs. 37.5% (SOC) ($p < 0.01$) |

*N = 103*  

**ADRs** adverse drug reactions, **CRP** C-reactive protein, **CP** convalescent plasma, **CrCl** creatinine clearance, **CQ** chloroquine, **hs cTn** high sensitivity troponin C, **LPV/r** lopinavir/ritonavir, **PNA** pneumonia, **SaO₂** oxygen saturation, **SOC** standard of care
5.2.2 Remdesivir

Remdesivir is an investigational adenosine nucleotide analog that causes premature termination of viral RNA transcription (Table 5.1). It has been shown to have broad-spectrum activity against RNA viruses including Ebola, Marburg, respiratory syncytial virus (RSV), as well as MERS and SARS-CoV. In addition, it showed in vitro activity against SARS-CoV2, which identified it as a promising therapy [29].

Gilead Sciences accepted requests for compassionate use of remdesivir in hospitalized patients with SARS-CoV-2 infection, oxygen saturation (\( \text{SaO}_2 \) \( \leq \) 94% on room air, creatinine clearance (\( \text{CrCl} \)) > 30 mL/min, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) within five times the upper limit of normal [31]. The drug was administered as a 200 mg intravenous infusion on the first day followed by 100 mg intravenously daily for a total duration of 5 days. In this compassionate use cohort, 57% of patients received mechanical ventilation. Patients were followed up for a mean of 18 days. Out of the patients who were intubated at baseline, 57% were extubated. Overall, 47% of patients were discharged and 13% died.

Following compassionate use, a multicenter, randomized controlled trial from China was published [18]. The trial was terminated early prior to attaining the prespecified sample size. The study showed no statistically significant clinical benefit in the primary endpoint, time to clinical improvement up to day 28. Clinical improvement was defined as a decline of two levels on a 6-point ordinal scale of clinical status (1 = discharged, 6 = death). A few limitations of this trial include low baseline use of mechanical ventilation (7%) and a high rate of corticosteroid use (66%).

A preliminary report of the Adaptive Covid-19 Treatment Trial (ACTT-1) sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), from 60 trial sites in the United States, Europe, Asia, and Latin America, was subsequently published [19]. Based on preliminary data that showed shorter time to recovery in the remdesivir group compared to the placebo group, the data and safety monitoring board recommended early unblinding of the data. A total of 1059 patients were included in this analysis (538 in the remdesivir group and 521 in the placebo group). Patients in the remdesivir group had a median time to recovery of 11 (95% CI; 9–12) days vs. 15 (95% CI; 13–19) days in the placebo group (\( p < 0.001 \)). There was no mortality difference between both groups. A subgroup analysis showed that patients who received remdesivir within 10 days as well as those who received it after 10 days of symptoms onset benefited from the therapy and had a shorter time to recovery. The authors also analyzed time to recovery according to the patients’ baseline oxygen requirement. This showed that the benefit of remdesivir on time to recovery decreased as baseline oxygen requirement increased. Patients receiving mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (\( n = 272 \)) did not have a benefit with remdesivir treatment compared to placebo: RR of recovery = 0.95 (95% CI; 0.64–1.42). This study shed some insight suggesting that even though remdesivir reduced time to recovery in the overall cohort, additional or different therapeutics may be needed in patients with a more severe disease course.
Finally, an open-label phase 3, randomized controlled trial evaluated the efficacy of 5 vs. 10 days of remdesivir therapy [20]. At baseline, patients in the 10-day course had worse clinical status on a 7-point ordinal scale than patients in the 5-day course ($p = 0.02$). There was no difference in the primary outcome, clinical improvement at day 14 between both duration of therapies despite adjustment for baseline clinical status: 64% (5-day) vs. 54% (10-day); baseline-adjusted difference $-6.5\%$ (95% CI, $-15.7$ to $2.8$). The most common adverse events reported in this study with remdesivir use included nausea (9%), worsening respiratory failure (8%), elevated alanine transferase level (7%), and constipation (7%).

Based on the results of the ACCT-1 trial, the Food and Drug Administration (FDA) issued an emergency use authorization (EUA) on May 1, 2020, for the use of remdesivir in patients with severe disease [10]. Patients qualified for the EUA if they met all of the following criteria: hospitalized patients with a laboratory confirmed SARS-CoV-2 infection, severe disease with $\text{SaO}_2 \leq 94\%$ on room air, requiring oxygen supplementation, mechanical ventilation or ECMO. Clinicians should evaluate the risk/benefit ratio in pregnant patients or patients with renal dysfunction ($\text{CrCl} <30\; \text{mL/min}$) or hepatic dysfunction. The recommended duration of therapy was a 5-day course except for patients receiving mechanical ventilation or ECMO, suggested to receive a 10-day course of therapy. Multiple guidelines have released recommendations to prioritize the limited supply of remdesivir for patients requiring oxygen support [4, 5] (Table 5.2).

5.2.3 Lopinavir/Ritonavir

Lopinavir is a protease inhibitor used to treat human immunodeficiency virus and has been shown to be effective at inhibiting viral replication in vitro against SARS-CoV [32]. It is given as a fixed dose in combination with ritonavir, which is a potent inhibitor of cytochrome P450 3A4 (CYP3A4), inhibiting the metabolism of lopinavir and effectively increasing plasma concentrations. Specifically, lopinavir inhibits a viral enzyme present in coronaviruses, the enzyme 3-chymotrypsin-like protease (3CLpro), which cleaves and processes polyproteins translated from the viral RNA [33].

There are currently two randomized controlled trials published evaluating the efficacy and safety of lopinavir/ritonavir 400/100 mg two times daily for 7–14 days in patients with COVID-19. Cao and colleagues randomized 199 patients with severe disease in a 1:1 fashion to receive either lopinavir/ritonavir plus standard of care (SOC) vs. SOC alone [21]. The primary endpoint was time to clinical improvement, defined as improvement of two points on a seven-category scale (1 = not hospitalized; 7 = death) or discharge from the hospital, whichever came first. The investigators found that lopinavir/ritonavir was not associated with a more rapid time to clinical improvement compared to SOC (HR 1.31; 95% CI 0.95–1.80). In the modified intention to treat group, however, lopinavir/ritonavir led to a shorter median time to clinical improvement by 1 day compared to SOC. Overall, adverse drug reactions were similar between groups, but gastrointestinal-related adverse
reactions were more common in the lopinavir/ritonavir group, and serious adverse reactions (respiratory failure, acute kidney injury, secondary infection) were more common in the SOC group. Notable limitations include the lack of blinding and use of concurrent pharmacologic agents, which may have confounded results. In the study done by Li and colleagues, 86 patients with mild-to-moderate disease were randomized in a 2:2:1 fashion to receive lopinavir/ritonavir + SOC vs. umifenovir (a fusion inhibitor) + SOC vs. SOC alone [22]. The primary outcome was the rate of conversion from positive to negative COVID-19 pharyngeal swab from the first day of treatment to day 21. The investigators found no difference in any of the primary or secondary outcomes between groups; however adverse reactions were higher in the lopinavir/ritonavir group compared to umifenovir and SOC (35.5% vs. 14.3% vs. 0%, respectively), with diarrhea being the most common adverse drug reaction.

Other published studies that have evaluated the use of lopinavir/ritonavir for patients with COVID-19 were primarily observational and/or descriptive in nature. In a study done by Ye and colleagues, patients with mild disease (no mechanical ventilation) received lopinavir/ritonavir (400/100 mg orally two times daily or 800/200 mg orally once daily for 10 days) plus SOC vs. SOC alone [34]. Investigators found no difference in change in body temperature over 10 days between groups, although the lopinavir/ritonavir group returned to normal body temperature approximately 2.5 days sooner than the control group (4.8 ± 1.94 vs. 7.3 ± 1.53 days, \( p = 0.0364 \)). In addition, the time to a negative viral swab was shorter in the lopinavir/ritonavir group (7.8 ± 3 vs. 12 ± 0.82 days, \( p = 0.0219 \)). In contrast, a study by Zhu and colleagues who compared lopinavir/ritonavir (400/100 mg orally two times daily for 7 days) to umifenovir (0.2 g orally three times daily for 7 days) in patients with mild disease found that the day 14 viral load was undetectable in all patients in the umifenovir group and still detectable in 44.1% of patients in the lopinavir/ritonavir group [35]. Finally, a descriptive study by Wang and colleagues where all patients received lopinavir/ritonavir (no dose disclosed) for 7 days, viral swabs turned negative 4–21 days after diagnosis. In all observational studies, lopinavir/ritonavir was well tolerated [36].

Well-designed, randomized, controlled, double-blind trials assessing the efficacy and safety of lopinavir/ritonavir for use in COVID-19 are lacking. Based on current literature, it appears that lopinavir/ritonavir may not be efficacious in treating COVID-19. Overall, it does not seem that lopinavir/ritonavir decreases time to clinical improvement, and data regarding shortening the time to negative viral swab is conflicting. Due to the open-label or retrospective nature of the available literature, there is a risk for confounding factors that may have influenced the outcomes. For example, not all groups were similar in baseline characteristics (uneven distribution of baseline viral loads) and investigators were not able to control for other treatments patients may have received. In addition, many of these studies were single-center, therefore limiting the external validity. As more studies become available, a definitive conclusion regarding the role of lopinavir/ritonavir in treating patients with COVID-19 will be possible. If utilized, providers must consider drug interactions, gastrointestinal toxicities, and the risk/benefit of use in each patient. In particular, use of lopinavir/ritonavir in patients with COVID-19 may exacerbate hepatotoxicity
and other gastrointestinal toxicities caused by the virus itself. In addition, hepatic transaminitis is a common exclusion criterion for clinical trials on investigational agents (e.g., remdesivir, although not a contraindication for the emergency use authorization); therefore use of Lopinavir/ritonavir may hinder patient access to these trials should adverse reactions occur.

5.2.4 Hydroxychloroquine or Chloroquine with or Without Azithromycin

Hydroxychloroquine or chloroquine has been proposed to increase the endosomal pH, inhibiting fusion of SARS-CoV-2 and the host cell membrane. In addition, chloroquine inhibits glycosylation of the cellular angiotensin-converting enzyme 2 receptor [29]. Both agents have been combined with azithromycin that can induce interferon-stimulated gene that attenuates viral replication, enhance neutrophil activation, attenuate inflammatory cytokines (IL-6 and IL-8) in epithelial cells, and inhibit fibroblast growth factor in airway smooth muscle cell.

A randomized study, CloroCOVID-19, included hospitalized patients with clinical suspicion of COVID-19 with a respiratory rate > 24 rpm and/or a heart rate > 125 bpm and/or peripheral oxygen saturation lower than 90% in ambient air and/or shock [23]. The patients received high-dose chloroquine 600 mg orally twice daily for 10 days or low-dose chloroquine 450 mg twice daily for 1 day then 450 mg daily for 4 days concomitantly with antibiotic therapy and oseltamivir if influenza was suspected. The results in the interim analysis of low-dose vs. high-dose chloroquine included viral RNA detection in 31 of 40 (77.5%) vs. 31 of 41 (75.6%) and lethality until day 13 documented in 6 out of 40 (15%) vs. 16 out of 41 (39%) patients, respectively. Notable adverse events included QTc interval prolongation greater than 500 ms, occurring in 11.1% of patients in the low-dose group vs. 18.9% of patients in the high-dose group. Patients in the high-dose group were older and had a higher incidence of baseline heart disease.

In China, a multicenter, open-label, randomized controlled trial enrolled 150 total patients with ongoing SARS-CoV-2 infection confirmed in upper or lower respiratory tract specimens though RT-PCR [24]. Patients received hydroxychloroquine 1200 mg daily for 3 days followed by a maintenance dose of 800 mg daily for a total treatment duration of 2 or 3 weeks for patients with mild to moderate or severe disease, respectively. All patients received SOC in both groups concomitantly with varying regimens of antiviral agents, antibiotics, and systemic glucocorticoids. The probability of negative conversion by 28 days in the SOC plus hydroxychloroquine group was 85.4% (95% CI 73.8–93.8%), similar to that in the SOC group of 81.3% (95% CI 71.2–89.6%).

In addition to the paucity of data showing positive outcomes, the safety of hydroxychloroquine was assessed with a focus on QTc interval prolongation, particularly when in combination with azithromycin [37]. In a non-critically ill patient population, the combination of hydroxychloroquine 200 mg twice daily with azithromycin 500 mg daily for at least 3 days showed QTc interval prolongation,
particularly in patients with high levels of transaminases [38]. In addition, although not explicitly stated, a mix of ICU and non-ICU patients were given chloroquine/hydroxychloroquine with azithromycin that led to a significantly greater increase in the QTc interval when compared with monotherapy as well as a discontinuation rate of 3.5% due to QTc interval prolongation with no reported cases of TdP in the cohort [39].

The safety and efficacy of hydroxychloroquine or chloroquine combined with azithromycin as well as other investigational therapies have been studied in small retrospective clinical trials, case series, and observational reports that have shown mixed outcomes across a spectrum of illness in the COVID-19 patient population. Although few studies have shown positive outcomes, an overwhelming majority of published data have shown no difference in intubation, probability to negative conversion at a predetermined time point, survival without transfer to the ICU, acute respiratory distress syndrome (ARDS), or overall survival in patients that received treatment with hydroxychloroquine or chloroquine [40–43]. In addition, the FDA revoked the emergency use authorization to use hydroxychloroquine and chloroquine to treat COVID-19 in certain hospitalized patients outside of a clinical trial setting due to lack of benefit [44].

### 5.3 Immunomodulatory Agents

Cytokines play a pivotal role in the immune response to viral pathogens. This response, however, can become dysregulated, leading to a cytokine release syndrome with downstream complications including end-organ damage such as ARDS. Cytokine release syndrome is a major cause of morbidity in patients infected with SARS-CoV-2. Serum elevations in IL-6 and IL-1 correlate to respiratory failure, ARDS, and adverse clinical outcomes. IL-6 has proinflammatory properties due to the cis- and trans-signaling pathways. In the trans-signaling pathway, high circulating concentrations of IL-6 bind to the soluble form of IL-6 receptor and form the IL-6-sIL-6R-JAK-STAT3 complex that activates cells downstream resulting in a cytokine storm. During the cytokine storm phase, numerous factors including vascular endothelial growth factor, monocyte chemoattractant protein-1, and IL-8 are expressed that contribute to vascular permeability. Consequently, alveolar-capillary permeability to fluid, proteins, and blood cells is increased and respiratory failure occurs [45–48].

#### 5.3.1 Interleukin 6 Inhibitors

Tocilizumab, sarilumab, siltuximab, and olokizumab are IL-6 inhibitors commercially available in different countries, while clazakizumab is undergoing clinical trials. Tocilizumab, the most widely researched IL-6 inhibitor in COVID-19, is a recombinant humanized monoclonal antibody that binds to both membrane-bound and soluble forms of the IL-6 receptor [47, 48].
Chronic administration in patients with rheumatologic diseases such as rheumatoid arthritis can shed light on common adverse reactions that may manifest with short-term administration in the SARS-CoV-2 patient population. Serious and potentially fatal infections, including active tuberculosis, invasive fungal, bacterial, viral, protozoal, and other opportunistic infections, have been reported in chronic therapy, especially in patients treated with concomitant immunosuppressive therapy. Although adverse effects were reported in published literature in the COVID-19 patient population, including infection, many outcomes were limited to short-term endpoints [49].

In a retrospective ICU cohort study, patients with laboratory confirmed severe COVID-19 with elevated C-reactive protein (CRP) levels were administered tocilizumab at a median total dose of 5.7 mg/kg (IQR 4.8–9.5 mg/kg) [50]. Patients also received at least two concomitant investigational antiviral agents. Results obtained on day 1, 3, and 7 showed a decrease in median oral temperature, CRP, number of patients requiring invasive ventilation, and radiological improvement. Twenty-three (92%) patients in the study experienced at least one adverse event, most frequently anemia, ALT rise, and QT prolongation. Due to the patients receiving concomitant investigational therapies, assessing adverse effects could be difficult to ascertain.

In a non-ICU retrospective cohort in patients with COVID-19, tocilizumab was administered at 400 mg with a second dose of 400 mg being administered after 24 h in case of respiratory worsening [51]. The patients enrolled had hyper-inflammation, defined as either CRP ≥ 100 mg/L or ferritin >900 ng/mL in the presence of increased LDH, and severe respiratory involvement in the presence of an oxygen saturation ≤92% while breathing ambient air or a PaO₂:FiO₂ ratio ≤ 300 mmHg. The patients did not receive other anti-inflammatory drugs or glucocorticoids and were not enrolled in other clinical trials. During the 28-day follow-up, 69% of the tocilizumab patients experienced a clinical improvement compared to 61% of the standard treatment group (p = 0.61). Mortality was 15% in the tocilizumab group and 33% in the standard treatment group (p = 0.15). Between the tocilizumab and standard care group, there were no statistically significant increases in bacterial infections, pulmonary thrombosis, or increases in AST or ALT, although there was a difference in neutropenia reported in 16% of patients in the tocilizumab group (p = 0.024) [51].

Patients enrolled in the tocilizumab treatment arm at Michigan Medicine had severe COVID-19 present and required invasive mechanical ventilation. Patients received a dose of 8 mg/kg (maximum 800 mg) once, with additional doses discouraged. Patients in both groups received concomitant therapy with overall rates being 23% hydroxychloroquine, 3% remdesivir, and 25% corticosteroids. Survival probability was significantly higher among tocilizumab treated compared to untreated patients (p = 0.089). Patients who received tocilizumab were more than twice as likely to develop superinfection compared to untreated controls (54% vs. 25%; p < 0.001), driven primarily by ventilator associated pneumonia, although case fatality rates were similar in infected and uninfected tocilizumab-treated patients [52].

Numerous published case reports and retrospective cohort papers are available to interpret, while many other clinical trials are still enrolling patients. Clinicaltrials.
gov has over 60 registered studies with interleukin-6 inhibitors. When reviewing the available literature, many papers were single arm retrospective reviews with IL-6 inhibitor treatment spanning from ICU to non-ICU patients [53–55]. Given that IL-6 inhibitors were commonly used with concomitant investigational therapies for SARS-CoV-2, one should take into consideration the results from all clinical trials to parse out if the trial result is a cumulative outcome due to a multi-modal treatment approach or due to a single medication given.

5.3.2 Corticosteroids

The use of corticosteroids in patients diagnosed with COVID-19 is controversial given mixed results in the existing literature. Steroids exhibit their anti-inflammatory effects that could have a beneficial effect in suppressing the cytokine-related lung injury in patients with severe COVID-19. Diffuse alveolar damage, inflammatory infiltrates, and microvascular thrombosis are features recognized on autopsy reports [5, 25]. There are three suggested phases of SARS-CoV-2 that include early infection in phase 1, pulmonary involvement with and without hypoxia in phase II, and systemic hyperinflammation in phase III. The viral response phase is thought to occur in stage I with overlap into stage II, while the host inflammatory response phase occurs at the end of stage II into stage III. During the host inflammatory response phase, glucocorticoids have been proposed to play a role [56]. The NIH recommends use of dexamethasone (at a dose of 6 mg/day for up to 10 days) in mechanically ventilated COVID-19 patients and in patients who require supplemental oxygen [5]. In the RECOVERY trial, investigators compared dexamethasone 6 mg daily to SOC in patients with clinically suspected or laboratory confirmed SARS-CoV-2 infection. Overall, the study showed a reduced 28 day mortality \( (p < 0.001) \) as well as a larger proportion of patients being discharged at 28 days \( (p = 0.002) \) in the dexamethasone group [25]. Dexamethasone had varying results based upon the level of respiratory support; specifically, there were reduced deaths in patients receiving mechanical ventilation (29% vs. 40.7%, \( p < 0.001 \)) and patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25%, \( p = 0.002 \)), but there was no difference in mortality in patients not receiving respiratory support (17% vs. 13.2%; \( p = 0.14 \)).

Investigators studied methylprednisolone in varying doses and severity of illness in the SARS-CoV-2 patient population through mostly observational reviews that produced both positive and negative results. In a systematic review, the percentage of patients taking corticosteroids ranged from 7.6 to 44.9% of the cohorts included [57]. Of the four studies reviewed, two studies by Liu et al. and Wang et al. did not show a significant benefit. Wang et al. found that glucocorticoid therapy was associated with a greater risk of ICU admission. In addition, Ling et al. showed that duration of viral RNA detection for oropharyngeal and fecal swabs in the corticosteroids treatment group was longer than that in the non-corticosteroid treatment group. Lastly, in a study published by Wu et al., the administration of methylprednisolone reduced the risk of death in subjects having ARDS for COVID-19. In Spain, patients diagnosed with COVID-19 pneumonia complicated by ARDS and/or
hyperinflammatory syndrome were treated with 1 mg/kg/day methylprednisolone or a steroid pulse with additional investigational therapies at the discretion of the treating physician. Of the various investigational therapies available, the patients in the steroid cohort received statistically more hydroxychloroquine (99.5% vs. 92.5%, \( p = 0.001 \)) and tocilizumab (44.9% vs. 18.5%, \( p < 0.001 \)). Patients received steroid treatment in a median of 10 days after onset of symptoms. In-hospital mortality was lower in patients treated with steroids than in controls (13.9% vs. 23.9%, HR 0.51 [0.27–0.96]). In-hospital mortality was not different between initial regimens of 1 mg/kg/day of methylprednisolone and steroid pulses [58]. Additional retrospective papers have reported similar results including reduced escalation of care from ward to ICU, decreased mortality, decreased ICU length of stay and hospitalization, and decreased inflammatory markers [59, 60].

In the GLUCOCOVID trial, a partially randomized preference, open-label, controlled, parallel-group trial, patients over 18 years of age with confirmed diagnosis of SARS-CoV-2 infection with symptom duration of at least 7 days, radiological evidence of lung disease, moderate-to-severe disease with abnormal gas exchange, and laboratory parameters indicative of hyper-inflammatory state were enrolled [26]. Patients were excluded if they were intubated or mechanically ventilated, were hospitalized in the ICU, or were treated with corticosteroids or immunosuppressive drugs at the time of enrollment. The treatment included methylprednisolone 40 mg every 12 h for 3 days followed by 20 mg every 12 h for 3 days with standard care vs. standard care alone. The composite endpoint, including in-hospital all-cause mortality, escalation to ICU admission, or progression of respiratory insufficiency that required non-invasive ventilation, was reduced in the intention-to-treat, age-stratified analysis (RR 0.55, 95% CI 0.33–0.91, \( p = 0.024 \)). In the per-protocol analysis, RR was 0.11 (0.01–0.82) in patients aged 72 years or less, RR 0.61 (0.32–1.17) in those over 72 years of age, and RR 0.37 (0.19–0.74) in the whole group after age-adjustment by stratification.

### 5.3.3 Anakinra

Anakinra is an IL-1 antagonist that inhibits the proinflammatory cytokines IL-1\( \alpha \) and IL-1\( \beta \) [11]. It is indicated for treatment of rheumatoid arthritis; however, based on its mechanism of action, it was hypothesized that it may benefit patients with COVID-19 with a severe inflammatory component. Anakinra is administered subcutaneously, and although it is generally well-tolerated, severe adverse reactions such as reactivation of tuberculosis (TB), hypersensitivity reactions, secondary infection, and neutropenia are possible.

The data for use of anakinra in patients with COVID-19 is limited to case reports, small case series, and retrospective studies. In the two largest observational studies to date, patients with moderate to severe ARDS (non-invasive mechanical ventilation, not in the ICU) received anakinra in addition to lopinavir/ritonavir and/or HCQ/azithromycin or SOC (including lopinavir/ritonavir and/or HCQ/azithromycin) [12, 61]. In both studies, baseline characteristics were not evenly distributed between groups and
may have affected outcomes. In the study by Cavalli et al., at 21 days, survival was 90% in the anakinra group and 56% in the control group ($p = 0.009$); however there was no difference in mechanical ventilation-free survival or adverse reactions [12]. In the study by Huet et al., admission to ICU for mechanical ventilation or death was significantly lower in the anakinra vs. SOC group (25% vs. 73% (HR 0.22, 95% CI 0.11–0.41)) and results were not affected by multivariate analysis [61]. There were more adverse reactions (elevated LFTs, thromboembolic events) in the anakinra group. Other case reports and case series have reported improvement in inflammatory markers and respiratory status [62–64]. Although results are encouraging, these studies are limited by non-randomized design, uneven distribution of baseline characteristics, and confounders including inter-provider variability in the SOC regimen.

There are currently four studies registered with clinicaltrials.gov assessing the role of anakinra in patients with COVID-19. The results of these randomized controlled trials will be imperative in guiding providers on the most judicious use of this agent, given the paucity of current data does not define a cohort of patients that would benefit most, and expanded use is cost prohibitive and possibly unsafe.

### 5.3.4 Colchicine

Recently, colchicine has become a drug of interest in treating the inflammatory aspects of COVID-19. Although colchicine’s primary mechanism of action is inhibition of the polymerization of microtubules, colchicine also has significant anti-inflammatory properties, particularly on neutrophils. The dosing of colchicine will vary by indication, and the most appropriate dose of colchicine in patients with COVID-19 is yet to be determined. Colchicine commonly causes gastrointestinal symptoms, particularly diarrhea, nausea, and vomiting; however in rare instances, colchicine can cause bone marrow suppression [13, 14].

There is currently only one trial evaluating the role of colchicine in treating the inflammatory aspects of COVID-19. This study by Deftereos and colleagues was an open-label, randomized, controlled trial that assessed colchicine plus SOC vs. SOC alone on various inflammatory markers and clinical outcomes [27]. Patients were enrolled if they had a positive SARS-CoV-2 swab and a temperature $\geq 37.5$ °C plus two or more of the following: sustained cough, sustained sore throat, anosmia and/or ageusia, fatigue and/or tiredness, $O_2$ sat $<95$% on room air and did not require ventilator support. Fifty-five patients were randomized to a colchicine loading dose followed by maintenance dosing and SOC and 50 patients received SOC only. The study was stopped early because of slow enrollment and did not meet power; however for the patients that were included, baseline characteristics were similar between groups. The investigators found no significant differences in biochemical outcomes such as CRP or high-sensitivity troponin-C (hs cTn). There was, however, a significant difference in clinical outcomes (time to deterioration, cumulative event-free 10-day survival) favoring the colchicine group. Diarrhea was significantly more frequent in the colchicine group but only caused discontinuation of therapy in two cases and was not associated with electrolyte abnormalities.
There are currently seven studies registered with clinicaltrials.gov assessing colchicine in patients with COVID-19. Currently, data for the use of colchicine in patients with COVID-19 is limited to one small, underpowered, open-label study. In addition, colchicine has never been studied in patients with severe disease requiring intubation and the risk benefit is unknown. Until further information is available, its use cannot be recommended.

5.3.5 Convalescent Plasma

This therapy uses the antibodies from patients recovered from COVID-19 and provides adaptive immunotherapy. It has been shown to be successful in the treatment of other viral infections including SARS, MERS, and H1N1 influenza A [65, 66].

A small prospective observational cohort of 10 patients in China who received a dose of convalescent plasma showed that all patients cleared the viremia and improved within 3 days of administration [67]. This study showed that convalescent plasma could be a promising treatment modality in COVID-19 patients [66].

There is one randomized controlled trial evaluating convalescent plasma, conducted in seven medical centers in Wuhan, China [28]. This study included 103 patients who were randomized to convalescent plasma or standard of care. The study was terminated early due to poor enrollment and therefore has limited power. Most patients (86.4%) were enrolled after 14 days from symptoms onset. The primary outcome evaluated was time to clinical improvement within 28 days, defined as hospital discharge or decrease in 2 points on a 6-point disease severity scale (1 = discharge to 6 = death).

Adverse effects associated with the use of blood products should be considered when deciding whether to administer convalescent plasma. These include transfusion-related lung injury (TRALI), transfusion-associated circulatory overload (TACO), thrombotic events, and transfusion associated infections. A total of 5000 patients who received convalescent plasma as part of the US FDA Expanded Access Program for COVID-19 were analyzed to evaluate the safety. Rate of serious adverse events was <1% [68].

To date, use of convalescent plasma is recommended as part of a clinical trial [4, 5]. More data is needed to evaluate its role in this patient population.

5.3.6 Vitamins and Minerals

Patients with COVID-19 likely have evidence of oxidative stress, characterized by the production of reactive oxygen species and a concomitant deficiency of antioxidants. Given the potential of ascorbic acid, vitamin D, and zinc to influence the immune response, reactive oxygen species, and nitrogen species, these agents may be useful as adjunctive therapy in SARS-CoV-2 infection [69].

Ascorbic acid, also known as vitamin C, functions as an antioxidant by salvaging reactive oxygen species, decreasing the gene expression of proinflammatory
cytokines, and enhancing microbial killing in certain cell types. Although there are currently no published studies assessing the use of ascorbic acid in patients with SARS-CoV-2 infection, high doses of ascorbic acid have been studied in the ARDS and septic shock patient populations [69, 70]. CITRIS-ALI trial suggested that giving intravenous vitamin C 50 mg/kg every 6 h for 96 h did not significantly alter disease severity scores, CRP levels, or thrombomodulin levels in patients with sepsis and ARDS. However, 28-day all-cause mortality was lowered and ICU-free days were shorter with vitamin C use [71]. The VITAMINS trial suggested that a combination of intravenous vitamin C, hydrocortisone, and thiamine did not improve duration of time alive or free from vasopressor administration compared to hydrocortisone alone in a population with septic shock [72]. Randomized controlled trials of vitamin C are registered on the NIH ClinicalTrials.gov website with a wide range in dosing strategies as well as varying concomitant investigational agents.

Zinc has a role in antibody and white blood cell production. A deficiency in zinc can increase proinflammatory cytokine concentrations (IL-1, IL-6, and TNF-alpha) and decrease the production of antibodies. Zinc supplementation may act in a synergistically when co-administered with the standard antiviral therapy. It has been shown that effectiveness of zinc against a number of viral species was best explained through the physical processes, such as viral attachment, infection, and uncoating [73]. Zinc may also stabilize the cell membrane that could help block of the virus entry into the cell. Finally, zinc may also inhibit viral replication by alteration of the proteolytic processing of the replicase polyproteins and RNA-dependent RNA polymerase in rhinoviruses, HCV, and influenza virus and diminish the RNA-synthesizing activity of noroviruses, to which SARS-CoV-2 belongs.

In addition, in vitro studies with vitamin D show immunomodulatory effects, anti-proliferative effects on T cells, modulating expression and secretion of type 1 interferon, and inhibition of proinflammatory cytokine expression. The largest study to date included over 10,000 individuals from 25 high-quality trials, concluded that oral vitamin D₃ supplementation reduced the risk of acute respiratory tract infections with stronger effects in patients with 25-hydroxyvitamin D levels <25 ng/mL [69, 70, 73].

Ascorbic acid, zinc, and vitamin D have biologic plausibility for the prevention and treatment of SARS-CoV-2 and are currently undergoing clinical trial analysis. Unless a patient has a true micronutrient deficiency, additional research is needed before providing doses of these agents above the recommended daily intake.

5.4 Controversial Agents

5.4.1 Renin Angiotensin Aldosterone Inhibitors

One of the key mechanisms responsible for the pathophysiology of COVID-19 is the dysregulation of the renin-angiotensin aldosterone system (RAAS). This is explained by the fact that the SARS-CoV2 spike protein uses the angiotensin converting enzyme 2 as an entry receptor into target cells [1]. Patients with hypertension
have been shown to have more severe disease, which has led to concerning state-
ments that it might be caused by RAAS inhibitor agents such as angiotensin con-
verting enzyme inhibitors (ACEis) and angiotensin receptor blockers (ARBs) used
to control blood pressure [74, 75]. Concerns regarding their use include the pos-
sibility of upregulation of cellular ACE2 expression, thereby increasing viral entry
and replication [76]. On the contrary, researchers have described potential benefit
of ACEis and ARBs because these agents reduce levels of angiotensin II, which is a
potent proinflammatory, pro-oxidative, pro-fibrotic hormone that contributes to the
pathophysiology of COVID-19 [77].

Multiple investigators have evaluated the association between the use of ACEis
and ARBs and the likelihood of testing positive for COVID-19 and did not find an
increased risk [78–80]. Additionally, a meta-analysis of retrospective cohort and
case-control studies did not find an association between the use of these agents and
the risk of developing severe/lethal COVID-19 disease [81]. The American College
of Cardiology, American Heart Association, and Heart Failure Society of America
as well as treatment guidelines recommend continuation of ACEis and ARBs in
patients prescribed these medications for cardiovascular disease [4, 5].

5.4.2 Non-steroidal Anti-inflammatory Drugs

Initial warning statements were released regarding potential harm with the use of
NSAIDs in COVID-19 patients due the risk of reduced antibody production and
increased ACE2 expression [82, 83]. Due to the lack of clinical evidence suggesting
benefit or harm associated with NSAIDs in COVID-19 patients, the FDA issued a
statement regarding their use [84]. The NIH guidelines recommend continuation
of NSAIDs in patients prescribed this class of medication. In addition, the panel
recommended the use of acetaminophen or NSAIDs as antipyretics in COVID-19
patients [5].

5.5 Summary and Future Research

Aside from the therapeutic options discussed in this text, numerous additional
pharmacologic treatment options are being investigated to target the virus itself as
well as the downstream inflammatory aspects of the disease. Some of these agents
include janus kinase inhibitors (baracitunib, ruxolitinib, tofacitinib), complement
pathway inhibitors (ravulizumab, eculizumab), granulocyte-macrophage colony-
stimulating factors (lenzilumab, mavrilimumab, sargramostim), ivermectin, famoti-
dine, nitazoxanide, dornase alfa, and anakinra/retinoic acid. This data is paramount
in providing insight to healthcare providers on the most safe and effective pharma-
cologic therapies of this disease and its associated complications.

Non-pharmacologic therapies are also being studied for treatment of COVID-19.
In patients with SARS-CoV-induced ARDS in the early 2000s, blood purification
strategies such as plasma exchange showed significant cytokine clearance. An
artificial-liver-blood purification system used in patients with severe H7N9 influenza filtered proinflammatory cytokines from the blood of these patients and showed significantly reduced levels of cytokines including TNF-α and various interleukins [85]. Recently, this artificial-liver-blood purification system was trialed in patients with COVID-19 and showed prevention of cytokine storm and adequate clearance of cytokines [86]. In April, the FDA issued four EUAs for blood purification systems, which are designed to filter proinflammatory cytokines from the blood of patients with COVID-19. These emergency use authorizations will facilitate patient access and provide opportunities to assess their safety and efficacy. Mesenchymal stem cell (MSC) therapy is also being investigated to target the inflammatory aspects of COVID-19 primarily due to their immunomodulatory effects. A small case series of seven patients with COVID-19 who were treated with MSC therapy showed improved respiratory function within 2 days of administration [87]. The FDA has granted compassionate use approval for MSC therapy.

The COVID-19 pandemic has globally burdened researchers to swiftly develop, test, assess, and approve or reappraise novel or existing therapies for the treatment of COVID-19. Much of the available literature is limited to case reports, case series, observational studies, or small, open-label studies. Expanded access programs have given patients with limited options access to investigational agents not yet approved by the FDA, European Medicine Agency, and other international equivalents, in the hopes that the benefits will outweigh the risks of treatment. Expert panels are constantly updating national guidelines to be consistent with the most recently published literature and, where data is limited or unavailable, are making recommendations based on expert consensus. Ultimately, until well-designed, large clinical studies are available, a critical assessment of the pros and cons of some of these agents in context of the clinical scenario will be necessary.

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