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Commentary

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Presently Available and Emerging Treatments for COVID-19

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Editorial

Supportive care is the standard treatment for COVID-19. Remdesivir taken for 5 days may shorten time to recovery in hospitalized patients with evidence of lower respiratory tract infection. The impact of remdesivir on survival is not established. In patients requiring respiratory support with at least supplemental oxygen, dexamethasone 6 mg daily for up to 10 days may improve survival. The optimal dosing and duration of glucocorticoids has not been fully established. Although many other therapies, including antiviral, antiinflammatory, and antibody-neutralizing medications, have been proposed to treat COVID-19, no evidence from randomized controlled trials (RCTs) currently exists to support use of these therapies. Clinical trials to evaluate potential therapies are ongoing. Favipiravir has shown promise as standalone therapy in in vitro models. Clinical data have shown no benefit for lopinavir-ritonavir as standalone therapy. Chloroquine and hydroxychloroquine with or without azithromycin have shown no clinical benefit in the treatment or prevention of COVID-19. Interleukin-6 (IL-6) and interleukin-1 (IL-1) inhibitors are being studied as a therapy in critically ill patients with severe respiratory failure and a pro-inflammatory state. Convalescent plasma has been used with success in other viral infections and appears safe in patients being supported by mechanical ventilation. Clinical trials are ongoing to explore its efficacy in the treatment of COVID-19.

Currently, supportive care is the standard treatment for COVID-19. The two pharmacologic therapies shown to have clinical benefit in prospective randomized trials are remdesivir and dexamethasone. Several clinical trials are ongoing to help determine the efficacy of various other treatments, including antiviral therapies, repurposed medications, and antiinflammatory medications. Because of the unknown benefit and limited medication availability, these medications should be used in consultation with an infectious diseases specialist and on a case-by-case basis. According to the National Institutes of Health (NIH)'s Coronavirus 2019 Treatment Guidelines, these medications should be given only as part of a research protocol to allow for further information to be garnered regarding their efficacy and safety.

Most patients with COVID-19 will only develop mild to moderate disease and will not require therapy beyond supportive care. However, a subset of patients develop severe pulmonary disease, critical illness, or both.1,2 For this subset of patients and for patients with risk factors for developing severe disease, antiviral, antiinflammatory, or repurposed medications may be considered. Risk factors for developing severe disease include age older than 60 years; active cigarette smoking; taking immunosuppressants; being immunocompromised; or having chronic pulmonary disease, obesity, and cardiovascular disease.

Several antiviral therapies have been proposed to treat COVID-19. These drugs include remdesivir, lopinavir/ritonavir with or without ribavirin, and favipiravir.

Remdesivir is a broad-spectrum antiviral agent initially developed to treat infections with Ebola and Marburg viruses. It is a prodrug nucleotide analogue with broad-spectrum antiviral activity against RNA viruses (eg, severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2; coronavirus]). This drug likely works by causing premature termination of viral RNA transcription. In lung-epithelial cell cultures and mouse models, remdesivir has demonstrated activity against the viruses responsible for Middle Eastern respiratory syndrome (MERS-CoV) and severe acute respiratory syndrome (SARS-CoV-1). Given the similarities between the viral structure of SARS-CoV-1 and SARS-CoV-2, it is speculated that remdesivir also has activity against SARS-CoV-2. Recent in vitro models support this supposition.

Initially, remdesivir was used to treat select cases of COVID-19, with the results reported in case reports/series. Recently, however, remdesivir has been used more liberally because of the favorable results of a double-blind, placebo-controlled, randomized trial. In this trial, remdesivir decreased the median time to recovery in hospitalized patients with lower respiratory tract infection compared with patients receiving placebo (11 vs 15 days, respectively). The 7-day mortality rate was approximately 10% in both groups, indicating that remdesivir alone may be inadequate to improve survival. The overall impact of remdesivir on survival remains unknown. Remdesivir appears to be well tolerated; transaminitis and acute kidney injury were the most commonly reported serious adverse events.

The optimal duration of treatment with remdesivir is unclear. Due to drug shortages and the results of an open-label, phase 3 clinical trial showing no difference in clinical outcomes in non-mechanically ventilated patients and 5 days of therapy vs 10 days, most experts, including those at the NIH, recommend 5 days of treatment.

Lopinavir-ritonavir is a combined protease inhibitor used for HIV treatment and postexposure prophylaxis (PEP). Lopinavir has in vitro activity against SARS-CoV-1. Ritonavir, a potent cytochrome P450 inhibitor, is combined with lopinavir to increase the plasma concentration of lopinavir. An open-label, RCT to evaluate the efficacy and safety of lopinavir-ritonavir for COVID-19 was conducted in China and included 199 patients with confirmed moderate or severe COVID-19 (99 received lopinavir-ritonavir and 100 received supportive care). No difference in mortality or viral load was observed between groups.

Because results from an open-label study previously published in 2004 suggested that lopinavir-ritonavir plus ribavirin reduced the risk of ARDS or death compared with ribavirin alone in SARS, optimism for lopinavir-ritonavir in combination with ribavirin as a potential therapeutic option in COVID-19 remains. If lopinavir-ritonavir in combination with ribavirin is effective in treating COVID-19, then it has several potential advantages over remdesivir; these medications are already widely available, and they have well-known side effects and drug interaction profiles. Before prescribing lopinavir-ritonavir, HIV testing should be completed because single-agent therapy may promote HIV resistance.

Favipiravir is a prodrug inhibitor of viral RNA polymerase. It has broad-spectrum activity against RNA viruses and was initially developed to treat neuraminidase-inhibitor-resistant influenza. Data on in vitro and clinical activity of favipiravir for SARS-CoV-2 are sparse, but clinical trials are ongoing. An open-label study comparing favipiravir with lopinavir-ritonavir in patients with COVID-19 found a shorter viral clearance time and more rapid resolution of chest imaging abnormalities in patients receiving favipiravir. This medication appears to be well tolerated, but the side effect profile is not well delineated, and the medication is not broadly available.

Both chloroquine and hydroxychloroquine have been proposed to treat COVID-19. Traditionally, chloroquine is used to prevent and treat malaria. Both chloroquine and hydroxychloroquine are effective antiinflammatory agents used for the treatment of rheumatoid arthritis and lupus erythematous. These medications have potential broad-spectrum antiviral activity; although their exact mechanisms of action are unclear, they are believed to interfere with viral-cell effusion. Hydroxychloroquine was found to be a more potent inhibitor of SARS-CoV-2 in vitro than chloroquine.

Although in vitro models suggest that hydroxychloroquine has anti-SARS-CoV-2 activity, hydroxychloroquine with or without azithromycin has not been shown to improve clinical outcomes in an RCT of patients with mild to moderate disease or in a large observational study of hospitalized patients. A widely publicized, single-arm study in France of 20 patients with mild to moderate disease who were treated with hydroxychloroquine showed reduced nasopharyngeal viral loads compared with the viral loads of patients from another center. Clinical benefit was not reported.

Hydroxychloroquine has also been proposed for PEP. An RCT of 821 participants with high-risk exposure found no difference in symptomatic infection rates between those receiving hydroxychloroquine as PEP compared with those receiving placebo.

Chloroquine and hydroxychloroquine are generally well tolerated, but they have the potential to cause QT prolongation and hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency. Hydroxychloroquine can also cause visual disturbances. The NIH guideline panel recommends that hydroxychloroquine not be used for treatment of COVID-19.

Cytokine storm and viral evasion of the cellular immune system may play key roles in disease severity. Cytokine storm can lead to and cause progression of ARDS. It has been proposed that a reduction in the host's inflammatory response to SAR-CoV-2 in a select subgroup of patients may improve survival.

Glucocorticoids have previously been shown to have no benefit in SARS, MERS, and influenza, and observational data have shown increased viral shedding, increased mortality, and more secondary infections compared with other agents. Previously, in a retrospective cohort study of 84 patients with COVID-19 and ARDS, patients receiving methylprednisolone had a decreased risk of death, suggesting that a subset of patients with severe COVID-19 may benefit from corticosteroids. In the RECOVERY trial, which used an open-label design, hospitalized patients with COVID-19 were randomly assigned to receive dexamethasone 6 mg daily for up to 10 days or usual care. The researchers found that patients receiving dexamethasone had lower 28-day mortality rates than patients who received usual care. Specifically, mortality rates were lower in those patients whose symptoms began at least 7 days previously and who were receiving supplemental oxygen or invasive mechanical ventilation. No mortality difference was observed in those requiring no respiratory support. Research is ongoing to determine the appropriate dosing and duration of corticosteroids.

Tocilizumab and siltuximab are IL-6 inhibitors approved for the treatment of cytokine activation syndrome secondary to chimeric antigen receptor T-cell therapy. No randomized studies have been completed to evaluate the effectiveness of tocilizumab or siltuximab in the treatment of severe COVID-19. Preliminary observational studies show a possible survival benefit in patients with evolving cytokine release syndrome. These agents may be considered in critically ill patients with ARDS and elevated IL-6 levels because of the theoretical effect of cytokine storm on the progression of ARDS and multiorgan failure.

These medications may increase the risk of life-threatening opportunistic infections. Tocilizumab may have other serious side effects, including transaminitis and bone marrow suppression. Siltuximab may cause edema, hypotension, and thrombocytopenia. The NIH recommends that these agents only be used in the setting of an RCT.

Anakinra is an IL-1 inhibitor used to treat autoimmune conditions such as rheumatoid arthritis. Results from a phase 3 trial demonstrated a survival benefit with anakinra in critically ill patients who had sepsis and associated hyperinflammation. Secondary to the robust inflammatory response observed in critically ill patients with COVID-19, anakinra has been proposed as a therapeutic agent. Anakinra is a safe medication with a short half-life allowing for prompt discontinuation, a potential advantage over other immunomodulating agents. A retrospective cohort of 29 critically ill patients with COVID-19 showed a potential survival benefit with high-dose anakinra; however, prospective RCTs are needed to establish a benefit. The NIH recommends that this agent only be used in the setting of an RCT.

Convalescent plasma or immunoglobulins from recovered individuals have been used in the treatment of SARS, Ebola infection, and H1N1 influenza. These therapies work to suppress viremia, enhance humoral response, and accelerate viral clearance from infected cells. In SARS, convalescent plasma was associated with shorter length of hospital stays and lower rates of mortality. In H1N1 influenza, a prospective study showed a reduction in the risk of mortality in those treated with convalescent plasma without significant adverse effects.

Secondary to these prior successes, convalescent plasma has been proposed as a treatment option for COVID-19. A case series of five patients with severe COVID-19 and ARDS treated with convalescent plasma showed an overall improvement in clinical status, with three patients discharged from the hospital 51 to 55 days after transfusion. Data from the first 20,000 patients transfused with COVID-19 convalescent plasma demonstrate that use of convalescent plasma is safe and appears to have no excess risk of complications. Convalescent plasma may be associated with improved survival; however, this initial report does not establish efficacy. Clinical trials are ongoing to determine if convalescent plasma may be a potential therapy for COVID-19.