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The Medical Letter on Drugs and Therapeutics

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COVID-19 - Some Drug-Related Issues

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Note: This article will be updated as more information becomes available.

Read our blog post on this topic: Remdesivir: A Possible Treatment for 2019 Novel Coronavirus

Outline

The rapid spread and severity of COVID-19 (caused by SARS-CoV-2) have raised some questions about use of various drugs in patients with the disease and whether currently available drugs could be effective in treating it. Definitive answers are lacking, but some recommendations can be made. Updated information on COVID-19 is available from the CDC at www.cdc.gov/coronavirus/2019-ncov/hcp/index.html.

ACES AND ARBS — Patients with cardiovascular disease are at increased risk of severe COVID-19. Some researchers have suggested that this increase in risk may be due to use of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with diabetes, hypertension, or heart failure. The basis for this hypothesis is that ACE inhibitors and ARBs increase expression of ACE2 by epithelial cells in the lung, and pathogenic coronaviruses such as SARS-CoV-2 enter these cells via ACE2 receptors.[1] Others have suggested, however, that ACE2 may protect against lung injury in coronavirus infection and that taking an ACE inhibitor or an ARB might be beneficial.[2]

There is no clinical evidence that ACE inhibitors or ARBs increase or decrease the severity of COVID-19 infection. Multiple medical organizations have recommended that patients who take these drugs and subsequently develop COVID-19 continue to take them and have advised against starting these drugs to prevent COVID-19 infection.[3]

NSAIDS — The Health Minister of France recently warned that use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen (*Advil, Motrin*, and others) to reduce fever in patients with COVID-19 increases the risk of severe adverse events and recommended use of acetaminophen (*Tylenol*, and others) instead.[4] There is no convincing evidence that NSAIDs are especially dangerous for patients with COVID-19,[5] but they can cause GI bleeding, fluid retention, and renal dysfunction, adverse effects that may be dangerous for any critically ill patient. The World Health Organization (WHO) does not recommend against use of an NSAID for fever in patients infected with coronavirus. Controlled trials are lacking, but acetaminophen is an effective antipyretic and, in recommended doses, is less likely than an NSAID to cause serious adverse effects in most patients.

Continual fever suppression with either an NSAID or acetaminophen may reduce the immune response and prolong viral shedding. Patients who are taking NSAIDs for other reasons should not stop taking them because of COVID-19.

REPURPOSED DRUGS — In the absence of any FDA-approved treatment for COVID-19, many clinicians have turned to existing drugs to prevent or treat the disease. Some drugs that have been tried based on hypotheses or limited evidence include neuraminidase inhibitors used to treat influenza (e.g., oseltamivir), HIV protease inhibitors (e.g., lopinavir/ritonavir), ribavirin, interferon, chloroquine/hydroxychloroquine, and azithromycin.[6] Corticosteroids and IL-6 inhibitors (e.g., tocilizumab, sarilumab) have been used to suppress the inflammatory response. The available evidence supporting off-label use of any of these drugs for treatment or prevention of COVID-19 is limited.

Neuraminidase inhibitors are not expected to be effective for prevention or treatment of COVID-19 because the SARS-CoV-2 virus does not contain neuraminidase.

A recently published clinical trial in 199 hospitalized patients with severe COVID-19 infection found that the HIV protease inhibitor combination **lopinavir/ritonavir** *(Kaletra)* was no more effective than usual care.[7] Whether the combination might be effective in patients with less severe disease remains to be established. Lopinavir/ritonavir causes GI adverse effects and QT interval prolongation[8] and has the potential to interact with many drugs. The Society of Critical Care Medicine recommends against the use of lopinavir/ritonavir in critically ill patients.[9]

In some US hospitals, **chloroquine and hydroxychloroquine**, which are FDA-approved for prophylaxis of malaria and treatment of rheumatoid arthritis, are being used off-label for treatment of patients with moderate or severe COVID-19, based on preliminary data from China and France showing that these drugs can reduce viral load and shorten the duration of symptoms. In one open-label study in 42 patients hospitalized for COVID-19 in France, addition of **azithromycin** to hydroxychloroquine resulted in a more rapid decrease in viral load compared to treatment with hydroxychloroquine alone.[10] Clinical trials evaluating the efficacy and safety of these drugs for COVID-19 are underway here. Interactions with other drugs, particularly those that also prolong the QT interval,[8] are a concern with use of these drugs.

The CDC recommends that **corticosteroids** be avoided in most patients with COVID-19 because they may prolong viral replication; they are recommended for treatment of acute respiratory distress syndrome (ARDS) or refractory shock.[9,11] Other immunomodulating drugs such as **IL-6 inhibitors** (e.g., tocilizumab, sarilumab) may mitigate the effects of cytokines released in response to the virus and limit lung damage in patients with severe disease; clinical trials are in progress.

Improper prescribing or stockpiling of repurposed drugs could result in toxicity and an inadequate supply for treatment of severe COVID-19 and other important indications, such as influenza and rheumatoid arthritis, and should be avoided. Until clinical trials establish the efficacy and safety of any drug for treatment of COVID-19, the CDC recommends supportive treatment and appropriate management of complications, such as ARDS and bacterial pneumonia.[11] Patients should be asked to participate in clinical trials of direct and supportive treatments.[12]

REMDESIVIR — Remdesivir (Gilead), a broad-spectrum IV antiviral drug that is active against SARS-CoV-2 and other coronaviruses *in vitro* and in animal models,[13] is currently being studied in controlled trials in China and the US for treatment of severe COVID-19. Remdesivir is a prodrug that requires activation by CYP3A4; whether inhibitors of CYP3A4,[14] such as ritonavir, would reduce the efficacy of remdesivir is unknown.

Gilead has temporarily stopped honoring requests for individual compassionate use of remdesivir, except for pregnant women and children ≤18 years old with severe disease. Enrollment in clinical trials is recommended instead (https://rdvcu.gilead.com).

CONVALESCENT SERA — Until a vaccine becomes available, use of passive antibody therapy using the apheresed serum of recovered patients (no residual virus, high titers of neutralizing antibodies), which has been used in other viral epidemics, may be an option for prevention or early treatment of COVID-19. Limited data from the current COVID-19 outbreak in China suggest that use of convalescent sera reduced viral load and was safe. It might be especially beneficial for healthcare workers or family members of recently diagnosed patients.[15]

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