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IN THIS ISSUE

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Some Drugs for COVID-19

Note: The print/PDF version of this article is limited by space and the speed by which new information becomes available. This article is continually updated on our website (medicalletter.org/TML-article-1595a).

The severity and rapid spread of COVID-19 (caused by SARS-CoV-2) have raised questions about the use of some 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 or 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 to date that ACE inhibitors or ARBs increase or decrease the severity of COVID-19 and multiple medical organizations have advised against starting or stopping these drugs to prevent COVID-19 infection. Patients who are taking an ACE inhibitor or an ARB and subsequently develop COVID-19 should continue to take the drug.[3]

NSAIDS — The Health Minister of France has 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 in any patient, which can be dangerous for the critically ill. 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. Use of an NSAID or acetaminophen for continual fever suppression may reduce the immune response and prolong viral shedding. Patients who are taking NSAIDs for other indications should not stop taking them.

REPURPOSED DRUGS — In the absence of any FDA-approved drugs for treatment of 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, HIV protease inhibitors, ribavirin, interferon, chloroquine/hydroxychloroquine, and azithromycin.[6] Corticosteroids and interleukin-6 (IL-6) inhibitors have been used to suppress the inflammatory response. Evidence supporting off-label use of any of these drugs for treatment or prevention of COVID-19 is limited.

Neuraminidase inhibitors (e.g., oseltamivir) are not expected to be effective for prevention or treatment of COVID-19 because SARS-CoV-2 does not contain neuraminidase.

In a recently published clinical trial in 199 hospitalized patients with severe COVID-19 illness, addition of the HIV protease inhibitor combination **lopinavir/ritonavir** *(Kaletra)* to standard care was no more effective than standard care alone.[7] Whether the combination might be effective in patients with less severe disease remains to be established. Lopinavir/ritonavir can cause GI adverse effects and QT interval prolongation,[8] and it has the potential to interact adversely with many drugs.[9] The Society of Critical Care Medicine recommends against use of lopinavir/ritonavir in critically ill COVID-19 patients.[10]

In some US hospitals, **chloroquine and hydroxychloroquine** (*Plaquenil*, and generics) 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** (*Zithromax*, and generics) to hydroxychloroquine resulted in a more rapid decrease in viral load compared to treatment with hydroxychloroquine alone.[11] Clinical trials evaluating the efficacy and safety of these drugs for COVID-19 are in progress. These drugs can prolong the QT interval; 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 other indications such as asthma and for treatment of acute respiratory distress syndrome (ARDS) or refractory shock.[10,12] Other immunomodulating drugs such as **IL-6 inhibitors** (e.g., tocilizumab *[Actemra]*, sarilumab *[Kevzara]*) 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 lupus 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.[12] Patients should be asked to participate in clinical trials of direct and supportive treatments.[13]

REMDESIVIR — Remdesivir (Gilead), an investigational broad-spectrum IV antiviral drug that is active against SARS-CoV-2 and other coronaviruses *in vitro* and in animal models,[14] is currently being studied in controlled trials in China and the US for treatment of severe COVID-19.

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, 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] Studies in seriously ill patients will be conducted in the US. ■

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