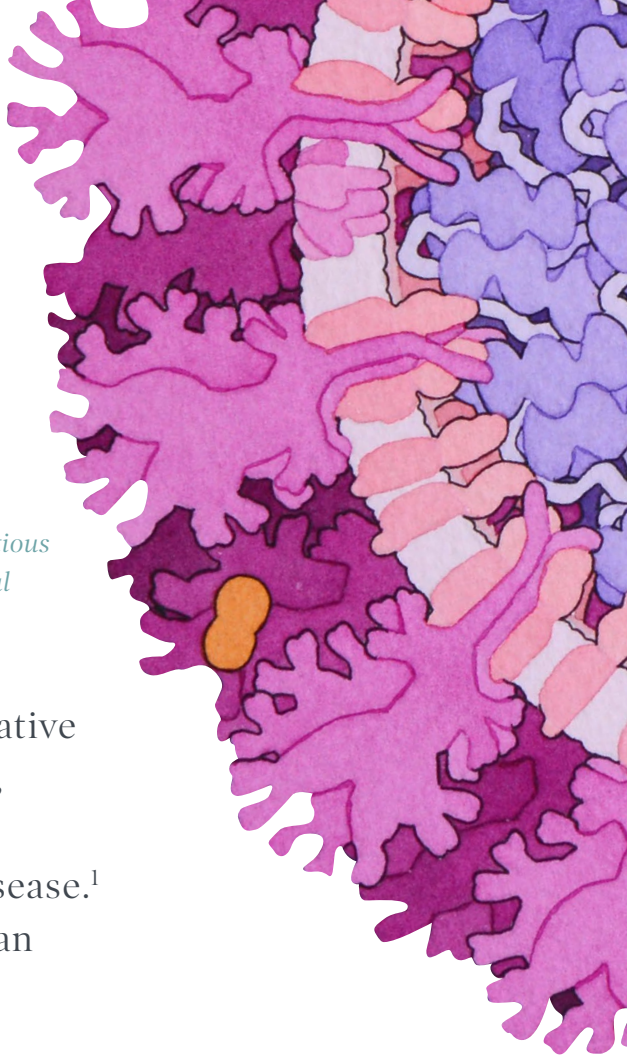

INFECTIOUS DISEASE ALERT

Pharmacotherapy Considerations for COVID-19

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The 2019 novel coronavirus (2019-nCoV) is the causative pathogen of 2019 coronavirus disease (SARS-CoV-2), an acute respiratory illness, which can range from asymptomatic carriage to life-threatening, severe disease.[1] At the time of this writing, there have been more than 1,000 reported cases in the United States.[2]

The global outbreak of 2019-nCoV has spawned interest in potential treatment options, particularly for those with more severe illness. This article provides a brief summary of selected pharmacotherapy options proposed for COVID-19.

REMDESIVIR

Remdesivir is a prodrug of an adenosine nucleoside, which inhibits viral RNA-dependent RNA polymerase.[3,4] At the time of this writing, remdesivir is not approved by the Food and Drug Administration (FDA) and is available only as an investigational drug through Gilead Sciences.[5] It was studied originally for Ebola virus disease and found to have no benefit vs. comparators. Despite this, remdesivir has been found to have a broad spectrum of activity against various coronaviruses, including SARS-CoV, MERS-CoV, and 2019-nCoV in preclinical studies.[6,7]

Although reports on clinical outcomes of remdesivir therapy are limited, it was used in the first confirmed case of COVID-19 in the United States. Initially the patient presented with mild symptoms, but after the first week of largely supportive care,

Coronavirus Illustration by David S. Goodsell, RCSB Protein Data Bank

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had progression of the disease to pneumonia requiring supplemental oxygenation, which prompted the initiation of remdesivir through compassionate use. The patient's clinical condition subsequently improved.[8]

At the time of writing, multiple randomized clinical trials (NCT04252664, NCT04257656, and NCT04280705) are being conducted on remdesivir for treatment of COVID-19 in the United States. In these trials, remdesivir is given as either a five-day or 10-day course, dosed at 200 mg intravenously on day 1, and 100 mg intravenously daily thereafter. Exclusions vary between trials, but, notably, they generally exclude patients 17 years of age or younger, those with severe hepatic or renal impairment, and pregnant or breastfeeding women.[9-11]

CHLOROQUINE OR HYDROXYCHLOROQUINE

Chloroquine has been proposed as another pharmacotherapy consideration for COVID-19 and has been found to have in vitro activity against SARS-CoV-2.[7] Its antiviral activity may be afforded by an increase in endosomal pH and interference with glycosylation of cellular receptors of SARS-CoV.[12]

Initial reports from more than 100 patients asserted that there was superiority of chloroquine to control treatment in inhibiting exacerbation of pneumonia, promoting negative conversion, and shortening the disease. However, this information is per a news briefing in China and, at the time of this writing, no patient data has been released yet.[12] The purported treatment dosage of chloroquine is 500 mg orally twice daily for 10 days.[13] There is an ongoing Phase III, placebo-controlled clinical trial (NCT04261517) of hydroxychloroquine for pneumonia caused by 2019-nCoV. In this trial, the treatment regimen is hydroxychloroquine 400 mg orally daily for five days.[14]

LOPINAVIR

Lopinavir is an HIV protease inhibitor that has been reported to have activity against SARS-CoV-2. It is unclear whether inhibitors of HIV protease (in the aspartic protease family) can effectively inhibit that of 2019-nCoV (in the cysteine protease family).[15] Use for COVID-19 is based largely on trials in severe acute respiratory syndrome (SARS) suggesting that lopinavir was associated with improved clinical outcomes and mortality.[16,17]

As opposed to remdesivir and chloroquine, however, several detailed reports on clinical experience with lopinavir have been published. That said, the data are not encouraging. In a study of five patients with COVID-19 in Singapore who received lopinavir/ritonavir, the clinical benefit was equivocal, and progressive disease occurred in two patients. Of note, this study used a lower dose (200/100 mg orally twice daily) of lopinavir/ritonavir.[18] In a study of four patients in Shanghai with COVID-19, two with mild disease and two with severe disease, who received lopinavir/ritonavir (400/100 mg orally twice daily for six to 15 days), along with other treatments including arbidiol and traditional Chinese medicine. Three patients improved, two of whom had negative viral testing at the

Image from CDC, via Unsplash

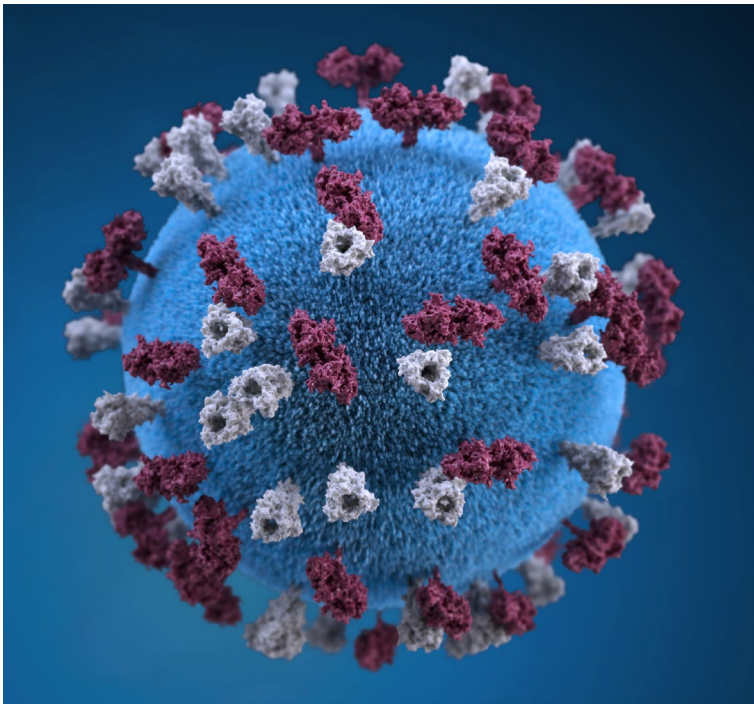

Table 1*— Selected Potential Antiviral or Adjunctive Therapies for COVID-19*[15, 20, 22]

Remdesivir
Chloroquine
Hydroxychloroquine
Lopinavir/Ritonavir
Darunavir/Cobicistat
Ribavirin
Nitazoxanide
Nelfinavir
Penciclovir
Mefloquine
Oseltamivir
Tocilizumab
Interferon Alfa (nebulized)
Intravenous Immunoglobulin
Baricitinib

end of data collection. The fourth patient, with severe COVID-19, showed signs of improvement at the end of data collection.[19]

Guidelines for 2019-nCoV pneumonia from the Zhongnan Hospital of Wuhan Novel Coronavirus Management and Research Team provided a weak recommendation for the use of lopinavir/ritonavir based on benefits found in patients with SARS or Middle East respiratory syndrome (MERS), especially with earlier administration.[20]

ADJUNCTIVE THERAPIES

Adjunctive corticosteroids have not shown clinical benefit, have delayed viral RNA clearance in other coronavirus disease (SARS and MERS), and may increase the risk of side effects (e.g., psychosis, diabetes, and avascular necrosis) and increased mortality in influenza.[21] Chinese guidance has suggested the use of tocilizumab for cytokine storm in patients with severe disease (e.g., acute respiratory distress syndrome) and elevated interleukin-6 levels.[22]

SOURCE— *Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies (letter). BioSci Trends 2020 Feb. 19. doi:10.5582/bst/2020.01047. [Epub ahead of print].*

WHICH TREATMENT FOR SARS COV-2 IS BEST?

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A hot topic of conversation this week is how best to treat our three critically ill SARS-CoV-2 patients in the intensive care unit (ICU). Facilities nearby are using ***remdesivir,*** *and another is using* ***hydroxychloroquine****.*

CHLOROQUINE *has been found to block SARS-CoV-2 infection, with cytotoxic activity demonstrated in vitro by increasing the endosomal pH, interfering with viral fusion, and interfering with glycosylation of cellular receptors. The National Health Commission of the People's Republic of China has been quickly conducting several clinical trials of various agents, including hydroxychloroquine and chloroquine.[1] In a comparison of inhibiting the exacerbation of pneumonia, improved lung findings, and shortening the disease course, chloroquine to a "control" treatment of more than 100 patients,*

researchers found active treatment was superior to the control in and in promoting clearance of the virus in respiratory specimens.

It was fairly well tolerated, with no severe adverse reactions. Chloroquine will be included in the upcoming version of China's treatment guidelines.

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