Emerging Treatment of Acute COVID-19 Infection in Adults with Repurposed Antiviral Medication

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus that causes coronavirus disease 2019 (COVID-19).[1] The coronavirus outbreak of 2019 initiated a severe pandemic and started a global health crisis.[2] Globally, as of May 20, 2021, there have been 164 409 804 confirmed cases of COVID-19, including 3 409 220 deaths.[2,8] In the United States, COVID-19 has infected over 32 million people and killed over 580 000.[2,5] The spectrum of clinical manifestations of COVID-19 in adults ranges from asymptomatic to mild respiratory symptoms to acute respiratory distress syndrome (ARDS) and multiorgan dysfunction.[3] The mortality rate of COVID-19 is approximately 1 to 2%.[4]

Most patients with COVID-19 have mild or moderate disease; up to 10% of patients present with severe or life-threatening illness.[3] The typical manifestations of COVID-19 include fever, sore throat, fatigue, cough, headaches, muscle aches, loss of taste or smell and shortness of breath.[3]

Transmission of COVID-19 is most likely via droplet spread to close contacts, typically within 6 feet.[5] Adults over the age of 70 and those with multiple medical co-morbidities are at increased risk of poor outcomes from the virus.[6] The greatest risk for severe illness from COVID-19 is among those aged 85 or older.[6] For deaths involving COVID-19 through December 31, 2020, the virus was the only cause of death mentioned in 6% of cases.[8] For the remaining 94% of deaths, patients had, on average, an additional 2.9 comorbidities.[7]

Vaccinations have recently emerged as a tool to reduce symptomatic infection, but vaccines do not treat acute disease. Therefore, there is an urgent need for effective and specific treatment for acute viral illness. According to Anthony Fauci, MD, Director of the National Institute of Allergy and Infectious Diseases, “You have to treat the elderly and those with underlying conditions to protect them because they are vulnerable.”[9]

Currently, supportive care measures remain the standard of care because there is no specific treatment established for patients with acute COVID-19 infection.[10,11] Supportive care for acute illness includes the use of agents such as antiviral medications, inflammation inhibitors/antirheumatic drugs, low molecular weight heparins, plasma, and hyperimmune immunoglobulins.[10,11]

Antiviral medications previously tested for other coronaviruses, like SARS-CoV and MERS-CoV (Middle Easters Respiratory Syndrome-Coronavirus), shortened the course of disease by interfering with the viral cycle inside the host cell, reducing viral load and viral shedding.[12,13] The antivirals administered shortly after the onset of symptoms both decreased the length of clinical illness and reduced infectiousness to others.[13] This supports early treatment with antivirals against SARS-CoV-2. Effective early treatment is essential to curtail the impact of subsequent local waves of COVID 19.[14] Currently in the United States, all oral antiviral COVID-19 treatments are under investigation and should not be prescribed in the ambulatory setting outside of a clinical trial.[18,27]

The antiviral medications favipiravir and lopinavir/ritonavir may be given to adults presenting for care in ambulatory settings within 72 hours of onset of COVID-like symptoms.[12,23] Remdesivir is currently approved for emergency use in the United States but is only available intravenously to those patients who are already hospitalized.[36]

Overall, favipiravir has shown promising results in multiple international clinical studies and more trials are underway in several countries including the USA, the UK, and India.[12] Recently, treatment guidelines from many countries and some states from India have included favipiravir in their treatment protocols.[12] To date, favipiravir has only been tested in adults 18 years and older. Compared with lopinavir/ritonavir, favipiravir showed greater efficacy in decreasing the length of fever and cough; favipiravir also

demonstrated a greater efficacy in the rate of viral clearance at 96 hours after treatment initiation when compared to lopinavir/ritonavir.[12] However, ongoing trials in several countries did not show a significant decrease in all-cause mortality from COVID-19 in patients who received favipiravir.[12,24,25,26]

Lopinavir/ritonavir has also demonstrated efficacy in treating acute COVID-19 infection. Twelve studies evaluated treatment with lopinavir/ritonavir in addition to standard care versus standard care alone in adults with COVID-19.[13] The evidence from two randomized trials demonstrates that lopinavir/ritonavir may reduce mortality (relative risk, 0.77; 95% CI, 0.45 to 1.3; *P*<.01) in patients with moderate to severe disease.[13] Lopinavir/ritonavir also had a slight reduction in the risk of requiring mechanical ventilation and developing either respiratory failure or acute respiratory distress syndrome.[13] However, treatment with lopinavir/ritonavir did not lead to any difference in the duration of hospitalization and may lead to an increase in the number of total adverse effects.[13]

EDUCATIONAL ANALYSIS

Gap #1: Clinicians may be unaware of emerging antiviral treatments for acute COVID-19 infection

Learning Objective #1: Describe the timeline of COVID-19 illness progression and antiviral treatment effectiveness pertinent to the adult, outpatient practice setting.

SARS-CoV-2 is a positive-sense single-stranded ribonucleic acid (RNA) virus, which has an incubation period of up to 14 days and an infectivity rate (R_0) from 1.5 to more than 6 in some regions.[12] Viral shedding may be seen 1-2 days before symptom onset and may continue for 1-2 weeks in mild to moderate cases.[12] Symptoms usually appear between 2 and 14 days after exposure.[12]

Antiviral medication administered shortly after the onset of symptoms can shorten the course of clinical illness.[14,16] It has been reported that if a patient receives antiviral therapy in the early phase of infection, there is a significant reduction of viral shedding.[17] Hence, an efficient means to limit viral burden is to treat with antivirals early, possibly at the presymptomatic phase before the peak viral load.[17] Furthermore, high-risk patients with progressing symptomatic disease are currently limited to treatment in the hospital; hospitalization for COVID-19 is independently associated with high mortality.[18] An outpatient management protocol that treats acute disease and prevents hospitalization is therefore needed.[20]

Favipiravir is a repurposed drug for COVID-19 that was originally developed as an anti-influenza medication.[12] Favipiravir is an inhibitor of RNA-dependent RNA polymerase (RdRp) of RNA viruses.[12] Favipiravir has proven efficacy against a broad range of influenza viruses, including H1N1, H5N1, and H7N9 avian virus.[12] Additionally, it may halt the replication of several other RNA viruses, including arenaviruses, phleboviruses, hantaviruses, flaviviruses, Western equine encephalitis virus, noroviruses, and ebola virus.[12] Recent in vitro studies and clinical trials reported the efficacy of favipiravir to reduce viral load of SARS-CoV-2 infected patients with acute symptoms.[14,15,16,17,18,19,34,35] Recommended treatment of acute COVID-19 with favipiravir is as follows: 1800 mg twice a day on day 1, followed by 800 mg twice a day up to a maximum of 14 days in mild to moderate COVID-19 patients.[12]

Lopinavir/ritonavir is an HIV protease inhibitor and is indicated in combination with other antiretroviral medication for the treatment of human immunodeficiency virus (HIV) in infected individuals.[31] In a phase 2 study recently published in *The Lancet*, a total of 127 patients with mild to moderate COVID-19 infection were randomized to receive either a 14-day combination of lopinavir/ritonavir (400mg/100mg), 14 days of ribavirin, or three doses of interferon beta-1b over two weeks.[32] The authors suggested that early antiviral therapy with lopinavir/ritonavir might be effective in mild to moderate illness. Subsequently, it has been suggested that lopinavir/r may be combined with ribavirin as a treatment option for COVID-19.[32]

Gap #2: Clinicians may be unaware of the mechanism of action of emerging antiviral treatments for COVID-19

Learning Objective #2: Identify the mechanism of action of COVID-19 antiviral treatment options for non-hospitalized adults.

RNA-dependent RNA polymerase (RdRp) plays an essential role in coronavirus replication.[26,28,29,33] RdRp is an enzyme that facilitates viral replication and increases viral load, which causes acute symptomatic illness and host infectivity.[33]

Favipiravir binds to and inhibits RdRp, which ultimately prevents viral transcription and replication.[12] Favipiravir is a prodrug with a purine base analog that is converted to active favipiravir ribofuranosyl-5B-triphosphate (favipiravir-RTP) by intracellular phosphoribosylation.[12] Favipiravir-RTP is a selective inhibitor of RdRp in RNA viruses.[38] Favipiravir-RTP is incorporated into the nascent viral RNA by RdRp, which leads to chain termination and viral mutagenesis.[36-38] Hence, after RNA viral incorporation, favipiravir works as a mutagen that reduces the number of viral RNA and infectious particles.[33]

Lopinavir/ritonavir is a protease inhibitor (PI), which is a class of drugs best known for efficacy against HIV. PI medications block the final step of virion assembly of the human immunodeficiency virus.[42] Lopinavir/ritonavir binds competitively to the substrate site of the viral protease.[36] This enzyme is responsible for the release of functional viral proteins, allowing them to function correctly in replication, transcription and maturation.[38,39,40] Inhibition of viral protease results in the production of immature virus particles.[39] Coronavirus proteases contain a 3C-like proteinase, which enables the formation of the viral replication complex.[41] It is postulated that the 3CLpro-inhibiting activity of lopinavir/ritonavir contributes to its activity against SARS-CoV-2.[42]

Gap #3: Clinicians may be unaware of the safety profiles of emerging antiviral treatments for acute COVID-19 infection

Learning Objective #3: Evaluate the safety profiles of repurposed, antiviral medication for COVID-19 and subsequently choose the most appropriate therapy to offer adults with an acute, symptomatic infection.

The common adverse effects of favipiravir include gastrointestinal symptoms, uric acid elevations, decrease of neutrophil count, increase of aspartate aminotransferase (ALT), increase of alanine transaminase (AST), psychiatric symptoms, and increase in blood triglycerides.[43,44] Favipiravir is contraindicated in pregnant and lactating women because of its teratogenic potential in animal studies.[44]

Additionally, favipiravir is contraindicated in patients with severe hepatic impairment and severe renal impairment.[43,44] Favipiravir should be administered with care in patients with gout or a history of gout, with hyperuricemia.[43,44] Favipiravir may be safe and tolerable in short-term use, but more evidence is needed to assess the longer-term effects of treatment.[44]

The common adverse effects of lopinavir-ritonavir include gastrointestinal symptoms, loss of appetite, elevation of alanine aminotransferase (ALT), elevation of aspartate aminotransferase (AST), and an increased incidence of upper respiratory tract infections.[45] Other adverse effects include thrombocytopenia, prolonged QT, sleep disturbance, neutropenia, rash, leukopenia, lymphopenia, anemia, and abdominal discomfort.[45] Because of its longstanding use in the treatment of HIV, lopinavir-ritonavir may be safe and tolerable in short- and long-term use, but more evidence is needed to assess the longer-term effects of treatment in patients with COVID-19.[45]

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CONCLUSION

COVID-19 is associated with high morbidity and mortality among adults greater than 70 years of age. No established treatment currently exists for acute COVID-19 infection. Acute treatment is particularly important for the elderly and those patients at high risk for serious complications due to underlying health conditions. Physicians must be well-informed and equipped to provide accurate information and timely treatment to patients to minimize serious outcomes and disease spread. The development of novel therapies is a time-consuming, labor-intensive process and often takes years before a new drug is available for use. This makes attractive the use of already-existing antiviral medications that can be repurposed for use in treatment of COVID-19. The antiviral medications favipiravir and lopinavir/ritonavir appear to be useful in the management of acute COVID-19 infection, particularly mild to moderate disease. However, large randomized controlled trials are required to demonstrate whether this effect translates to clinical benefits such as shortening the disease course, reducing transmission, decreasing time to hospital discharge, and reducing mortality. Current evidence is limited, but more clinical trials and ongoing research can provide evidence to inform researchers and decision-makers.

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