COVID-19 One Year Later: A Focused Review of Treatment Options

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Learning Objectives:

After completion of the activity, the participant will be able to:

1. Describe the epidemiology, pathophysiology, and circulating variants of a novel coronavirus, SARS-CoV-2.
2. Identify treatments for mild, moderate, and severe COVID-19 disease available under emergency use authorization in the United States.

Outline – Focused review of FDA EUA products

I. Background
    a. COVID-19 epidemiology (global and US)
    b. Pathophysiology/risk factors
    c. Current environment with circulating variants
II. Prevention
    a. Infection control practices
    b. Vaccines
III. Treatment
    a. Outpatient for mild/moderate disease
        i. Monoclonal antibodies
        ii. Colchicine
    b. Inpatient for moderate/severe disease
        i. Remdesivir
        ii. Dexamethasone
        iii. Baricinitib combination
    c. Thrombotic complications and management

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Background

Cases of a novel coronavirus disease (SARS-CoV-2) were first reported in Wuhan, China in December 2019.[1,2,3] In approximately one year the number of confirmed cases of COVID-19 exceeded 120 million worldwide, including more than 2.5 million deaths, with the United States accounting for nearly 25% of all cases and more than 500,000 deaths.[5] In mid-December 2020, the Food and Drug Administration authorized the emergency use of two vaccines for COVID-19 prevention.[6,7] Clinical trials and mass vaccination efforts are urgently occurring worldwide, especially as SARS-CoV-2 variants have emerged in various regions.[8]

Coronaviruses are single stranded ribonucleic (RNA) viruses and are categorized into four subgroups: alpha (a), beta (b), gamma (g), and delta (δ) coronavirus. SARS-CoV-2 belongs to the b subgroup and shares similar genomic sequence as the SARS and MERS coronaviruses.[2,3,4] Coronaviruses cause respiratory, gastrointestinal, hepatic, and neurological diseases in humans and animals. The primary mode of transmission is inhalation of respiratory droplets from an infected person, although airborne transmission can also occur.[9] The median incubation period is four to five days and can range up to 14 days from exposure.[1] Effective prevention strategies include physical distancing of at least six feet, wearing a mask that covers the nose and mouth, washing hands often with soap and water, and avoiding crowds especially while indoors.

Spike proteins on the SARS-CoV-2 virus bind to human angiotensin-converting enzyme 2 (ACE2) receptors present on epithelial cells in the lung, heart, kidney, and gastrointestinal tract.[2,4] Similar to other respiratory viral infections, signs and symptoms include fever or chills, cough, shortness of breath, fatigue, and myalgias. Based on its viral tropism, other symptoms may include new onset ageusia, anosmia, nausea, vomiting, and diarrhea[10] While disease can range from mild symptoms to severe disease, risk factors for severe disease include older age, pregnancy, and certain medical conditions such as cancer, cardiovascular diseases, chronic kidney disease, chronic obstructive pulmonary disease, obesity, and type 2 diabetes mellitus.[11,12,13] Approximately 10% of people who recover from COVID-19 experience long-term symptoms lasting weeks or months. Symptoms experienced by “long haulers” include chronic and sometimes debilitating fatigue, myalgias and joint pain, headaches, and brain fog. Ongoing research is being conducted to better understand these long-term effects.[14]

Prevention of COVID-19: Inpatient Settings

Infection Prevention and Control (IPC)

Evidence supports and recommends several infection prevention and control measures in health care settings. For patients this entails universal use of personal protective equipment (PPE) with masks, face shields, or respirators to cover the nose and mouth, as well as physical distancing. For healthcare providers, IPC measures include universal PPE utilization with well-fitting N95 respirators or equivalent, or a well-fitting surgical mask, and eye protection.[15,16] Hand hygiene is also necessary, either with 60-95% alcohol-based hand sanitizer before and after every patient encounter, or with soap and water for at least 20 seconds if hands are visibly soiled.[17,18] Gloves and gowns are necessary during encounters with patients suspected or confirmed to have COVID-19. Healthcare personnel must wear N95(or higher-level) respirators, eye protection, gloves, and a gown during aerosol generating procedures such as endotracheal intubation/extubation, bronchoscopy, and cardiopulmonary resuscitation.[19]

Vaccines

In December 2020, the FDA issued an emergency use authorization (EUA) for two vaccines for the prevention of COVID-19. The two vaccines are manufactured by Pfizer/BioNTech and Moderna and are both messenger RNA (mRNA) based vaccines.[6,7] Following administration, the mRNA encodes for the SARS-CoV-2 spike protein, which the host cells will express. Thereafter, antibodies to the spike proteins will be produced.[20,21] These are considered inactive vaccines and can be safely administered to patients who are immunosuppressed though efficacy data in this population is lacking.[20,21] These vaccines are each two-dose series, separated by 21 days (Pfizer/BioNTech) or 28 days (Moderna). The Pfizer-BioNTech vaccine can be administered to people ≥12 years whereas the Moderna vaccine is limited to those ≥18 years. Efficacy rates for preventing COVID-19 illness are approximately 95% and protection is observed within seven days and two weeks following the second dose for the Pfizer/BioNTech and Moderna vaccines respectively.[20,21] Similar to other vaccines, the most common side effects include injection site pain, fatigue, headache, joint pain, and muscle pain.[20,21] While severe allergic reactions have been reported, these remain rare at rates less than 1%.[20,21] The logistical challenge posed by these mRNA vaccines is the ultra-low temperatures (-80 to -60°C for Pfizer-BioNTech) and cold chain requirement, which affects their storage, delivery, and stability.

At the end of February 2021, the FDA issued an EUA for the Johnson & Johnson's Janssen (J&J) COVID-19 vaccine in adults ≥18 years. Notable differences with this vaccine

include that it is a single dose, does not require ultra-low temperatures for storage, and it is the first viral vector COVID-19 vaccine available in the United States. The vaccine contains a recombinant adenovirus vector that expresses the SARS-CoV-2 spike protein. The immune system is expected to respond to this adenovirus vector. Efficacy rates for preventing COVID-19 illness are approximately 67% at 14- and 28-days post-vaccination. The vaccine appears effective at preventing severe disease across all age groups. While the adenovirus vector may be novel for some people, it may not be the case for all. In these cases, the efficacy may be diminished. Serious thrombotic events have been reported in the clinical trial.[22] While not currently available in the United States, the Astra Zeneca COVID-19 vaccine is another viral vector vaccine with reports of thrombotic events that led to the trials being halted in several European countries.[23] Further data are needed to better understand and compare between mRNA and viral vector vaccines. As with treatment options under investigation, it is also important to understand how effective these vaccines are against circulating virus variants.

With new variants of SARS-CoV-2 becoming prevalent around the world, including the B.1.1.7, B.1.351, P.1 and B.1.427/B.1.429 variants, there are concerns as to whether available vaccines will continue to be effective at preventing COVID-19 illness. In vitro data for both the Moderna and Pfizer vaccines against recombinant SARS-CoV-2 suggests effectiveness is maintained in these newer strains.[24,25] Additionally, the J&J vaccine trials were conducted in Brazil and South Africa when the P.1 and B.1.351 became prevalent and was shown to be efficacious in this setting.[23] Nonetheless, continued viral surveillance and vaccine studies are needed to appropriately assess continued effectiveness of currently available vaccines. Several other vaccine candidates including live attenuated vaccines and inactivated vaccines are in various stages of clinical trials.[23]

Outpatient COVID-19 Treatment: Early Administrations for Mild to Moderate Disease

SARS-CoV-2 Monoclonal Antibodies

Bamlanivimab (LY-CoV555) plus etesevimab (LY-CoV016), and casirivimab plus imdevimab (REGEN-COV) are two combination monoclonal antibody products administered as one-time intravenous infusions that have been authorized by the FDA for emergency use in non-hospitalized patients with mild to moderate COVID-19. Preliminary data have shown that these products decrease the number of emergency department visits or hospitalizations when administered immediately following a positive SARS-CoV-2 test result or within 10 days of symptom onset. The criteria for use are similar for both products and use is authorized in adults and pediatric patients ≥12 years old who weigh ≥40 kg with mild to moderate disease (i.e.,

commonly in outpatient settings) who are at high risk for progression to severe disease and/or hospitalization. Risk factors for worsening disease include age ≥65 years as well as several chronic conditions such as classes 2 and 3 obesity, chronic kidney disease, diabetes, and immunosuppressive disease or treatment, to name a few. Hypersensitivity and infusion-related reactions are common and therefore, patients must be monitored for at least an hour following the infusion. Supportive measures include stopping or slowing down the infusion rate and administering supportive medications (e.g., diphenhydramine, epinephrine).[26] Presently, the National Institutes of Health (NIH) treatment guidelines recommend the use of monoclonal antibodies to treat outpatients with mild to moderate COVID-19 who are at high risk of disease progression as defined above.[27]

Bamlanivimab and etesevimab

The Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies Trial (BLAZE-1) is an ongoing randomized, double-blind, placebo-controlled clinical trial designed to assess the safety and efficacy of bamlanivimab alone or bamlanivimab plus etesevimab for the treatment of symptomatic COVID-19 in the outpatient setting. In the phase 2/3 portion of the trial, 613 patients with laboratory confirmed mild to moderate COVID-19 infection were randomly assigned to receive an intravenous infusion of bamlanivimab in one of three doses (700 mg, 2800 mg, and 7000 mg), bamlanivimab 2800 mg plus etesevimab, or placebo. The primary outcome measured was the change from baseline in SARS-CoV-2 viral load at day 11 (±4 days) after positive testing results. When treated with bamlanivimab plus etesevimab, the SARS-CoV-2 viral load was associated with a statistically significant reduction when compared to placebo. No significant difference in viral load reduction was found for bamlanivimab monotherapy.[28]

Concerns with bamlanivimab resistance has emerged as circulating SARS-CoV-2 variants with amino acid substitutions in the spike proteins have shown resistance to certain monoclonal antibodies including bamlanivimab alone. The combination with etesevimab was granted EUA status in February 2021 and *in vitro* data has shown it to be effective against the B.1.1.7 variant (United Kingdom origin). However, this combination was less effective against the variants from South Africa (B.1.351), Brazil (P.1), California (B.1.427/B.1.429), and New York (B.1.526).[29] The phase 3 portion of BLAZE-1, comparing bamlanivimab 2800 mg plus etesevimab 2800 mg versus placebo and bamlanivimab 700 mg plus etesevimab 1400 mg versus placebo, is currently ongoing and measures the percentage of patients who experience COVID-19 related hospitalizations or all-cause mortality.[30]

Casirivimab and imdevimab (REGEN-COV)

The combination of casirivimab and imdevimab has been shown *in vitro* to retain its activity against the known variants circulating the world in spring of 2021.[31] It remains unknown if and how these *in vitro* data results correspond to clinical outcomes. Furthermore, it is possible for cross-resistance to occur wherein the variant can develop resistance to multiple monoclonal antibodies. Additional surveillance tracking and data are necessary, along with clinical data, to inform clinicians of the role of monoclonal antibodies in the treatment of mild to moderate COVID-19 cases.

Colchicine

The use of anti-inflammatory drugs may potentially mitigate or prevent inflammation associated with COVID-19 infection. Colchicine has several potential mechanisms of action that may decrease inflammation, such as reducing chemotaxis of neutrophils, inhibiting inflammasome signaling, and decreasing the production of cytokines. The Colchicine Coronavirus SARS-CoV-2 (COLCORONA Trial) is a randomized, double-blind, placebo-controlled trial that enrolled 4,488 patients with confirmed COVID-19 infection, who were not hospitalized, and had one risk factor for COVID-19 complication.[32] Subjects were randomized to receive either colchicine 0.5 mg twice daily for 3 days then once daily for 27 days or placebo. The primary outcome was a composite outcome of death or hospitalization due to COVID-19 infection 30 days after randomization. For those treated with colchicine, while there was a lower rate of composite death and hospitalization, the difference was not statistically significant compared to those treated with placebo. Additionally, participants in the colchicine group were more likely to experience diarrhea.[32] Currently, the NIH COVID-19 Treatment Guidelines states that there is insufficient evidence to recommend either for or against the use of colchicine for the treatment of non-hospitalized patients with COVID-19 infection.[1]

Inpatient COVID-19 Treatment Options: Early Administrations for Patients Requiring Supplemental Oxygenation

The NIH COVID-19 Treatment Guidelines recommend remdesivir, dexamethasone, or the combination of both in hospitalized patients who require supplemental oxygenation through non-invasive means (e.g., high-flow cannula, non-invasive ventilation). In the most severe cases wherein patients require mechanical ventilation or extracorporeal membrane oxygenation (ECMO), dexamethasone monotherapy is the only recommended drug for severe COVID-19

treatment. Of note, the combination of remdesivir and dexamethasone has not been studied in clinical trials. Furthermore, the NIH endorses the combination of baricitinib and remdesivir if corticosteroids cannot be given.[1]

Remdesivir (Veklury®)

On October 22, 2020, remdesivir became the first FDA-approved drug for use in adults and children ≥12 years old and weigh ≥40 kg hospitalized with COVID-19. Remdesivir is currently authorized for emergency use in hospitalized pediatric patients <12 years old and weight >3.5 kg. In the early stages of SARS-CoV-2 infection, the pathogenesis involves rapid viral replication and its associated acute respiratory symptoms. Therefore, antiviral therapies like remdesivir are likely to have the greatest effect when administered earlier on.[1] Remdesivir, marketed under the brand name Veklury®, is an injectable antiviral drug developed by Gilead Sciences. Remdesivir is a nucleotide analog RNA polymerase inhibitor that was identified as a potential antiviral against SARS-CoV-2 because of its *in vitro* activity against SARS-CoV-1 and MERS-CoV.[33] The recommended dosage for patients who do not require mechanical ventilation nor ECMO is a single loading dose of 200 mg administered intravenously on day 1 followed by daily intravenous administrations of 100 mg on days 2-5. Treatment may be extended by five days for a 10-day course in patients who do not clinically respond. The treatment course is 10 days for patients requiring mechanical ventilation or ECMO.[34]

Several randomized controlled trials have been conducted to determine the efficacy of remdesivir alone, in combination with other therapies, optimal treatment duration, and safety outcomes. The Adaptive COVID-19 Treatment Trial (ACTT-1) was a multinational, phase 3 randomized, double-blind, placebo-controlled clinical trial that enrolled more than 1,000 adults hospitalized with mild, moderate, and severe COVID-19 between February and April 2020.[33] A total of 541 subjects were randomized to the remdesivir arm and 521 subjects to the placebo arm. Subjects were required to have evidence of lower respiratory tract infection either through radiographic imaging, low oxygen saturations, or supplemental oxygen requirements. Disease severity was determined by various respiratory status indicators. Mild/moderate disease was defined as oxygen saturation via pulse oximetry of >94% on room air and respiratory rate <24 breaths/minute. Approximately 10% of subjects had mild/moderate disease with an equal distribution in both study groups. Severe disease was defined as oxygen saturation ≤94% on room air, respiratory rate ≥24 breaths/minute, supplemental oxygen requirement, or mechanical ventilation requirement. The majority of subjects (90%) had severe disease.

The primary outcome was the time to recovery within 29 days following randomization. Recovery was assessed daily using an eight-category ordinal scale previously proposed for influenza treatment trials.[35] The eight categories (Table 1) ranged from discharged and able to resume daily activities to death. Recovery was defined as the first day when a subject met criteria for categories 1, 2, or 3. There were many secondary outcomes and key ones included clinical status at day 15 (assessed via the ordinal scale), time to improvement, changes in the National Early Warning Score (NEWS), time to hospital discharge, length of hospital stay, and mortality at 14- and 28-days following enrollment. The median time to recovery was significantly shorter at 10 days in the remdesivir arm compared to 15 days in the placebo arm. Subgroup analyses showed that subjects with severe disease experienced significantly shorter time to recovery (11 versus 18 days in the remdesivir and placebo arms, respectively). While time to recovery was shorter in the remdesivir arm for subjects with mild/moderate disease, these results were not statistically significant. Similarly, mortality rates at day 15 were nearly halved in the remdesivir arm (6.7% versus 11.9% for placebo), but these results were not statistically significant. Rates of adverse effects were similar in both arms and included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine, and increased blood glucose. The authors concluded that remdesivir was superior to placebo in shortening the time to recovery for adults hospitalized with COVID-19.[33]

The results of this trial formed the basis of the clinical evidence for FDA approval of remdesivir. This drug is recommended for COVID-19 treatment in hospitalized patients requiring supplemental oxygen.[1,33] However, it is not recommended for patients requiring mechanical ventilation due to the lack of data demonstrating benefit for these more severe cases.

While the ACTT-1 trial treated subjects with a 10-day course of remdesivir, there is a need to identify the shortest duration of effective treatment.[33] In addition to limiting adverse effects associated with remdesivir, identifying a shorter duration of therapy may reduce hospital length of stay and preserve the supply of remdesivir available.[36] The SIMPLE trial is a phase 3 randomized open-labeled study that evaluated the efficacy and safety of remdesivir treatment for five or 10 days in patients with severe COVID-19 infection. The primary outcome was clinical status at day 14, assessed on a seven-point ordinal scale. While overall, the patients in the 10-day group had worse clinical status than those in the 5-day group, this trial did not show a significant difference in clinical improvement between the two treatment courses.[1,33] A second SIMPLE trial will evaluate the safety and efficacy of five-day and 10-day dosing compared to standard of care therapy.[37]

Dexamethasone

Administration of dexamethasone in hospitalized patients requiring supplemental oxygen can decrease mortality, especially among patients requiring mechanical ventilation. The dexamethasone dose is 6 mg daily and can be administered either parenterally or enterally for 10 days or until hospital discharge. Equivalent doses of other corticosteroids may be considered during dexamethasone drug shortages.[38]

Anticoagulation

Patients with COVID-19 are also at high risk for developing a venous thromboembolism (VTE). The cause of hypercoagulability is not fully understood, but increased release of inflammatory mediators, endothelial damage, and dysregulation of fibrinolysis are implicated.[39] Current guidelines from the NIH, the American Society of Hematology (ASH), and the American College of Chest Physicians (CHEST) all favor VTE prophylaxis over no prophylaxis in hospitalized patients with COVID-19 who have no contraindication to prophylactic anticoagulation.[40,41,42] Evidence for the efficacy of prophylactic anticoagulation is mixed. Meta-analyses showed no effect on mortality for hospitalized patients with COVID-19 who received anti-coagulation compared to those who did not.[43,44] A recent cohort study, however, showed early initiation of prophylactic anticoagulation was associated with reduced mortality in hospitalized patients with COVID-19 compared to those who received late or no anticoagulation.[45] There is a lack of good quality evidence comparing different anticoagulation strategies and their effects on clinical outcomes in patients with COVID-19, though several RCTs including the REMAP-CAP, ACTIV-4, and ATTACC studies hope to shed light on this topic.[40] As data is still being collected, it is important to review the most current evidence and refer to guidelines from reliable organizations such as NIH, ASH, and CHEST.

Conclusion

As the COVID-19 pandemic evolves and new literature is published, the treatment considerations presented in this article will likely change. Therefore, it is crucial for healthcare professionals to refer to reputable resources such as COVID-19 treatment guidelines published by the NIH and Infectious Diseases Society of America, as well as FDA alerts regarding Emergency Use Authorization products. While effective treatments have been identified for certain disease severities, and vaccines may be effective at preventing severe disease, there remains many knowledge gaps that are currently being evaluated and addressed. Trials such as

the ACTT-3, ACTT-4, SIMPLE2, and WHO SOLIDARITY should provide clarity and guidance to further improve the management of COVID-19.

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