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Current Therapeutics Effective against SARS-CoV-2 Omicron Sub-Variants

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Abstract

Severe acute respiratory syndrome coronavirus 2 that causes coronavirus disease 2019 (COVID-19) is changing at a rapid pace due to accumulated mutations in the viral genetic code over time. As new variants of the virus continue to emerge and replace previous versions of the variants, therapeutics and vaccines are being constantly monitored and reviewed for their efficacy against the new strains. With the surge in new omicron sub-variants across the nation, U.S. Food and Drug Administration issued emergency use authorization to a new monoclonal antibody therapy called bebtelovimab replacing the previous sotrovimab that was effective against Omicron BA.1. The main objective of the paper is to review the current treatment options available to treat non-hospitalized mild-to-moderate COVID-19 caused by the new omicron sub-variants BA.2, BA.4, and BA.5. Scientists, pharmaceutical companies, and researchers have been proactive in conducting randomized, double-blinded, placebo-controlled clinical trials to test the safety and efficacy of therapeutics in managing COVID-19 in addition to testing the vaccine efficacy against new strains. The paper focuses on reviewing the results of these randomized controlled trials. The oral antiviral options paxlovid and molnupiravir, and intravenous (IV) bebtelovimab continue to show their efficacy against the new sub-variants BA.4 and BA.5. It is important for everyone to stay well-informed of the new treatment options and only opt for those medications that are currently authorized for use in treating mild-to-moderate COVID-19.

Keywords: SARS-CoV-2, COVID-19, omicron, sub-variant, therapeutics, antivirals, paxlovid, molnupiravir, bebtelovimab.

INTRODUCTION

The world has seen a massive spike in coronavirus disease (COVID-19) cases in the recent times due to the emergence of novel variants delta and omicron and their sub-variants. Globally as of April 2022, around 497 million confirmed cases of COVID-19 and more than 6.2 million deaths have been recorded (World Health Organization [WHO], 2022). COVID-19 classified as an infectious disease is known to be caused by a virus termed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (WHO, n.d.). The first ever COVID-19 disease outbreak was reported in Wuhan, China in December 2019 which then rapidly started to spread its wings across other countries (Holshue *et al.*, 2020). The World Health Organization (WHO) professed COVID-19 outbreak as a global pandemic in March 2020 (Cucinotta, 2020). The SARS-CoV-2 virus spreads from an infected person to others through respiratory droplets (e.g., when an infected person coughs, sneezes, sings, or speaks) which is the main route of transmission (WHO, n.d.). The severity of illness can be categorized based on the symptoms as asymptomatic, mild illness, moderate illness, and severe illness (National Institute of Health [NIH], 2022a). The individuals infected with the virus experience mild-to-moderate respiratory illness like fever, cough, sore throat, and chills and generally get well without the necessity for any special treatment (Wu *et al.*, 2020). But this isn't the case with everyone; some might experience serious illness needing medical attention or hospitalization. Those who are at higher risk for developing serious illness are older adults and people with underlying medical conditions such as cancer, chronic heart disease, chronic lung disease, chronic kidney disease, HIV, diabetes, and immunocompromised status such as chemotherapy,

organ transplant etc. (Centers for Disease Control and Prevention [CDC], 2022a). A significant percent with COVID-19 develop critical illness like acute respiratory distress syndrome or respiratory failure requiring in-patient intensive care support either via mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (Bartlett *et al.*, 2020). These events can often be life- threatening, with the potential for immediate death (Elezkurtaj *et al.*, 2021).

The SARS-CoV-2 virus is evolving incessantly as a result of genetic mutations that take place during genome replication. Though mutations occur frequently, characteristics of the virus change only at certain times (CDC, 2022b). While some variants emerge and replace previous variants, some emerge and disappear without increased or continued spread. Mutations in the virus spike protein may increase the rate of transmissibility and severity of the disease which can have a noticeable impact on the response rate of vaccines and therapeutics resulting in vaccine breakthrough infections (CDC, 2022c). SARS-CoV-2 has many lineages, all of which cause the COVID-19 disease. A lineage is referred to as a group of closely related viruses that belong to a common ancestor. A variant on the other hand is a viral genome that can have single or multiple mutations. CDC makes use of the genomic surveillance to identify and track the variants of SARS-CoV-2 (CDC, 2022c). Multiple variants of the SARS-CoV-2 virus have been reported globally since 2019. A US government interagency group (SIG) established a variant classification scheme that classifies the variants into four different classes namely variant being monitored (VBM), variant of interest (VOI), variant of concern (VOC), and variant of high consequence (VOHC) (CDC, 2022c). Delta (B.1.617 and AY lineages) and Omicron (B.1.1.529; BA.1, BA.1.1, BA.2, BA.3, BA.4, BA.5 lineages) have been classified as variants of concern till date (CDC, 2022d). All the Omicron subvariants share around 39 mutations in the spike protein, with BA.2 carrying 27 additional mutations and 10 unique mutations. Omicron BA.2 has a higher transmissibility rate compared to BA.1 (Callaway, 2022). BA.4 and BA.5 are more similar to BA.2 with unique mutations in the spike protein (Callaway, 2022). Currently, BA.4 and BA.5 are the new subvariants of Omicron that are taking over the dominant status over Omicron BA.2 and Delta in United States as well many countries across the globe (Callaway, 2022).

Many pharmaceutical companies have developed COVID-19 vaccines and boosters to prevent severe illness, hospitalization, and death. While Pfizer-BioNTech and Moderna vaccines received FDA approval, Janssen vaccine is available under EUA for prevention of COVID-19 (US Food and Drug Administration [FDA], 2022a). But vaccines are not 100% effective; they limit the spread of virus and provide maximum protection needed to fight serious illness and death from COVID-19 (CDC, 2022e). Unvaccinated, partially vaccinated, and even fully vaccinated people can become infected with the virus again and experience illness if the body elicits a weaker immune response (CDC, 2022e). In addition to vaccines, those infected with the virus, having mild-to-moderate symptoms with comorbidities and immunocompromised, need medications to stop the progression to severe disease.

MATERIALS AND METHODS

Effective therapeutic options are necessary because of constant viral mutations, accessibility and availability of vaccines, waning of vaccine protection, and hesitancy of the public to get vaccinated. Researchers and pharmaceutical companies have been working relentlessly to identify the variant of concern, research, and develop drugs that prevent the progression of mild-to-moderate COVID-19 to serious illness with the intent to decrease COVID-19 related hospitalization and mortality rates. Various therapeutic options have now become available for treating non-hospitalized adults with mild-to-moderate symptoms of COVID-19 and who are at high risk of progression to severe illness (US Department of Health and Human Services [HHS], 2022a). These include oral and IV options (Fig.1). Oral therapeutics include paxlovid (ritonavir-boosted nirmatrelvir) and molnupiravir. IV therapeutics include remdesivir and monoclonal antibody (mAb) bebtelovimab. All these therapies have found to be effective against the omicron sub-variants (CDC, 2022f). This therapeutics hinders viral replication and propagation either by lethal mutagenesis, by limiting activity of viral proteases, or by blocking virus from entering the cell (HHS, 2022a).

There are a multitude of factors that need to be considered when selecting a treatment option for each individual patient. Some of these factors include clinical efficacy of the drug, availability of the drug, potency of the drug against the specific variant prevalent in the region (e.g., the presence of Omicron sub-variant may impact the use of monoclonal antibody therapy prescribed for the patient), feasibility of administering oral or parenteral medications (e.g., paxlovid, molnupiravir, monoclonal antibody, remdesivir), significant drug-drug interactions (e.g., paxlovid has many drug interactions that need to be considered before prescribing), and clinical condition of the patient (e.g., monoclonal antibodies are not prescribed for a patient admitted to hospital and needing oxygen above baseline) (NIH, 2022b). The main objective of this paper is to provide a review of the preferred therapeutic options and alternate therapies available to treat all omicron subvariants that are currently prevalent. The literature review includes valuable information such as safety and efficacy of drugs with supporting outcome data from randomized clinical trials.

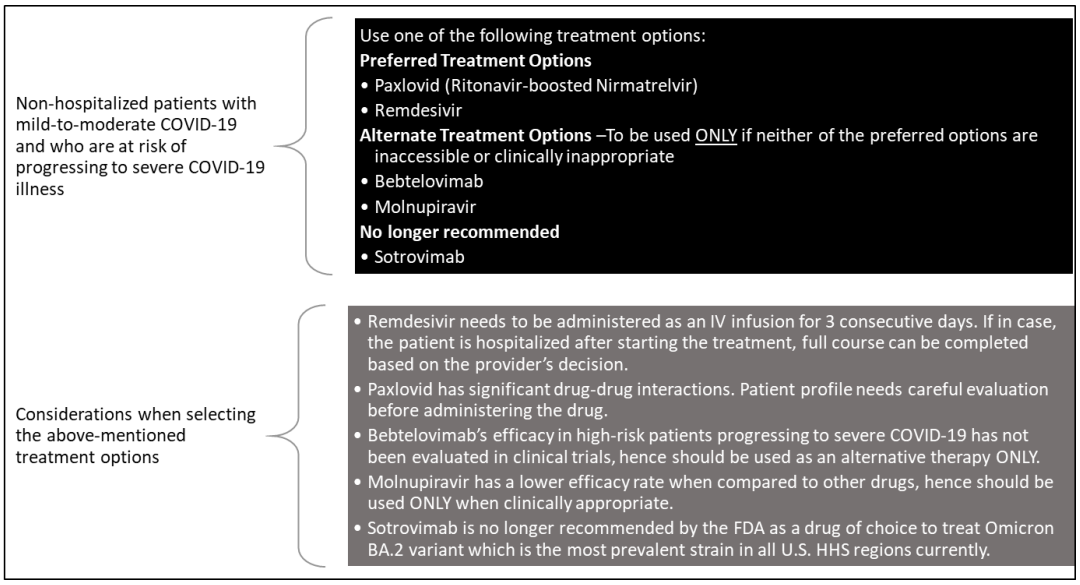

Fig. 1: Antiviral Options in managing non-hospitalized adults with mild-to-moderate COVID-19

COVID-19 Coronavirus Disease 2019, *IV* Intravenous, *FDA* Food and Drug Administration, *US* United States, *HHS* Health and Human Services

*****The above data is current based on FDA and NIH reports (NIH, 2022b)

RESULTS AND DISCUSSION

Remdesivir

Remdesivir was one of the first IV drugs approved for use in inpatient settings by the FDA to treat hospitalized patients with severe COVID-19 and results from clinical trials have demonstrated an improved recovery rate (Beigel *et al.*, 2020). It was also found to be safe and effective in treating outpatients based on the clinical trial data published by Gottlieb *et al.*, in November 2021 and was approved by FDA as an alternate therapy to paxlovid. Remdesivir can be administered as an IV infusion for duration of 3 days in non-hospitalized patients with mild-to-moderate COVID-19 symptoms with higher risk of progressing to severe illness or death. For adults and pediatric patients aged 12 years or older and weighing at least 40kg, it is given at a dosage of 200mg IV on day 1 followed by a dosage of 100 mg on day 2 and day 3 (Veklury, 2020). Remdesivir, a nucleotide prodrug acts directly by inhibiting the SARS-CoV-2 virus RNA- dependent RNA polymerase, which is critical for viral replication to take place and hence the production of virions that freely circulate in the host body. When the prodrug is distributed into cells, it gets metabolized to an active form called remdesivir triphosphate which acts as an analog to ATP. It gets incorporated into emerging viral RNA resulting in delayed chain termination ultimately disrupting the replication of viral RNA (Veklury, 2020). Remdesivir also exhibits powerful nanomolar activity in the epithelial cells of human airways (Pizzorno *et al.*, 2020).

Gottlieb *et al.*, conducted a phase 3 (NCT04501952), randomized, double-blinded, placebo-controlled study to evaluate the efficacy and safety of remdesivir in treating patients with COVID-19 in outpatient settings (Gottlieb *et al.*, 2022; NIH, 2021). It was conducted on non-hospitalized patients aged 12 years or older and with at least one risk factor for progressing to severe disease and had symptoms within 7 days of symptom onset. Those hospitalized and receiving supplemental oxygen, those with previous history of COVID-19, or those who received COVID-19 vaccine were excluded from the study. As part of the trial, 584 non-hospitalized, non-vaccinated patients with confirmed SARS-CoV-2 infection and symptoms were randomly selected to receive either remdesivir (n=292) or placebo (n=292). 22 of these patients were excluded from the efficacy and safety analyses since they did not receive an infusion. Of the remaining 562 patients, 279 received 200 mg remdesivir on day 1 and 100 mg on the next days 2 and 3, and 283 of them received placebo (Gottlieb *et al.*, 2022; NIH, 2021a). The primary efficacy outcome measure was to evaluate the percent of COVID-19 related hospitalization or death by day 28 and it was found to be significantly lower in remdesivir group (0.7%) when compared to the placebo group (n=5.3%). The primary safety outcome measure which was to determine the occurrence of adverse events was lower in the remdesivir group (42.3%) when compared to the placebo group (46.3%) (Gottlieb *et al.*, 2022). None of the patients died through day 28. The secondary outcome measure that intended to evaluate the COVID-19 related medical visit or death by day 28 was found to be lower in the remdesivir group (1.6%) than the placebo (8.3%) (Gottlieb *et al.*, 2022). In summary, a 3-day IV course of remdesivir in non-hospitalized patients with mild-to-moderate symptoms was found to reduce the risk of hospitalization or death by 87% when compared with those who received

placebo. In vitro data has confirmed that remdesivir is effective against omicron variant (Vangeel *et al.*, 2022).

Oral Antivirals

Though remdesivir is shown to have a proven efficacy in non-hospitalized patients, limitations exist with this IV route of administration such as limited access to the drug, a required visit to the hospital, staffing shortage, IV supplies etc. (Kunal *et al.*, 2022). In December 2021, FDA granted EUA for two oral antiviral drugs called paxlovid (nirmatrelvir tablets co-packaged with ritonavir tablets) and molnupiravir (FDA, 2021). To date, Paxlovid and Molnupiravir have been the first oral pills authorized for the treatment of COVID-19 (FDA, 2021).

Paxlovid

Paxlovid (Ritonavir-Boosted Nirmatrelvir) developed by Pfizer Inc. laboratories has not been officially approved but has been granted EUA by FDA in December 2021 (FDA, 2021). It includes a SARS-CoV-2 main protease inhibitor called nirmatrelvir and a HIV-1 protease inhibitor called ritonavir. Paxlovid is used for treating mild-to-moderate COVID-19 in adults and pediatric patients (aged 12 years or older and weighing at least 40kg) with positive SARS-CoV-2 results, within 5 days of symptom onset and as soon as possible after the diagnosis, and who are at high risk of progressing to severe illness, hospitalization, or death. Paxlovid is usually administered orally at a dosage of 300 mg nirmatrelvir (2 tablets each 150mg) with 100mg ritonavir (1 100mg tablet) twice a day for 5 days. Dose reduction to 150mg nirmatrelvir with 100mg ritonavir is needed in patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥30 to <60 mL/min) (FDA, 2022b). Paxlovid is not recommended in patients with severe renal impairment (eGFR value is below 30ml/min) and severe hepatic impairment (Child-Pugh Class C) (NIH, 2022c; FDA, 2022b). Paxlovid has the potential to result in significant drug-drug interactions mainly because of the ritonavir component. The reason why a patient's medical profile and medication lists need a careful review by the clinicians before prescribing (NIH, 2022c; FDA, 2022b).

Paxlovid was particularly designed to retain its activity against various variants of coronavirus that predominantly have mutations in their spike proteins. Nirmatrelvir is a protease inhibitor that acts by inhibiting SARS- CoV-2 main protease (Mpro) which plays a critical role in virus replication (FDA, 2022b; Pfizer, 2022). The resulting inhibition of Mpro makes the virus incapable to process viral polyprotein precursors thereby preventing viral replication. Ritonavir on the other hand, is a HIV-1 protease inhibitor that acts by inhibiting the cytochrome P450 CYP3A-facilitated metabolism of nirmatrelvir, boosting plasma concentrations of nirmatrelvir to the target therapeutic range (FDA, 2022b; Pfizer, 2022). Using other medications alongside paxlovid that either inhibit or induce CYP3A might decrease or increase paxlovid concentrations to a significant extent which can lead to adverse reactions or fatal events (FDA, 2022b).

Paxlovid received FDA EUA based on the results of EPIC-HR (NCT04960202), which was a phase 2/3, randomized, double-blinded, and placebo-controlled study (Hammond *et al.*, 2022; NIH, 2021b; Pfizer, 2021). It was conducted on adults 18 years and above, with confirmed SARS-CoV-2 infection who did not require any kind of hospitalization and had at least one risk factor for progressing to severe disease and had symptoms within 5 days of onset. As part of the study, 2,246 non-hospitalized, non-vaccinated, adults with confirmed SARS-CoV-2 infection and symptoms were randomly selected to receive either paxlovid (n=1,039) at a dosage of 300mg/100mg or placebo (n=1,046) orally for 5 days taken every 12 hours (Hammond *et al.*, 2022; NIH, 2021b; Pfizer, 2021). 66% of the subjects had symptoms that started within 3 days from the initiation of treatment. The subjects enrolled in the study had no history of infection with COVID-19. The analyses included subjects that did not receive any kind of COVID-19 monoclonal antibody treatment at baseline. 6% of the subjects were excluded from the analyses as they were expecting to receive monoclonal antibody therapy. The clinical trial's main intent was to determine the percent of subjects who were admitted to the hospitals due to COVID-19 or who died through day 28. The efficacy results indicate that paxlovid significantly reduced the COVID-19 related hospitalization or death rate by 89% in subjects within 3 days of symptom onset and by 88% in subjects within 5 days of symptom onset when compared with placebo (Hammond *et al.*, 2022; NIH, 2021b; Pfizer, 2021). COVID-19 related hospitalization or death that resulted from any cause during the 28-day period was around 0.8% in subjects who received paxlovid while higher (6.3%) in the placebo group. In addition, viral load appeared to reduce by nearly 10-fold when compared to placebo. No subject died due to Paxlovid by day-28, while 12 (1.1%) subjects died in the placebo group. The primary SARS-CoV-2 variant that was common among all the treatment subjects was the Delta (98%) (Hammond *et al.*, 2022; NIH, 2021b; Pfizer, 2021). In summary, paxlovid was found to be significantly effective in reducing the hospitalization risk in unvaccinated subjects who were at high risk for progressing to severe illness. Paxlovid is found to show its antiviral activity against all variants of concern including the prevalent omicron sub-variants (CDC, 2022f). Recently, there have been reports of COVID-19 rebound following treatment with Paxlovid. CDC Health Alert Network (HAN) released a guidance for clinicians stating that the return of symptoms for a brief period could be attributed to a natural history of COVID-19 infection in few people and is independent

of treatment with Paxlovid irrespective of the vaccination status (CDC, 2022f).

Molnupiravir

Molnupiravir developed by Merck & Co. Inc. is the first oral antiviral drug that received FDA EUA in December 2021 (NIH, 2022d). Molnupiravir is used for treating mild-to-moderate COVID-19 in adults with positive SARS-CoV-2 results, within 5 days of symptom onset and as soon as possible after the diagnosis, and who are at high risk for progression to severe illness, hospitalization, or death. Molnupiravir is usually administered orally at a dosage of 800 mg (4 capsules each 200mg) every 12 hours for 5 days (NIH, 2022b; FDA, 2022c). Due to its lower antiviral efficacy when compared to other therapeutic options, it is prescribed only if alternate COVID-19 treatments authorized by FDA are inaccessible or inappropriate. It is not authorized for use in pregnancy due to risk of embryo-fetal toxicity and in patients aged 18 years or less due its impact on bone and cartilage growth (NIH, 2022b; FDA, 2022c). No specific drug-drug interactions have been documented based as per the limited clinical data available (NIH, 2022b; FDA, 2022c).

Molnupiravir is a prodrug that exhibits antiviral activity against the virus SARS-CoV-2 through a mechanism called viral lethal mutagenesis (Kabinger *et al.,* 2021). It interrupts the process of replication or production of new viruses by causing a change in the viral code. Molnupiravir acts by metabolizing to an analogue of ribonucleoside, beta- D-N4-hydroxycytidine (NHC) that closely resembles cytidine (NIH, 2022d; FDA, 2022c; Kabinger *et al.,* 2021). The NHC that is distributed to cells is phosphorylated to active ribonucleoside triphosphate, NHC-TP, the incorporation of which into the viral RNA via viral RNA polymerase results in errors in viral genome thereby inhibiting the process of replication (FDA, 2022c; Kabinger *et al.,* 2021).

Molnupiravir received FDA EUA based on the results of MOVe-OUT (NCT04575597), which was a phase 2/3, randomized, double-blinded, and placebo-controlled study (Jayk Bernal *et al.,* 2022). It was conducted on adults 18 years and older with mild to moderate symptoms of COVID-19 within 5 days of onset and at least one risk factor for severe illness from COVID-19. Those subjects that needed hospitalization in the next 48 hours, those on dialysis or eGFR less than 30ml/min, immunosuppressive conditions, and history of hepatitis B or C with cirrhosis, end-stage liver disease, hypersensitivity, neutropenia, pregnancy, and lower platelet count were excluded from the study (Jayk Bernal *et al.,* 2022). As part of the study, 1,433 non-hospitalized, non-vaccinated, adults with confirmed SARS-CoV-2 infection and symptoms were randomly selected to receive either molnupiravir (n=709) or placebo (n=699) at a dosage of 800mg twice orally for 5 days taken every 12 hours (Jayk Bernal *et al.,* 2022). The clinical trial's primary intent was to determine the percent of subjects who were admitted to the hospitals due to COVID-19 or who died through day 29. The risk of hospitalization or death due to any cause through day 29 was 7.3% in subjects who received molnupiravir while higher (14.1%) in the placebo group. The percentage of those who were hospitalized or died due to any reason through day 29 appeared to be lower (6.8%) in the subjects who received molnupiravir than the placebo group (9.7%) (Jayk Bernal *et al.,* 2022). The time to event analysis indicates that molnupiravir decreased the COVID-19 related hospitalization and death through day 29 by 31% in those who took molnupiravir than placebo. There was also a significant reduction in baseline viral mRNA when compared to placebo at days 5 and 10. 1 subject died due to molnupiravir by day-29, while 9 subjects died in the placebo group (Jayk Bernal *et al.,* 2022). In summary, it was found that the risk of hospitalization or death in high-risk unvaccinated adults with confirmed COVID-19 was significantly lower when treated early with molnupiravir. In a study conducted by Zou *et al.,* (2022) 147 patients with COVID-19 were randomized to receive molnupiravir (n=80) and control (n=36). Following exclusions, 77 of them received 800mg molnupiravir twice daily for 5 days and 31 were in the control group (Zou *et al.,* 2022). Treatment with molnupiravir was found to significantly reduce the viral load in collected pharyngeal swabs. It was effective in treating the prevalent Omicron sub-variants (Zou *et al.,* 2022).

Monoclonal Antibodies

Antibodies in general are produced in the body to fight infection. They play a key role by blocking the virus from entering the cell (Arribas *et al.,* 2022). Lack of antibodies or lower immunity makes it easy for the virus to enter the cells and cause infection. Monoclonal antibodies also called mAbs are antibodies that are produced in the laboratory and infused intravenously into a patient helping the body fight infection (Arribas *et al.,* 2022). Monoclonal antibodies are being studied to evaluate their efficacy in treating and preventing COVID-19. To date, FDA authorized EUA for many investigational mAbs both for pre-exposure prophylaxis and managing post-exposure mild-to-moderate COVID-19 based on their clinical trial potency against a virus strain (Mornese Pinna *et al.,* 2021). These include casirivimab and imedevimab, bamlanivimab and etesevimab, sotrovimab, tocilizumab, and bebtelovimab (Mornese Pinna *et al.,* 2021). Due to the increased frequency of omicron sub-variants BA.2, BA.4, and BA.5 in U.S. HHS regions, casirivimab and imedevimab, bamlanivimab and etesevimab, and sotrovimab are no longer authorized for post-exposure prevention of COVID-19 until further notice by the FDA. Tixagevimab together with cilgavimab is being used for pre-exposure prophylaxis and is found to be

potent enough against new sub-variants (Mornese Pinna *et al.*, 2021).

Sotrovimab

Sotrovimab received FDA EUA based on the results of COMET-ICE (NCT0454060), which is a phase 1/2/3, randomized, double-blinded, and placebo-controlled study (US Centers for Medicare and Medicaid Services [CMS], 2022; NIH, 2022; Gupta *et al.*, 2022). In summary, the outcome measures of the trial indicate that a single IV dose of sotrovimab has the potential to reduce the risk of progression to severe disease in patients with mild-moderate COVID- 19 symptoms (CMS, 2022; NIH, 2022; Gupta *et al.*, 2022). Sotrovimab was found to be effective against Delta (B.A.617.2, AY.1/AY.2 lineages) and Omicron (B.1.1.529/BA.1) but not Omicron BA.2 sub-variant (Gupta *et al.*, 2022).

CDC has been making use of the viral genomic surveillance for tracking COVID-19 variants. A new sub-variant of Omicron called the BA.2 was first identified in U.S in December 2021 (FDA, 2022d). FDA updated the sotrovimab EUA on April 5, 2020, that it is no longer authorized for treating COVID-19 cases in any of the U.S. HHS regions due to spike in COVID-19 cases caused by the BA.2 sub-variant (CDC, 2022g). Data in the FDA issued fact sheet for health care providers indicate that the current approved dose of sotrovimab is unlikely to show its potential and has a lower neutralizing power against BA.2 sub-variant (Gupta *et al.*, 2022). In a study published on BioRxiv, the researchers tested a panel of 19 monoclonal antibody treatments that mainly target the virus spike protein against all the Omicron sub- variants (FDA, 2022e). The results revealed that 17 out of the 19 antibody treatments failed to show neutralizing capacity or had impaired neutralizing effects against the BA.2 variant. Unfortunately, sotrovimab was one among the panel that failed to show its efficacy against BA.2 (FDA, 2022e). Several states across the U.S. started to see a decline in BA.2 cases. As of July 2022, the new sub-variants of Omicron called BA.4 and BA.5 became the dominant strains rapidly transmitting across all parts of United States. BA.4 and BA.5 currently make up 53.6% and 16.5% of all cases across the country. The two sub-variants tend to have mutations that are closely linked to escaping immunity (Schnirring, 2022).

Bebtelovimab

Sotrovimab, the monoclonal antibody which was found to be effective against Omicron BA.1 variant, was found to be ineffective against the other sub-variants of Omicron (FDA, 2022f). Bebtelovimab is used for treating mild-to- moderate COVID-19 in adults and pediatric patients (aged 12 years or older and weighing at least 40kg) with positive SARS-CoV-2 results and who are at high risk for progression to severe illness, hospitalization, or death (FDA, 2022f). Bebtelovimab is administered at the earliest possible usually immediately after a positive test result and within 7 days of symptom onset, intravenously at a dosage of 175 mg over at least 30 seconds and monitored for an hour for any infusion reactions. It is contraindicated in patients who require increased baseline oxygen flow rate and in those who are hospitalized requiring respiratory support (FDA, 2022f). Bebtelovimab provides passive immunity to the human antibodies protecting oneself from the virus effects. It is a recombinant neutralizing human IgG1gamma mAb that acts by binding the spike protein to a dissociation constant Kd, blocking the attachment of viral spike protein to the human angiotensin converting enzyme 2 (ACE2) receptor, thereby preventing the virus from entering the target cells (FDA, 2022f).

Bebtelovimab received FDA EUA recently based on the results of BLAZE-4 trial (NCT04634409), which is a phase 2, randomized, single-dose, and placebo-controlled study (FDA, 2022g; NIH, 2022e; Kreuzberger *et al.*, 2021). The study evaluated the efficacy of bebtelovimab in treating non-hospitalized adults with mild to moderate COVID-19 symptoms. Bebtelovimab was assessed alone and together with bamlanivimab and etesevimab in low-risk adults those that were not at high-risk of progressing to severe illness and were compared to placebo control arm, and in high-risk adults and pediatric subjects (aged 12 years and older weighed at least 40kg) who received open label active treatment (FDA, 2022g; NIH, 2022e; Kreuzberger *et al.*, 2021). Due to the availability of other therapeutic options, a placebo control arm was not employed to be used to treat high-risk patients. In the placebo-controlled portion (includes low-risk subjects), 127 received 700mg bamlanivimab, 1400mg etesevimab, and 175mg bebtelovimab together; 125 received 175mg bebtelovimab alone; and 128 received placebo. In the open-label randomized portion (includes high-risk subjects), 50 received 700mg bamlanivimab, 1400mg etesevimab, and 175mg bebtelovimab together and 100 received 175mg bebtelovimab alone. In the open-label non-randomized portion (includes high-risk subjects), 176 received 700mg bamlanivimab, 1400mg etesevimab, and 175mg bebtelovimab together [48, 49, 50]. The data from BLAZE-4 trial indicate that bebtelovimab improved symptoms in subjects with confirmed mild-to-moderate COVID-19. In addition, a significant reduction in viral load was observed on day 5 when compared to placebo (FDA, 2022g; NIH, 2022e; Kreuzberger *et al.*, 2021). In summary, bebtelovimab may be beneficial for the treating patients with mild-to-moderate COVID-19 to decrease the severity or risk of progression to hospitalization or death (FDA, 2022g). Though it was found to be active in vitro against all the circulating subvariants of Omicron, there isn't enough data to show its clinical efficacy from placebo-controlled trial in high-risk

patients (NIH, 2022b). Therefore, bebtelovimab should only be considered as a preferred treatment option in those patients for whom alternate treatment options authorized by FDA are deemed clinically inappropriate (NIH, 2022b).

CONCLUSION

Data from the clinical trials indicate that early treatment with antivirals have the potential to result in a significant reduction in the hospitalization and mortality rates in unvaccinated and low-immunity adults with mild-to- moderate COVID-19. It is critical for clinicians and pharmacists to stay abreast on the drug therapies approved for specific variants and cautiously prescribe medications only after thoroughly reviewing a patient's profile. Indiscriminate use of drugs that are not authorized for use or that lack efficacy and safety evidence should be strongly discouraged.

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Conflicts of Interest/Competing Interests

The author declares no relevant financial or non-financial interests to disclose related to the work submitted. The corresponding author (the only author for this paper) states that there is no conflict of interest.

Ethical approval

This is a review paper that does not contain any human or animal studies performed by the author. The author has confirmed that no ethical approval is required.

Consent to participate

This is a review paper and did not require any form of informed consent.

Consent to publish

The author confirms that informed consent is not applicable for this review paper.

Availability of data and material

Since this paper is a review, data is obtained from recent literature and clinical controlled trials.

Code availability

The author did not make use of any software application or custom code for the paper.

Author Contributions

Mounica Soma contributed her work for all sections of the manuscript that includes design, conception, writing, draft preparation, literature search, review, and editing. Mounica Soma read and approved the final version of the manuscript.

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