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Letter to the Editor

Molnupiravir: a new hope in the treatment of COVID-19

Sir,

Coronavirus disease-19 (COVID-19), a highly contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been causing pandemic since its first emergence in Wuhan, China in December 2019.[1] Most of the people with COVID-19 experience mild to moderate respiratory illness and recover without requiring special treatment. The common presentations of the disease include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting and diarrhea.[2] However, upto 20% patients develop severe disease requiring hospitalization.[3] Older adults and people with underlying medical conditions like heart or lung disease or diabetes are at higher risk for developing more serious complications such as pneumonia, acute respiratory distress syndrome, cardiac injury, arrhythmia, septic shock, liver dysfunction, acute kidney injury, multi-organ failure and death of the patients.[2,4] The pandemic has presented a major threat to public health worldwide. As of 13 March 2022, World Health Organization (WHO) reported a total of 452,201,564 confirmed cases of COVID-19 with 6,029,852 deaths (case fatality: 1.33%).[5]

Scientists have been working faster than ever to develop and produce vaccines that can stop the spread of COVID-19. On 31 December 2020, within almost a year since the pandemic started, WHO listed the Comirnaty COVID-19 mRNA vaccine for emergency use, making the Pfizer/BioNTech vaccine the first to receive emergency validation from WHO.[6] According to Global Alliance for Vaccines and Immunization (Gavi), 21 vaccines are now being currently rolled out in countries worldwide and there are now 137 COVID-19 vaccine candidates undergoing clinical trials and 194 candidates in pre-clinical development.[7] The vaccines are considered best strategy for protection against COVID-19 but they are associated with some disadvantages which include: providing only short-term immunity and need for booster doses, severe allergic reactions and unknown long-term side effects.[8] Also, the current rate of vaccination is still not adequate to control the infection. As of 13 March 2022, WHO has reported that only 56.1% people have received full vaccination worldwide and over 11 million new cases of COVID-19 are still being reported weekly.[5]

Several agents such as chloroquine, hydroxychloroquine, favipiravir, antisense RNA, corticosteroids, convalescent plasma were used in the past but these agents did not show much promising results. Remdesevir and monoclonal antibodies received emergency use authorization from the U.S. Food and Drug Administration (FDA) for treatment of COVID-19. However, they have some limitations. Remdesivir requires intravenous administration, and is only approved for the treatment of hospitalized patients. Monoclonal antibodies are indicated for outpatients with mild to moderate COVID-19 but have significant limitations: a) They require parenteral administration b) clinical monitoring is needed during infusion and for ≥1 hour following infusion c) they induce hypersensitivity reactions and d) they may be less effective to emerging SARS-CoV-2 variants.[9] Thus, there was a need of approved antiviral agent which could be taken orally and be effective against the virus.

Pfizer's Paxlovid (nirmatrelvir tablets and ritonavir tablets, co-packaged for oral use) was the first oral drug which received emergency use authorization from U.S. FDA on 22 December 2021 for the treatment of mild-to-moderate coronavirus disease (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg or about 88 pounds) with positive results of direct SARS-CoV-2 testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death.[10] However, this drug has not yet been approved by WHO for global use.

Merck's Molnupiravir was the 2nd oral antiviral agent that received emergency use authorization from FDA on December 23, 2021.[11] It is an oral prodrug of beta-D-N4-hydroxycytidine, a ribonucleoside which has broad antiviral activity against RNA viruses.[12] The drug acts on viral RNA-dependent RNA-polymerases and results in viral mutations and lethal mutagenesis.[12] Various clinical trials found this drug to be effective for mild to moderate COVID-19.[13,14] In the MOVe-OUT trial, molnupiravir reduced the rate of hospitalization or death by 30% compared to placebo.[14] The drug has been authorized by FDA for the treatment of mild-to-moderate COVID-19 in adults with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options authorized by the FDA are not accessible or clinically appropriate.[11] It is also indicated that the drug should be initiated as soon as possible after diagnosis of COVID-19 and within five days of symptom onset.[11]

Molnupiravir is the first oral antiviral drug approved by WHO to be included in the treatment guidelines for

COVID-19.[15] On 03 March 2022, WHO has recommended Molnupiravir for the treatment of non-severe COVID-19 patients with the highest risk of hospitalization. Those people include the people who have not received a COVID-19 vaccination, older people, people with immunodeficiencies and people living with chronic diseases. WHO bases its recommendation on results from six randomized controlled trials with a total of 4,796 participants.

Since Molnupiravir can be administered orally, it would be convenient for its global use in community setting. Though there is a need of strong data on its safety and affordability information, this drug shows a new hope in the treatment of COVID-19 and is expected to save many lives in the future.

Rama Paudel*

School of Biomedical Sciences, Trinity Medical Sciences University, Kingstown, St. Vincent and the Grenadines

***Correspondence to:**
Dr. Rama Paudel
Email: paudelrama2015@gmail.com

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