Will molnupiravir be a game changer in our efforts to safe COVID-19 outpatients?

To the editor Our race to combat the COVID-19 pandemic was accelerated when safe and effective COVID-19 vaccines were approved in December 2020.[1] Unfortunately, for many reasons, following over a year of the largest vaccination programs ever, there are still relatively large populations of unvaccinated people all over the world who are prone to COVID-19 and special risk groups of patients with certain immunosupressive medical conditions that are vulnerable to severe SARS-CoV-2 infection despite vaccination.[2] Therefore, SARS-CoV-2–specific oral antiviral agents easy to use in COVID-19 outpatients have long been awaited.[3-5] December 2021 brought us a licensure of molnupiravir, which was approved in many countries for use in adults from certain groups of patients at a high risk of severe COVID-19, based on positive results of the MOVe-OUT trial published recently in *New England Journal of Medicine*.[6]

Molnupiravir is the oral prodrug of beta-D-N4-hydroxycytidine (NHC), a ribonucleoside that has broad antiviral activity against RNA viruses.[3] NHC uptake by viral RNA-dependent RNA polymerases results in viral mutations and lethal mutagenesis.[3] The drug is named after Mjölnir, the hammer of the Norse god, Thor, as it was intended to have a destructive effect on SARS-CoV-2 by hammering down its replication. MOVe-OUT participants were unvaccinated adults with mild-to-moderate COVID-19 and at least one of the following risk factors for severe COVID-19: age over 60 years, active cancer, chronic kidney disease, chronic obstructive pulmonary disease, obesity (BMI ≥30 kg/m^2), major heart disease (heart failure, coronary artery disease, or cardiomyopathy), or diabetes mellitus.[6] Will molnupiravir be a real game changer in our efforts to reduce COVID-19–related hospital admissions and mortality? The answer is a bit complicated—the real-life effect will depend not only on the properties of the agent itself (as revealed by the MOVe-OUT trial) and its effects on different SARS-CoV-2 variants, but also on its effective distribution and timely administration to those selected patients who will potentially benefit the most from its use. The latter may be even more important to maximize the potential benefits of molnupiravir from the public health perspective, and to reduce potential harms (there is a theoretical risk that molnupiravir will be metabolized by the human host cell and incorporated into the host DNA, leading to mutations).[3] This barrier must be strongly considered in the recommendations on how to use molnupiravir in clinical practice, and is solely dependent on the organization of the primary health care system in a particular country, cost of the drug, and local availability of effective, cheaper, and safe alternatives. Therefore, following the publication of the MOVe-OUT trial results, there is much to do for local experts before country-specific recommendations for molnupiravir (or other oral antivirals) are developed and efficiently implemented into practice.

After molnupiravir manufacturer's press release following the results of the interim analysis, announcing a 50% relative reduction in risk (RRR) of the composite end point of hospitalization or death in 29-day follow-up,[7] the publication of the final MOVe-OUT trial results came somehow subdued, reporting finally an approximately 30% RRR of COVID-19–related hospitalization or death, with rather wide 95% confidence intervals (relative risk [RR], 0.69; 95% CI, 0.49–1.00).[6] Interim analyses are prone to over- or underestimation of the true effect, so they should always be interpreted with caution. In the final report, molnupiravir was also associated with a greater chance for symptom improvement by days 10 (odds ratio [OR], 1.58; 95% CI, 1.14–2.2) and 15 (OR, 1.36; 95% CI, 1.03–1.78). These results were generated in patients treated very early in the course of COVID-19, no later than 5 days from symptom onset (48% within the first 3 days). This approach will require a very well established and easily accessible system of testing for SARS-CoV-2 infection in primary care and patients' awareness that timely detection of COVID-19 within a very narrow time-frame is critical for the best effects of treatment.

The results of the MOVe-OUT trial suggest that molnupiravir might also have an impact on mortality; however, due to a very low number of these events in that population of outpatients (all-cause mortality: 1 [0.1%] vs 9 [1.3%] cases), the precision and certainty of this estimate are

low (RR, 0.11; 95% CI, 0.01–0.86; number needed to treat [NNT], 88; 95% CI, 50–376).[6]

Certainly, the major impact is on the reduction in the need for hospitalization, which is important both from an individual patient's and the public health perspectives. The authors reported this effect was numerically greater in vulnerable patients without serological evidence of prior or current SARS-CoV-2 infection, defined as anti–SARS-CoV-2 nucleocapsid (N) antibodies–negative (RR, 0.59; 95% CI, 0.40–0.86; NNT, 20; 95% CI, 12–66).[6] Although this finding came from prespecified subgroup analysis, it should be interpreted with caution due to a very low number of events in the anti-N seropositive group. Clearly, this is currently not an indication for serological testing prior to treatment, but it may suggest that a patient who recovered from previous COVID-19 infection or who already mounted an antibody response to the current one may have a different level of benefit. It is possible that the earlier this drug is administered (preferably within the first 3 days of symptom onset), the more likely it is to have a beneficial effect.[8]

The likely conclusion for guideline developers is that proper selection of the most vulnerable risk groups and establishing mechanisms that ensure timely initiation of therapy in local practice, especially during the period of limited supplies of the drug, will result in lower NNT and more effect for the effort. It also seems rational not to use molnupiravir in hospitalized patients with COVID-19, since the need for hospitalization usually occurs later in the disease course, with inflammatory mechanism being dominant.[3-5]

Are there any other approved easy-to-use, effective, safe, more accessible, and inexpensive alternative treatments for COVID-19 at the prehospital stage? Despite early encouraging results,[9] subsequent trials have not shown a consistent reduction in hospitalization and improved outcomes with colchicine.[3,10] Inhaled budesonide is one that potentially showed promise, but at this stage the trials were relatively small or revealed positive effect of primarily more surrogate outcomes, although building an early evidence base for this agent.[11,12] This evidence will be discussed in January 2022 by experts involved in the development of the World Health Organization (WHO) living guideline for COVID-19,[5] but so far, inhaled budesonide is not considered neither in the National Institutes of Health nor the Infectious Diseases Society of America COVID-19 guidelines.[3,4] However, since this therapy is relatively inexpensive, safe, and easily available, inhaled budesonide is a suggested option to be considered at the prehospital stage in some countries (eg, in Poland).[13,14] Whether coadministration of molnupiravir and budesonide would result in better efficacy is unknown at this point, but there are no theoretical concerns either that it would be detrimental.

Recently, the United States Food and Drug Administration approved another oral small molecule antiviral agent active against SARS-CoV-2 (ritonavir-boosted nirmatrelvir), with a different mechanism of action—nirmatrelvir is a protease inhibitor active against the main protease (M^{PRO}) of all human coronaviruses (a viral protease that plays an essential role in viral replication by cleaving the 2 viral polyproteins), and ritonavir is a potent cytochrome P450 3A4 inhibitor required to increase nirmatrelvir serum concentrations to the therapeutic level.[3,15] In the EPIC-HR trial (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients), this agent was indirectly potentially more effective than molnupiravir (the peer-reviewed publication has not been released yet).[15] Most of our remarks for guideline developers concerning molnupiravir refer also to this new drug, and since at this early stage supplies of both oral antivirals are limited, both of them will probably play some role in clinical practice. It is also important to consider significant contraindications or precautions related to these agents while developing recommendations and selecting patients which may benefit the most (eg, potential mutagenesis of molnupiravir in humans, including negative impact on reproductive health and fetal development, or selections of viral resistance; many drug interactions of ritonavir-boosted nirmatrelvir).[3] Although specific data are lacking, both agents are expected to be active against the Omicron variant of SARS-CoV-2, as well as against other variants of concern.[3]

Balance of benefits and harms (including cost) for molnupiravir seems to be close, so there will likely be differences in recommendations among groups of experts and patients in particular countries. American National Institutes of Health guidelines have recently been updated to include a conditional (optional) recommendation for the use of molnupiravir within 5 days of symptom onset for nonhospitalized patients with mild-to-moderate COVID-19 who are at high risk of disease progression ONLY when other options cannot be used (listed in order of preference: oral ritonavir-boosted nirmatrelvir [licensed in patients ≥12 years old] or intravenous sotrovimab or intravenous ritonavir).[3] The Infectious Diseases Society of America has also issued a conditional recommendation (based on low certainty of evidence) for the use of molnupiravir in the same group of patients who have no other treatment options, and for the use of ritonavir-boosted nirmatrelvir (with no preference over intravenous monoclonal antibodies or remdesivir).[4] The WHO living guideline for COVID-19 panel is expected to release its recommendations for both oral antivirals soon.[5]

To conclude, if and once experts consider a positive recommendation for the use of oral antiviral agents for prehospital treatment of COVID-19, we suggest that guidelines include practical and specific criteria for optimal patient selection and prioritization (especially during the period of limited drug supply). Such guidelines should also consider local systems of timely drug distribution

ensuring optimal use and maximum impact. Otherwise, the real-life effect and public health impact of these drugs may be markedly reduced.

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