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EDITORIAL

Molnupiravir: Is It Time to Move In or Move Out?

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With more than 250 million diagnosed cases and 5 million deaths, Covid-19 is our epoch-defining pandemic — and it is still ongoing. Despite the development of several effective Covid-19 vaccines, there are a limited number of antiviral treatments to reduce disease progression, risk of hospitalization, and death once the infection occurs. In this editorial, we examine the results of the phase 2 randomized, placebo-controlled, double-blind trials evaluating the safety and efficacy of molnupiravir, an oral drug that inhibits viral replication by introducing errors in the viral genome beyond the threshold required for viral viability in nonhospitalized (MOVe-OUT)[1] and hospitalized (MOVe-IN)[2] adults with Covid-19.

In the MOVe-OUT trial, 302 nonhospitalized patients with mild to moderate Covid-19 with symptom onset 7 days or less before randomization received 200, 400, or 800 mg of molnupiravir or placebo twice daily for 5 days. The side-effect and adverse event profile of active treatment was not clinically limiting; the adverse effects observed were comparable to placebo. Evidence suggestive of a clinical benefit was observed in the combined molnupiravir arm, as fewer participants were hospitalized or died through day 29 versus placebo (3.1% vs. 5.4%). The largest clinical benefit was seen for patients older than 60 years of age (3.6% vs. 21.4%) and for those at increased risk for severe illness and whose treatment began less than 5 days from symptom onset (3.7% vs. 11.8%). However, treatment effects should be interpreted with caution because the study was not powered for dose finding–based clinical outcomes.

In the MOVe-IN trial, the same molnupiravir or placebo treatment used in the outpatient study was given to 304 hospitalized patients. Again, no dose-limiting side effects or laboratory safety concerns were identified. Although there were many adverse events reported, the same events were also common in the placebo group. Regarding efficacy, the median time to sustained recovery at day 29 (81.5% to 85.2%) was comparable in the active and placebo arms. Even in the subgroup of hospitalized patients who had symptoms for fewer than 5 days from treatment initiation, — when antiviral treatments are more effective at blunting disease progression — no treatment effect was observed. Alternatively, oral antiviral agents may not be sufficient to provide optimal lung parenchyma penetration when patients progress to Covid-19 pneumonia compared with intravenous antiviral agents. Reinforcing this idea, in clinical trials evaluating the effectiveness of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)–neutralizing monoclonal antibodies for treating Covid-19 in hospitalized individuals, equivalent time-dependent treatment effects have been reported.[3]

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Taken together, the results of both the MOVe-OUT and MOVe-IN trials suggest that molnupiravir appears to be most effective when treatment is started early in the disease course for patients who do not require hospitalization (outpatient setting), have mild to moderate Covid-19, and are at high risk for severe disease. Unlike other drugs for Covid-19 approved by the Food and Drug Administration (FDA) for Emergency Use Authorization (EUA), molnupiravir is an orally bioavailable antiviral with excellent pharmacokinetic properties.[4] This could make its use practical in logistically difficult-to-reach communities if the lack of immediate access to SARS-CoV-2 testing could be remedied.[5] Despite the wide geographic distribution of participants in these trials, the sample sizes are small, limiting the ability to explore outcomes in specific subgroups. None of the participants were vaccinated; pregnant and immunosuppressed individuals were excluded. This is appropriate for an early phase study, but both groups are known to be at the highest risk for disease progression and likely to benefit the most from early therapies, as long as the benefits outweigh the risk. One could easily imagine a future scenario in which outpatient testing and treatment could make Covid-19 a disease that will not overwhelm health care facilities — but before we can imagine this, more work is needed.

Mean mutation rates per 10,000 nt at the end of therapy were 5.9 with 800 mg of molnupiravir versus 2.8 for placebo. Molnupiravir may be mutagenic to host DNA[6] based on in vitro studies in which cells were exposed to high doses for long periods of time. However, molnupiravir was clinically tested on a short-term basis (5 days), possibly limiting mutagenesis of host mRNA and adverse events. More safety data is needed from a phase 3 trial before its widespread use.

One of the main challenges faced during this Covid-19 pandemic is understanding the interface between SARS-CoV-2 viral replication and the human immunologic response.[7] We know that the primarily intense viral replication can be followed either by an immunologic response that can appropriately eliminate the SARS-CoV-2 and prevent the disease progression (regulated immune response) or by an immunologic response that cannot eliminate or prevent the viral disease progression (dysregulated immune response) and may in fact be detrimental to the host. The limiting factor that prevents a more refined approach to different treatment interventions is related to the fact that nasal SARS-CoV-2 viral load correlates neither with disease severity at presentation nor with progression to a more severe infectious process; thus, it is not surprising that there was no apparent effect on the nasal titers of SARS-CoV-2 RNA between treatment arms in the molnupiravir trial. In addition, the viral load in one site (e.g., nasal) does not correlate with another site (e.g., lungs). In fact, in the progression to severe Covid-19 pneumonia, we have observed that some patients may develop a negative nasal PCR result while having a very high viral load detected in a bronchoalveolar lavage specimen. Because no validated viral or immunologic biomarkers that can establish the timing, duration, and magnitude of the viral replication or immunologic regulation/dysregulation have been discovered to date, direct anti-viral treatment early in the course of Covid-19 illness when replication rather that host immune response is the predominant culprit makes sense. The two molnupiravir trials (MOVe-OUT and MOVe-IN), the FDA approval of remdesivir,[8] and the FDA EUA approval of monoclonal antibodies[3] all provide evidence for this approach. Until objective markers of disease onset can be identified, it seems reasonable to cautiously use timing of the symptoms of infection coupled with the patient's underlying risk for disease progression and presenting clinical, laboratory, and radiologic pictures (i.e., probability of active viral replication) as clinical markers that could be used to optimize the benefits and reduce the risks of different treatment interventions. In the same vein, immunosuppressive drugs such as steroids given at this early stage could be harmful by delaying viral clearance and adversely affecting the necessary immune response.[9,10]

The MOVe-OUT and MOVe-IN phase 2 trials on molnupiravir provided the scientific justification to design and perform the phase 3 trial in nonhospitalized patients newly diagnosed with SARS-CoV-2 infection reported concurrently in the *New England Journal of Medicine*.[11] Notably, independent of their results – both positive and negative trials are relevant to patient care and public health – these trials are also a testimony of the critical need for rigorous science through placebo-controlled, double-blind, randomized studies to discover new effective and safe treatments for Covid-19.[12] Let's move out.

Disclosures

Author disclosures are available at evidence.nejm.org.

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