EDITORIAL

Molnupiravir — A Step toward Orally Bioavailable Therapies for Covid-19

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The Covid-19 pandemic has resulted in substantial global morbidity and mortality as well as disruption of the economies of virtually every country.[1] Some of this tragedy could have been averted with the development of deliverable, orally bioavailable, direct-acting antiviral therapeutics. Molnupiravir, the orally bioavailable prodrug of N4-hydroxycytidine (NHC), begins to address this need. Synthesized at the Emory Institute for Drug Development (EIDD), molnupiravir is active against influenza as well as multiple other RNA viruses, including SARS-CoV-2.[2] As the coronavirus pandemic emerged, EIDD developed molnupiravir for the treatment of pathogenic coronavirus infections rather than influenza. This decision was based on an extensive body of work performed in cell culture and in animal models of SARS, MERS, and ultimately, SARS-CoV-2.[3-5] NHC is phosphorylated intracellularly to its triphosphate derivative, which is incorporated into viral RNA, leading to fatal errors in replication. An added benefit is a high genetic barrier to resistance.

Jayk Bernal and colleagues now report in the *Journal* the results of a phase 2–3 placebo-controlled trial of molnupiravir that may begin to address this global problem. The drug was administered orally (800 mg [four tablets] twice daily for 5 days) and compared with a matching placebo.[6] Patients with mild-to-moderate disease and at least one risk factor for progression to severe illness (including age >60 years, obesity, diabetes, or cardiovascular disease) were eligible for enrollment. The primary end point was a composite of hospitalization or death at 29 days. At the planned interim analysis, 775 patients who were infected with SARS-CoV-2 and had symptoms of no more than 5 days' duration were enrolled; 387 patients received molnupiravir and 388 received placebo. The prespecified interim analysis was performed at approximately 50% of the planned enrollment. In the molnupiravir group, the risk of hospitalization or death was 7.3% (28 of 385 patients), as compared with 14.1% (53 of 377) in the placebo group ($P=0.001$); no deaths had occurred in the molnupiravir group at the time of this interim analysis. However, the final analysis of these peer-reviewed data shows a more modest effect. In the final data, 1433 infected volunteers were randomly assigned to molnupiravir (716 patients) or placebo (717 patients). A primary end-point event occurred in 48 of 709 molnupiravir recipients (6.8%) and 68 of 699 placebo recipients (9.7%), an absolute difference of approximately 3 percentage points. One death occurred in the treatment group, and nine among placebo recipients. Numerous potential reasons for the lessening of the drug effect include preexisting SARS-CoV-2 nucleocapsid antibodies and lower viral load at enrollment.

In the patients with available sequence data, molnupiravir was found to be active against the three predominant circulating variants (delta, gamma, and mu) and showed a modest antiviral effect. Adverse events were similar in the two groups.

This clinical trial potentially provides a tool in the management of Covid-19, pending evaluation by the Food and Drug Administration (FDA), the European Medicines Agency, and other licensing bodies. Several points warrant emphasis. First, molnupiravir therapy was initiated within 72 hours after symptom onset in nearly 50% of patients;

however, we must strive for therapy to begin within 72 hours in all patients, as shown in studies of influenza.[7] Since SARS-CoV-2 infection must be confirmed, a point-of-care companion diagnostic test would be of value. Molnupiravir is less beneficial when administered late in the disease course — namely, after patients have had symptoms for more than 3 to 5 days or after they are hospitalized, as shown in reports of two phase 2 trials of molnupiravir.[8,9] Second, the safety database is small and will require careful monitoring for the emergence of side effects. Third, potential mutagenic toxicity has been a concern, since the drug is mutagenic in Chinese hamster ovary cells.[10] However, there is a body of data that address concerns related to the potential mutagenicity and genotoxicity of molnupiravir.[11] Given the totality of data, regulatory authorities in the United Kingdom have stated that the risk of mutagenicity or genotoxicity in the clinical use of molnupiravir is low, and it was licensed for use in the United Kingdom on November 4, 2021.[12] The U.K. summary report on molnupiravir recommends licensure for SARS-CoV-2–infected persons 18 years of age or older who have one risk factor for progression to severe illness — a population similar to that described in the article by Jayk Bernal et al. The report notes a low risk of genotoxicity, a concern for some physicians.[10] Molnupiravir was not recommended for women who are pregnant or breast-feeding or for those who might become pregnant during treatment. The FDA will review these data, most likely before the end of the year, in considering an Emergency Use Authorization. Fourth, the sponsor has indicated in the lay press that drug patents will be made available to the World Health Organization patent pool and to manufacturers of generic drugs so that molnupiravir can be produced for developing countries, ideally at low cost.

Vaccines must be the primary mode of protection against SARS-CoV-2; however, orally bioavailable medications will become an essential tool for physicians in the management of this horrible disease. Of note, although the data have not been peer-reviewed, Pfizer has announced the efficacy of its orally bioavailable protease inhibitor, Paxlovid, and Gilead has reported a benefit of ambulatory therapy with remdesivir. Data for both medications demand peer review. The availability of medications with different mechanisms of action offers the opportunity for creating combination therapies that are potentially synergistic and less likely to lead to resistance.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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