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BRIEFING

Covid-19: What is the evidence for the antiviral molnupiravir?

Merck's drug was originally claimed to halve hospital admissions and deaths in people with covid-19, leading some governments to stockpile it as the pandemic continued. Andy Extance looks at the published evidence for its effectiveness

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What is molnupiravir?

Molnupiravir (marketed as Lagevrio) is an antiviral drug, slightly modified from a compound known as NHC (β-d-N^4-hydroxycytidine) that a team at Emory University in Atlanta, Georgia, first described in 2003.[1] It is available as hard capsules that are swallowed and absorbed from the gut so is easy to take at home. That contrasts with some other covid-19 drugs such as the monoclonal antibody tocilizumab or the antiviral remdesivir, which must be administered by intravenous infusion in hospitals. In October 2021 the UK government announced the procurement of 480 000 courses of molnupiravir (as well as 250 000 courses of the Pfizer antiviral Paxlovid (nirmatrelvir)).

Molnupiravir had been due to enter clinical trials against influenza, but during the pandemic Emory University struck a deal with the biotechnology company Ridgeback Biotherapeutics to test it as a treatment for covid-19.[2] Ridgeback then partnered with the pharmaceutical giant Merck in May 2020 for clinical trials and scale-up.[3]

Antiviral drugs for acute respiratory infections need to be used as early as possible after infection if they are to help prevent disease progression, hospital admissions, and deaths. This normally means within three days, but the drug may still be beneficial up to five days after onset of symptoms. The current advice is to give 800 mg of molnupiravir (four 200 mg tablets) every 12 hours for five days, within five days of symptom onset.[4]

How does molnupiravir work?

Like many antivirals, its chemical structure resembles the nucleotide bases that link together to make the long RNA chains that are a virus's genetic material. After ingestion, molnupiravir breaks down to form NHC. NHC then targets an enzyme called RNA dependent RNA polymerase (RdRP) that SARS-CoV-2 uses to make more copies of its genetic instructions.[5]

RdRP picks up and links NHC into the growing RNA chain instead of natural nucleotides, creating errors in the virus's genetic code. Eventually this builds up to an "error catastrophe" that stops the virus functioning.[6] For comparison, remdesivir works by shutting down RdRP's function altogether.

A key challenge for these kinds of "nucleotide-mimic" drugs is that healthy cells might also integrate them into RNA, which could cause mutations and kill the cells. This happened with the hepatitis C antiviral candidate BMS-986094, for which clinical trials were abandoned quickly after a death and hospital admissions arising from heart and liver toxicity.[7 8]

What is the peer reviewed evidence for molnupiravir?

The most informative evidence comes from an international phase 2/3 clinical trial, called MOVe-OUT, involving people with mild or moderate covid-19. Merck published early results of the trial, which started in October 2020,[9] in a press release in October 2021.[10] Reporting on 762 patients, the study found that the number who needed to be admitted to hospital or who died was about halved among those taking molnupiravir when compared with placebo. But results for the full set of 1433 participants published in the *New England Journal of Medicine* in December 2021 showed that hospital admissions and deaths were only about 30% lower in the molnupiravir group.[11] The proportion of patients experiencing adverse events were similar in the two groups.

What seems like a small drop in efficacy between October and December could be a serious concern. Some critics have said that this means that people taking molnupiravir were at greater risk of hospital admission or death during the October-December period than those given placebo.[12]

With only a single pivotal trial, the supporting evidence is "still quite limited," Steve Pearson, president of the independent US non-profit Institute for Clinical and Economic Review, told the *BMJ*. "The relative risk reduction was modest," he added.

Furthermore, even before those trial results were released, concerns about molnupiravir's potential for causing mutations had been raised. These followed a whistleblower complaint from Rick Bright, former head of the US government's Biomedical Advanced Research and Development Authority, about improper use of research funds in molnupiravir's development.[13] In May 2020 investigative reporting in *Science* reported Bright's discomfort with the pressure that Emory researchers had put on him to grant funding before molnupiravir had been tested in humans.

Raymond Schinazi, an Emory University chemist who has developed many antiviral drugs, including NHC, told *Science* that his former pharmaceutical company Pharmasset had dropped development of NHC because of mutagenicity. He doubted that the small

chemical change that turned NHC into molnupiravir could avoid this. However, George Painter, another Emory University chemist who led molnupiravir's commercialisation,[14] told *Science* that his team hadn't "seen robust evidence for any sort of mutagenicity."

Then, in August 2021, a team that included Schinazi noted in the *Journal of Infectious Diseases* that NHC caused mutations in experiments involving mouse cell cultures.[15] Merck responded in a letter to the journal that the experiments were not relevant to what the drug did in living animals.[16] Chris Butler, professor of primary care at the University of Oxford, likewise told *The BMJ* that "there's no evidence that this drug is mutagenic in the human host so far."

What does molnupiravir cost?

In the US a five day course costs around $700 (£540), which the Institute for Clinical and Economic Review estimates equates to $63 000 for each hospital admission averted in that country.[17] "The value—both clinical and economic—of these treatments depends on how much risk patients are at for progressing to more serious covid-19," commented Pearson. "Given the current landscape, with omicron being the dominant variant, the risk of hospitalisation is high enough to justify the current pricing of these treatments. If hospitalisation rates drop further, the cost effectiveness of the drugs will worsen."

In parallel with its drug trials, Merck built a global supply chain for manufacturing partners and put together a deal with the Medicines Patent Pool for easier licensing with manufacturers of generic drugs. This enables tiered pricing for lower income countries, with a five day course as low as $10. The World Health Organization says that molnupiravir is not yet widely available but that steps like the licensing agreements should increase access. WHO's Access to COVID-19 Tools Accelerator initiative is also making a limited supply available where the drug is most needed.

Which countries are using molnupiravir—and which are not?

On 4 November 2021 the UK Medicines and Healthcare Products Regulatory Agency became the first to authorise molnupiravir through a conditional marketing authorisation.[18] On 23 December 2021 the US Food and Drug Administration also granted molnupiravir early use authorisation (EUA).[19] The EUA notice indicated the drug's use for the treatment of mild to moderate covid-19 in at-risk adults for whom alternative covid-19 treatment options are not accessible or clinically appropriate. The next day the Japanese Ministry of Health, Labour and Welfare's Pharmaceutical Evaluation and Control Division issued a *Report on the Deliberation Results* and granted "special approval."[20] However, these approvals have been criticised for a lack of transparency and scientific rigour.[21] South Korea has also issued emergency approval of the drug, as well as of Pfizer's Paxlovid, after a steep rise in cases in March.[22]

France had ordered 50 000 doses of molnupiravir in October but cancelled its order in December, citing efficacy concerns.[23] The European Medicines Agency is yet to grant conditional marketing authorisation. The *Financial Times* reported that the EMA was now unlikely to do so.[24] And on 13 January 2022 the Indian Council of Medical Research excluded molnupiravir from its covid treatment guidelines over toxicity concerns.[25]

In March 2022 WHO said that molnupiravir should be provided only to those patients with non-severe covid-19 who had the highest risk of hospital admission.[26] This means older people, those who are unvaccinated, and those with immunodeficiencies or who have chronic disease. It said that children and pregnant and breastfeeding people should not be given molnupiravir and that those who take it should have a contraceptive plan.

Are further trials of molnupiravir planned?

In December 2021 a government funded effectiveness study in the UK called Panoramic started studying molnupiravir's efficacy in a much larger group. Its aim was to see how the efficacy shown by the drug in initial trials translated to a largely vaccinated population in the real world, said Butler, who is leading the study.

Panoramic had planned to recruit 10 000 patients, assuming a 3% rate of hospital admission for standard care, reduced to 2% for patients taking molnupiravir. However, fewer people now need to be admitted to hospital, Butler underlined, requiring more participants to be able to show a difference.

At the time of writing Panoramic had recruited 22 744 patients. After follow-up after 28 days, then analysis of the trial's data, results will appear in late May at the earliest. Panoramic will then follow up patients at six months and could enable long term follow-up to assess mutagenicity concerns. Butler emphasised the importance of getting clear data as quickly as possible "so we have that evidence available for use within the pandemic but also for future generations."

Also, in March 2022 WHO launched a pharmacovigilance programme in low and middle income countries to gather international data on molnupiravir's safety.[27]

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