



Kent

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Covid-19: Molnupiravir does not cut hospital admissions or deaths in vaccinated people at high risk, trial finds

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The antiviral drug molnupiravir does not reduce hospital admissions or deaths among vaccinated high risk patients with covid-19 infection, show the results of a landmark trial that included more than 25 000 participants.¹

However, the oral treatment was associated with reduced viral detection and load, and patients recovered around four days more quickly than those who received usual care. The Panoramic study, now peer reviewed and published in the *Lancet*, was first available as a preprint in October.²

In November 2021 the UK was the first country to authorise Merck Sharp & Dohme's molnupiravir (Lagevrio) for the treatment of mild to moderate covid-19 in adults with at least one risk factor for severe illness. The government bought 2.23 million doses at an estimated cost of £1bn, and the then health secretary Sajid Javid called it a "gamechanger for the most vulnerable and the immunosuppressed."^{3 4} However, the government was criticised for overhyping the antiviral drug in official press releases.^{5 6}

Trial with vaccinated patients

Before the emergence of the omicron variant, trials of molnupiravir were previously done in largely unvaccinated participant groups. This new trial was carried out in a mostly vaccinated population where most covid infections involved omicron, and it is therefore more applicable to the current situation in the UK.

A total of 25 786 study participants were randomly assigned through general practices to receive either molnupiravir (taken as an 800 mg dose twice daily for five days) or the usual standard of NHS care. All participants had a confirmed omicron covid-19 infection and were enlisted within five days of symptom onset. The participants were either aged over 50 in good health or aged 18-50 with an underlying health condition that made them clinically more vulnerable. About 6% of participants were from ethnic minorities.

No benefit was seen in terms of hospital admissions or death rates. The group treated with molnupiravir had 105 cases of death or hospital admission (0.8%), and the control group had 98 cases of death or hospital admission (also 0.8%).

The median average length of illness in patients who took molnupiravir was nine days, which compared with 15 days in the control group. After adjusting for other factors the study authors found that patients taking molnupiravir recovered 4.2 days more quickly than patients in the control group.

The study found modest evidence that patients who were treated with the antiviral drug sought less further GP care (20% of molnupiravir patients v 24% of the control group). No safety concerns were identified in the study, which was funded by the National Institute for Health and Care Research.

Chris Butler, professor of primary care in the Nuffield Department of Primary Care Health Sciences at Oxford University and co-chief investigator, said, "During swine flu we gave out Tamiflu in large quantities but didn't know if we were doing more good than harm. This trial represents a sea change in how we evaluate treatments. We have generated evidence within a pandemic to guide care within the same pandemic," he told a Science Media Centre briefing.

Other possible benefits

Although the trial found no benefit from molnupiravir for its primary outcome of reducing the likelihood of hospital admission or death, the treatment could have other benefits such as a faster recovery time and reduced follow-up with health services, said Butler. "This could help to ease the burden on UK health services through the treatment of selected patients at home, during times of high disease burden and pressure on key services," he said.

A seven day course of molnupiravir in the US costs around \$700 (£580; €660), but the price paid by the UK government is confidential. Richard Hobbs, Nuffield professor of primary care at Oxford and co-investigator, told the briefing, "Molnupiravir is a high cost antiviral. Its deployment will depend on how much a mean four days' improvement in symptoms will benefit the country."

A Department of Health and Social Care spokesperson told *The BMJ* that its response to beating the pandemic "continues to be guided by robust data . . . Molnupiravir will continue to be available to high risk patients this winter, alongside other medicines, free testing, and vaccination, to help reduce the risk of hospitalisation and improve recovery for the most vulnerable."

Trial still open

The Panoramic trial is still open and is now studying a second oral antiviral, Paxlovid. The researchers said that the drug's cost effectiveness and effect on long covid would be analysed later. Molnupiravir is also undergoing assessment by the National Institute for Health and Care Excellence.

Ly-Mee Yu, coauthor from the University of Oxford, said that it was critical that people who were likely to benefit from antiviral treatments received them but that "using antivirals to treat patients who are unlikely to benefit carries the risk of further driving

antimicrobial resistance, wasting resources, and exposing people to unnecessary harm.”

Jonathan Van-Tam, pro-vice-chancellor for the Faculty of Medicine and Health Sciences at the University of Nottingham and study coauthor, said that the latest research in a vaccinated population demonstrated that the vaccine protection was so strong that there was no obvious benefit from the drug in terms of further reducing hospital admissions and deaths. But he added, “However, symptom duration and virus shedding are both markedly reduced, and we have to wait much longer to know if there will be any discernible effects on long covid.”

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