NPO Japan Institute of Pharmacovigilance, Tennoji-ku, Osaka, Japan 543-0043

gec00724@nifty.com

Cite this as: *BMJ* 2022;377:o977
http://dx.doi.org/10.1136/bmj.o977
Published: 26 April 2022

MOLNUPIRAVIR'S PREMATURE AUTHORISATION

Imbalance in baseline characteristics in molnupiravir trials

Rokuro Hama *medical doctor*

Brophy emphasises the dangers of making decisions based on a single prematurely terminated trial.[1] The molnupiravir trials have several more problems[2 3]:

- The risk of hospital admission or death associated with molnupiravir was not significant in the all randomised population when adjusted for sex (hazard ratio 0.69, 95% confidence interval 0.48 to 1.01).
- Molnupiravir may worsen covid-19 outcomes after the interim analysis—simply calculating the rate of hospital admission or death in the population of participants who were included in the final analysis but not the interim analysis shows that the molnupiravir group had a non-significant higher risk (6.2%) than the placebo group (4.7%).
- The Move-Out trial has serious imbalances in baseline risk factors that favour molnupiravir. Patients with chronic obstructive pulmonary disease were assigned at a significantly lower rate to the molnupiravir group (odds ratio 0.31, P=0.0043).[4] The sum of the percentages of the participants with risk factors other than obesity was significantly lower in the molnupiravir group (43.4%) than in the placebo group (51.8%) (OR 0.71, P=0.019). With restriction to four risk factors (diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and active cancer), risk was almost 40% lower in the molnupiravir group (OR 0.61, P=0.0043).[4] These findings suggest that blinding might have been broken before the interim analysis.
- Significant imbalances (except obesity) were also observed in the all randomised population (OR=0.79, P=0.031[4]), which raises doubts about fair randomisation.
- Contradictory results were seen in moderate to severe covid-19. In subgroup analysis, molnupiravir seemed significantly effective in patients with moderate covid-19 and the effect size was greater than in those with mild covid-19.[5] But two randomised controlled trials targeting moderate covid-19 have been terminated because of futility.[6]
- The Move-In trial also has a serious imbalance in severity of covid-19 at baseline. Patients with score 6 covid-19 (admitted to hospital and given oxygen by non-invasive ventilation or high flow therapy) were significantly less common in the molnupiravir groups (2.3%) than in the placebo group (8.0%) (OR 0.27, P=0.025). But a non-significant higher risk of death (6.0%) was reported compared with placebo (2.7%) (OR 4.69, P=0.105). The ratio of mortality OR to OR of baseline score 6 was 17.38 (95% confidence interval 1.6 to 188.8) by Kolassa's method.[7]
- Molnupiravir has been associated with irreversible myelosuppression in dogs[5] and with DNA damage, bone marrow toxicity, and mutations in humans.[8] Were the deaths observed in the Move-In trial[3] associated with bone marrow toxicities?

Full clinical study reports of antivirals including molnupiravir and remdesivir[9] should be disclosed, and a reanalysis is needed as in the systematic reviews on neuraminidase inhibitors.[10]

Competing interests: None declared.

Full response at: https://www.bmj.com/content/376/bmj.o443/rr.

1 Brophy JM. Molnupiravir's authorisation was premature. *BMJ* 2022;376:o443. doi: 10.1136/bmj.o443 pmid: 35241455
2 Jayk Bernal A, Gomes da Silva MM, Musungaie DB, etalMOVe-OUT Study Group. Molnupiravir for oral treatment of covid-19 in nonhospitalized patients. *N Engl J Med* 2022;386:509-20. doi: 10.1056/NEJMoa2116044 pmid: 34914868
3 Arribas JR, Bhagani S, Lobo SM, etalRandomized trial of molnupiravir or placebo in patients hospitalized with covid-19. *NEJM Evid* 2022;1:EVIDoa2100044. doi: 10.1056/EVIDoa2100044.
4 MedCheck Editorial Team. Antivirals for COVID-19: molnupiravir (Lagevrio). Doubt about efficacy due to serious baseline inbalance. Med Check in English 2022;8:11-16. https://www.npojip.org/english/MedCheck/Med%20Check%20TIp-23-2022-04.pdf
5 Medicines and Healthcare Products Regulatory Agency. Public assessment report national procedure Lagevrio 200mg hard capsules (molnupiravir). https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1042560/Lagevrio_Public_Assessment_Report.pdf
6 Singh AK, Singh A, Singh R, Misra A. Molnupiravir in COVID-19: A systematic review of literature. *Diabetes Metab Syndr* 2021;15:102329. doi: 10.1016/j.dsx.2021.102329 pmid: 34742052
7 Kolassa S. Calculate 95% CI for ratio of odds ratio. https://stats.stackexchange.com/questions/471805/calculate-95-ci-for-ratio-of-odds-ratio
8 Kabinger F, Stiller C, Schmitzová J, etal. Mechanism of molnupiravir-induced SARS-CoV-2 mutagenesis. *Nat Struct Mol Biol* 2021;28:740-6. doi: 10.1038/s41594-021-00651-0 pmid: 34381216
9 MedCheck Editorial Team. Remdesivir (trade name: Veklury). Most likely ineffective for COVID-19. *MedCheck in English* 2020;6:39-45. https://www.npojip.org/english/MedCheck/Med%20Check%20Tip-18-2020-08-21.pdf.
10 Jefferson T, Jones MA, Doshi P, etal. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2012;1:CD008965. doi: 10.1002/14651858.CD008965.pub4. pmid: 22258996