Journal of Infection 86 (2023) 121–122

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Review

Molnupiravir for SARS-CoV-2 infection: Public health and policy implications

Edward J. Gray[a], Jonathan S. Nguyen-Van-Tam[b,*]

[a] Formerly, UK Antivirals Task Force, United Kingdom
[b] Lifespan and Population Health Unit, Nottingham UKMedicine, University of Nottingham School of Medicine, Nottingham, United Kingdom

ARTICLE INFO

Article history:
Accepted 30 October 2022
Available online 23 December 2022

This week, The Lancet reports the initial results from the PANORAMIC study, which evaluates molnupiravir for community treatment of test-confirmed SARS-CoV-2 infection in higher risk patients.[1]

This has been the fastest recruiting clinical trial ever in the UK, and a testament to the combined research capability of the National Health Service (NHS), National Institute for Health Research (NIHR), United Kingdom Health Security Agency (UKHSA) and UK primary care researchers. The study concept is novel, by making it possible for patients to enrol, on-line, from their own homes (as well as in clinical settings) and receive timely study medication via courier. Bringing the trial to patients, rather than relying purely on bringing patients to the trial undoubtedly trailblazes how future research can and should be conducted in primary care. Significant credit should be given to the senior authors (Butler, Hobbs, Yu and Little) and the PANORAMIC Team for conducting a nationwide community-based study of this scale to measure real-world results of new treatments during an ongoing pandemic.

Molnupiravir was granted Conditional Marketing Authorisation in the UK in November 2021, on the basis of clinical trials data showing an approximate 30% reduction in hospitalisation in community patients diagnosed with SARS-CoV-2 infection.[2] This is a seemingly large public health benefit and based on these data, molnupiravir was quickly deployed by the UK Government to treat highest-risk patients alongside other options such as monoclonal antibodies via Covid Medicine Delivery Units (CMDUs).[3]

Why then was a trial such as PANORAMIC conducted, in the face of convincing Phase 3 data and subsequent licensure? Data from the pivotal Phase 3 'MOVe-OUT' trial, whilst impressive, were obtained in unvaccinated patients in 2021, during the pre-Omicron era.[2] These results do not therefore address the current policy relevant question pertaining to the effects of molnupiravir when pitched against the less virulent Omicron variants and in populations who are already highly vaccinated, and who have, so far, typically received a primary immunisation course (two doses) of Covid-19 vaccine, followed by one or two boosters (a mixture of heterologous and homologous). 25,783 patients across the UK were randomised into the molnupiravir arm of the study and the interim analysis is based on 97% of collected data, spanning a wide range of included patients.

The initial analysis of the results indicate that early treatment with molnupiravir for test-confirmed, symptomatic COVID-19 in the community significantly shortens recovery times in treated patients, reduces demand on primary care, and reduces viral load and duration of shedding - the latter two potentially impinge on secondary transmission - albeit in PANORAMIC there was no effect seen on transmission to household members. However, the risk of hospital admission or death is not reduced.

The findings were replicated across sub-groups within the study, demonstrating that the overall results do not conceal particular patient groups who would benefit more than others in either reducing hospitalisation / death or recovery time. Importantly, it is not yet possible to determine if treatment will impact on the incidence or duration of long-COVID, but, given time, the study almost certainly has sufficient statistical power to address this important public health question.

As we start to analyse these results, we need to ensure they are fully understood, both in the context of the study and of the potential benefit that antivirals will have as societies begin to live with SARS-CoV-2 as an endemic or recurrent epidemic virus.

The results of PANORAMIC have been generated almost entirely during a period dominated by the Omicron variants, which produce far lower rates of hospitalisation for COVID-19, compared with Alpha and Delta predecessors.[4] It is also known that first

* Corresponding author.
E-mail address: jvt@nottingham.ac.uk (J.S. Nguyen-Van-Tam).

https://doi.org/10.1016/j.jinf.2022.10.040

generation, monovalent, vaccines offer very substantial protection against hospitalisation and death.[5] However, despite the recent deployment of bivalent (Wild type and Omicron) vaccines in the UK Autumn 2022 booster programme,[6] it is plausible that a future variant could emerge which is significantly vaccine escaping with higher future rates of hospitalisation and a need to reformulate vaccines.

To date, the findings from the PANORAMIC trial offer an interesting combination of encouraging benefits related to early recovery and possibly reduced spread but counterbalanced by no meaningful reductions in hospitalisations and mortality in the context of current milder virulence attributable to the Omicron variants. The complete clinical impact and cost-effectiveness of molnupiravir will not be known until all planned analyses are completed and the longer-term evolution of variants is better understood.

National and international policymakers now need time to assimilate and consider these new data, and subsequent analyses, when formulating and then evolving clinical policy for access to molnupiravir and future antivirals (initially Paxlovid®) as these are evaluated in subsequent arms of the PANORAMIC study. Whilst it is clear that meaningful reductions in hospitalisations and deaths cannot be realised currently in vaccinated populations through use of molnupiravir, policy makers may need to consider the disease impact profile of future variants and the wider benefits that antivirals may bring to UK citizens beyond reducing hospitalisation and death, such as the reduced recovery time shown in the study and potential gains in business continuity, as well as treatment for groups unable to benefit from vaccination due to immune dysfunction or clinical contraindications. These issues will likely involve complex considerations about targeted and setting-specific deployment, response to future variants, particularly if vaccine-escape necessitates antigenic reformulation, cost-effectiveness, and opportunity costs within constrained healthcare budgets.

Disclaimers

EJG was Chair of the UK Government Antivirals Task Force (UKAVTF), Department of Health and Social Care, England (DHSC) from June 2021 to March 2022. JSN-V-T was seconded to DHSC as Deputy Chief Medical Officer from October 2017 to March 2022. He was a clinical adviser to UKAVTF. JSN-V-T co-conceived the PANORAMIC study (with C. Butler) and is a member of the PANORAMIC study team. The views expressed in this article are personal, and not necessarily those of UKAVTF, DHSC or the PANORAMIC study team. Neither author declares any financial conflict related to Merck Inc. or Pfizer. JSN-V-T has performed a paid internal lecture for Gilead Sciences and a paid external lecture for AstraZeneca.

References

1. Butler C., Hobbs F.D.R., Gbinigie O., Rahman N.M., Hayward G., Richards D., et al. Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): preliminary analysis from1 the United Kingdom Randomised, controlled open-label, platform adaptive trial. Pre-print available online at: (2022), https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4237902 (last accessed, 19.10.22).
2. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, Martín-Quirós A, Caraco Y, Williams-Diaz A, Brown ML, Du J, Pedley A, Assaid C, Strizki J, Grobler JA, Shamsuddin HH, Tipping R, Wan H, Paschke A, Butterton JR, Johnson MG, De Anda C. MOVe-OUT study group. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med* 2022;**386**(6):509–20. Feb 10Epub 2021 Dec 16. PMID: 34914868; PMCID: PMC8693688. Available online at https://www.nejm.org/doi/full/10.1056/NEJMoa2116044 (last accessed, 19.10.22).
3. National Health Service England. Covid-19 community-based treatments, (2022). Available online at: https://www.england.nhs.uk/coronavirus/community-treatments/. (last accessed, 19.10.22).
4. Nyberg T, Ferguson NM, Nash SG, Webster HH, Flaxman S, Andrews N, et al. Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study. *Lancet* 2022;**399**(10332):1303–12. Apr 2Epub 2022 Mar 16. PMID: 35305296; PMCID: PMC8926413. Available online at https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02597-1/fulltext .
5. Kirsebom FCM, Andrews N, Stowe J, Toffa S, Sachdeva R, Gallagher E, et al. COVID-19 vaccine effectiveness against the omicron (BA.2) variant in England. *Lancet Infect Dis* 2022;**22**(7):931–3. JulEpub 2022 May 24. PMID: 35623379; PMCID: PMC9129256. Available online at https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00309-7/fulltext (last accessed, 19.10.22).
6. UK Health Security Agency. A guide to the COVID-19 autumn booster. (2022), Available online at: https://www.gov.uk/government/publications/covid-19-vaccination-autumn-booster-resources/a-guide-to-the-covid-19-autumn-booster (last accessed, 19.10.22)