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Learning and confirming in publicly funded antiviral trials



Reporting the phase 2 results from the UK AGILE CST-2 study of molnupiravir for SARS-CoV-2 in *The Lancet Infectious Diseases*, Saye H Khoo and colleagues¹ present output from a platform trial with public funding that has taken an approach inspired by commercial drug developers. The COVID-19 pandemic exposed our lack of potent oral antivirals and, given the previous two decades of outbreaks of RNA viruses, including SARS-CoV, MERS-CoV, and Ebola virus, one could argue that we should have been better prepared.

However, developing drugs for acute infections is fraught with difficulties. One single pivotal phase 3 trial without positive results can lead to a company going out of business and the commercial case for developing agents used as a short course against a virus with pandemic potential is limited. Thus, public funding is required.

Drug development follows cycles of learning and confirming.² For antivirals, this process means an initial preclinical cycle, in which it is learned whether a compound has in-vitro activity and then this activity is confirmed in animal models. This first cycle would have ruled out any possible efficacy of hydroxychloroquine for patients with COVID-19,³ for example.

During clinical drug development, we learn about drug safety and dose–response in phases 1 and 2, which are then followed by pivotal, confirmatory phase 3 trials. To ensure that results are robust to regulatory scrutiny, double-blinding and placebo control are usually used. To maximise the probability of success, trials target the phase of disease during which interventions are most likely to be efficacious. In the case of SARS-CoV-2, this approach means treating patients within the first few days of symptom onset, as was known from preprints of viral dynamic models from March, 2020.⁴ Continuous learning via secondary endpoints, such as pharmacokinetics, viral load, sequencing and viability measures, and markers of immune function, is particularly important in phase 2 trials.

Unlike Khoo and colleagues, the leaders of national and international SARS-CoV-2 platform trials sought to shortcut this tried and tested approach. Taking antiviral monotherapies with little or questionable in-vitro activity straight to confirmatory phase 3 trials, often in late-stage COVID-19 when viral replication has

slowed, very predictably, does not work.⁵ A paucity of systematic collection of secondary data in SARS-CoV-2 drug trials further undermines the ability to understand why interventions have failed. A notable exception has been the DISCOVERY trial, published in *The Lancet Infectious Diseases*, which showed why remdesivir does not have clinical benefit in late COVID-19: it does not reduce viral load.⁶

The rapid setup and roll-out of high-quality clinical learning studies is perfectly possible in an emergency setting: Khoo and colleagues opened recruitment to AGILE CST-2 in November, 2020. The double-blind, 2 × 2 factorial FLARE trial⁷ investigating favipiravir with or without lopinavir–ritonavir for the treatment of patients with COVID-19 opened recruitment in September, 2020, without UK Research and Innovation funding or Urgent Public Health badging. But, in both cases, these high-quality trials requiring 180 patients (AGILE CST-2) or 240 patients (FLARE) took more than 1 year to recruit.

Accordingly, were resources used for rapidly deployed phase 3 platform trials well directed? Had the FLARE trial design been adopted for a platform oral antiviral study, for example, with only 960 participants, eight drugs and their 2 × 2 combinations could have been ruled appropriate or inappropriate for a phase 3 trial.

With large portions of the population having been vaccinated, infected with SARS-CoV-2, or both, rates of so-called hard or severe clinical endpoints, such as hospitalisation and death, have plummeted. Low event rates mean larger sample sizes will be required to detect an effect, threatening the future viability of both antiviral and vaccine phase 3 trials.

The development of COVID-19 vaccines, conducted largely by commercial developers, followed a compressed traditional path, in that no vaccine was taken into a phase 3 trial without first showing it could produce an antibody response in phase 2. A low event rate for traditional phase 3 endpoints is now leading to discussion about so-called correlates of protection:⁸ what level of antibody response can be considered sufficient for licensing a vaccine without large-scale efficacy trials? Perhaps now is the time to start considering a similar approach for antivirals. The modest effect on viral load by favipiravir in early COVID-19⁷ predicted favipiravir's phase 3 failure,⁹ and retrospective



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Lancet Infect Dis 2022

Published Online

October 19, 2022

[https://doi.org/10.1016/](https://doi.org/10.1016/S1473-3099(22)00665-X)

[S1473-3099\(22\)00665-X](https://doi.org/10.1016/S1473-3099(22)00665-X)

See Online/Comment

[https://doi.org/10.1016/](https://doi.org/10.1016/S1473-3099(22)00644-2)

[S1473-3099\(22\)00644-2](https://doi.org/10.1016/S1473-3099(22)00644-2)

studies highlight the relationship between viral load and clinical outcome.¹⁰

In the study by Khoo and colleagues,¹ molnupiravir shortened the time to negative PCR compared with placebo (8 days [95% CI 8–9] vs 11 days [10–11]), although the predefined threshold for recommending molnupiravir for further testing was not reached. As half the participants in the study were unvaccinated and the median age of the study cohort was 43 years (IQR 28–55), whether results will be similar in a largely vaccinated, older population remains to be seen. It is also unknown whether a correlate of protection based only on viral load is possible and whether secondary virological endpoints, such as the evolution of the viral genome sequence or infectivity with time on treatment, correlate with clinical outcome.

JFS received funding for COVID-19 antiviral projects as principal investigator from the Medical Research Council (MR/W015560/1) and as co-investigator from the National Institute for Health and Care Research (PANORAMIC 135366) and LifeArc and is a member of the independent data safety and monitoring committee for the GSK sotrovimab paediatric trial (VIR-7831-5005). AAA is employed on the Medical Research Council grant MR/W015560/1.

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