

What is the place in therapy for nirmatrelvir/ritonavir?

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The COVID-19 pandemic presents substantial challenges for governments and providers keen to provide effective treatments. The tensions between supply, uncertainty of which patient populations optimally benefit, time-limited effectiveness (due to need for rapid initiation of treatment on an individual level, and viral evolution and potential development of resistance on a population level), and action bias (ie, most providers to want to 'do something' for an ailing patient) have incentivised rapid authorisation of therapeutic agents with relatively broad use criteria.¹

Nirmatrelvir/ritonavir (Paxlovid, Pfizer) is a combination protease inhibitor that prevents viral replication of SARS-CoV-2 and was authorised for emergency use in December 2021 for patients age ≥ 12 and weight ≥ 40 kg who have proven mild to moderate COVID-19 and who are considered at high risk for progression to severe disease.² This analysis summarises what is currently known about nirmatrelvir/ritonavir and the discord between clinical trial evidence and real-world usage. We will highlight that the evidence on which the drug was granted emergency approval (high-risk unvaccinated patients during the delta wave) and the patients who are being predominantly treated (including vaccinated patients infected with omicron and its sublineages) differ in expected benefit and that large-scale government purchasing and promotion has been based on the former. Indeed, the influence of vaccine-derived and infection-derived immunity on treatment effect remains largely unknown and non-evidence-based use continues to occur widely.

Efficacy demonstrated in Evaluation of protease inhibition for COVID-19 in high risk

The first available data for nirmatrelvir/ritonavir came from the EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) trial.³ This was a randomised clinical trial in symptomatic, unvaccinated individuals at high-risk for complications of SARS-CoV-2 infection who were treated with either nirmatrelvir/ritonavir or placebo within 5 days of onset of symptoms. 'High risk' referred to those having at least one of the following medical conditions: ≥ 60 years of age; body mass index > 25 kg/m²; cigarette smoking; immunosuppressive disease or prolonged immunosuppression; chronic lung, cardiovascular, kidney or sickle cell disease; hypertension; diabetes;

cancer; neurodevelopmental disorders or other medically complex conditions; or medical-related technological dependence. Patients were excluded if they had a known prior SARS-CoV-2 infection.

Study subjects were enrolled in EPIC-HR during a period when the delta variant predominated and before the global emergence of the Omicron variant. EPIC-HR control patients (ie, placebo-treated patients) had a rate of hospitalisation due to COVID-19 of 6.31%, which was reduced to 0.77% with nirmatrelvir/ritonavir treatment. This 5.5% absolute reduction equated to a number needed to treat (NNT) to prevent one hospitalisation of 18 (95% CI 14 to 25). These findings were the main driver behind global authorisations of this combination product.

Unclear efficacy in present day patients

While the reduction in the need for hospitalisation or death demonstrated in EPIC-HR was impressive, the benefit in the current COVID-19 landscape is unknown. First, it is unknown if the effect size (an 88% relative reduction) would be the same against the less severe Omicron variant and its subvariants. Optimistically, if the relative effect size is fully maintained, the NNT would be expected to be higher as the estimated HR for hospitalisation with Omicron, compared with delta, is 0.41 (0.39–0.43).⁴ Applying the upper bound of the CI for omicron to the risks of hospitalisation in EPIC-HR, the estimated NNT to prevent one hospitalisation becomes 42 (95% CI 29 to 76).

More importantly, the benefit in vaccinated patients, patients with previous infection-based immunity, or patients with hybrid immunity also remains largely unknown. Vaccines and recovery from prior infection have dramatically reduced the risk of infection causing hospitalisation and/or death for most patients. The impact of immune response on these outcomes was demonstrated in EPIC-HR, where the seropositive population (52% of total cohort) demonstrated a lower hospitalisation rate (1.5% untreated vs 0.2% treated, estimated NNT 75 (95% CI 41 to 441)). Adjusting for omicron, the NNT becomes 131 (95% CI 67 to 5561). This is in stark contrast to the benefit demonstrated in seronegative patients at trial enrolment, where treatment with nirmatrelvir/ritonavir decreased the rate of hospitalisation from 11.5% to 1.4%, for an NNT of 10.

A second trial, EPIC-SR (EPIC in Standard-Risk Patients), was designed to investigate the impact of nirmatrelvir/ritonavir on outcomes in standard-risk patients, defined as either

unvaccinated without a high-risk medical condition or vaccinated with a high-risk medical condition. The study enrolled patients from late August to early December 2021, during the delta wave of the pandemic. Interim results from 80% of the study population were announced via press release in December 2021, stating the study was 'fully enrolled' and further data on the rest of the cohort was 'expected to be released later (that) month'.⁵ Unfortunately, the full results of EPIC-SR were not made available until June 2022.⁶ In the interval 6 months, nirmatrelvir/ritonavir use in patients with medical comorbidities beyond those included in EPIC-HR and regardless of vaccination or prior infection has been actively encouraged in broad populations by certain government authorities and national guidelines. Indeed, a report on nirmatrelvir/ritonavir usage in 5287 persons in the USA from 31 December 2021 to 26 May 2022 found 73% of nirmatrelvir/ritonavir recipients had received at least three doses of a COVID-19 vaccine and 43% had no underlying medical conditions.⁷

Unfortunately, the final data from EPIC-SR are only currently available as a press release.⁶ In the overall cohort, there was a non-significant difference in the rate of hospitalisation or death between participants receiving placebo (10/569 (1.8%)) and nirmatrelvir/ritonavir (5/576 (0.9%)). Results were similar in the vaccinated subgroup of 721 adults with at least one risk factor for progression to severe COVID-19 where there were 7/360 (1.9%) hospitalisations in the control arm and 3/361 (0.8%) in the nirmatrelvir/ritonavir arm (RR 0.43; 95%CI 0.11 to 1.64). Despite this unclear benefit on hospitalisation, Pfizer halted the trial, stating 'due to a very low rate of hospitalisation or death observed in the standard-risk patient population, Pfizer has decided to cease enrolment into EPIC-SR and include available data in this month's planned New Drug Application submission to the US Food and Drug Administration (FDA) to support the use of nirmatrelvir/ritonavir in appropriate individuals at high risk of progression to severe illness'.⁶ The findings of EPIC-SR do not necessarily support this statement since benefit was not demonstrated in vaccinated high-risk individuals.

Whether or not an adequately powered EPIC-SR would have demonstrated a statistically significant reduction in hospitalisation with nirmatrelvir/ritonavir is left unknown. However, even if the numerical benefit demonstrated in EPIC-SR held true, this would represent an NNT to prevent one hospitalisation during the delta wave of 91, which is an estimated NNT of 212 for omicron. At this NNT, the cost to prevent one hospitalisation would be estimated at US\$112360 whereas the Medicare cost of a hospitalisation in the unvaccinated era, when outcomes for COVID-19 were worse than today, was estimated at US\$21 752.⁸

While multiple, real-world observational studies have attempted to ascertain the benefit with nirmatrelvir/ritonavir on preventing hospitalisation or death in high-risk vaccinated patients during omicron, these data have numerous biases (eg, immortal time bias, confounding by indication and residual confounding including by vaccine and prior infection status) and for the purposes of drug licensure these are methodologically inappropriate.^{9 10} Even accepting these analyses at face value, no benefit could be demonstrated in patients younger than age 60–65. It remains unclear if nirmatrelvir/ritonavir significantly reduces hospitalisation or death in omicron-infected patients, particularly those who are younger or with vaccine-derived or infection-derived immunity. The ongoing UK PANORAMIC trial may provide more clarity¹¹; however, with control hospitalisation rates of 0.8% in their high-risk molnupiravir trial,¹² the minimal NNT would be 125 even with perfect protection.

Beyond hospitalisation

If hospitalisation will remain an infrequent outcome in vaccinated and/or previously infected individuals, there are other potential benefits to antiviral therapy which merit consideration. First, patients are interested in feeling better, and therefore, a reduction in time to symptom resolution would be an important patient-centred outcome for consideration in treatment decisions. Unfortunately, there is currently no evidence nirmatrelvir/ritonavir impacts this outcome. While symptom resolution was a preregistered secondary outcome in the EPIC-HR trial, these data have not yet been reported in a peer reviewed publication.¹³ In the EPIC-SR press release,⁵ the manufacturer reported no significant difference in the primary outcome of time to sustained symptom resolution. At the interim analysis, the median times to achieving this endpoint was 13 days (95%CI 12 to 15 days) with nirmatrelvir/ritonavir and 13 days (95%CI 11 to 14 days) with placebo.¹⁴

Reduced disease transmission is another potential benefit of antiviral therapy. Given the impressive reduction in viral load over time with receipt of nirmatrelvir/ritonavir in EPIC-HR, this is an often given reason for widespread usage. However, to date, no study has assessed this endpoint, and enthusiasm for significantly reducing transmission in a non-immune naïve population is tempered by both the more modest benefit on viral load demonstrated in seropositive patients in the EPIC-HR trial and the press-release reporting no significant benefit of nirmatrelvir/ritonavir in postexposure prophylaxis study.¹⁵

Moreover, attention is now being turned to a paradoxical relapse of symptoms, associated with increased nasopharyngeal viral load, following completion of treatment with nirmatrelvir/ritonavir. Importantly, the incidence of this phenomenon, whether it is more common with receipt of nirmatrelvir/ritonavir versus untreated patients with omicron, or whether retreatment offers any benefit is currently unknown; however, it was estimated at 2% in EPIC-HR.^{16 17} This is clearly an area that needs further investigation, for if it is causally associated with receipt of nirmatrelvir/ritonavir in vaccinated patients, it may paradoxically prolong the duration of symptoms, the length of time needed in isolation, and/or the transmission risk of a given patient, and this would need to be weighed against risk of progression to severe disease.

Finally, whether nirmatrelvir/ritonavir reduces 'Long Covid' is also of great interest, but without a formal and accepted case definition for the post-COVID-19 condition and studies specifically evaluating treatment against blinded controls, any impact on this outcome is purely speculative. In summary, there is a lack of evidence supporting significant impact on any secondary targets of antiviral therapy.

Political and public demand for care of low or unproven value

When the topline results were first announced by Pfizer via press release, nirmatrelvir/ritonavir was widely touted as a 'game-changer'. Indeed, in the unvaccinated, high-risk population studied, the efficacy was comparable to or better than all other agents studied. Therefore, in the interest of public health, governments made substantial advanced purchases of this antiviral despite no public release of the specific data beyond the press releases. To date, there has not been transparency about which data was used to support these purchases and it is unclear what will support purchase decisions moving forward. Pfizer projects US\$22 billion in sales for 2022,¹⁸ with most sales going to high-income countries; 20 million courses were sold to the USA alone.¹⁹

Care that is medically unnecessary and provides no appreciable health benefits to patients is low value. High-income countries are burdened by low value care. For instance, low value care is estimated to cost the US healthcare system US\$76–US\$101 billion annually.²⁰ It includes overtreatment—typified by antimicrobial overuse—and is driven by multiple factors on both treatment demand and supply sides. With the COVID-19 pandemic, an easy to access, relatively cheap (for the patient) treatment that could prevent severe illness and hospitalisation has been highly sought after. The arrival of nirmatrelvir/ritonavir, touted as a ‘risk-free cure’, has raised patient expectations of being able to abandon pandemic public health measures. Governments have encouraged this behaviour, and many have lowered the threshold to receive nirmatrelvir/ritonavir below those in EPIC-HR. The result is that millions of patients are being exposed to a drug which is relatively untested at a cost of billions of dollars. The side effects and drug–drug interactions are potentially understated, as patients are encouraged to take a medication that is potentially not beneficial but likely to cause significant dysgeusia and create need for adjustment/management of concomitant medications. In addition, patients residing in areas of high social vulnerability are still underrepresented and untreated, further widening social and economic gaps.²¹

Conclusions and future directions

Based on what is currently known, the benefit from the routine use of nirmatrelvir/ritonavir for immunocompetent patients who are vaccinated and/or have already recovered from COVID-19 on hospitalisation or death remains uncertain. While there are an increasing number of retrospective, observational studies supporting use of nirmatrelvir/ritonavir in ‘high-risk’ vaccinated patients, they suffer from varying degrees of immortal time bias, confounding by indication and residual confounding by vaccine status, and therefore, likely represent the most optimistic view of efficacy.

Unfortunately, the non-evidence-based approach to use of this oral antiviral agent will continue and likely be exacerbated by full FDA approval. There will remain a critical need for reassessment of what constitutes optimal, cost-effective care with nirmatrelvir/ritonavir. The haste with which COVID-19 therapeutics moved in 2020 and 2021 may no longer be necessary in 2022 and beyond. Unfortunately, SARS-CoV-2 is now here for the long term, and it seems reasonable to make judgements for how we will purchase and prioritise therapies with this in mind prior to repeating lessons from the past.²²

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