Oral antivirals for acute symptoms and post-acute sequelae in SARS-CoV-2 infection

In *The Lancet Infectious Diseases*, Huwen Wang and colleagues[1] reported the outcomes of all adults admitted to hospital in Hong Kong with COVID-19 between March, 2022, and October, 2023. The study was a nationwide, retrospective cohort study, and examined 50 055 patients, of whom 15 242 (30%) were treated with nirmatrelvir–ritonavir within 5 days of symptom onset. Starting after 3 weeks of first positive test for SARS-CoV-2, those who were treated with nirmatrelvir–ritonavir had significantly lower hazards of death, and heart, lung, and kidney complications than patients with COVID-19 who did not receive nirmatrelvir–ritonavir.[1] The benefit of nirmatrelvir–ritonavir was more pronounced in patients aged 65 years and older and in those who had completed the three-dose SARS-CoV-2 vaccination schedule, although subgroup analyses relied on smaller numbers than the main analysis and some had sparse data.

Previous studies assessing the benefit of nirmatrelvir–ritonavir for post-acute death and complications had been conducted in patients at high risk of poor outcomes, with mild to moderate COVID-19, who had not been admitted to hospital. One study conducted in the USA showed a protective effect of nirmatrelvir–ritonavir,[2] whereas another two studies found no protective effect on post-acute death or sequelae.[3,4] Therefore, to our knowledge, Wang and colleagues' study is the first showing that nirmatrelvir–ritonavir benefits patients admitted to hospital with COVID-19, reducing post-acute death and mid-term to long-term complications.

Several caveats of the study should be taken into account. First, patients had to survive the first 21 days after COVID-19 diagnosis to be evaluated. Thus, premature deaths were not assessed, a fact that could have influenced the results. Second, patients should have no contraindications for nirmatrelvir–ritonavir use, including the use of drugs with potential serious drug–drug interactions (eg, amiodarone, rifampicin, phenobarbital, carbamazepine, and phenytoin). Nearly 13% of patients were excluded from the study for this reason. Third, criteria for nirmatrelvir–ritonavir prescription were not uniform, and instead relied on individual physician decision. Because the study was observational and retrospective, unnoticed biases might have occurred in this real-world analysis. Fourth, almost all patients with COVID-19 in Hong Kong during the study period had their first SARS-CoV-2 infection when omicron (BA.2.2) was the predominant circulating variant. Compared with the previous delta variant (B.1.617.2 and its sublineages), omicron has been associated with milder disease severity.[5]

Nirmatrelvir–ritonavir targets the SARS-CoV-2 main protease, an enzyme crucial for viral replication. Ritonavir boosts the effect of nirmatrelvir by inhibiting the enzyme CYP3A4, which is responsible for its metabolism.[6] More antivirals are needed for patients who cannot be treated with nirmatrelvir–ritonavir owing to the risk of drug–drug interactions, and for individuals in whom vaccines are less effective, such as immunocompromised patients.

A phase 3 trial, reported in 2023, assessed the efficacy and safety of mindeudesivir, an oral derivate of remdesivir, a coronavirus polymerase inhibitor.[7] In adults with mild-to-moderate COVID-19 who were at risk for progression, mindeudesivir was non-inferior to nirmatrelvir–ritonavir with respect to the time to sustained clinical recovery, with fewer safety concerns. Mindeudesivir does not inhibit or induce major drug-metabolising enzymes or inhibit major drug transporters, so interaction with concomitant medications is unlikely.

Ensitrelvir and leritrelvir are other new oral antivirals that block the SARS-CoV-2 main protease after binding covalently to its catalytic site. Both depict a longer half-life than nirmatrelvir and do not need to be boosted pharmacokinetically with ritonavir. Of note, all these coronavirus protease inhibitors share cross-resistance to some extent, which might compromise their use after treatment failure with one of them. Ensitrelvir has already been approved in Japan[8] and leritrelvir in China to treat SARS-CoV-2.[9]

After the first unprecedented 2 years of the COVID-19 pandemic and the success of vaccination,[10] post-acute sequelae of COVID-19 either measured at 3 weeks and beyond after first diagnosis (as in Wang and colleagues'

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Lancet Infect Dis 2024

Published Online
May 3, 2024
https://doi.org/10.1016/S1473-3099(24)00258-5

See Online/Articles
https://doi.org/10.1016/S1473-3099(24)00217-2

study) or after 3 months, defined as long COVID,[11] have become a major research area. Post-COVID-19 condition might affect 10% of people with acute SARS-CoV-2 infection and seems to be caused by immune activation and inflammatory processes triggered by the initial viral replication. Current data, including the results from Wang and colleagues' study,[1] support a mechanistic view in which reducing viral replication might be important for improving mid-term to long-term clinical outcomes.

Given that the benefit conferred by nirmatrelvir–ritonavir is not complete and combination with intravenous monoclonal antibodies such as sotrovimab has already shown to enhance protection,[12] it would be worth exploring whether combination therapy with oral antivirals with distinct inhibitory mechanisms could improve clinical outcomes in both outpatients and inpatients in terms of ameliorating acute symptoms and sequelae of COVID-19.

In summary, oral antiviral agents given promptly could help mitigate hospitalisation burden, facilitate post-exposure prophylaxis, reduce post-COVID-19 sequelae, and potentially minimise household transmission of SARS-CoV-2 infection. Thus, clinical development of antivirals against SARS-CoV-2 should remain a priority. Antivirals are a powerful complement to vaccines and will help to further ameliorate the global clinical burden of COVID-19 in the coming years.

We declare no competing interests.

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