Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Early oral antiviral use in patients hospitalised with COVID-19

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Nearly 2 years after the emergence of SARS-CoV-2, two oral antiviral drugs, molnupiravir and nirmatrelvir–ritonavir, which reduce the risk of COVID-19 progression and death in patients at high risk, were approved for emergency use.

In *The Lancet Infectious Diseases*, Carlos K H Wong and colleagues[1] reported the results of a retrospective analysis evaluating the effectiveness of these two antivirals in patients with mild-to-moderate COVID-19 in a real-world setting. The study included patients admitted to hospital during the SARS-CoV-2 omicron BA.2 wave in Hong Kong between Feb 26, 2022, and April 26, 2022, and who did not require supplemental oxygen at the time of admission. From a cohort of 40 776 hospitalised adult patients with SARS-CoV-2 infection confirmed by RT-PCR or rapid antigen test, the analyses included 1856 patients who received molnupiravir and 890 who received nirmatrelvir–ritonavir who were propensity-score matched (1:1) with control patients (those not treated with either oral antiviral) for comparison. For both antivirals, treatment was started within 2 days of admission to the hospital. In patients with a known date of symptom onset (almost half of the patients), the median time from symptom onset to drug administration was 1 day (IQR 1–3) for both drugs. Early administration of oral antivirals in patients with mild-to-moderate COVID-19 was associated with a significantly lower risk of all-cause mortality (hazard ratio 0·48 [95% CI 0·40–0·59], p<0·0001 for molnupiravir *vs* matched controls; 0·34 [0·23–0·50], p<0·0001 for nirmatrelvir–ritonavir *vs* matched controls). Reduced risk of the composite outcome of disease progression (which consisted of all-cause mortality, initiation of invasive mechanical ventilation, admission to an intensive care unit, or the need for oxygen therapy) was also found in oral antiviral recipients compared with their respective control groups (0·60 [0·52–0·69], p<0·0001 for molnupiravir; 0·57 [0·45–0·72], p<0·0001 for nirmatrelvir–ritonavir). Additionally, a low viral load (cycle threshold value ≥30 on RT-PCR) was reached more rapidly in oral antiviral recipients than in the corresponding matched control groups.

The study was not a head-to-head comparison between the two antivirals because of the imbalance in baseline characteristics between the groups. Mean age was higher in molnupiravir recipients (80·8 years [SD 13·0]) than in nirmatrelvir–ritonavir recipients (77·2 years [14·1]), as was the proportion of patients older than 65 years (87·6% *vs* 82·6%), while the proportion of fully vaccinated patients, defined as those who had received at least two doses of Comirnaty or three doses of CoronaVac, was lower (6·2% *vs* 10·5%). The burden of comorbidities also differed, with a higher mean score on the Charlson's Comorbidity Index in molnupiravir recipients (5·8 [SD 1·9]) than in nirmatrelvir–ritonavir recipients (5·1 [1·7]). Unfortunately, detailed information about the type of comorbidities was not available.

These are, to our knowledge, the first published data on the use of both molnupiravir and nirmatrelvir–ritonavir in a real-world setting during a pandemic wave dominated by the SARS-CoV-2 omicron variant. This analysis of the use of these oral antivirals in clinical practice[1] supports the results of in-vitro studies documenting the drugs' efficacy against the omicron variant.[2] The added value of Wong and colleagues' study is the inclusion of a cohort consisting mainly of older adults with multiple pre-existing comorbidities who were not fully vaccinated—a group with a high risk of fatal disease progression. For patients with such characteristics, the US Food and Drug Administration issued an emergency use authorisation for both oral antivirals in late December, 2021, although this was based on data from the randomised trials MOVe-OUT[3] and EPIC-HR,[4] conducted in non-hospitalised patients before the period of omicron dominance. Although the analysis by Wong and colleagues[1] looks at hospitalised patients, the baseline characteristics of the cohort are more similar to those of the outpatient populations in the MOVe-OUT[3] and EPIC-HR[4] studies than to those of the hospitalised patients included in the MOVe-IN study[5] of molnupiravir (which was discontinued because of a lack of benefit), in which most participants had moderate-to-severe COVID-19 and about half required oxygen supplementation. Notably, the MOVe-IN study

included patients infected with previous variants of SARS-CoV-2. Another real-world study, from Poland, which also included inpatients from the omicron wave period, showed that molnupiravir administered in the first 5 days after symptom onset reduced the frequency of death among patients older than 80 years by more than half.[6] Three more real-world analyses evaluating the use of nirmatrelvir–ritonavir during the omicron wave are also available.[7–9] One study from the USA that included patients aged 50 years and older,[7] one from Israel that analysed a subgroup of patients aged 65 years and older,[8] and another from Israel that included patients with a mean age of 68·5 years,[9] showed that early nirmatrelvir–ritonavir therapy was associated with reductions in the risks of hospitalisation or death, or both, in these groups of patients with COVID-19.

In summary, the results of Wong and colleagues' study, conducted in a real-world setting, support the early use of oral antiviral drugs in patients with mild-to-moderate COVID-19 who are at high risk, regardless of whether they are in outpatient or inpatient care.

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1 Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. Real-world effectiveness of early molnupiravir or nirmatrelvir–ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: an observational study. *Lancet Infect Dis* 2022; published online Aug 24. https://doi.org/10.1016/S1473-3099(22)00507-2.

2 Vangeel L, Chiu W, De Jonghe S, et al. Remdesivir, molnupiravir and nirmatrelvir remain active against SARS-CoV-2 omicron and other variants of concern. *Antiviral Res* 2022; **198:** 105252.

3 Jayk Bernal A, Gomes da Silva MM, Musungaie DB, et al. Molnupiravir for oral treatment of COVID-19 in nonhospitalized patients. *N Engl J Med* 2022; **386:** 509–20.

4 Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N Engl J Med* 2022; **386:** 1397–408.

5 Arribas JR, Bhagani S, Lobo SM, et al. Randomized trial of molnupiravir or placebo in patients hospitalized with COVID-19. *NEJM Evidence* 2022; **1:** EVIDoa2100044.

6 Flisiak R, Zarębska-Michaluk D, Rogalska M, et al. Real-world experience with molnupiravir during the period of SARS-CoV-2 omicron variant dominance. *Pharmacol Rep* 2022 (in press). https://doi.org/10.1007/S43440-022-00408-6.

7 Dryden-Peterson S, Kim A, Kim AY, et al. Nirmatrelvir plus ritonavir for early COVID-19 and hospitalization in a large US health system. *medRxiv* 2022; published online June 17. https://doi.org/10.1101/2022.06.14.22276393 (preprint, version 2).

8 Arbel R, Sagy YW, Hoshen M, et al. Oral nirmatrelvir and severe COVID-19 outcomes during the omicron surge. *Research Square* 2022; published online June 1. https://doi.org/10.21203/rs.3.rs-1705061/v1 (preprint).

9 Najjar-Debbiny R, Gronich N, Weber G, et al. Effectiveness of Paxlovid in reducing severe COVID-19 and mortality in high risk patients. *Clin Infect Dis* 2022; published online June 2. https://doi.org/10.1093/cid/ciac443.