

COVID-19 residual symptoms and adverse drug reactions after oral antiviral therapy in the Singapore primary care setting

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Dear Editor,

The COVID-19 pandemic remains a significant public health threat with over 7 million deaths worldwide (as of 14 January 2024).¹ In Singapore, oral antivirals (OAVs) nirmatrelvir/ritonavir and molnupiravir were approved in 2022 for treating mild-to-moderate COVID-19 in adults at risk of progression to severe disease.^{2,3} Clinical trials in Western populations showed nirmatrelvir/ritonavir having higher efficacy in reducing hospitalisations and mortality by 88% compared to 30% for molnupiravir.^{2,4} A Singapore study showed nirmatrelvir/ritonavir's effectiveness in reducing hospitalisation and severe COVID-19.⁵ However, further research is needed on potential adverse drug reactions (ADRs) and control of COVID-19 symptoms in Asian populations. This study focused on the short-term safety and efficacy of nirmatrelvir/ritonavir and molnupiravir, examining associations between OAV type and dose on the incidence of ADRs and COVID-19 residual symptoms 7 days post-treatment.

A retrospective review was performed on COVID-19 patients from primary care polyclinics treated with OAVs within 5 days of symptom onset, from July 2022 to October 2022. Patients were prescribed 1 of the following for 5 days: (1) nirmatrelvir 300 mg/ritonavir 100 mg twice daily (full dose), (2) nirmatrelvir 150 mg/ritonavir 100 mg twice daily (renally adjusted dose) if impaired renal function or (3) molnupiravir 800 mg twice daily if contraindicated to nirmatrelvir/ritonavir.^{2,3} OAV eligibility, type, dose and potential drug interactions were reviewed by physicians and pharmacists following guidelines from National Centre for Infectious Diseases.⁶ Renal function was assessed using estimated glomerular filtration rate (eGFR) (Chronic Kidney Disease Epidemiology Collaboration) if <75 years or creatinine clearance (Cockcroft-Gault) if ≥75 years, considering eGFR may overestimate kidney function in the elderly.

Follow-up occurred 7 days post-treatment over phone interviews by pharmacists. Patients who

were uncontactable or did not start OAVs were excluded. The following outcomes on day 7 were compared across the 3 OAV cohorts: (1) ADRs reflecting short-term safety, categorised into allergic reactions or side effects, and (2) COVID-19 residual symptoms reflecting short-term efficacy on COVID-19 symptom control. Hypothesis testing and multivariable logistic regression were used to evaluate associations between OAV type, dose, adherence and demographics on the outcomes. Statistical analyses were performed using R statistical software version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria), with $P < 0.05$ deemed significant.

The study population comprised 902 patients, 66.6% on nirmatrelvir/ritonavir full dose, 21.1% on nirmatrelvir/ritonavir renal dose and 12.3% on molnupiravir. Nirmatrelvir/ritonavir renal dose patients were the oldest, followed by molnupiravir then nirmatrelvir/ritonavir full dose (mean age 77 versus [vs] 72 vs 64 years, $P < 0.001$). The 3 cohorts were similar for sex, ethnicity and OAV adherence. Overall, patients were adherent to completing the 5-day course (nirmatrelvir/ritonavir full dose 90.2% vs nirmatrelvir/ritonavir renal dose 88.4% vs molnupiravir 85.6%, $P = 0.33$).

The incidence of allergic reactions was low (molnupiravir 7.2% vs nirmatrelvir/ritonavir full dose 5.5% vs nirmatrelvir/ritonavir renal dose 2.1%, $P = 0.07$). However, gastrointestinal side effects were most common. Nirmatrelvir/ritonavir full dose had the highest incidence of diarrhoea, followed by nirmatrelvir/ritonavir renal dose, then molnupiravir (28.8% vs 20.0% vs 9.9%, $P < 0.001$). Dysgeusia was also more common with nirmatrelvir/ritonavir full dose than renal dose, but none for molnupiravir (18.8% vs 9.5% vs 0%, $P < 0.001$).

After adjusting for baseline age, sex, ethnicity and OAV adherence, molnupiravir was associated with significantly less gastrointestinal side effects compared to nirmatrelvir/ritonavir full dose, with an

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adjusted odds ratio (OR) of 0.42 (95% confidence interval [CI] 0.24–0.75, Table 1). OAV type and dose were otherwise not significantly associated with allergic reactions.

Although molnupiravir was associated with more COVID-19 residual symptoms, it was not statistically significant with an adjusted OR of 1.32 (95% CI 0.86–2.04, Table 1). OAV type and dose were thus not significantly associated with COVID-19 residual symptoms, with similar incidence (40%) across the 3 cohorts ($P=0.65$).

In this retrospective review, molnupiravir was associated with significantly less gastrointestinal

and dysgeusia ADRs than nirmatrelvir/ritonavir full dose. Both OAVs were well tolerated with low incidence of allergic reaction and consistent with clinical trials.^{2–4} However, observed incidence of diarrhoea (9.9–28.8%) and dysgeusia (9.5–18.8%) were higher compared to Western populations (diarrhoea 2–4%, dysgeusia 6%).^{2,3} A Korean study found similar high incidence of dysgeusia (23.8%) for nirmatrelvir/ritonavir,⁷ thus suggesting poorer tolerance in Asians. They reported lower incidence of diarrhoea (1.7–3.3%) contrary to our results, which could be due to ethnic differences or confounded by diarrhoea also being early symptoms of COVID-19.⁸

Table 1. Regression analysis of adverse drug reactions and COVID-19 residual symptom on day 7.

	Safety outcomes: allergic reactions ^a		Safety outcomes: gastrointestinal side effects ^b		Efficacy outcomes: COVID-19 residual symptoms ^c	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age	0.98 (0.95–1.00)	0.06	0.98 (0.96–0.99)	0.002	0.98 (0.96–0.99)	<0.001
Sex						
Female	Reference					
Male	0.76 (0.40–1.42)	0.39	0.81 (0.59–1.09)	0.17	0.73 (0.55–0.96)	0.02
Ethnicity						
Chinese	Reference					
Malay	0.12 (0.02–0.88)	0.04	0.51 (0.30–0.86)	0.01	1.02 (0.67–1.56)	0.92
Indian	0.38 (0.09–1.67)	0.20	0.73 (0.40–1.31)	0.29	0.42 (0.24–0.76)	0.004
Others ^d	0.00 (0 to infinity)	0.98	0.73 (0.18–2.90)	0.66	0.89 (0.26–3.05)	0.86
Completed OAV course						
No ^e	Reference					
Yes	0.16 (0.08–0.31)	<0.001	0.69 (0.44–1.11)	0.13	0.84 (0.54–1.30)	0.42
OAV prescribed						
Nirmatrelvir/ritonavir full dose	Reference					
Nirmatrelvir/ritonavir renal dose	0.43 (0.14–1.31)	0.14	0.78 (0.51–1.20)	0.26	1.22 (0.83–1.79)	0.31
Molnupiravir	1.41 (0.60–3.34)	0.43	0.42 (0.24–0.75)	0.003	1.32 (0.86–2.04)	0.21

CI: confidence interval; OAV: oral antiviral; OR: odds ratio

^a Allergic reactions included rash, itch, eye swelling or unspecified reactions.

^b Gastrointestinal side effects included diarrhoea, nausea or vomiting.

^c COVID-19 residual symptoms included cough, sore throat, flu-like symptoms, blocked nose or phlegm.

^d Others refer to 5 European and 6 unspecified.

^e Patients reporting “No” discontinued the OAV from days 2 to 4. Reasons for OAV discontinuation were adverse drug reaction, improvement of condition, subsequent negative antigen rapid test results or hospital admission.

For short-term efficacy, no significant differences in COVID-19 residual symptoms were observed between both OAVs. Despite nirmatrelvir/ritonavir's higher efficacy in reducing hospitalisations and mortality,²⁻⁴ our study demonstrated that both OAVs appeared similarly effective in reducing COVID-19 residual symptoms by day 7. Another study also found similar rates of persistence of COVID-19-related symptoms at 30 days between nirmatrelvir/ritonavir (15.9%) and molnupiravir (11.2%).⁹ However, a confounder not assessed in our study was OAV administration timing. Early OAV administration may result in improved efficacy by targeting the initial rapid viral replication phase.⁴ Patients should thus be counselled on possible symptom persistence regardless of the OAV prescribed.

Comparing nirmatrelvir/ritonavir full and renal dose showed no significant difference in ADRs or COVID-19 residual symptoms. This may be due to similar resultant drug exposure between both cohorts after accounting for impaired renal clearance by dose reduction. Literature suggests OAVs have heterogeneous outcomes in different populations,⁴ thus future studies could guide nirmatrelvir/ritonavir dose optimisation in various comorbidities.

Both OAVs also showed similar high adherence rates, reflecting patients' tolerability and acceptance. The cost of OAVs and ancillary investigations (e.g. COVID-19 testing) were fully subsidised to ensure treatment access. OAV adherence would thus ensure cost-effective use of healthcare resources, as OAVs are increasingly prescribed in primary care.

The study limitations include absence of a control group of COVID-19 positive patients without OAV therapy, due to the retrospective design and small sample of such patients in primary care. There were unmeasured confounders, such as comorbidities or vaccination status, although OAV adherence and baseline demographics were adjusted for. To our knowledge, this study is the first in Singapore's primary care to provide real-world data on the short-term safety and efficacy outcomes of OAVs, potentially encouraging OAV uptake for timely treatment to mitigate the disease burden of COVID-19. Future studies could explore long-term outcomes of OAVs such as COVID-19 rebound in multiethnic Asian populations.

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Ethics statement

The study was approved by the National Healthcare Group Domain Specific Review Board (2023/00464) and granted a waiver of informed consent owing to the de-identified data and retrospective nature.

Declaration

The authors declare there are no affiliations with or involvement in any organisation or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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