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RESEARCH LETTER

Oral antiviral therapies for COVID-19 in patients with advanced chronic kidney disease or kidney failure

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As of December 2022, over 651 million people have been diagnosed with coronavirus disease 2019 (COVID-19) and 6.6 million people have died of COVID-19 [1]. Chronic kidney disease (CKD) is an important independent risk factor for hospitalization and death due to COVID-19 [2, 3]. Although case fatality has decreased since the introduction of effective vaccines, patients with advanced CKD and kidney failure requiring kidney replacement therapy remain at high risk for severe COVID-19 outcomes; a recent report by Bell and colleagues found a 7% 30-day mortality risk after COVID-19 diagnosis in fully vaccinated patients with kidney failure [4]. Vaccine effectiveness may be attenuated in patients with kidney failure, and monoclonal therapies are no longer effective against current Omicron variants [5, 6]. Thus, there is a pressing need for effective antiviral therapies to decrease morbidity and mortality in this population. Nirmatrelvir/ritonavir and molnupiravir each received emergency use authorization (EUA) from the Food and Drug Administration in December 2021. Patients with advanced CKD [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2] and kidney failure were excluded from the trials that led to the approval of these agents [7, 8]. The EUA for molnupiravir includes all levels of eGFR because pharmacokinetic studies demonstrated that kidney impairment had a small impact on drug levels [8]; however, there are limited data on its use in advanced CKD and kidney failure. In contrast, a pharmacokinetic study of nirmatrelvir/ritonavir demonstrated significantly higher drug exposures in patients with impaired kidney function which led to the recommendation that the dose be reduced to 150/100 mg twice daily for patients with eGFR 30–59 mL/min/1.73 m^2, and that nirmatrelvir/ritonavir be avoided in patients with eGFR <30 mL/min/1.73 m^2 [9]. Because limited data exist on the use of either molnupiravir or nirmatrelvir/ritonavir in patients with eGFR <30 mL/min/1.73 m^2, we sought to characterize real-world use within our healthcare network.

In a large healthcare system providing care for 1.5 million patients in Massachusetts and New Hampshire, we identified patients who were prescribed molnupiravir or nirmatrelvir/ritonavir between January and October 2022, during which Omicron and its subvariants have been the predominant strains in the USA [10]. We included those with eGFR <30 mL/min/1.73 m^2 or kidney failure before beginning oral antiviral therapy. We defined baseline eGFR as the median of all eGFR measurements between 14 and 365 days prior to diagnosis of COVID-19 [11]. We reviewed all clinical documentation between the start date and 4 weeks after therapy completion to identify potential adverse events (AEs). This study was approved by the Mass General Brigham Institutional Review Board; the need for informed consent was waived.

A total of 27 patients met the inclusion criteria; 15 received molnupiravir and 12 received dose-reduced nirmatrelvir/ritonavir. Baseline characteristics, comorbidities, concurrent monoclonal antibody use, vaccination status and type of COVID-19 diagnostic tests are shown in Table 1. Overall, the majority had pre-dialysis CKD, and more patients with kidney failure were prescribed molnupiravir (Table 1). All patients had previously received the primary series of COVID-19 vaccination prior to infection; the majority (77.7%) had received at least one booster. Diagnosis was confirmed in the outpatient setting in all cases, using an antigen test (N = 12, 44%) or reverse transcriptase polymerase chain reaction testing (N = 15, 56%). Fever and cough were the most common presenting symptoms (Table 1).

AEs were more common in patients receiving nirmatrelvir/ritonavir; eight patients (66.7%) reported at least one AE (Table 1). AEs that occurred in more than one patient receiving nirmatrelvir/ritonavir included dysgeusia, gastrointestinal upset, dyspnea and fatigue. One patient (8.3%) discontinued nirmatrelvir/ritonavir early due to

Table 1: Patient characteristics and adverse events.

Patient characteristics	Molnupiravir $N = 15$	Nirmatrelvir/ritonavir $N = 12$
Age (years), median (IQR) mean (Range)	76 (49–96)	76 (51–96)
Female sex, *n* (%)	10 (66.7)	3 (25)
Time from symptom onset to medication start (days), median (IQR)	2 (0–5)	1.9 (0–4)
Race/ethnicity, *n* (%)		
White	14 (93.3)	10 (83.3)
Black	0 (0)	1 (8.3)
Hispanic	0 (0)	0 (0)
Asian	1 (6.7)	1 (8.3)
Other	0 ()	0 (0)
Comorbidities, *n* (%)		
Hypertension	14 (93.3)	12 (100)
Coronary artery disease	8 (53.3)	8 (66.7)
Diabetes mellitus	9 (60)	10 (83.3)
Cirrhosis	0 (0)	0 (0)
Medication use, *n* (%)		
ACEi/ARB	11 (73.3)	12 (100)
Proton pump inhibitors	10 (66.7)	8 (66.7)
Diuretics	11 (73.3)	9 (75)
Immunosuppressants[a]	4 (26.7)	1 (8.3)
CKD stage, *n* (%)		
Stage 4 (eGFR 15–30 mL/min/1.73 m^2)	11 (73.3)	11 (91.7)
Stage 5 (eGFR <15 mL/min/1.73 m^2)	1 (6.7)	0 (0)
Stage 5D, receiving KRT	3 (20)	1 (8.3)
Baseline labs, median (IQR)		
Serum albumin (g/dL)	3.8 (2.4–4.5)	4.2 (3.7–4.5)
Hemoglobin (g/dL)	9.9 (7.4–12.6)	11.9 (9.1–16.1)
Platelet count (1000/μL)	255.5 (94–333)	180.6 (120–252)
AST (U/L)	19.4 (14–38)	20 (15–24)
ALT (U/L)	14.9 (5–39)	17 (10–19)
COVID-19 vaccination status, *n* (%)		
Primary series	15 (100)	12 (100)
At least 1 booster dose	11 (73.3)	10 (83.3)
COVID-19 symptoms at presentation, *n* (%)		
Cough	12 (80)	6 (50)
Fever	9 (60)	1 (8.3)
Congestion	4 (26.7)	3 (25)
Shortness of breath	2 (13.3)	2 (16.7)
Gastrointestinal upset	2 (13.3)	2 (16.7)
Asymptomatic prior to initiating antiviral therapy	0 (0)	1 (8.3)
Concurrent treatment with monoclonal antibody	2 (13.3)	1 (8.3)
Adverse event summary[b], *n* (%)		
Any AE	3 (20)	8 (66.7)
AE leading to treatment discontinuation[c]	3 (20)	2 (16.7)
Hospitalization within 4 weeks	2 (13.3)	2 (16.7)
Hospitalized for severe COVID-19	0 (0)	0 (0)
Adverse events reported, *n* (%)		
Gastrointestinal upset	3 (20)	2 (16.7)
Dysgeusia	0 (0)	3 (25)
Dry mouth	0 (0)	1 (8.3)
Fatigue	0 (0)	2 (16.7)
Dizziness	0 (0)	1 (8.3)
Dyspnea	1 (6.7)	2 (16.7)
Myalgia	0 (0)	1 (8.3)
Insomnia	1 (6.7)	0 (0)
Delirium	1 (6.7)	0 (0)
Gout	0 (0)	1 (8.3)
Worsening kidney function[d]	0 (0)	1 (8.3)
Unresolved COVID-19 symptoms	0 (0)	3 (25)
Drug–drug interaction requiring medication adjustment[e], *n* (%)	0 (0)	7 (58.3)

Among the patients with kidney failure, the three treated with molnupiravir included two receiving hemodialysis and one receiving peritoneal dialysis. The one patient with kidney failure who was treated with nirmatrelvir/ritonavir was receiving hemodialysis.

[a]Immunosuppressant therapy used in molnupiravir-treated patients were prednisone and mycophenolate; nirmaltrelvir/ritonavir-treated patients were on daratumumab and dexamethasone.

[b]Adverse events included any adverse events that occurred within 4 weeks of initiating oral antiviral therapy.

[c]Molnupiravir (discontinued on Day 1 and 3 of the regimen due to gastrointestinal upset), an additional patient discontinued on Day 4 due to hospitalization for hallucinations (see text); nirmaltrevir/ritonavir (discontinued on Day 1 of the regimen due to gastrointestinal upset).

[d]Worsening kidney function was defined by hospitalization for worsening kidney function or a rise in serum creatinine rising $\geq$1.5 times baseline anytime during treatment or within 4 weeks of treatment completion.

[e]The drugs withheld due to drug–drug interaction were apixaban, oxycodone, atorvastatin, hydrocodone, tamsulosin and dexamethasone.

IQR, interquartile range; AST, aspartate aminotransferase; ALT, alanine transaminase; ACEi/ARB, angiotensin-converting enzyme inhibitor or angiotensin II receptor blockade; KRT, kidney replacement therapy.

gastrointestinal upset. Two patients (16.7%) were hospitalized within 4 weeks of medication completion. One was hospitalized due to an acute gout flare 2 weeks after completing nirmatrelvir/ritonavir, and another was hospitalized 4 days after completing nirmatrelvir/ritonavir due to fatigue and worsening kidney function; her serum creatinine had increased from 1.6 mg/dL pre-treatment to 2.4 mg/dL, but she had also been prescribed trimethoprim (800 mg)/sulfamethoxazole (160 mg) twice per day for a skin infection during this time. Her creatinine quickly normalized with intravenous hydration. Drug–drug interactions were common in patients treated with nirmatrelvir/ritonavir; seven patients (58.3%) required an adjustment to one or more medications due to the FDA-reported significant drug interactions (Table 1 footnote).

Only three (20%) molnupiravir-treated patients experienced AEs. The only AE affecting more than one molnupiravir-treated patient was gastrointestinal upset in three cases (20%), which caused two to discontinue therapy early (13.3%) (Table 1). Two patients (13.3%) were hospitalized within 4 weeks. One had an exacerbation of schizoaffective disorder and was admitted on Day 3 of therapy due to worsening insomnia and visual hallucinations triggered by either molnupiravir or COVID-19. Another patient, who had discontinued therapy early due to gastrointestinal upset, was admitted 7 days later due to an exacerbation of congestive heart failure attributed to COVID-19. Neither required supplemental oxygen nor additional therapy for COVID-19.

In our healthcare system, we found that oral antiviral use was uncommon in patients with advanced CKD and kidney failure; we identified only 27 treated patients in the first 10 months since EUA. Due to the retrospective nature of the study and limited availability of follow-up labs and clinical documentation in certain patients, causality of AEs could not be ascertained from our observations; however, molnupiravir and nirmatrelvir/ritonavir were reasonably well tolerated in patients with advanced CKD and kidney failure, with only five patients discontinuing treatment due to AEs [three patients (20%) on molnupiravir and two patients (16.7%) on nirmatrelvir/ritonavir]. None of the patients hospitalized within 4 weeks was admitted due to severe COVID-19 nor were their admissions convincingly related to an adverse drug reaction. Another recent report also found that that modified dose of nirmaltrelvir/ritonavir (300/100 mg on Day 1 followed by 150/100 mg daily from Days 2–5) was well-tolerated in patients with kidney failure, with very high rates of treatment completion, no severe AEs and no COVID-19-related deaths within 30 days [12]. There are drawbacks to each antiviral: drug–drug interactions are common in patients receiving nirmatrelvir/ritonavir, whereas molnupiravir has lower efficacy and potential to accelerate the rate of mutations, some of which may be transmitted [8, 13].

As monoclonal antibodies are no longer authorized for the early treatment of COVID-19, there remains a tremendous need for more data to inform the safety and effectiveness of COVID-19 therapies in patients with advanced CKD and kidney failure.

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