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Safety and efficiency of molnupiravir for COVID-19 patients with advanced chronic kidney disease

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Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is particularly life threatening in patients who are immunocompromised, including those with advanced chronic kidney disease (CKD) [1,2]. Despite the implementation of a third dose of a messenger RNA (mRNA) vaccine, the efficacy of SARS-CoV-2 vaccination on humoral and cellular immunities is reduced in the population with CKD, resulting in an increased incidence of severe infection and mortality, including in fully vaccinated patients [3].

In this context, several antiviral therapies or monoclonal antibodies are being investigated for treatment of COVID-19. These drugs prevent viral replication through various mechanisms, including neutralization, blocking SARS-CoV-2 entry, and inhibiting RNA polymerase or proteases activity [4,5]. However, patients with CKD are frequently excluded from clinical trials evaluating new drugs.

Although sotrovimab and casirivimab/imdevimab have been shown to confer satisfactory protection against the COVID-19 Delta variant, they have limited neutralizing activity against the Omicron variant [4]. Remdesivir, nirmatrelvir/ritonavir, bebtelovimab, and molnupiravir seem to be effective against the Omicron variant [5]. U.S. Food and Drug Administration product labels do not recommend remdesivir or nirmatrelvir/ritonavir in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 due to a lack of data concerning the risk of drug accumulation in this population. Indeed, nirmatrelvir and one of the excipients contained in remdesivir (betadex sulfobutyl ether sodium) are renally cleared and can accumulate in patients with abnormal kidney function. The appropriate dose for patients with severe renal impairment has not been determined. Bebtelovimab is only available in the United States. Thus, molnupiravir is the only antiviral drug that could potentially be used for CKD patients with the COVID-19 Omicron variant outside of the United States. Molnupiravir is an inhibitor of the RNA-dependent RNA polymerase of SARS-CoV-2. Although a phase III double-blind, placebo-controlled study of molnupiravir as an oral treatment for COVID-19 in nonhospitalized adults (MOVe-OUT) showed good efficacy, patients with eGFR of <30 mL/min or on dialysis were excluded [6]. To our knowledge, this is the first report on the efficacy and safety of molnupiravir in advanced CKD patients.

Three patients were on maintenance hemodialysis, one had received a transplant and had CKD G4 (eGFR, 18 mL/min/1.73 m^2), and one had CKD G5 (eGFR, 11 mL/min/1.73 m^2) (Table 1). Patients 1, 2, and 4 were under

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Table 1. Baseline and COVID-19 characteristics of patients treated with molnupiravir

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (yr)	56	71	46	60	57
Sex	Male	Male	Female	Male	Male
Cause of CKD	CNI toxicity	MPGN	FSGS	MCD	Tubulo-interstitial disease
Dialysis modality (CKD stage)	In-center HD (CKD G5D)	No dialysis (CKD G4)	Home HD (CKD G5D)	No dialysis (CKD G5)	In-center HD (CKD G5D)
Immunosuppressive therapy	Tac/MMF	Tac/Cs	No	Csa	No
Reason for immunosuppressive therapy	Cardiac transplant	Renal transplant	No	MCD	No
Cardiovascular disease	Cardiac transplant Ischemic cardiomyopathy	Aortic valve stenosis	No	No	Atrial fibrillation
Hypertension	Yes	No	Yes	Yes	No
Diabetes mellitus	Type II	No	No	No	No
Body mass index (kg/m^2)	30	22	25	24	29
Chronic liver disease	Liver cirrhosis due to NASH	Nodular regenerative hyperplasia			
Chronic pulmonary disease	No	No	No	No	No
Other relevant comorbidities	CML	CLL	Failed kidney transplant		Spina bifida
Symptom					
Fever	Yes	No	Yes	Yes	No
Cough	Yes	Yes	Yes	Yes	Yes
Dyspnea	No	No	No	No	No
Diarrhea	Yes	No	No	No	No
Time between symptom onset and molnupiravir administration (day)	2	4	3	3	5
Vital sign at presentations					
Blood pressure (mmHg)	98/52	135/80	151/93	138/89	73/33
Heart rate (beats/min)	106	85	110	99	82
Oxygen saturation (%)	93	100	100	98	98
Need for supplemental oxygen	No	No	No	No	No
Baseline laboratory test results					
hsCRP (mg/L)	34	16	7	224	46
Platelets (×10^3/μL)	125	118	129	131	150
Lymphocytes (μL^{-1})	630	1370	410	770	770
eGFR (mL/min/1.73 m^2)	Dialysis	18		11	Dialysis
Serum albumin (g/L)	30	27	40	43	34
Glucose level (mg/dL)	190	99	80	159	NA
SARS-CoV-2 variant	Omicron BA.5.1	Omicron BA.5.1.3	NA	Omicron BA.5.2.1	Omicron BA.5.1.3
SARS-CoV-2 viral load on nasopharyngeal swabs					
Day 0 (copies/mL)	20,335,411	18,222,021	4,700	1,761,144	43,275,421
Day 6 or 7 (copies/mL)	<1,000	<1,000	<1,000	250,722	348,467
Day 13 (copies/mL)	NA	NA	NA	1,685	2,071
Long-term prognosis					
eGFR after treatment (mL/min/1.73 m^2)	NA	24	NA	19	NA
Remaining symptoms	Tiredness Loss of appetite	No	No	No	No

CKD, chronic kidney disease; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CNI, calcineurin inhibitor; COVID-19, coronavirus disease 2019; Cs, corticosteroid; Csa, cyclosporin A; eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; HBP, high blood pressure; HD, hemodialysis; hsCRP, high sensitivity C-reavtive protein; MCD, minimal change disease; MMF, mycophenolate mofetil; MPGN, membranoproliferative glomerulonephritis; NA, not available; NASH, nonalcoholic steatohepatitis; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Tac, tacrolimus.

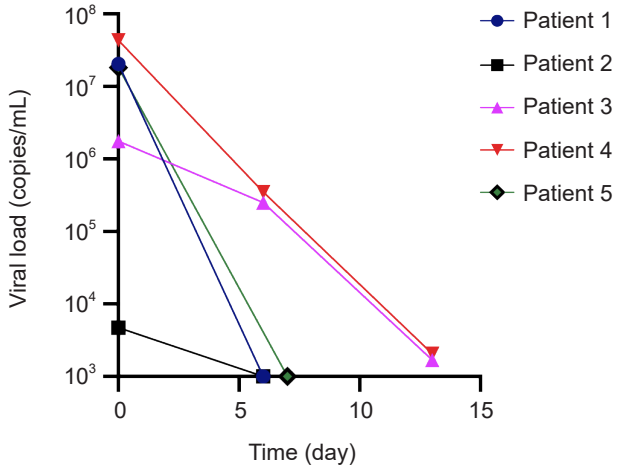

Figure 1. Evolution of the SARS-CoV-2 viral load on nasopharyngeal swabs.
SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

immunosuppressive therapy (heart transplantation, renal transplantation, and treatment of minimal change disease, respectively). All five were fully vaccinated (four doses of the mRNA BNT162b2 vaccine [Pfizer-BioNTech]). They received molnupiravir at a dosage of 800 mg twice daily for 5 days (given after hemodialysis on dialysis day) for mild-to-moderate COVID-19. Quantitative reverse transcription polymerase chain reaction was performed on nasopharyngeal swabs at diagnosis, on day 6 or 7 to evaluate the time to clearance of the virus, and on day 13 for patients 4 and 5 (Fig. 1). Three patients showed <1,000 copies/mL at day 6 or 7. Patients 4 and 5 had results of 1,685 and 2,071 copies/mL on day 13, respectively, and rapid symptom resolution. No adverse effects were observed in any patient. Renal function remained stable in the two CKD patients who were not on dialysis (Table 1). One month after treatment, four patients were entirely asymptomatic and feeling well. Patient 1 still reported tiredness and loss of appetite. None of the five patients experienced delayed immune events or early recurrence of SARS-CoV-2 infection.

Molnupiravir is a prodrug that is metabolized to the ribonucleoside analogue N-hydroxycytidine (NHC). NHC is distributed into cells where it is incorporated into viral RNA by the viral RNA polymerase, which inhibits replication [7]. NHC is eliminated by cellular metabolism to uridine and/or cytidine through the same pathways involved in endogenous pyrimidine metabolism [8]. Renal clearance is not a meaningful route of elimination for NHC. For these reasons, no dose adjustments in patients with any degree of kidney impairment are recommended on the product label [7,8].

Molnupiravir is a safe drug with no contraindications (except during pregnancy and in patients aged <18 years because it may affect bone and cartilage growth). Side effects are limited; the most common (incidence ≥ 1%) include diarrhea, nausea, and dizziness [6]. No drug interactions have been identified (unlike for nirmatrelvir-ritonavir); although ritonavir is a potent CYP3A4 inhibitor and an inducer of other cytochrome p450 substances, oral administration allows treatment outside the hospital, while remdesivir or bebtelovimab requires an intravenous route.

In conclusion, this real-life observational study reported the safety of molnupiravir use in advanced CKD and its relative effectiveness on symptoms and virus clearance.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization: AD, LL
Data curation: ID
Investigation: ID, HG, PD
Formal analysis: ID, AD, EG, LL
Supervision and validation: LL, AD, EG, JDG
Ressources: AS, CB
All authors read and approved the final manuscript.

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