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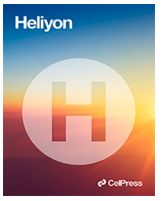

Case report

Safety, efficacy, and pharmacokinetics of nirmatrelvir and ritonavir in patients with severe COVID-19 and renal impairment: A case report

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ABSTRACT

Nirmatrelvir/ritonavir (N/r) has received emergency use authorization for mild-to-moderate COVID-19 treatment in adult and pediatric patients (aged and weighing at least 12 years and 40 kg, respectively) presenting positive direct SARS-CoV-2 viral testing results and a high risk of disease progression to severe COVID-19. However, information remains limited concerning the corresponding drug safety, efficacy, and pharmacokinetics in patients with severe renal impairment. In this study, we present the case of a 91-year-old Chinese man who, despite exhibiting recurrent positive SARS-CoV-2 results and progression to severe COVID-19, was treated with N/r. Due to severe renal impairment and concurrent administration of continuous renal replacement therapy (continuous venovenous hemofiltration) during medication, we aimed to determine the serum N/r drug concentration in the patient. Our analysis revealed C_{max} values of 12.42 and 2.001 μg/mL for nirmatrelvir and ritonavir, respectively. Despite the particularly high serum N/r concentration in this patient, the clinical and laboratory test analyses confirmed that the treatment was safe and effective. Nevertheless, N/r should be used with caution and at lower doses in patients with severe renal impairment to avoid potential high N/r concentration-related adverse reactions and events.

1. Introduction

Nirmatrelvir functions as a peptidoid inhibitor targeting the main protease (Mpro) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), prohibiting polyprotein precursor processing, thereby preventing viral replication. Ritonavir complements the aforementioned effect by inhibiting the CYP3A-mediated metabolism of nirmatrelvir, thereby increasing the blood concentration of the latter [1].

Following its emergency approval in 2021 [1,2], nirmatrelvir/ritonavir (N/r) has gained widespread use, with reported efficacy in reducing the risk of severe illnesses and mortality in non-hospitalized patients [3]. Moreover, a limited number of studies suggest that N/r exhibits improved efficacy in older and immunosuppressed patients as well as those with underlying neurological or

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cardiovascular diseases [4]. However, N/r therapeutic efficacy and safety in patients with severe disease progression remain inadequately substantiated. In addition, the recommended dose adjustment for patients with moderate renal impairment (estimated glomerular filtrate rate [eGFR] $\geq$ 30 to <60 mL/min) is 150/100 mg N/r every 12 h [1]. Nonetheless, N/r use is not recommended for patients with severe renal impairment (eGFR <30 mL/min) due to insufficient data, encompassing patients with end-stage renal disease undergoing hemodialysis [5]. Nevertheless, several recent studies focusing on N/r safety and pharmacokinetics in patients with end-stage renal disease and undergoing hemodialysis, demonstrated the safety and efficacy of this treatment for this patient cohort [6–9]. Hiremath et al. argue that N/r dosage for COVID-19 treatment in patients with severe renal impairment (eGFR < 30 mL/min) should be as follows: not on dialysis: 300/100 mg N/r on day 1, then 150/100 mg N/r once a day for 4 more days; in dialysis: 300/100 mg N/r on day 1, then 150/100 mg N/r once a day for 4 more days, to be dosed after dialysis [6].Although these studies examined N/r pharmacokinetics and the appropriate dosage, most patients display mild symptoms. Therefore, N/r administration conditions for COVID-19 treatment in patients with severe renal impairment should be further addressed. Herein, we provide real-world data to aid treatment decision-making by studying the pharmacokinetics of N/r in patients with severe renal impairment.

2. Case report

In this report, we present the case of a 91-year-old man who had undergone prolonged hospitalization from 2002 due to type 2 diabetes accompanied by multiple complications. The medical history of the patient encompassed several conditions, including advanced onset Alzheimer's disease, cerebral infarction sequelae, chronic obstructive pulmonary disease, coronary atherosclerotic heart disease, and chronic renal insufficiency. During hospitalization, the patient did not receive pacemaker installation, hemodialysis, or other related invasive treatment. The drug use history of the patient is complex (Table 1). In January 2023, his first nucleic acid test yielded positive results (cycle threshold [CT] value: 28.21). However, it yielded negative results after symptomatic treatment with 5 mg once-daily oral azvudine for 5 days. After 10 days of continued hospitalization, the oxygen saturation of the patient decreased. Blood oxygen saturation under the Venturi mask was 83%, which could not be maintained above 90% after applying noninvasive ventilator support. The patient underwent tracheal intubation and ventilator-assisted ventilation, then he was transferred to the intensive care unit (ICU). The aforementioned intervention involved ventilator parameters as follows: 6 cm H_2O positive end-expiratory pressure (PEEP) and 19 cm H_2O pressure control (PC), restoring blood oxygen saturation to 100% at a fraction of inspired oxygen (FiO_2) of 60%. However, bedside hemofiltration could not be corrected due to renal failure, systemic edema, oliguria, and persistent hyperkalemia. Instead, the patient underwent continuous venovenous hemofiltration with sodium citrate anticoagulation. The applied parameters were as follows: replacement fluid flow rate of 1600 mL/min, blood flow rate of 150 mL/min, and a treatment duration of approximately 12 h daily, resulting in an ultrafiltration volume of approximately 7500 mL.

After 4 days in the ICU, the patient exhibited a positive nucleic acid retest (CT value: 35.04). During this time, the ventilator parameters were as follows: 3 cm H_2O PEEP, 20 cm H_2O PC, and 40% FiO_2. Moreover, the patient started oral N/r treatment at 300 mg every 12 h. After 5 days of treatment, the condition of the patient improved, yielding lower ventilator parameters than before (i.e., PEEP, 3 cm H_2O; PC, 14 cm H_2O, and FiO_2, 30%). Following these improvements, we attempted to transition the patient to offline ventilation. However, due to weakened spontaneous respiration ability, this endeavor proved unsuccessful. Consequently, the patient remained in the ICU and continued to receive support from the tracheal intubation ventilator. However, the COVID-19 test did not yield any further positive results.

We measured serum N/r concentrations on the third day of administration at specific intervals, i.e., 0, 0.5, 1, 3, 6, 9, and 12 h post-administration (Table 2). We collected blood samples from the hemodialysis catheter before the blood entered the pipeline during hemofiltration. Next, we analyzed the blood samples using ultra-high-performance liquid chromatography with tandem mass

Table 1
Previous experience of the drugs.

Drugs	Dosage
Insulin Glargine Injection	10 units, i.h., QN
Insulin Injection	6 units, 6 units, 4 units, i.h., 30 minutes before each meal
Repaglinide Tablets	1 mg, p.o., before each meal
Sitagliptin Tablets	25 mg, p.o., QD
Mecobalamin Tablets	0.5 mg, p.o., TID
Clopidogrel Bisulfate Tablets	25 mg, p.o., QD
Isosorbide Mononitrate Sustained-Release Tablets	40 mg, p.o., QN
Policosanol Tablets	10 mg, p.o., QD
Furosemide Tablets	20 mg, p.o., QD
Memantine Hydrochloride Tablets	10 mg, p.o., QD
Levodopa and Benserazide Hydrochloride Tablets	250 mg, p.o., TID
Olanzapine Tablets	5 mg, p.o., QN
Calcitonin (Salmon) for Injection	10 units, i.m., BIW
Thymalfasin for Injection	1.6 mg, i.h., BIW
Pantoprazole Sodium Enteric Capsules	40 mg, p.o., QN

QN = Once Every Night; i.h. = injected subcutaneously; TID = Three Times Daily; p.o. = Oral administration; QD = Once Daily; i.m. = intramuscular injection; BIW = Twice Weekly.

spectrometry. We detected the 0-, 3-, and 12-h concentrations as follows: for nirmatrelvir, 7.77, 12.42, and 10.59 μg/mL, respectively (Fig. 1a), and for ritonavir, 0.614, 1.95, and 1.03 μg/mL, respectively (Fig. 1b).

3. Discussion

Despite the reduction of the ventilator parameters of the patient and attempts to transition to offline treatment, continuous norepinephrine administration remained necessary to maintain stable blood pressure. In addition, we could not perform a computed tomography examination. Therefore, the efficacy assessment of oral N/r administration in treating the novel coronavirus infection in this patient remained limited to clinical observation and laboratory examination. After 5 days of 300 mg N/r oral treatment every 12 h, the ventilator parameters decreased, the serum interleukin-6 levels reduced from 163.4 pg/mL to 25.7 pg/mL, and the nucleic acid tests continued to yield negative results, although the hemodynamic status of the patient remained poor. However, this status was attributed to the underlying disease and secondary bacterial infection of the patient. Therefore, we maintain our conclusion that N/r was effective for this patient. Additionally, factors such as ventilator support, hormone application, and others may have contributed to the improvement of the patient.

Throughout the treatment, we detected neither adverse reactions in response to N/r nor severe drug-induced adverse events, although the patient exhibited severely impaired renal function (eGFR < 30 mL/min). In addition, certain related adverse reactions might have been masked by certain factors, such as confusion, hindered expression while under continuous sedation, and supportive treatment implementation (e.g., ventilators and continuous blood purification). Taken together, we considered that N/r was safe for the patient.

Compared to healthy participants following the administration of a single 300/100 mg oral N/r dose [1], the nirmatrelvir and ritonavir C_{max} as well as AUC values in our patient were 462% and 457% as well as 3917% and 985% higher, respectively (Table 3). A previous study described that, compared to healthy controls with no renal impairment, the C_{max} and AUC values of nirmatrelvir in patients with severe renal impairment were 48% and 204% higher, respectively, following administration of a single 100/100 mg oral N/r dose [1]. This description is generally consistent with our findings. Therefore, in patients with severe renal impairment also receiving blood purification therapy, the administered dosage should probably remain below 100/100 mg.

Compared to the serum drug concentration in other patients with severely impaired renal function using N/r [5,7], that of our patient was higher, which could be attributed to the dosage-related difference. Our patient received a conventional dose of 300/100 mg N/r every 12 h instead of the recommended 150/100 mg dose every 12 h for moderate renal function impairment. Despite the multiple dosages, we could not observe similar patterns in the serum drug concentrations, potentially related to patients receiving blood purification treatments that extended beyond 12 h. When comparing the serum drug concentration of patients at 0 h (before the first dose) and 12 h (before the second dose), we discovered that the blood purification treatment time significantly impacted nirmatrelvir serum drug concentration. However, based on the relationship between blood purification treatment and serum drug concentration (Fig. 2), we observed that even with continuous blood purification exceeding 12 h, we could not revert nirmatrelvir serum drug concentration to the normal level. Regrettably, we could not collect blood samples after the 12 h time point, which would have provided a comprehensive assessment of how the different blood purification treatment periods could affect nirmatrelvir metabolism.

During the treatment of this patient, we observed that N/r therapy could be effective for patients with reconfirmed positive SARS-CoV-2 viral testing and disease progression approaching severe COVID-19. Although we observed no N/r-related adverse reactions or events following the administration of the standard dose, the patient exhibited increased serum drug concentrations. Other studies have demonstrated that halving the dosage is insufficient to normalize serum drug concentrations in individuals with severe renal impairment [5]. Concerning efficacy, higher blood drug concentrations did not result in significant benefits, potentially due to the small number of cases. This underscores the importance of administering a smaller dose to patients with severe renal impairment. In addition, the degree of change in the serum drug concentration indicated that the blood purification treatment duration significantly impacted nirmatrelvir serum drug concentration. Based on our observation of this patient, more than 12 h, compared to 9 h, of blood purification could reduce the valley concentration by approximately 26%. However, the potential occurrence of a similar trend for the entire cohort receiving blood purification and N/r treatments should be validated through clinical studies with large sample sizes.

In summary, we observed that the conventional N/r dose can be considered safe and effective even in patients with severe renal impairment and hemodialysis duration might affect N/r blood concentrations. These results provide some guidance into treatment decisions in patients with severe COVID-19 combined with severe renal failure.

This study has some limitations. First, because this is a single case report, although the results are consistent with other case reports,

Table 2
Nematavir/ritonavir serum drug concentrations.

Time (h)	Nematavir (μg/mL)	Ritonavir (μg/mL)
0	7.766	0.614
0.5	9.664	1.903
1	9.865	2.0015
3	12.420	1.9485
6	11.469	1.3695
9	10.671	1.155
12	10.585	1.0275

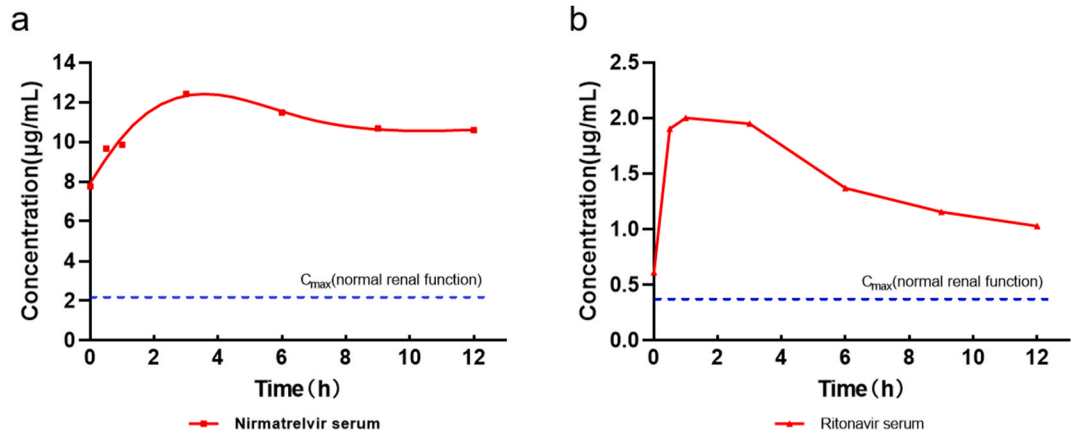

Fig. 1. Day 3 serum concentration following administration of nirmatrelvir/ritonavir 300 mg/100 mg every 12h. Fig. 1a. The serum concentration of nirmatrelvir. Fig. 1b. The serum concentration of ritonavir.

Table 3
N/r pharmacokinetic properties in healthy persons and our patient.

Pharmacokinetic Parameter	Nirmatrelvir		Ritonavir	
	Healthy persons	our patient	Healthy persons	our patient
AUCinf (μg*h/mL)	23.01	924.250	3.599	39.05
Cmax (μg/mL)	2.21	12.42	0.359	2.002
Tmax (h)	3.00	3.00	3.98	1

AUC_{inf} = area under the plasma concentration-time profile from time zero extrapolated to infinite time; C_{max} = the observed maximum concentration; T_{max} = the time to reach C_{max}.

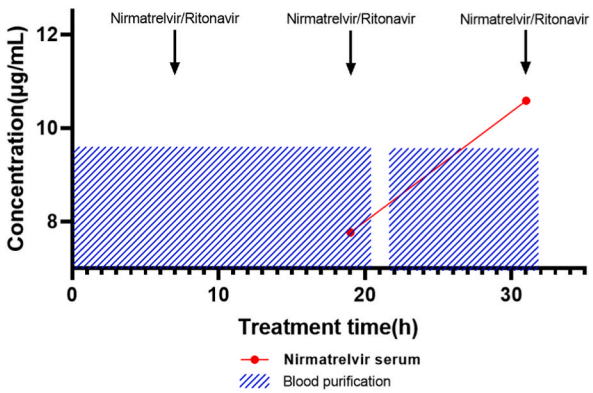

Fig. 2. Compared to 9h of blood purification, More than 12h of blood purification can reduce the valley concentration of nirmatrelvir by approximately 26%.

the generality of these results needs to be further confirmed in prospective, multicenter, large-sample studies. Second, based on the condition of the patient, we are not collecting more blood samples for testing to further support the view that hemodialysis time may affect the plasma concentration of N/r.

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Ethical approval

This study was reviewed and approved by the Medical Ethics Committee of Red Cross Hospital, with the approval number: 2022107.

CRediT authorship contribution statement

Ren Zheng: Writing – original draft, Formal analysis, Data curation. **Xudong Fan:** Validation, Supervision, Project administration. **Feng Zhou:** Software, Project administration, Methodology. **Xiqian Ye:** Supervision, Project administration, Methodology. **Jing Sun:** Visualization, Validation, Supervision. **Junjie Cheng:** Methodology, Formal analysis, Data curation. **Yuan Yuan:** Formal analysis, Data curation, Conceptualization. **Yu Wang:** Formal analysis, Data curation, Conceptualization. **Xinjun Cai:** Writing – review & editing, Supervision, Project administration. **Anqi Wei:** Visualization, Validation, Resources, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28069.

References

[1] US Food and Drug Administration, Fact Sheet for Healthcare Providers: Emergency Authorization for Paxlovid, 2022. Available at: https://www.fda.gov/media/155050/download. (Accessed 30 April 2022).
[2] US Food and Drug Administration, Emergency Use Authorization 105, 2021. Available at: https://www.fda.gov/media/155049/download. (Accessed 30 April 2022).
[3] J. Hammond, H. Leister-Tebbe, A. Gardner, P. Abreu, W. Bao, W. Wisemandle, M. Baniecki, V.M. Hendrick, B. Damle, A. Simón-Campos, R. Pypstra, J.M. Rusnak, EPIC-HR Investigators, Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19, N. Engl. J. Med 386 (15) (2022 Apr 14) 1397–1408.
[4] R. Najjar-Debbiny, N. Gronich, G. Weber, J. Khoury, M. Amar, N. Stein, L.H. Goldstein, W. Saliba, Effectiveness of paxlovid in reducing severe coronavirus disease 2019 and mortality in high-risk patients, Clin. Infect. Dis. 76 (3) (2023 Feb 8) e342–e349.
[5] S.S. Toussi, J.M. Neutel, J. Navarro, R.A. Preston, H. Shi, O. Kavetska, R.R. LaBadie, M. Binks, P.L.S. Chan, N. Demers, B. Corrigan, B. Damle, Pharmacokinetics of oral nirmatrelvir/ritonavir, a protease inhibitor for treatment of COVID-19, in subjects with renal impairment, Clin. Pharmacol. Ther. 112 (4) (2022 Oct) 892–900.
[6] S. Hiremath, M. McGuinty, C. Argyropoulos, K.S. Brimble, P.A. Brown, Z. Chagla, R. Cooper, S. Hoar, D. Juurlink, D. Treleaven, M. Walsh, A. Yeung, P. Blake, Prescribing nirmatrelvir/ritonavir for COVID-19 in advanced CKD, Clin. J. Am. Soc. Nephrol. 17 (8) (2022 Aug) 1247–1250.
[7] T. Lingscheid, M. Kinzig, A. Krüger, N. Müller, G. Bölke, P. Tober-Lau, F. Münn, H. Kriedemann, M. Witzenrath, L.E. Sander, F. Sörgel, F. Kurth, Pharmacokinetics of nirmatrelvir and ritonavir in COVID-19 patients with end-stage renal disease on intermittent hemodialysis, Antimicrob. Agents Chemother. 66 (11) (2022 Nov 15) e0122922.
[8] S. Hiremath, P.G. Blake, A. Yeung, M. McGuinty, D. Thomas, J. Ip, P.A. Brown, M. Pandes, A. Burke, Q.Z. Sohail, K. To, L. Blackwell, M. Oliver, A.K. Jain, Z. Chagla, R. Cooper, Early experience with modified dose nirmatrelvir/ritonavir in dialysis patients with coronavirus disease 2019, Clin. J. Am. Soc. Nephrol. 18 (4) (2023 Apr 1) 485–490.
[9] S. Ahamad, H. Ali, I. Secco, M. Giacca, D. Gupta, Anti-fungal drug anidulafungin inhibits SARS-CoV-2 Spike-induced Syncytia formation by targeting ACE2-Spike protein interaction, Front. Genet. 13 (2022 Mar 25) 866474, https://doi.org/10.3389/fgene.2022.866474.