Real-world risk evaluation of remdesivir in patients with an estimated glomerular filtration rate of less than 30 mL/min

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged as a potential global infectious threat in late 2019, originating in China, and has since rapidly spread across the globe, resulting in a pandemic.[1] In May 2020, remdesivir received emergency use authorization from the Food and Drug Administration and has since been approved for the treatment of coronavirus disease 2019 (COVID-19).[1]

Remdesivir is a nucleotide analog that inhibits RNA polymerase, preventing replication of the SARS-CoV-2 virus. Its parent compound, metabolites, and excipient, sulfobutylether-β-cyclodextrin (SBECD), primarily undergo renal elimination, creating a risk for adverse events in patients with renal impairment.[2] Renal toxicity has been observed with other nucleotide analogs such as tenofovir, but this toxicity has primarily been associated with prolonged use.[2] Adverse events from SBECD accumulation have been observed in animals, but at 50 times the dose used in patients in a 5-day course of remdesivir.[2] A case report of a patient undergoing double-lung transplantation provided pharmacokinetic data on removal of remdesivir and its primary metabolite, GS-441524, by hemodialysis. Predialysis levels of remdesivir and GS-441524 were less than 1 ng/mL and 563 ng/mL, respectively. After dialysis, remdesivir and metabolite concentrations were less than 1 ng/mL and 226 ng/mL, respectively.[3] Three patients in a case series showed an increase in the concentration of GS-441524, but no adverse effects aside from mild transaminitis in one patient were documented.[4] In hemodialysis, 46% of SBECD is removed by filtration.[5] Even with the absence of data from clinical trials owing to exclusion, it appears that remdesivir use in patients with an estimated glomerular filtration rate (eGFR) of <30 mL/min can be considered.

A retrospective cohort study, approved by the Saint Luke's Health System investigational review board, included all inpatients who were positive for COVID-19 and treated with remdesivir from May to July of 2020. Data collected included incidence of patients treated with an eGFR of <30 mL/min, incidence of liver function test (LFT) increases, incidence of acute kidney injury (AKI), and duration of remdesivir therapy (Table 1).

In all patients (n = 151), the incidence of AKI starting with the initiation of remdesivir was 6% (n = 9) and LFT adverse events in which levels were more than 5 times the upper limit of normal (ULN) occurred in 5% of patients (n = 8); no patients had treatment stopped because of infusion reactions. Among all patients, 21 had an eGFR below 30 mL/min at the time of remdesivir initiation, 11 of whom were on chronic dialysis. Adverse event rates in this subgroup were similar to those for all evaluated patients. The median duration of treatment was 5 days, no AKI events were seen after initiation, 1 patient (5%) had an LFT increase of more than 5 times ULN, and 2 patients discontinued therapy before completion of treatment. The 2 patients with an eGFR below 30 mL/min who discontinued therapy did so for reasons unrelated to adverse events; therapy was instead discontinued owing to decisions to withdraw care. Among the patients on hemodialysis (n = 11), no patient had a reported adverse event or discontinued therapy early. The single patient with an LFT increase of more than 5 times ULN developed the increase 3 days after completion of therapy, developed multiorgan failure, and died 12 hours after the LFT abnormality was detected.

Multiple case reports are now available suggesting that remdesivir can be safely used in patients with an eGFR below 30 mL/min.[3,4,6,7] In one study of 157 patients with COVID-19 and AKI or chronic kidney disease, 46 patients were treated with remdesivir. The study did not attribute any renal function abnormalities to the drug or stop treatment due to LFT

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Table 1. Demographic and Outcome Data

Characteristic	All Patients (*n* = 151)	Patients with eGFR <30 mL/min (*n* = 21)
Age, mean, years	61.6	72.1
Charlson comorbidity index, mean	4.6	8
Body mass index, mean, kg/m^2	34.6	32.9
ICU admission, No. (%)	82 (54)	13 (62)
Duration of ventilator use (per patient), mean, days	3.63	4.10
Acute kidney injury, No. (%)	9 (6)	0
LFT increase >5 times ULN, No. (%)	8 (5)	1 (5)
Duration of remdesivir, median, days	5	5

Abbreviations: eGFR, estimated glomerular filtration rate; ICU, intensive care unit; LFT, liver function test; ULN, upper limit of normal.

increases.[6] A second study identified 40 patients with renal impairment and found no statistical difference in end-of-treatment AKI or early discontinuation due to LFT increases.[7]

There is a scarcity of safety data in patients with an eGFR below 30 mL/min, and our study adds to current literature suggesting that there is a low toxicity risk with short exposures to remdesivir. Our findings are in line with 2 other published studies suggesting no increased risk of nephro- or hepatotoxicity in renally impaired patients. This analysis sheds light on a population not represented in clinical trials and provides real-world support for the safe consideration of short courses of remdesivir in patients with an eGFR below 30 mL/min.

1. COVID-19 Treatment Guidelines Panel, National Institutes of Health. Coronavirus disease 2019 treatment guidelines. Accessed October 16, 2020. https://www.covid19treatmentguidelines.nih.gov/
2. Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol*. 2020;31(7):1384-1386.
3. Lê MP, Le Hingrat Q, Jaquet P, et al. Removal of remdesivir's metabolite GS-441524 by hemodialysis in a double lung transplant recipient with COVID-19. *Antimicrob Agents Chemother*. 2020;64(11):e01521-20. doi:10.1128/AAC.01521-20
4. Davis MR, Pham CU, Cies JJ, et al. Remdesivir and GS-441524 plasma concentrations in patients with end-stage renal disease on haemodialysis. *J Antimicrob Chemother*. 2021;76(3):822-825. doi:10.1093/jac/dkaa472
5. Luke DR, Wood ND, Tomaszewski KE, Damle B. Pharmacokinetics of sulfobutylether β-cyclodextrin (SBECD) in subjects on hemodialysis. *Nephrol Dial Transplant*. 2012;27(3):1207-1212.
6. Thakare S, Gandhi C, Modi T, et al. Safety of remdesivir in patients with acute kidney injury or CKD. *Kidney Int Rep*. 2021;6(1):206-210. doi:10.1016/j.ekir.2020.10.005
7. Ackley TW, McManus D, Topal JE, Cicali B, Shah S. A valid warning or clinical lore: an evaluation of safety outcomes of remdesivir in patients with impaired renal function from a multicenter matched cohort. *Antimicrob Agents Chemother*. 2021;65(2):e02290-20. doi:10.1128/AAC.02290-20

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Disclosures: This work was supported by Saint Luke's Health System. No funding source was utilized. The authors have declared no potential conflicts of interest.

Keywords: coronavirus, COVID-19, dialysis, remdesivir, renal

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DOI 10.1093/ajhp/zxab245