function should be offered remdesivir treatment, because this is a potentially life-saving treatment for such a vulnerable population.

We agree with the authors that accumulation of the carrier sulfobutylether-β-cyclodextrin is likely to be of no concern because there is clinical experience with other agents, such as voriconazole. However, with respect to remdesivir and its metabolite GS-441524, to our knowledge, there are no human data to claim its safety in people with impaired renal function because they were excluded from the clinical trials.[2] It should be emphasized that, in repeat-dose toxicity studies in rats and monkeys, the kidney (*i.e.*, tubular epithelium) was identified as the primary target organ of remdesivir toxicity.[3] Furthermore, although remdesivir exhibits low renal excretion as an intact drug (<10% of the administered dose), 49% was recovered as GS-441524, and a total of 74% of a radiolabeled dose was recovered in urine.[3,4] Not surprisingly, a recent pharmacokinetic study showed higher GS-441524 levels in a patient with renal dysfunction.[5] Apparently, because GS-441524 will be removed by hemodialysis, toxicity of remdesivir or its metabolite will not be an issue in patients who are already on hemodialysis.[6] In contrast, in patients with COVID-19 and CKD, it cannot be excluded that remdesivir treatment might lead to an urgent need for RRT, and that remdesivir in this patient population might even have a negative risk-benefit ratio. The recent signal on potential renal side effects of remdesivir also holds concern about its use in patients with CKD.[7]

Therefore, we would like to discourage remdesivir as routine treatment in patients with COVID-19 and CKD (eGFR of <30 ml/min per 1.73 m^3). Its use should be reserved to the context of clinical trials to improve our knowledge on safety and efficacy.

DISCLOSURES

All authors have nothing to disclose.

FUNDING

None.

REFERENCES

1. Adamsick ML, Gandhi RG, Bidell MR, Elshaboury RH, Bhattacharyya RP, Kim AY, et al.: Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol* 31: 1384–1386, 2020
2. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al.; ACTT-1 Study Group Members: Remdesivir for the treatment of Covid-19—Final report. *N Engl J Med* 383: 1813–1826, 2020
3. European Medicines Agency: Summary on compassionate use. Remdesivir Gilead, 2020. Available at: https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf. Accessed October 16, 2020
4. Jorgensen SCJ, Kebriaei R, Dresser LD: Remdesivir: Review of pharmacology, pre-clinical data, and emerging clinical experience for COVID-19. *Pharmacotherapy* 40: 659–671, 2020
5. Tempestilli M, Caputi P, Avataneo V, Notari S, Forini O, Scorzolini L, et al.; COVID 19 INMI Study Group: Pharmacokinetics of remdesivir and GS-441524 in two critically ill patients who recovered from COVID-19. *J Antimicrob Chemother* 75: 2977–2980, 2020
6. Lê MP, Le Hingrat Q, Jaquet P, Wicky PH, Bunel V, Massias L, et al.: Removal of remdesivir's metabolite GS-441524 by hemodialysis in a double lung transplant recipient with COVID-19. *Antimicrob Agents Chemother* 64: e01521–20, 2020
7. European Medicines Agency: Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 28 September - October 1, 2020, 2020. Available at: https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-28-september-1-october-2020. Accessed October 16, 2020

See related reply, "Authors' Reply," on pages 519–520, and original perspective article, "Remdesivir in Patients with Acute or Chronic Kidney," in Vol. 31, Iss. 7, on pages 1384–1386.

Sanna Gevers[1], Jan Welink[1], and Cees van Nieuwkoop[1,2]

[1]Dutch Medicines Evaluation Board, Utrecht, The Netherlands
[2]Department of Internal Medicine, Haga Teaching Hospital, The Hague, The Netherlands

JASN 32: 518–519, 2021.
doi: https://doi.org/10.1681/ASN.2020101535

Authors' Reply

In their letter, Gevers and colleagues[1] highlight concerns that remdesivir and its metabolite, GS-441524, may carry a risk of toxicity to the renal tubular epithelium, and that risks may be more considerable for patients with predialysis CKD. We agree that the potential risks of remdesivir and the concern for nephrotoxicity are likely greater in patients with predialysis CKD who have an eGFR of <30 ml/min per 1.73 m^2 compared with patients receiving dialysis.

There have been two important updates in the literature regarding coronavirus disease 2019 since we originally wrote our perspective. First, the Solidarity Trial—an unblinded, randomized trial that assigned 2750 patients to remdesivir—found that remdesivir did not reduce mortality, initiation

*The original coauthors are Meagan L. Adamsick, Ronak G. Gandhi, Monique R. Bidell, Ramy H. Elshaboury, Roby P. Bhattacharyya, Arthur Y. Kim, Sagar Nigwekar, Eugene P. Rhee, and Meghan E. Sise.

Published online ahead of print. Publication date available at www.jasn.org.

Correspondence: Dr. Meghan E. Sise, Nephrology Division, Massachusetts General Hospital, 165 Cambridge Street, Suite 302, Boston, MA 02114. Email: msise@partners.org

of ventilation, or hospitalization duration compared with standard of care, which has led many to question the effectiveness of remdesivir.[2] Second, three retrospective studies now provide clinical experience of remdesivir use in patients with an eGFR of <30 ml/min per 1.73 m^2. Thakare *et al.*[3] reported no cases of worsening kidney function attributed to remdesivir in 46 patients with an eGFR of <30 ml/min per 1.73 m^2; 30 of these patients were not on dialysis at baseline. Estiverne *et al.*[4] reported no severe liver-function abnormalities attributed to remdesivir among 18 patients with an eGFR of <30 ml/min per 1.73 m^2; among 13 patients who were not on dialysis, multiple patients had improving kidney function on remdesivir, with only one case of worsening kidney function considered likely to be related to remdesivir by the study investigators. Ackley *et al.*[5] found that, among 40 patients receiving remdesivir with an eGFR of <30 ml/min per 1.73 m^2, only two patients had a >50% increase in creatinine during treatment with remdesivir, and both patients had alternative explanations for AKI.

Although these new data are reassuring, we reiterate the statement we made in our perspective that "conclusive data on the safety of remdesivir among individuals with eGFR <30 ml/min per 1.73 m^2 are lacking." We also enthusiastically agree, and reiterate, that only through well-designed, randomized, placebo-controlled trials that include patients with an eGFR of <30 ml/min per 1.73 m^2 can we truly understand the safety and efficacy of remdesivir in patients with advanced kidney disease. Currently, our hospital's approach is to consider remdesivir (lyophilized powder formulation) in patients with an eGFR of <30 ml/min per 1.73 m^2 who are deemed most likely to benefit (hospitalized within 10 days of symptom onset, requiring supplemental oxygen for pneumonia associated with coronavirus disease 2019, and not yet mechanically ventilated). After discussing risks and benefits with the infectious-diseases and nephrology consult teams, we engage in shared decision making with patients and caregivers, highlighting the lack of trial data in patients with an eGFR of <30 ml/min per 1.73 m^2.

DISCLOSURES

M.E. Sise has received research funding from Abbvie, Gilead, Merck, and EMD Serono; has served as a scientific advisory board member for Gilead in the area of viral hepatitis; has consultancy agreements with Bioporto; and has received honoraria from lecturing for the International Society of Hemodialysis–Hemodialysis University. All remaining authors have nothing to disclose.

FUNDING

None.

REFERENCES

1. Gevers S, Welink J, van Nieuwkoop C: Remdesivir in COVID-19 patients with impaired renal function. *J Am Soc Nephrol* 32: 518–519, 2021
2. Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, et al.; WHO Solidarity Trial Consortium: Repurposed antiviral drugs for covid-19 - interim WHO solidarity trial results [published online ahead of print December 2, 2020]. *N Engl J Med* 10.1056/NEJMoa2023184
3. Thakare S, Gandhi C, Modi T, Bose S, Deb S, Saxena N, et al.: Safety of remdesivir in patients with acute or chronic kidney disease [published online ahead of print October 10, 2020]. *Kidney Int Rep* 10.1016/j.ekir.2020.10.005
4. Estiverne C, Strohbehn IA, Mithani Z, Hirsch JS, Wanchoo R, Goyal PG, et al.: Remdesivir in patients with estimated glomerular filtration rate < 30mL/min/1.73m^2 or on renal replacement therapy [published online ahead of print November 27, 2020]. *Kidney Int Rep* 10.1016/j.ekir.2020.11.025
5. 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 [published online ahead of print November 23, 2020]. *Antimicrob Agents Chemother* 10.1128/AAC.02290-20

See related letter to the editor, "Remdesivir in COVID-19 Patients with Impaired Renal Function," on pages 518–519, and original perspective article, "Remdesivir in Patients with Acute or Chronic Kidney," in Vol. 31, Iss. 7, on pages 1384–1386.

Meagan L. Adamsick[1], Roby P. Bhattacharyya[2,3], and Meghan E. Sise[4], on behalf of the coauthors*

[1]Division of Pharmacy, Massachusetts General Hospital, Boston, Massachusetts
[2]Division of Infection Diseases, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts
[3]Infectious Disease and Microbiome Program, Broad Institute, Cambridge, Massachusetts
[4]Nephrology Division, Massachusetts General Hospital, Boston, Massachusetts

JASN 32: 519–520, 2021.
doi: https://doi.org/10.1681/ASN.2020121692