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Captisol and GS-704277, but Not GS-441524, Are Credible Mediators of Remdesivir's Nephrotoxicity

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A recent paper published by Le and colleagues in Antimicrobial Agents and Chemotherapy describes the use of remdesivir (GS-5734) in a patient with a double lung transplant and afflicted with COVID-19 (1). The patient experienced a progressive decline in renal function 3 days after initiating remdesivir treatment, which prompted hemodialysis. Due to acute kidney impairment (AKI), remdesivir therapy was discontinued 1 week after initiation despite a lack of clinical improvement. The authors suggest that accumulation of the main remdesivir metabolite, GS-441524, and the remdesivir excipient, sulfobutylether-β-cyclodextrin (SBED; Captisol) may lead to AKI and offer hemodialysis as a possible solution to remove both GS-441524 and Captisol and maintain remdesivir treatment. While we agree with the authors' well-supported assertion that renal clearance of Captisol (2, 3) likely contributes to the nephrotoxicity associated with remdesivir treatment (4), we refute the assumption that GS-441524 is a major driver of AKI. We further contend that removal of GS-441524 likely hampers the overall efficacy of remdesivir, given its documented ability to exert anti-SARS-CoV-2 activity (5, 6).

A central issue with the authors' analysis lies in their incomplete description of the remdesivir bioactivation scheme. While it is true that GS-441524 is the major persistent metabolite following intravenous administration of remdesivir (7–11), the authors fail to consider the role of the intermediate L-alanine metabolite (GS-704277) in their discussion of renal toxicity, omitting GS-704277 from their bioactivation schematics. GS-704277 is a low-molecular-weight (MW = 441 g/mol) anionic molecule. Administration of remdesivir results in transient appearance of GS-704277 before further hydrolysis to GS-441524 (12). Studies conducted by Gilead Sciences in rats have demonstrated that GS-704277, but not GS-441524 or remdesivir, is an effective substrate of OAT3 and likely contributes to renal adverse events in rats (13). Though the interaction between GS-704277 and human OATs has not yet been characterized, pharmacokinetic (PK) studies in humans point to the extensive renal clearance of GS-704277 rather than GS-441524. A study by Tempestilli and colleagues documented the PK of remdesivir and GS-441524 in a patient with normal kidney function and in a patient with renal impairment (14). While the patient with renal impairment retained higher levels of GS-441524 throughout the 24-h experiment (Fig. 2 in reference 14), the identical decay kinetics (slope) of GS-441524 for both patients implies that the higher levels of GS-441524 result from reduced clearance of the intermediate GS-704277. If renal impairment resulted in reduced clearance of GS-441524, then the half-life of GS-441524 in the renally compromised patient would be much longer than that observed for the uncompromised patient. However, this is not the case. The rate of clearance and half-life of GS-441524 is essentially identical for both patients, implicating the ability for GS-704277 to be extensively cleared by the kidneys.

In addition to overlooking the significance of GS-704277, the authors erroneously claim that the 50% effective concentration (EC_{50}) of GS-441524 against SARS-CoV-2 has

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not been reported. Pruijssers and colleagues have demonstrated that GS-441524 exhibits similar or superior efficacy to remdesivir in Calu3 and VeroE6 cells infected with SARS-CoV-2 (5). The authors' recommendation for hemodialysis assumes that remdesivir is the main contributor to antiviral activity despite the fact that its half-life pales in comparison to that of GS-441524 (11). We acknowledge that hemodialysis may alleviate remdesivir-related AKI by removing Captisol and GS-704277. However, we assert that GS-441524 is an unlikely culprit behind AKI. We thus caution the authors of potential reductions in treatment efficacy that could be associated with removing GS-441524, given its low micromolar anti-SARS-CoV-2 activity (5, 6). Hemodialytic removal of GS-441524 may further diminish the therapeutic effects of remdesivir treatment.

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REFERENCES

1. Lê MP, Le Hingrat Q, Jaquet P, Wicky P-H, Bunel V, Massias L, Visseaux B, Messika J, Descamps D, Mal H, Timsit J-F, Peytavin G. 31 August 2020. Removal of remdesivir's metabolite GS-441524 by hemodialysis in a double lung transplant recipient with COVID-19. Antimicrob Agents Chemother https://doi.org/10.1128/AAC.01521-20.
2. Stella V, He Q. 2008. Cyclodextrins. Toxicol Pathol 36:30–42. https://doi.org/10.1177/0192623307310945.
3. Hoover RK, Alcorn H, Lawrence L, Paulson SK, Quintas M, Luke DR, Cammarata SK. 2018. Clinical pharmacokinetics of sulfobutylether-β-cyclodextrin in patients with varying degrees of renal impairment. J Clin Pharmacol 58:814–822. https://doi.org/10.1002/jcph.1077.
4. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, Hohmann E, Chu HY, Luetkemeyer A, Kline S, Lopez de Castilla D, Finberg RW, Dierberg K, Tapson V, Hsieh L, Patterson TF, Paredes R, Sweeney DA, Short WR, Touloumi G, Lye DC, Ohmagari N, Oh M, Ruiz-Palacios GM, Benfield T, Fätkenheuer G, Kortepeter MG, Atmar RL, Creech CB, Lundgren J, Babiker AG, Pett S, Neaton JD, Burgess TH, Bonnett T, Green M, Makowski M, Osinusi A, Nayak S, Lane HC, ACTT-1 Study Group Members. 22 May 2020. Remdesivir for the treatment of Covid-19 — preliminary report. N Engl J Med https://doi.org/10.1056/NEJMoa2007764.
5. Pruijssers AJ, George AS, Schäfer A, Leist SR, Gralinksi LE, Dinnon KH, Yount BL, Agostini ML, Stevens LJ, Chappell JD, Lu X, Hughes TM, Gully K, Martinez DR, Brown AJ, Graham RL, Perry JK, Du Pont V, Pitts J, Ma B, Babusis D, Murakami E, Feng JY, Bilello JP, Porter DP, Cihlar T, Baric RS, Denison MR, Sheahan TP. 2020. Remdesivir inhibits SARS-CoV-2 in human lung cells and chimeric SARS-CoV expressing the SARS-CoV-2 RNA polymerase in mice. Cell Rep 32:107940. https://doi.org/10.1016/j.celrep.2020.107940.
6. Schooley RT, Carlin AF, Beadle JR, Valiaeva N, Garretson AF, Smith VI, Murphy J, Hostetler KY. 27 August 2020. Rethinking remdesivir: synthesis of lipid prodrugs that substantially enhance anti-coronavirus activity. bioRxiv https://doi.org/10.1101/2020.08.26.269159.
7. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L, Neville S, Carra E, Lew W, Ross B, Wang Q, Wolfe L, Jordan R, Soloveva V, Knox J, Perry J, Perron M, Stray KM, Barauskas O, Feng JY, Xu Y, Lee G, Rheingold AL, Ray AS, Bannister R, Strickley R, Swaminathan S, Lee WA, Bavari S, Cihlar T, Lo MK, Warren TK, Mackman RL. 2017. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-*f*] [triazin-4-amino] adenine *C*-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. J Med Chem 60:1648–1661. https://doi.org/10.1021/acs.jmedchem.6b01594.
8. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, Siegel D, Perron M, Bannister R, Hui HC, Larson N, Strickley R, Wells J, Stuthman KS, Van Tongeren SA, Garza NL, Donnelly G, Shurtleff AC, Retterer CJ, Gharaibeh D, Zamani R, Kenny T, Eaton BP, Grimes E, Welch LS, Gomba L, Wilhelmsen CL, Nichols DK, Nuss JE, Nagle ER, Kugelman JR, Palacios G, Doerffler E, Neville S, Carra E, Clarke MO, Zhang L, Lew W, Ross B, Wang Q, Chun K, Wolfe L, Babusis D, Park Y, Stray KM, Trancheva I, Feng JY, Barauskas O, Xu Y, Wong P, et al. 2016. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 531:381–385. https://doi.org/10.1038/nature17180.
9. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, Leist SR, Pyrc K, Feng JY, Trantcheva I, Bannister R, Park Y, Babusis D, Mo C, Mackman RL, Spahn JE, Palmiotti CA, Siegel D, Ray AS, Cihlar T, Jordan R, Denison MR, Baric RS. 2017. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Transl Med 9:eaal3653. https://doi.org/10.1126/scitranslmed.aal3653.
10. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, Schulz J, Van Doremalen N, Leighton I, Yinda CK, Pérez-Pérez L, Okumura A, Lovaglio J, Hanley PW, Saturday G, Bosio CM, Anzick S, Barbian K, Cihlar T, Martens C, Scott DP, Munster VJ, de Wit E. 2020. Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. Nature 585:273–276. https://doi.org/10.1038/s41586-020-2423-5.
11. Humeniuk R, Mathias A, Cao H, Osinusi A, Shen G, Chng E, Ling J, Vu A, German P. 2020. Safety, tolerability, and pharmacokinetics of remdesivir, an antiviral for treatment of COVID-19, in healthy subjects. Clin Transl Sci 11:896–906. https://doi.org/10.1111/cts.12840.
12. Yan VC, Muller FL. 2020. Advantages of the parent nucleoside GS-441524 over remdesivir for Covid-19 treatment. ACS Med Chem Lett 11:1361–1366. https://doi.org/10.1021/acsmedchemlett.0c00316.
13. European Medicines Agency. 2020. Summary on compassionate use for Remdesivir Gilead. EMA/178637/2020 - Rev. 2. https://www.ema.europa.eu/en/documents/other/summary-compassionate-use-remdesivir-gilead_en.pdf.
14. Tempestilli M, Caputi P, Avataneo V, Notari S, Forini O, Scorzolini L, Marchioni L, Bartoli TA, Castilletti C, Lalle E, Capobianchi MR, Nicastri E, D'Avolio A, Ippolito G, Agrati C, COVID 19 INMI Study Group. 2020. Pharmacokinetics of remdesivir and GS-441524 in two critically ill patients who recovered from COVID-19. J Antimicrob Chemother 75:2977–2980. https://doi.org/10.1093/jac/dkaa239.