AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

Remdesivir for COVID-19: Why Not Dose Higher?

Victoria C. Yan,[a] Florian L. Muller[a]

[a]Department of Cancer Systems Imaging, University of Texas MD Anderson Cancer Center, Houston, Texas, USA

KEYWORDS COVID-19, GS-441524, drug metabolism, prodrug, remdesivir

A recent article by Xu et al. (1) examined the on- and off-target toxicity of remdesivir (RDV) and its parent nucleoside, GS-441524. Notably, primary human hepatocytes (PHHs) and HepG2 cells (liver cancer cell line) were exceptionally sensitive to RDV treatment. Still, the authors conclude, "In clinical settings of COVID-19 [coronavirus disease 2019] treatment in hospitalized patients, the risk associated with possible RDV-related liver enzyme elevations is substantially lower compared to its established benefits in hospitalized COVID-19 patients." Whereas we commend the authors' rigorous study, we deplore the omission of citations of key clinical studies demonstrating no clear benefit with RDV (2, 3). The clinical efficacy of RDV is contentious; major clinical trials conducted with RDV yield mixed results (Table 1). The claim of "established benefits in hospitalized COVID-19 patients" rests on favorable results of a single double-blind, randomized controlled trial (RCT) (4) and at the omission of unfavorable interim results from the WHO Solidarity trial (3) and a double-blinded RCT by Wang et al. (2). By undermining these trial results (5, 6), Gilead implicitly acknowledges that the clinical benefits of RDV are modest, requiring the most stringent trial design to extract a favorable, statistically significant result (4). Ironically, Gilead dismisses the interim results from Solidarity on the basis of potential heterogeneity in controls and its open-label nature (6) yet touts their self-sponsored, open-label trials (7, 8) lacking a control group (7). Beyond its questionable clinical efficacy, it is unclear whether the current RDV regimen effectively reduces viral loads in patients' lungs (2, 9). Wang et al. (2) found no difference in viral reduction in the upper respiratory tracts of RDV-treated versus placebo groups. Given RDV's limited clinical and antiviral efficacy, we ask, why not dose higher?

In a phase 1 trial with RDV in healthy volunteers, graded transaminase elevations were observed in 25% of participants in the 7-day multiple-ascending-dose (MAD) cohort (150 mg daily, 1,050 mg cumulative dose) and in 75% of participants in the 14-day MAD cohort (150 mg daily, 2,100 mg cumulative dose) (10), which concurs with the unique sensitivity of PHHs to RDV *in vitro* (1, 11). Comparing the magnitude of hepatotoxicity in healthy participants ties transaminase elevations to total dose exposure (Table 2); hepatotoxicity was not observed in the 225-mg single-dose cohort (10). For reference, the recommended dosage (200-mg loading dose, 100-mg maintenance) results in total doses of 600 mg (5 days) and 1,100 mg (10 days), which fall below the threshold for hepatotoxicity (1,050 to 2,100 mg). If viral suppression is a C_{max} (maximum concentration)-driven effect and the degree of hepatotoxicity relates to cumulative exposure, then it may be possible to compress the dosing schedule to enable higher dosing while maintaining the same cumulative dose. For instance, a 300-mg loading dose with 200-mg maintenance for 5 days yields a cumulative dose of 1,100 mg. Although we foresaw these shortcomings with RDV some time ago and have advocated for clinical investigation of GS-441524 in regard to safety (12–16), investigating dose modifications with RDV may benefit patients more readily (17), and we urge Gilead to do so.

Citation Yan VC, Muller FL. 2021. Remdesivir for COVID-19: why not dose higher? Antimicrob Agents Chemother 65:e02713-20. https://doi.org/10.1128/AAC.02713-20.

For the author reply, see https://doi.org/10.1128/AAC.00085-21.

Accepted manuscript posted online 8 February 2021

Published 18 March 2021

TABLE 1 Clinical efficacy of RDV, by major clinical trial

Study (reference)	Comparison	*n*	Double blind?	Controlled?	Primary endpoint	Outcome
Goldman et al. (7)	5- vs 10-day RDV in severe COVID-19	397	No	No	Clinical status at day 14 by 7-point ordinal scale	No statistically significant difference between treatment groups
Wang et al. (2)	RDV vs placebo in severe COVID-19	237	Yes	Yes (placebo)	Time to clinical improvement up to day 28	No statistically significant difference between placebo and RDV groups
Beigel et al. (4)	RDV vs placebo in severe COVID-19	1,062	Yes	Yes (placebo)	Time to recovery, discharge from hospital vs. hospitalization	Shortened median time to recovery in RDV vs placebo groups (10 vs 15 days)
Spinner et al. (8)	5- vs 10-day RDV vs SOC[a] in moderate COVID-19	596	No	Yes (SOC)	Clinical status at day 11 by 7-point ordinal scale	5-Day RDV had statistically significant higher odds of better clinical status
WHO Solidarity Trial Consortium (3)	One of trial drug regimens (including RDV) vs local SOC in severe COVID-19	2,750	No	Yes (local SOC)	In-hospital mortality	No effect on mortality for patients hospitalized with COVID-19

[a]SOC, standard of care.

TABLE 2 Dose-dependent hepatotoxicity of RDV in healthy volunteers

Cohort	*n*	Dose[a] (mg i.v.)	Total dose (mg)	Duration (days)	ALT/AST elevations[c]
SAD 5	4	150 (solution)	150	1	0/4
SAD 8	4	150 (lyophilized powder)	150	1	0/4
SAD 6[b]	4	225 (solution)	225	1	0/4
MAD 1	8	150 QD, 7 days	1,050	7	**2/8**
MAD 2	8	150 QD, 14 days	2,100	14	**6/8**

[a]Doses of RDV trialed in the SAD and MAD arms of the phase 1 trial for a 50- to 70-kg human (10). Long-term repeated dosing at 150 mg yields transaminase elevations.
[b]No participants experienced transaminase elevations in the 225-mg SAD cohort.
[c]Boldface indicates that transaminase elevations are dose dependent and emergent even in healthy human volunteers.

ACKNOWLEDGMENT

We thank Steve Kirsch and the COVID-19 Early Treatment Fund (CETF) for financial support.

REFERENCES

1. Xu Y, Barauskas O, Kim C, Babusis D, Murakami E, Kornyeyev D, Lee G, Stepan G, Perron M, Bannister R, Schultz BE, Sakowicz R, Porter D, Cihlar T, Feng JY. 2020. Off-target *in vitro* profiling demonstrates that remdesivir is a highly selective antiviral agent. Antimicrob Agents Chemother 65:e02237-20. https://doi.org/10.1128/AAC.02237-20.
2. Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu Y, Luo G, Wang K, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang Y, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang Y, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C. 2020. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 395:1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9.
3. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, Preziosi MP, Sathiyamoorthy V, Abdool Karim Q, Alejandria MM, Hernández García C, Kieny MP, Malekzadeh R, Murthy S, Reddy KS, Roses Periago M, Abi Hanna P, Ader F, Al-Bader AM, Alhasawi A, Allum E, Alotaibi A, Alvarez-Moreno CA, Appadoo S, Asiri A, Aukrust P, Barratt-Due A, Bellani S, Branca M, Cappel-Porter HBC, Cerrato N, Chow TS, Como N, Eustace J, García PJ, Godbole S, Gotuzzo E, Griskevicius L, Hamra R, Hassan M, Hassany M, Hutton D, Irmansyah I, Jancoriene L, Kirwan J, Kumar S, Lennon P, Lopardo G, Lydon P, Magrini N, Maguire T, Manevska S, Manuel O, McGinty S, Medina MT, Mesa Rubio ML, Miranda-Montoya MC, Nel J, Nunes EP, Perola M, Portolés A, Rasmin MR, Raza A, Rees H, Reges PPS, Rogers CA, Salami K, Salvadori MI, Sinani N, Sterne JAC, Stevanovikj M, Tacconelli E, Tikkinen KAO, Trelle S, Zaid H, Røttingen JA, Swaminathan S. 2020. Repurposed antiviral drugs for Covid-19 — Interim WHO Solidarity trial results. N Engl J Med:NEJMoa2023184. https://doi.org/10.1056/NEJMoa2023184.
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. 2020. Remdesivir for the treatment of Covid-19—final report. N Engl J Med 383:1813–1826. https://doi.org/10.1056/NEJMoa2007764.
5. Norrie JD. 2020. Remdesivir for COVID-19: challenges of underpowered studies. Lancet 395:1525–1527. https://doi.org/10.1016/S0140-6736(20)31023-0.
6. Gilead Sciences. 2020. Gilead Sciences statement on the Solidarity trial. Gilead Sciences, Foster City, CA.
7. Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn M-Y, Nahass RG, Chen Y-S, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A, GS-US-540–5773 Investigators. 2020. Remdesivir for 5 or 10 days in patients with severe Covid-19. N Engl J Med 383:1827–1837. https://doi.org/10.1056/NEJMoa2015301.
8. Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, Ogbuagu O, Malhotra P, Mullane KM, Castagna A, Chai LYA, Roestenberg M, Tsang OTY, Bernasconi E, Le Turnier P, Chang S-C, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wang H, Gaggar A,

Brainard DM, McPhail MJ, Bhagani S, Ahn MY, Sanyal AJ, Huhn G, Marty FM, GS-US-540–5774 Investigators. 2020. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate COVID-19. JAMA 324:1048–1057. https://doi.org/10.1001/jama.2020.16349.
9. Parker M, Shepherd J, Alders N, Bamford A, Grandjean L. 2020. Remdesivir induced viral RNA and subgenomic RNA suppression, and evolution of viral variants in SARS-CoV-2 infected patients. medRxiv https://doi.org/10.1101/2020.11.18.20230599.
10. 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 13:896–906. https://doi.org/10.1111/cts.12840.
11. 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, Braun MR, Flint M, McMullan LK, Chen SS, Fearns R, Swaminathan S, Mayers DL, Spiropoulou CF, Lee WA, Nichol ST, Cihlar T, Bavari S. 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.
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. Yan V, Muller F. 2020. Comprehensive summary supporting clinical investigation of GS-441524 for Covid-19 treatment. OSF Preprints. https://doi.org/10.31219/OSF.IO/MNHXU.
14. Pedersen NC, Perron M, Bannasch M, Montgomery E, Murakami E, Liepnieks M, Liu H. 2019. Efficacy and safety of the nucleoside analog GS-441524 for treatment of cats with naturally occurring feline infectious peritoniti. J Feline Med Surg 21:271–281. https://doi.org/10.1177/1098612X19825701.
15. Dickinson PJ, Bannasch M, Thomasy SM, Murthy VD, Vernau KM, Liepnieks M, Montgomery E, Knickelbein KE, Murphy B, Pedersen NC. 2020. Antiviral treatment using the adenosine nucleoside analogue GS-441524 in cats with clinically diagnosed neurological feline infectious peritonitis. J Vet Intern Med 34:1587–1593. https://doi.org/10.1111/jvim.15780.
16. Li Y, Cao L, Li G, Cong F, Li Y, Sun J, Luo Y, Chen G, Li G, Wang P, Xing F, Ji Y, Zhao J, Zhang Y, Guo D, Zhang X. 2020. Remdesivir metabolite GS-441524 efficiently inhibits SARS-CoV-2 infection in mouse model. bioRxiv https://doi.org/10.1101/2020.10.26.353300.
17. Food and Drug Administration. 2020 VEKLURY (remdesivir).