Research Correspondence

Hepatobiliary adverse drug reactions associated with remdesivir: The WHO international pharmacovigilance study

Min Seo Kim, MD[1,2]*, Se Yong Jung, MD[3]*, Seung Won Lee, MD, PhD[4]*, Han Li[5], Ai Koyanagi, MD, PhD[6,7,8], Andreas Kronbichler, MD, PhD[9], Elena Dragioti, BSc, MSc, PhD[10], Kalthoum Tizaoui, PhD[11], Paul Wasuwanich[5], Sung Hwi Hong, MD, MPH[12,13], Ramy Abou Ghayda, MD, MHA, MPH[12,14], Hae Won Yoo, MD[15], Hanna Kim[16], Louis Jacob, MD, PhD[6,17], Joe-Elie Salem, MD, MPharm, PhD[18], Karel Kostev, DMSc, PhD[19], Youn Ho Shin, MD, PhD[20], So Young Kim, MD[21], Gabriele Gamerith, MD[22], Dong Keon Yon, MD[23]†, Jae Il Shin, MD, PhD[3]†, Lee Smith, BSc, MSc, PhD[24]

*These authors contributed equally to this work.
†Corresponding author

[1] Korea University, College of Medicine, Seoul, Republic of Korea; minseolike@naver.com
[2] Genomics and Digital Health, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea; minseolike@naver.com
[3] Division of Pediatric Cardiology, Department of Pediatrics, Yonsei University College of Medicine, Seoul, Republic of Korea; jung811111@yuhs.ac (SY Jung), shinji@yuhs.ac (JI Shin)
[4] Department of Data Science, Sejong University College of Software Convergence, Seoul, Republic of Korea; lsw2920@gmail.com
[5] University of Florida College of Medicine, Gainesville, FL 32610, USA; lih2@ufl.edu (H.L.); p.wasuwanich@ufl.edu (P.W.)
[6] Research and Development Unit, Parc Sanitari Sant Joan de Déu, Universitat de Barcelona, Fundació Sant Joan de Déu, CIBERSAM, 08830 Barcelona, Spain; a.koyanagi@pssjd.org, louis.jacob.contacts@gmail.com
[7] ICREA, Pg. Lluis Companys 23, 08010 Barcelona, Spain
[8] Instituto de Salud Carlos III, Centro de Investigación Biomédica en Red de Salud Mental, CIBERSAM, 28029 Madrid, Spain
[9] Department of Internal Medicine IV, Medical University Innsbruck, Anichstraße 35, 6020 Innsbruck, Austria; andreas.kronbichler@i-med.ac.at
[10] Pain and Rehabilitation Centre, and Department of Health, Medicine and Caring Sciences, Linköping University, SE-581 85 Linköping, Sweden; elena.dragioti@liu.se
[11] Department of Basic Sciences, Medicine Faculty of Tunis, Tunis El Manar University, 15 Rue Djebel Lakdar, Tunis 1007, Tunisia; kalttizaoui@gmail.com
[12] Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA; sunghwihong@gmail.com (S.H.H.);

ramy.aboughayda@gmail.com (R.A.G.)
[13] Yonsei University College of Medicine, Seoul 03722, Republic of Korea
[14] Urology Institute, University Hospitals System, Case Western Reserve University School of Medicine, Cleveland, OH, USA.
[15] Division of Gastroenterology and Hepatology, Soon Chun Hyang University Bucheon Hospital, Soonchunhyang University College of Medicine, Bucheon, Republic of Korea; uhyewon90@gmail.com
[16] College of Medicine, Ewha Womans University, Seoul, Republic of Korea; znrznr93@gmail.com
[17] Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, 78180, Montigny-le-Bretonneux, France
[18] Sorbonne Université, INSERM, CIC-1901 Paris-Est, CLIP² Galilée, UNICO-GRECO Cardio-oncology Program, and Department of Pharmacology, Pitié-Salpêtrière Hospital, Assistance Publique–Hôpitaux de Paris, F-75013 Paris, France; joe-elie.salem@aphp.fr
[19] University Clinic of Marburg, Marburg, Germany; Karel.Kostev@gmx.de
[20] Department of Pediatrics, CHA Gangnam Medical Center, CHA University School of Medicine, Seoul, Republic of Korea; epirubicin13@gmail.com

[21] Department of Otorhinolaryngology-Head & Neck Surgery, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, Republic of Korea; sossi81@hanmail.net

[22] Internal Medicine V, Department of Hematology and Oncology, Medical University Innsbruck, 6020 Innsbruck, Austria; gabriele.gamerith@i-med.ac.at

[23] Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; yonkkang@gmail.com
[24] The Cambridge Centre for Sport and Exercise Sciences, Anglia Ruskin University, Cambridge CB1 1PT, UK; lee.smith@aru.ac.uk

Corresponding authors:

Prof. Jae Il Shin, MD, PhD

Department of Pediatrics, Yonsei University College of Medicine, Seoul 03722, Republic of

Korea; Address: 50-1 Yonsei-ro, Seodaemun-gu, C. P. O. Box 8044; Tel: +82-2-2228-2050

Email: shinji@yuhs.ac

Dr. Dong Keon Yon, MD, FACAAI

Department of Pediatrics, Seoul National University College of Medicine, 103 Daehak-ro,

Jongno-gu, Seoul, 03080, South Korea

Phone: +82-2-6935-2476

Fax: +82-504-478-0201

Email: yonkkang@gmail.com

Author Contributions

Drs DKY and JIS had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. *Conception and design*: JIS; *Analysis and interpretation of the data*: MSK, SYJ, SWL, DKY, and JIS; *Drafting of the article*: MSK, SYJ, SWL, HL, PW, and DKY; *Critical revision of the article for important intellectual content*: all authors; *Final approval of the article:* all authors; *Statistical expertise*: MSK, SYJ, and DKY; *Administrative, technical, or logistic support:* MSK, SYJ, SWL, DKY, and JIS; *Collection and assembly of data:* MSK, SYJ, SWL, DKY, and JIS. DKY and JIS are guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Financial Support

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (NRF2019R1G1A109977912). The funders had no role in the design, analyses, or interpretation of the study,

Conflict of interests

All authors declare no conflict of interest. Please refer to the accompanying ICMJE disclosure forms for further details

Ethical approval

The study protocol was approved by the Institutional Review Board of Yonsei University (No. 4-2020-0868), and the requirement for written consent was waived by the ethics committee because anonymous data were used.

Data availability statement

Study protocol, *Statistical code*: Available from Prof. Shin (e-mail, shinji@yuhs.ac).

Data set: Available from the WHO Program for International Drug Monitoring through a data use agreement.

Abbreviations

ADRs, adverse drug reactions; ALT, alanine aminotransferase; aOR; adjusted odds ratio; AST, aspartate aminotransferase; CI, confidence interval; COVID-19, coronavirus disease 2019; FDA, Food and Drug administration; GI, gastrointestinal; IC, information component; IC_{025}, information component with 95% credibility interval lower endpoint; ICSRs, individual case safety reports; MedRA, *Medical Dictionary for Regulatory Activities*; OR; odds ratio; US, United States; RCTs, randomized placebo-controlled trials; ROR, reported odds ratio;; WHO, World Health Organization;

Acknowledgement

We appreciate members of the custom search team at the Uppsala Monitoring Centre (Uppsala, Sweden) research section, who were invaluable to the successful performance of this study. The supplied data from VigiBase was obtained from various sources and the likelihood of a causal relationship was not the same in all reports. Finally, the results and conclusions of this study do not represent the opinion of the WHO.

INTRODUCTION

Remdesivir was granted emergency use authorized by the US FDA and approved as the first drug for the treatment of patients with COVID-19 [1, 2]. These approvals have accelerated demand for remdesivir worldwide, but potential toxicities associated with this drug remain largely unknown and warrant urgent safety evaluation. Altough hepatotoxicity is one of the most frequent complication observed in COVID-19 patients, the association between remdesivir and gastrointestinal adverse drug reactions (GI-ADRs) in RCT is conflicting to date [2-6]. Furthermore, elevated liver enzymes as part of the clinical course in certain COVID-19 patients complicated the differentiation of GI-ADRs induced by remdesivir from clinical course of COVID-19.

In this study, we aimed to detect a diverse spectrum of GI-ADRs associated with remdesivir, using the VigiBase, WHO's international pharmacovigilance database of individual case safety reports (ICSRs).

METHODS

We obtained ICSRs of VigiBase, which included records from over 20 million individuals across 130 countries [7,8]. Information component (IC) with 95% credibility interval was calculated by Uppsala Monitoring Centers [8]. We used multivariate logistic model for covariate adjustments (age, sex, geographic region, and COVID-19 medications). Detailed methods were described in the Supplement Materials.

RESULTS

There were 2,107 all-ADRs associated with remdesivir reported from February 1, 2020 to August 30, 2020, and among them 752 (35.7%) were GI-ADRs. We identified that the risk of following eight GI-ADRs were significantly increased after remdesivir treatment (Table 1): alanine aminotransferase (ALT) elevation (IC_{025}, 5.58; ROR, 120.7; 95% CI, 107.2–136.0); aspartate aminotransferase (AST) elevation (IC_{025}, 5.17; ROR, 15.0; 95% CI, 12.0–18.9); ischemic hepatitis (IC_{025}, 3.22; ROR, 371.2; 95% CI, 171.2–805.3); increased serum bilirubin (IC_{025}, 3.19; ROR, 24.5; 95% CI, 17.3–34.8); acute hepatic failure (IC_{025}, 1.85; ROR, 22.2; 95% CI, 10.9–44.5); retroperitoneal hemorrhage (IC_{025}, 0.75; ROR, 63.5; 95% CI, 22.7–177.1); intra-abdominal hemorrhage (IC_{025}, 0.31; ROR, 42.5; 95% CI, 13.2–136.7); and increased ammonia (IC_{025}, 0.10; ROR, 13.9; 95% CI 4.4–43.6). Most cases were reported as serious ADRs: increase of ALT, 259/371 [69.8%]; increase of AST, 181/236 [76.7%]; increase of serum bilirubin, 27/33 [81.8%]; acute hepatic failure, 6/8 [75.0%]; and ischemic hepatitis 9/10 [90.0%]).

We conducted a sensitivity analysis by comparing the effect of remdesivir and other drugs exclusively in the COVID-19 diagnosed population (n = 5408), offsetting the effect of COVID-19 in cases and non-cases. After further covariate adjusting, we found that COVID-19 patients treated with remdesivir had higher risk of elevated ALT levels (18.5% for remdesivir versus 2.5% for other all drugs; adjusted odds ratio (aOR), 5.48; 95% CI, 3.90–7.71), elevated AST levels (11.6% versus 2.1%; aOR, 3.05; 95% CI, 2.11–4.41), elevated serum bilirubin levels (1.8% versus 0.5%; aOR, 7.45; 95% CI, 2.72–20.38), and acute hepatic failure (0.4% versus 0.03%; aOR, 73.22; 95% CI, 4.61–1162.51).(Table S1)

To identify GI-ADRs that were not evident in well-controlled RCTs, we compared and analyzed pooled data from VigiBase and five published RCTs (Tables S2). In five previously

published RCTs, remdesivir was associated with nausea (odds ratio [OR], 3.24; 95% CI, 1.55–6.78), but not with ALT, AST, or serum bilirubin elevation, which was inconsistent with our main result.

DISCUSSION

This study is the first international pharmacovigilance study to investigate the diverse spectrum of GI-ADRs associated with remdesivir. We identified the following hepatobiliary ADRs that are potentially associated with remdesivir: serum ALT, AST, ammonia and bilirubin elevations, and acute hepatic failure after adjustment which was not evident in previous RCTs. The discrepancy between this large observational pharmacovigilance study and clinical trials [2-6] could be attributable to both from protocols of RCTs and pharmacovigilance study. It should be noted that all clinical trials excluded patients with severe hepatic impairment at enrollment and adopted the discontinuation protocol for those who experienced elevated liver enzymes (ALT >5 times the upper limit of normal) during remdesivir administration. These study protocols may have prevented elucidation of the genuine rate of hepatic damage induced by the drug in clinical trials. Since the clinical situations of COVID-19 were remarkably diverse, we did our best to minimize the noise signals but there are likely significant residual confounding factors such as heterogenous characteristics of patients and severity of COVID-19.

We also detected rare ADRs associated with remdesivir like hepatic failure and ischemic hepatitis from this pharmacovigilance study. While hepatic failure and ischemic hepatitis were more frequently associated with remdesivir use, their prevalence rates were low (0.4% and 0.4%, respectively) and thus irreversible damage of hepatobiliary system is less likely to pose a burden to a large population. Nonetheless, adequate hepatobiliary monitoring is still

encouraged to maintain a tolerable safety margin when using remdesivir.

References

[1] Rubin D, Chan-Tack K, Farley J, Sherwat A. FDA Approval of Remdesivir - A Step in the Right Direction. N Engl J Med 2020;383:2598-2600.

[2] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383:1813-1826.

[3] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-1578.

[4] Mulangu S, Dodd LE, Davey RT, Jr., Tshiani Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med 2019;381:2293-2303.

[5] Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020;383:1827-1837.

[6] Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Jama 2020;324:1048-1057.

[7] Salem J-E, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. The Lancet Oncology 2018;19:1579-1589.

[8] Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, et al. A Bayesian neural network method for adverse drug reaction signal generation. European journal of clinical pharmacology 1998;54:315-321.

Table 1

Table. 1. GI-ADRs associated with remdesivir in the full database from VigiBase.

	Remdesivir	Full database (since inception)*	IC/IC_{025}	Full database (since Feb 2020)†	ROR (95% CI)
Total numbers of individual case safety reports	2,107	22,728,189		1,403,532	
Alanine aminotransferase increased	**371 (17.61)**	**70,334 (0.31)**	**5.73/5.58**	**2847 (0.20)**	**120.7 (107.2-136.0)**
Aspartate aminotransferase increased	**236 (11.20)**	**56,589 (0.25)**	**5.36/5.17**	**2172 (0.15)**	**15.0 (12.0-18.9)**
Ischaemic hepatitis	**10 (0.47)**	**562 (0.00)**	**4.25/3.22**	**28 (0.00)**	**371.2 (171.2-805.3)**
Serum bilirubin increased	**33 (1.57)**	**21,900 (0.10)**	**3.73/3.19**	**942 (0.07)**	**24.5 (17.3-34.8)**
Acute hepatic failure	**8 (0.38)**	**5,950 (0.03)**	**3.01/1.85**	**249 (0.02)**	**22.2 (10.9-44.5)**
Retroperitoneal haemorrhage	**4 (0.19)**	**3,261 (0.01)**	**2.49/0.75**	**46 (0.00)**	**63.5 (22.7-177.1)**
Intra-abdominal haemorrhage	**3 (0.14)**	**1,937 (0.01)**	**2.36/0.31**	**50 (0.00)**	**42.5 (13.2-136.7)**
Ammonia increased	**3 (0.14)**	**3,129 (0.01)**	**2.15/0.10**	**147 (0.01)**	**13.9 (4.4-43.6)**
Nausea	30 (1.42)	1,252,290 (5.51)	-1.93/-2.50	83,896 (5.98)	NA
Vomiting	20 (0.95)	803,210 (3.53)	-1.87/-2.57	48,794 (3.48)	NA
Diarrhea	19 (0.90)	671,030 (2.95)	-1.69/-2.41	42,974 (3.06)	NA
Pancreatitis	6 (0.28)	47,376 (0.21)	0.41/-0.97	1,259 (0.09)	NA
Abdominal distension	2 (0.09)	92,629 (0.41)	-1/86/-4.45	6,264 (0.45)	NA
Abdominal pain	2 (0.09)	345,864 (1.52)	-3.70/-6.29	18,935 (1.35)	NA
Lipase increased	1 (0.05)	6,756 (0.03)	0.41/-3.38	275 (0.02)	NA
Amylase increased	1 (0.05)	7,069 (0.03)	0.38/-3.42	189 (0.01)	NA

Intestinal perforation	1 (0.05)	6,872 (0.03)	0.40/-3.40	231 (0.02)	NA
Epigastric discomfort	1 (0.05)	10,133 (0.04)	0.06/-3.74	732 (0.05)	NA
Constipation	1 (0.05)	206,993 (0.91)	-3.71/-7.51	13,470 (0.96)	NA

Values are n (%) unless otherwise indicated.

First reports of ADRs associated with remdesivir started in February 1, 2020

* IC and IC_{025} of GI-ADRs associated with remdesivir compared in the entire database from VigiBase from inception from November 14, 1967 to August 30, 2020.

† ROR with 95% CIs of GI-ADRs associated with remdesivir compared in the entire database from VigiBase from February 1 to August 30, 2020.

Numbers in bold indicate significant differences (P <0.05).

A positive IC_{025} value (>0) in bold is the traditional threshold used for statistical signal detection.

Supplementary Materials

Study design and data source

We obtained data from ICSRs of VigiBase, which includes records from over 20 million individuals from over 130 countries [7.8]. Relevant ADRs in VigiBase have been collected since 1967 as per the WHO Program for International Drug Monitoring, maintained by the Uppsala Monitoring Center, Uppsala, Sweden.

We included all ICSRs reported with remdesivir from February 1 to August 30, 2020 (n = 2,107). The GI-ADRs associated with remdesivir were identified using the MedDRA version 23.1. To detect rare but clinically important safety signals of GI-ADRs associated with remdesivir, we utilized data from whole drug ICSRs, from November 14, 1967 (inception of the VigiBase) to August 30, 2020 (n = 22,728,189) (Table 1) as a control. To replicate the analysis in a more relevant period of the pandemic, we conducted an identical analysis using ICSRs collected from February 1, 2020, when ADR of remedesivir was first reported to VigiBase, to August 30, 2020 (n = 1,403,532) as a background (Table 1). We used disproportionality analysis (case–non-case analysis of studies that reported the potential safety concern of remdesivir) and compared the proportion of ADRs in patients exposed to remdesivir (cases; n = 2,107) and those not exposed to remdesivir (non-cases). Disproportionality analysis were reported as IC/$IC_{025.}$ Calculation of IC using a Bayesian neural network method was developed and validated by the Uppsala Monitoring Center [7, 8]. IC compares observed and expected drug-related ADRs to find the specific drug-related ADRS signals, with identification of probability difference from the full database. When significant signal was detected (defined as IC_{025} >0), the ADRs were further analyzed for reporting odd ratio (ROR) with 95%

confidence from February 1 to August 30.

Furthermore, we extracted data from all COVID-19 patient case safety reports, from February 1 to August 30, 2020 (n = 5,408). To mitigate the confounding effect of the natural course of COVID-19, we validated the GI-ADRs signals associated with remdesivir in exclusive COVID-19 patients, offsetting the disease course in cases and non-cases (1,814 COVID-19 patients treated with remdesivir versus 3,594 treated with other drugs). We used multivariate logistic model for minimal adjusting (age, sex, and geographic region) and full adjusting (age, sex, geographic region, and COVID-19 medications [hydroxychloroquine/chloroquine, dexamethasone and equivalents, lopinavir-ritonavir, and interferon]).

Finally, we compared and analyzed pooled data from an international real-world database (VigiBase) and five published RCTs. To compare GI-ADRs between well-controlled RCTs and real-world practice settings, we conducted a literature search in PubMed, MEDLINE, Embase (Ovid), and Google Scholar for published RCTs and calculated pooled incidence rates. Three authors (MSK, DKY, and JIS) independently searched all databases up to December 12, 2020 and used the following search terms: “remdesivir”, “RCT”, “randomized controlled trial”, “effect”, “safety”, “COVID-19”, “SARS-CoV-2”, “Ebola”, and their variants. Finally, full-text review yielded 5 records (four COVID-19-related studies and one Ebola-related study) [2-6], that met the eligibility criteria and were included in our analysis.

Statistical significance was defined as two-tailed $p<0.05$. Statistical calculations were performed with IBM statistical package for the social sciences (SPSS) version 25.0 (IBM Corp, Armonk, NY) and R software version 3.6.0 (R Foundation, Vienna, Austria)

Supplementary Table 1. RORs and aORs with 95% CI for the potential GI-ADRs associated with remdesivir among patients with COVID-19 in the VigiBase

Specific GI-ADRs	Exposures	Cases	Total	ROR (95% CI)	Minimally aOR* (95% CI)	Fully aOR† (95% CI)
Alanine aminotransferase increased	Remdesivir	336 (18.5%)	1814	**8.85 (6.96-11.26)**	**6.71 (4.98-9.03)**	**5.48 (3.90-7.71)**
	Other drugs prescribed for COVID-19	90 (2.5%)	3594	1.00 (reference)	1.00 (reference)	1.00 (reference)
Aspartate aminotransferase increased	Remdesivir	211 (11.6%)	1814	**6.03 (4.62-7.89)**	**3.64 (2.63-5.03)**	**3.05 (2.11-4.41)**
	Other drugs prescribed for COVID-19	77 (2.1%)	3594	1.00 (reference)	1.00 (reference)	1.00 (reference)
Blood bilirubin increased	Remdesivir	32 (1.8%)	1814	**3.38 (1.91-5.98)**	**2.35 (1.14-4.88)**	**7.45 (2.72-20.38)**
	Other drugs prescribed for COVID-19	19 (0.5%)	3594	1.00 (reference)	1.00 (reference)	1.00 (reference)
Acute hepatic failure	Remdesivir	7 (0.4%)	1814	**13.92 (1.71-113.21)**	**25.70 (2.56-257.72)**	**73.22 (4.61-1162.51)**
	Other drugs prescribed for COVID-19	1 (0.03%)	3594	1.00 (reference)	1.00 (reference)	1.00 (reference)
Retroperitoneal haemorrhage	Remdesivir	1 (0.1%)	1814	5.95 (0.24-146.04)	NA	NA
	Other drugs prescribed for COVID-19	0 (0.0%)	3594	1.00 (reference)		
Ischaemic hepatitis	Remdesivir	8 (0.4%)	1814	**33.83 (1.95-586.37)**	NA	NA
	Other drugs prescribed for COVID-19	0 (0.0%)	3594	1.00 (reference)		
Intra-abdominal haemorrhage	Remdesivir	0 (0.0%)	1814	NA	NA	NA

	Other drugs prescribed for COVID-19	0 (0.0%)	3594			
Ammonia increased	Remdesivir	3 (0.2%)	1814	13.89 (0.72-269.05)	NA	NA
	Other drugs prescribed for COVID-19	0 (0.0%)	3594	1.00 (reference)		

Values are n (%) unless otherwise indicated.

*Adjusted variables were age, sex and region.

†Adjusted variables were age, sex, region, and COVID-19 treatment medications (hydroxychloroquine/chloroquine, corticosteroids (dexamethasone and equivalents), lopinavir-ritonavir, and interferon).

Numbers in bold indicate significant differences (P <0.05).

NA, not applicable

Supplementary Table 2. Pooled incidences of reported adverse gastrointestinal events from five clinical trials

	Remdesivir		Placebo		Remdesivir versus placebo
	Overall AEs	Severe AEs	Overall AEs	Severe AEs	OR (95% CI) for overall AEs
Increased total bilirubin	24/687 (3.5%)	1/155 (0.6%)	23/594 (3.9%)	0/78 (0%)	0.90 (0.50-1.61)
Increased AST	160/1436 (11.1%)	6/507 (1.2%)	102/776 (13.1%)	11/260 (4.2%)	0.83 (0.64-1.08)
Increased ALT	156/1285 (12.1%)	10/356 (2.8%)	95/698 (13.6%)	14/182 (7.7%)	0.88 (0.67-1.15)
Constipation	47/552 (8.5%)	0/155 (0%)	12/78 (15.4%)	0/78 (0%)	0.51 (0.26-1.01)
Nausea	82/936 (8.8%)	0/155 (0%)	8/278 (2.9%)	0/78 (0%)	**3.24 (1.55-6.78)**
Diarrhea	22/486 (4.5%)	0/155 (0%)	16/278 (5.8%)	0/78 (0%)	0.78 (0.40-1.50)
Vomiting	4/155 (2.6%)	0/155 (0%)	2/78 (2.6%)	0/78 (0%)	1.01 (0.18-5.62)

Values are n (%) unless otherwise indicated.

Numbers in bold indicate significant differences (P <0.05).

[2] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the Treatment of Covid-19 - Final Report. N Engl J Med 2020;383:1813-1826.

[3] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569-1578.

[4] Mulangu S, Dodd LE, Davey RT, Jr., Tshiani Mbaya O, Proschan M, Mukadi D, et al. A Randomized, Controlled Trial of Ebola Virus Disease Therapeutics. N Engl J Med 2019;381:2293-2303.

[5] Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020;383:1827-1837.

[6] Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Jama 2020;324:1048-1057.