**Research Correspondence**

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

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**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.

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**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](mailto: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; IC025, 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;

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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 (IC025, 5.58; ROR, 120.7; 95% CI, 107.2‒136.0); aspartate aminotransferase (AST) elevation (IC025, 5.17; ROR, 15.0; 95% CI, 12.0‒18.9); ischemic hepatitis (IC025, 3.22; ROR, 371.2; 95% CI, 171.2‒805.3); increased serum bilirubin (IC025, 3.19; ROR, 24.5; 95% CI, 17.3‒34.8); acute hepatic failure (IC025, 1.85; ROR, 22.2; 95% CI, 10.9‒44.5); retroperitoneal hemorrhage (IC025, 0.75; ROR, 63.5; 95% CI, 22.7‒177.1); intra-abdominal hemorrhage (IC025, 0.31; ROR, 42.5; 95% CI, 13.2‒136.7); and increased ammonia (IC025, 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.

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# Table 1

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| Table. 1. GI-ADRs associated with remdesivir in the full database from VigiBase. | | | | | |
|  | Remdesivir | Full database  (since inception)\* | IC/IC025 | 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 IC025 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 IC025 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/IC025. 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 IC025 >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)

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| **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  Other drugs prescribed for COVID-19 | 336 (18.5%)  90 (2.5%) |  | 1814  3594 | **8.85 (6.96-11.26)** | **6.71 (4.98-9.03)** | **5.48 (3.90-7.71)** |
| 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| **Aspartate aminotransferase increased** | Remdesivir  Other drugs prescribed for COVID-19 | 211 (11.6%)  77 (2.1%) |  | 1814  3594 | **6.03 (4.62-7.89)** | **3.64 (2.63-5.03)** | **3.05 (2.11-4.41)** |
| 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| **Blood bilirubin increased** | Remdesivir  Other drugs prescribed for COVID-19 | 32 (1.8%)  19 (0.5%) |  | 1814  3594 | **3.38 (1.91-5.98)** | **2.35 (1.14-4.88)** | **7.45 (2.72-20.38)** |
| 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| **Acute hepatic failure** | Remdesivir  Other drugs prescribed for COVID-19 | 7 (0.4%)  1 (0.03%) |  | 1814  3594 | **13.92 (1.71-113.21)** | **25.70 (2.56-257.72)** | **73.22 (4.61-1162.51)** |
| 1.00 (reference) | 1.00 (reference) | 1.00 (reference) |
| **Retroperitoneal haemorrhage** | Remdesivir  Other drugs prescribed for COVID-19 | 1 (0.1%)  0 (0.0%) |  | 1814  3594 | 5.95 (0.24-146.04) | NA | NA |
| 1.00 (reference) |
| **Ischaemic hepatitis** | Remdesivir  Other drugs prescribed for COVID-19 | 8 (0.4%)  0 (0.0%) |  | 1814  3594 | **33.83 (1.95-586.37)** | NA | NA |
| 1.00 (reference) |
| **Intra-abdominal haemorrhage** | Remdesivir  Other drugs prescribed for COVID-19 | 0 (0.0%)  0 (0.0%) |  | 1814  3594 | NA | NA | NA |
| **Ammonia increased** | Remdesivir  Other drugs prescribed for COVID-19 | 3 (0.2%)  0 (0.0%) |  | 1814  3594 | 13.89 (0.72-269.05) | NA | NA |
| 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 | | | | | | | |

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| **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).

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