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ARTICLE

Cardiovascular events and safety outcomes associated with remdesivir using a World Health Organization international pharmacovigilance database

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Abstract

On October 2020, the US Food and Drug Administration (FDA) approved remdesivir as the first drug for the treatment of coronavirus disease 2019 (COVID-19), increasing remdesivir prescriptions worldwide. However, potential cardiovascular (CV) toxicities associated with remdesivir remain unknown. We aimed to characterize the CV adverse drug reactions (ADRs) associated with remdesivir using VigiBase, an individual case safety report database of the World Health Organization (WHO). Disproportionality analyses of CV-ADRs associated with remdesivir were performed using reported odds ratios and information components. We conducted in vitro experiments using cardiomyocytes derived from human pluripotent stem cell cardiomyocytes (hPSC-CMs) to confirm cardiotoxicity of remdesivir. To distinguish drug-induced CV-ADRs from COVID-19 effects, we restricted analyses to patients with COVID-19 and found that, after adjusting for multiple confounders, cardiac arrest (adjusted odds ratio [aOR]: 1.88, 95% confidence interval [CI]: 1.08–3.29), bradycardia (aOR: 2.09, 95% CI: 1.24–3.53), and hypotension (aOR: 1.67, 95% CI: 1.03–2.73) were associated with remdesivir. In vitro data demonstrated that remdesivir reduced the cell viability of hPSC-CMs in time- and dose-dependent manners. Physicians should be aware of potential CV consequences following remdesivir use and implement adequate CV monitoring to maintain a tolerable safety margin.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
Remdesivir use is increasing, but its cardiovascular (CV) adverse drug reactions (ADRs) remain largely unknown. The toxicity profile derives from clinical trials with conflicting results and of insufficient size to identify rare, severe adverse CV reactions.

WHAT QUESTION DID THIS STUDY ADDRESS?
This study identifies CV ADRs associated with remdesivir by disproportionality analysis using VigiBase, a global individual case safety report database.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
This study identifies three previously unreported putative adverse CV reactions, namely, hypotension, cardiac arrest, and bradycardia, independently associated

with remdesivir usage after sensitivity analysis and adjustment for multiple confounders.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Patients with pre-existing CV comorbidities or receiving higher doses of remdesivir may benefit from additional cardiac monitoring. Further study is warranted to confirm the findings.

INTRODUCTION

In December 2019, the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the causative agent of outbreak of pneumonia and other associated symptoms like cytokine storm,[1] eventually termed coronavirus disease 2019 (COVID-19).[2] Remdesivir (GS-5734), an inhibitor of the RNA-dependent RNA polymerases of SARS-CoV-1 and Middle East respiratory syndrome (MERS)-CoV,[3] has shown protective effect against SARS-CoV-2 by effectively inhibiting its proliferation in vitro.[4,5] Subsequent randomized placebo-controlled trials (RCTs) and open-label trials have shown that remdesivir treatment lowered the median recovery time of patients with COVID-19,[6–8] with some trials demonstrating decreased mortality.[6] Based on this supporting evidence, the US Food and Drug Administration (FDA) approved remdesivir as the first drug treatment against COVID-19 on October 22, 2020.[9]

Although the efficacy of remdesivir has been extensively investigated, the associated adverse events (AEs) are not well-characterized. Because remdesivir has not been extensively used in clinical practice—other than against Ebola virus (EBOV) disease and COVID-19—sufficient safety evidence has not been accumulated. At present, clinical trials on COVID-19 are the sole source of information on cardiovascular (CV) toxicities associated with remdesivir, and recent RCTs have reported conflicting results; some RCTs have reported that remdesivir causes more serious CV AEs than the standard care,[10] whereas another suggested that the CV AEs induced by remdesivir is comparable to that induced by placebo.[8] Although RCTs provide reliable information on drug efficacy, observational studies with large sample size often outperform RCTs in capturing rare but fatal AEs, such as cardiac arrest or myocardial infarction.[11] The increasing use of remdesivir during the COVID-19 pandemic has created an urgent need to elucidate its safety profile, particularly for CV AEs that are often infrequent but lethal to patients with COVID-19.

Therefore, we conducted a large observational pharmacovigilance study using the World Health Organization (WHO) global database of individual case safety reports (ICSRs),[12] to detect CV signals with high resolution and characterize the CV AEs of remdesivir. The VigiBase incorporates the data of 20 million individuals from more than 130 countries and as the largest pharmacovigilance database, it provides discriminating findings on drug safety, as indicated in our previous studies.[13–16]

METHODS

Study design and data source

This large retrospective pharmacovigilance cohort study was conducted using data from VigiBase, the WHO global deduplicated ICSR database,[12] which contains records from greater than 130 countries and 20 million individuals, until September 1, 2020. Relevant adverse drug reaction (ADR) reports from across the globe have been collected to the database since 1967 as per the WHO Program for International Drug Monitoring (MDR), and is managed by the Uppsala Monitoring Center (UMC, Sweden). The data casemix was separated into case and non-case groups based on the target drug of interest (remdesivir), which were then used for the disproportionality analysis. VigiBase accepts reports from various credible sources, including healthcare workers, patients, and pharmaceutical companies, and the sources are generally provided with postmarketing notifications. We extracted remdesivir-associated ADR cases from the inception of the database to August 30, 2020. The ethics committee of Yonsei University Severance Hospital, Seoul, Korea, approved this study and granted a waiver of review from the formal institutional review board (no. 4-2020-0868) and informed consent because anonymous data were used. This study has been registered in clinicaltrial.gov NCT04314817.

Procedures and description of the pharmacovigilance cohort

As per the Medical Dictionary for Drug Regulatory Activities (MedDRA) version 23.1 (Table S1), all relevant CV-ADRs classified by group queries were prespecified

and extracted for analysis. Currently, there is a considerable lack of specific CV toxicity reports on remdesivir for its recent FDA approval (October 2020) and Emergency Use Authorization (EUA) from the FDA (2020) as well as approval and conditional marketing authorization in the European Union and very low accumulation of real-world data. Consequently, we used some specific cardiac and vascular preferred terms (PTs) for the analysis. Of note, ICSRs associated with remdesivir have been accruing in VigiBase since February 2020. The individual reports included patient characteristics (age, sex, and nationality), drug information (indications, dosage, regimen, administration route, and duration prescribed), ADR (reported AE, MedDRA classification terms, time to onset, nature and severity of ADR, fetal outcomes, and mortality), and general administrative information (date of report, reporter qualification, and country of origin). Because the time to ADR onset was not consistently reported for remdesivir, we used treatment duration as an alternative to assume the onset period. According to the WHO definition, a serious reaction was described as an ADR associated with death, life-threatening condition, hospital admission or prolongation of hospitalization, chronic incapacity or impairment, and consequences deemed clinically severe by the reporting physician.[17]

Sensitivity analysis

Because the natural disease course of COVID-19 is known to involve myocardial injury and further challenges the CV system,[18,19] it is crucial to distinguish drug-induced CV-ADRs from COVID-19 induced CV effects. Therefore, we further conducted a sensitivity analysis by comparing the effect of remdesivir and other drugs exclusively in the COVID-19 diagnosed population, offsetting the effect of COVID-19 in cases and non-cases. The COVID-19 subpopulation was defined by each case of COVID-19 related MedDRA term as the indication of remdesivir use.

Statistical analysis

As VigiBase incorporates a dataset comprising a large sample size collected worldwide, it provides a good fit for the study of disproportionality (also known as case–non-case analysis), for which sufficient sample size is indispensable to warrant applicable power and resolution.[20] We used the analysis to determine whether the proportion of CV toxicities reported for remdesivir differs from that occurring in the drug control group (full database). When patients exposed to a particular medication (cases) have a higher percentage of ADRs than those not exposed to that drug (non-cases), the link between the adverse reaction and the individual active drug may suggest a possible safety concern. Information component (IC) and reporting odds ratio (ROR) are indicator values used for the disproportionate reporting developed by UMC, where an $IC_{0.25}$ (the lower end of a 95% credible interval) greater than 0 or lower confidence interval (CI) of ROR greater than 1 indicates significant associations of specific ADRs with the drugs. ROR was calculated using the chi-square (χ^2) test as per the well-established reporting method of pharmacovigilance studies.[21] When the full database was not used as a comparator and sensitivity analyses were conducted, ROR was reported rather than the IC to express disproportionality.[15] Multivariate odds ratios (ORs) with 95% CIs were calculated using a logistic regression model to consider prespecified variables, such as age, sex, and multiple COVID-19 treatment drugs, including hydroxychloroquine, corticosteroid, lopinavir-ritonavir, and interferon.[22,23] Dexamethasone, hydrocortisone, prednisolone, and prednisone were included for corticosteroid variable as indicated in study protocol and guideline for COVID-19 treatment.[23,24]

The IC compares observed and expected values to identify AEs that are associated with particular drugs using the Bayesian neural network method developed by UMC.[25] Probabilistic logic in intelligent systems—proven useful in controlling big data—is reliable for handling missing data, and can be used for complex variables.[25] It is often vulnerable to spontaneous variability for rare events with low expected counts, but statistical shrinkage safeguards against spurious associations and the shrinkage observed-to-expected (OE) ratio offers a basic but efficient structure for large-scale pattern exploration.[26] This sensitive algorithm allows the identification of signals soon after drug approval by a regulatory agency, therefore, we used this method to detect early signals of remdesivir and identify any potential risk.

The following statistical formula was used:

$$IC = \log_2([N_{observed} + 0.5]/[N_{expected} + 0.5])$$

where $N_{expected} = [N_{drug} \times N_{reaction}]/N_{total}$.

$N_{expected}$ represents the number of case reports expected for the drug-effect combination, whereas $N_{observed}$ indicates the actual number of case reports for the drug-effect combination. Furthermore, N_{drug} and $N_{reaction}$ specify the number of case reports for the drug irrespective of AEs and for the effect irrespective of drug, respectively.[25,26] N_{total} correspond to the total number of case reports in the full database. Qualitative variables were described as count (percentage), and continuous variables were expressed as median with interquartile range (IQR). The remdesivir and full database cases were compared using the χ^2 test

or Fisher's exact test for qualitative variables and the unpaired Kruskal-Wallis test for continuous variables. Post hoc power analyses of the comparisons between the remdesivir and full database cases as well as the remdesivir and COVID-19 cases were performed using the Z test of independent proportions. All tests were two-sided, and *p* value less than 0.05 was considered significant. All analyses were conducted using IBM statistical package for the social sciences (SPSS) version 25.0 (SPSS Inc.) or R software, version 3.6.0 (R Foundation for Statistical Computing). Power analyses were performed with G*Power, version 3.1.9.6 (Heinrich-Heine-Universität-Düsseldorf).

Generation of human pluripotent stem cells-derived cardiomyocytes

The human pluripotent stem cells (hPSCs) lines, which include both human embryonic stem cells (hESC: H9: Wicell) and human-induced pluripotent stem cells (hiPSCs: CMC-hiPSC-011: KNIH) were maintained with the StemMACS iPS-BREW XF, human (Miltenyi Biotec) on Matrigel (Corning). For derivation into the cardiac lineage, hPSCs were plated onto an Matrigel-coated cell culture dish (Eppendorf) at 140,000 cells/cm^2 dish. At day 0, 6 μM/ml CHIR99021 (Tocris) was treated into the cultured hPSCs together with bovine serum albumin (BSA; Sigma-Aldrich) and ascorbic acid (Sigma-Aldrich). After 48 h, 2 μM/ ml of C59, a Wnt inhibitor (Stemgent Inc.) was for 48 h. Spontaneously contracting cardiac linage cells began to appear as early as differentiation day 8. Subsequently, L-lactic acid was added into the culture media to purify cardiomyocytes (CM)-derived hPSCs (hPSC-CMs).

Cell viability assay

Various concentrations of remdesivir (MedChem Express) was added to hPSC-CMs for 24 h or 48 h, and the cell viability was determined using the CellTiter 96 AQueous One Solution Cell Proliferation Assay (MTS; Promega) according to the manufacturer's instructions. Absorbance at 490 nm (A490) was measured using a SynergyTM H1 multi-mode microplate reader (Biotek). All the cell viability assays were performed at least three times.

RESULTS

CV-ADR signals

The number of ADRs reported for remdesivir was 2107 by August 30, 2020, and a total of 22,728,189 all-drug ADRs have been reported since the inception of the database. Because ADRs associated with remdesivir during the outbreak of EBOV was not reported to VigiBase, ADRs related to remdesivir were first recorded in VigiBase in February 2020, after the outbreak of COVID-19. The total number of all-drug ADRs corresponding to the interval of interest (from February 2020 to August 2020) was 1,403,532. The number of specific CV-ADRs is listed in Table 1. The total number of patients with COVID-19 included in our analysis was 5408, and the sensitivity analysis of the COVID-19 population alone is described in Table 2. Median (IQR) drug treatment duration (days) ranged from 0 (0–4) days for ventricular fibrillation to 4 (1–5) days for atrial fibrillation (Table 3). The indication for remdesivir was COVID-19-positive for all reported patients. Post hoc power analysis of the closest proportion comparison (atrioventricular block) revealed a power of 0.634, with the second closest comparison (myocarditis) revealing a power 0.996.

We identified eight candidates among 37 broad CV outcomes where CV-ADRs were significantly higher in remdesivir than they were in the entire database (non-cases; Table 1). Remdesivir was associated with higher reporting of cardiac arrest (ROR: 19.9, 95% CI: 16.1–24.5, $IC_{0.25}$: 3.19), bradycardia (ROR: 15.0, 95% CI: 12.0–18.9, $IC_{0.25}$: 2.83), shock (ROR: 17.8, 95% CI: 11.2–28.1, $IC_{0.25}$: 2.56), hypotension (ROR: 5.9, 95% CI: 4.7–7.3, $IC_{0.25}$: 1.76), atrial fibrillation (ROR: 7.3, 95% CI: 5.0–10.6, $IC_{0.25}$: 1.64), ventricular tachycardia (ROR: 17.8, 95% CI: 9.5–33.4, $IC_{0.25}$: 1.58), ventricular fibrillation (ROR: 22.1, 95% CI: 10.4–47.1, $IC_{0.25}$: 1.18), and acute myocardial infarction (AMI; ROR: 15.5, 95% CI: 8.0–30.0, $IC_{0.25}$: 1.06). The results were consistent with the those of sensitivity analyses restricted to the patients with COVID-19 only, except for cardiogenic shock, atrial fibrillation, and ventricular tachycardia (Table 2). After further adjustment for various confounders, including corticosteroid use, cardiac arrest (adjusted OR [aOR]: 1.88, 95% CI: 1.08–3.29), bradycardia (aOR: 2.09, 95% CI: 1.24–3.53), and hypotension (aOR: 1.67, 95% CI: 1.03–2.73) were significantly associated with the use of remdesivir. Post hoc power analysis of the closest proportion comparison (cardiogenic shock) revealed a power of 1.00.

Characteristics of patients

Remdesivir-associated CV toxicity is a novel clinical entity and represents a new problem for clinicians treating COVID-19, and, therefore, additional data were collected to facilitate the description of the clinical characteristics of remdesivir-associated CV-ADR in the 2107 identified patients (Table 3). All CV-ADRs associated with remdesivir occurred more frequently in male patients (51.6%-90.0%) than in female patients. Cardiac arrest, cardiogenic shock,

TABLE 1 Disproportionality analysis in VigiBase from the inception of the database to August 30, 2020

	Remdesivir	Full database (since inception)	IC/IC$_{025}$	Full database (since February 2020)	ROR (95% CI)
Total numbers of ICSRs available	2107	22,728,189		1,403,532	
Numbers of ICSRs by cardiovascular ADR subgroups					
Cardiac arrest	**93 (4.41)**	**83,581 (0.37)**	**3.50/3.19**	**3340 (0.24)**	**19.9 (16.1–24.5)**
Bradycardia	**79 (3.75)**	**90,496 (0.40)**	**3.16/2.83**	**3703 (0.26)**	**15.0 (12.0–18.9)**
Cardiogenic shock	**19 (0.90)**	**16,292 (0.07)**	**3.28/2.56**	**737 (0.05)**	**17.8 (11.2–28.1)**
Hypotension	**86 (4.08)**	**215,210 (0.95)**	**2.01/1.76**	**10,194 (0.73)**	**5.9 (4.7–7.3)**
Atrial fibrillation	**28 (1.33)**	**60,278 (0.27)**	**2.23/1.64**	**2624 (0.19)**	**7.3 (5.0–10.6)**
Ventricular tachycardia	**10 (0.47)**	**13,208 (0.06)**	**2.61/1.58**	**385 (0.03)**	**17.8 (9.5–33.4)**
Ventricular fibrillation	**7 (0.33)**	**9482 (0.04)**	**2.44/1.18**	**218 (0.02)**	**22.1 (10.4–47.1)**
Acute myocardial infarction	**9 (0.43)**	**17,645 (0.08)**	**2.15/1.06**	**397 (0.03)**	**15.5 (8.0–30.0)**
Sinus tachycardia	19 (0.90)	213,580 (0.94)	−0.06/−0.78	10,467 (0.75)	NA
Hypertension	13 (0.62)	176,559 (0.78)	−0.32/−1.21	7910 (0.56)	NA
Pulmonary embolism	10 (0.47)	75,522 (00.33)	0.49/−0.54	2074 (0.15)	NA
Chest pain	7 (0.33)	319,538 (1.41)	−2.00/−3.27	23,265 (1.66)	NA
Electrocardiogram QT corrected interval prolonged	4 (0.19)	21,278 (0.09)	0.86/−0.87	1746 (0.12)	NA
Ischemic stroke	3 (0.14)	9860 (0.04)	1.31/−0.74	429 (0.03)	NA
Systolic dysfunction	2 (0.09)	970 (0.00)	2.08/−0.51	189 (0.01)	NA
Atrial flutter	2 (0.09)	5118 (0.02)	1.36/−1.22	200 (0.01)	NA
Supraventricular tachycardia	2 (0.09)	8478 (0.04)	0.96/−1.63	249 (0.02)	NA
Bundle branch block right	2 (0.09)	2731 (0.01)	1.73/−0.86	105 (0.01)	NA
Jugular vein thrombosis	2 (0.09)	1010 (0.00)	2.07/−0.51	29 (0.00)	NA
Vertebral artery obstruction	1 (0.05)	123 (0.00)	1.55/−2.55	5 (0.00)	NA
Cerebral hemorrhage	1 (0.05)	36,338 (0.16)	−1.37/−5.16	1373 (0.01)	NA
Deep vein thrombosis	1 (0.05)	58,504 (0.26)	−1.98/−5.78	1276 (0.01)	NA
Lacunar infarction	1 (0.05)	1543 (0.01)	1.22/−2.58	20 (0.00)	NA
Right ventricle dysfunction	1 (0.05)	405 (0.00)	1.48/−2.32	31 (0.00)	NA
Sinus node dysfunction	1 (0.05)	1972 (0.01)	1.13/−2.66	34 (0.00)	NA
Transient ischemic attack	1 (0.05)	24,093 (0.11)	−0.87/−4.66	653 (0.05)	NA
Atrioventricular block	1 (0.05)	8770 (0.04)	0.19/−3.61	232 (0.02)	NA
Right ventricular failure	1 (0.05)	7102 (0.03)	0.37/−3.43	195 (0.01)	NA
Coronary artery stenosis	1 (0.05)	2651 (0.01)	1.01/−2.79	38 (0.00)	NA
Carotid artery occlusion	1 (0.05)	1994 (0.01)	1.13/−2.67	51 (0.00)	NA
ST segment elevation	1 (0.05)	1837 (0.01)	1.16/−2.64	67 (0.00)	NA
Hypertensive urgency	1 (0.05)	132 (0.00)	1.55/−2.25	16 (0.00)	NA
Torsade de pointes	1 (0.05)	5583 (0.02)	0.56/−3.24	154 (0.01)	NA
Myocarditis	1 (0.05)	7340 (0.03)	0.34/−3.45	411 (0.03)	NA
Pulmonary hypertension	1 (0.05)	16,720 (0.07)	−0.45/−4.25	514 (0.04)	NA
Syncope	1 (0.05)	124,759 (0.55)	−3.00/−6.81	4259 (0.30)	NA
Palpitations	1 (0.05)	215,552 (0.95)	−3.77/−7.57	14,559 (1.04)	NA

Note: Values are *n* (%) unless otherwise indicated. Information component (IC) and its 95% credibility interval lower end point (IC025) comparing cardiac ADRs associated with remdesivir versus entire database in VigiBase (from inception on November 14, 1967, to August 30, 2020). A positive IC$_{025}$ value (>0) is the traditional threshold used for statistical signal detection (in bold). For significant signals, ROR and its 95% CI were also calculated using entire database from February 1, 2020, to August 30, 2020, as comparator (contemporary control group for remdesivir, first remdesivir report in February 2020).

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; ICSR, individual case safety report; NA, not applicable; ROR, reporting odds ratio.

TABLE 2 Reporting and adjusted ors for association between cardiovascular adverse reactions and use of remdesivir for patients with COVID-19 in VigiBase

Specific ADRs	Exposures	Cases	Non-cases	Total	ROR (95% CI)	Minimally adjusted OR[a] (95% CI)	Fully adjusted OR[b] (95% CI)
Cardiac arrest	Remdesivir	65 (3.58%)	1749	1814	**3.78 (2.50–5.72)**	**3.91 (2.44-6.28)**	**1.88 (1.08–3.29)**
	Other drugs prescribed for COVID-19	35 (0.97%)	3559	3594	1 (reference)		
Bradycardia	Remdesivir	66 (3.64%)	1748	1814	**2.12 (1.49–3.00)**	**1.93 (1.32–2.82)**	**2.09 (1.24–3.53)**
	Other drugs prescribed for COVID-19	63 (1.75%)	3531	3594	1 (reference)		
Cardiogenic shock	Remdesivir	2 (0.11%)	1812	1814	1.98 (0.28–14.08)	2.67 (0.24–29.89)	0.99 (0.09–11.40)
	Other drugs prescribed for COVID-19	2 (0.06%)	3592	3594	1 (reference)		
Hypotension	Remdesivir	72 (3.97%)	1742	1814	**3.26 (2.24–4.75)**	**3.56 (2.31–5.47)**	**1.67 (1.03–2.73)**
	Other drugs prescribed for COVID-19	45 (1.25%)	3549	3594	1 (reference)		
Atrial fibrillation	Remdesivir	22 (1.21%)	1792	1814	1.75 (0.99–3.12)	1.39 (0.76–2.55)	2.25 (0.92–5.52)
	Other drugs prescribed for COVID-19	25 (0.70%)	3569	3594	1 (reference)		
Ventricular tachycardia	Remdesivir	10 (0.55%)	1804	1814	1.10 (0.51–2.39)	1.09 (0.47–2.52)	1.36 (0.42–4.41)
	Other drugs prescribed for COVID-19	18 (0.50%)	3576	3594	1 (reference)		
Ventricular fibrillation	Remdesivir	7 (0.39%)	1807	1814	**4.64 (1.20–17.95)**	**5.77 (1.15–28.89)**	3.96 (0.54–28.84)
	Other drugs prescribed for COVID-19	3 (0.08%)	3591	3594	1 (reference)		
Acute myocardial infarction	Remdesivir	9 (0.50%)	1805	1814	**8.96 (1.93–41.49)**	**7.22 (1.51–34.43)**	3.49 (0.51–23.95)
	Other drugs prescribed for COVID-19	2 (0.06%)	3592	3594	1 (reference)		

Statistically significant ADRs were presented in bold. Abbreviations: ADR, adverse drug reaction; COVID-19, coronavirus disease 2019; OR, odds ratio.

[a]Adjusted variables were age and sex.

[b]Adjusted variables were age, sex, and COVID-19 treatment medications including hydroxychloroquine/chloroquine, dexamethasone and equivalents, lopinavir-ritonavir, and interferon. We used the case non-case method, which is similar to case-control studies, but adapted for pharmacovigilance studies. We used reporting odds ratios (RORs) and their 95% confidence interval (95% CI) to calculate disproportionality. ROR is a ratio similar in concept to the OR in case control studies and corresponds to the exposure odds among reported cases of cardiovascular disorders over the exposure odds among reported non-case. Cases were individual case safety reports which showed significant signals (defined as $IC_{025} > 0$). Non-cases were individual case safety reports containing all other adverse events reported linked with the respective drug. To identify patients with COVID-19, any following keywords appearing in the indication field were included: COVID-19, COVID19, SARS-COV-2, SARS-COV2, and COVID with/without pneumonia. The relevant term of "coronavirus infection" was conceived as COVID-19 infection in remdesivir group. However, for non-remdesivir group, the term was excluded to avoid the false-positive results due to coronavirus infections not correspond to COVID-19.

TABLE 3 Characteristics of reported ICSRs with cardiac ADRs associated with remdesivir in VigiBase (last accessed August 30, 2020)

	Cardiac arrest ($n = 93$)	Bradycardia ($n = 79$)	Cardiogenicshock ($n = 19$)	Hypotension ($n = 86$)	A. fib ($n = 28$)	VT ($n = 10$)	AMI ($n = 9$)	V. fib ($n = 7$)
Regions reporting	**93 (100.0)**	**79 (100.0)**	**19 (100.0)**	**86 (100.0)**	**28 (100.0)**	**10 (100.0)**	**9 (100.0)**	**7 (100.0)**
Americas	91/93 (97.8)	78/79 (98.7)	19/19 (100.0)	82/86 (95.3)	27 (96.4)	9/10 (90.0)	8/9 (88.9)	6/7 (85.7)
Europe	2/93 (2.2)	1/79 (1.3)	0/19 (0.0)	3/86 (3.5)	1 (3.6)	1/10 (10.0)	1/9 (11.1)	1/7 (14.3)
Australia	0/93 (0.0)	0/79 (0.0)	0/19 (0.0)	1/86 (1.2)	0 (0.0)	0/10 (0.0)	0/9 (0.0)	0/7 (0.0)
Asia	0/93 (0.0)	0/79 (0.0)	0/19 (0.0)	0/86 (0.0)	0 (0.0)	0/10 (0.0)	0/9 (0.0)	0/7 (0.0)
Africa	0/93 (0.0)	0/79 (0.0)	0/19 (0.0)	0/86 (0.0)	0 (0.0)	0/10 (0.0)	0/9 (0.0)	0/7 (0.0)
Report from clinical trials	4/93 (4.3)	0/79 (0.0)	0/19 (0.0)	1/86 (1.2)	1 (3.6)	1/10 (10.0)	0/9 (0.0)	1/7 (14.3)
Reporting months	**93 (100.0)**	**79 (100.0)**	**19 (100.0)**	**86 (100.0)**	**28 (100.0)**	**10 (100.0)**	**9 (100.0)**	**7 (100.0)**
2020.02–2020.05	0/93 (0.0)	0/79 (0.0)	0 (0.0)	2 (2.3)	1/28 (3.6)	1/10 (10.0)	0 (0.0)	1/7 (14.3)
2020.06	1/93 (1.1)	7/79 (8.9)	6 (31.6)	22 (25.6)	6/28 (21.4)	2/10 (20.0)	0 (0.0)	4/7 (57.1)
2020.07	1/93 (1.1)	1/79 (1.3)	0 (0.0)	1 (1.2)	0/28 (0.0)	0/10 (0.0)	0 (0.0)	0/7 (0.0)
2020.08	91/93 (97.8)	71/79 (89.9)	13 (68.4)	61 (70.9)	21/28 (75.0)	7/10 (70.0)	9 (100.0)	2/7 (28.6)
Reporter	**91 (97.8)**	**77 (97.5)**	**18 (94.7)**	**81 (94.2)**	**26 (92.9)**	**10 (100.0)**	**9 (100.0)**	**7 (100.0)**
Health care professional	91/91 (100.0)	76/77 (98.9)	18/18 (100.0)	79/81 (97.6)	26/26 (100.0)	10/10 (100.0)	9/9 (100.0)	7/7 (100.0)
Non-health care professional	0/91 (0.0)	1/77 (1.0)	0/18 (0.0)	2/81 (2.4)	0 (0.0)	0/10 (0.0)	0 (0.0)	0/7 (0.0)
Age groups	**90 (96.8)**	**74 (93.7)**	**19 (100.0)**	**84 (97.6)**	**28 (100.0)**	**10 (10.0)**	**9 (100.0)**	**7 (100.0)**
<18 years	1/90 (1.1)	1/74 (1.4)	0/19 (0.0)	1/84 (1.2)	0/28 (0.0)	0/10 (0.0)	1 (11.1)	0/7 (0.0)
18–44 years	6/90 (6.7)	11 (14.8)	0/19 (0.0)	8/84 (9.5)	0/28 (0.0)	3/10 (30.0)	2 (22.2)	2/7 (28.6)
45–64 years	37/90 (41.1)	28 (37.8)	11/19 (57.9)	34/84 (40.5)	12/28 (42.9)	1/10 (10.0)	1 (11.1)	0/7 (0.0)
65–74 years	29/90 (32.2)	12 (16.2)	7/19 (36.8)	19/84 (22.6)	6/28 (21.4)	4/10 (40.0)	2 (22.2)	5/7 (71.4)
≥75 years	17/90 (18.3)	23 (31.1)	1/19 (5.3)	22/84 (26.2)	10/28 (35.7)	2/10 (20.0)	3 (33.3)	0/7 (0.0)
Sex	**93 (100.0)**	**78 (98.7)**	**19 (100.0)**	**85 (98.9)**	**28 (100.0)**	**10 (10.0)**	**9 (100.0)**	**7 (100.0)**
Male	48/93 (51.6)	41/78 (52.6)	13/19 (68.4)	45/85 (52.9)	16 (57.1)	9/10 (90.0)	5/9 (55.6)	4 (57.1)
Female	45/93 (48.4)	37/78 (47.4)	6/19 (31.6)	40/85 (47.1)	12 (42.9)	1/10 (10.0)	4/9 (44.4)	3 (42.9)
Serious ADRs	**93 (100.0)**	**79 (100.0)**	**19 (100.0)**	**86 (100.0)**	**28 (100.0)**	**10 (100.0)**	**9 (100.0)**	**7 (100.0)**
	91/93 (97.8)	65/79 (82.3)	19/19 (100.0)	86/86 (100.0)	26/28 (92.9)	8 (80.0)	9/9 (100.0)	7/7 (100.0)
Outcomes	**20 (21.5)**	**19 (24.1)**	**8 (42.1)**	**8 (9.3)**	**7 (25.0)**	**4 (40.0)**	**3 (33.3)**	**3 (42.9)**
Deaths	19/20 (95.0)	4/19 (21.1)	2/8 (25.0)	4/8 (50.0)	0 (0.0)	1 (25.0)	2/3 (66.7)	2/3 (66.7)

TABLE 3 (Continued)

	Cardiac arrest ($n = 93$)	Bradycardia ($n = 79$)	Cardiogenicshock ($n = 19$)	Hypotension ($n = 86$)	A. fib ($n = 28$)	VT ($n = 10$)	AMI ($n = 9$)	V. fib ($n = 7$)
Drug treatment duration	**81 (87.1)**	**61 (77.2)**	**16 (84.2)**	**74 (86.0)**	**23 (82.1)**	**8 (80.0)**	**8 (88.9)**	**7 (100.0)**
Median days (IQR, min-max)	2.0 (0.0–4.0, 0.0–13.0)	4.0 (0.0–4.0, 0.0–10.0)	2.0 (0.0–4.0, 0.0–9.0)	3.0 (1.0–4.0, 0.0–10.0)	4.0 (1.0–5.0, 0.0–9.0)	2.0 (0.8–4.0, 0.0–8.0)	1.0 (0.0–3.5, 0.0–9.0)	0.0 (0.0–4.0, 0.0–8.0)
Indications	**86 (92.5)**	**64 (81.0)**	**19 (100.0)**	**73 (84.5)**	**23 (82.1)**	**9 (90.0)**	**9 (100.0)**	**7 (100.0)**
COVID-19	86/86 (100.0)	64/64 (100.0)	19/19 (100.0)	73/73 (100.0)	23/23 (100.0)	9/9 (100.0)	9 /9(100.0)	7/7 (100.0)

Note: Values are *n* (%) or *n*/*N* (%), unless otherwise indicated. Availability of data is mentioned in bold and top rows. A severe ADR was defined as life threatening, causing to persistent or significant disability, or requiring hospitalization (first or prolonged) or when causing death.

Abbreviations: ADR, adverse drug reaction; A. fib, atrial fibrillation; AMI, acute myocardial infarction; COVID-19, coronarvirus disease 2019; ICSR, individual case safety report; IQR, interquartile range; min-max, minimum-maximum; V. fib, ventricular fibrillation; VT, ventricular tachycardia.

hypotension, and ventricular fibrillation were the commonly reported CV-ADRs in patients aged between 45 and 74 years. Bradycardia, atrial fibrillation, ventricular tachycardia, and AMI primarily occurred in patients greater than 75 years of age. The proportions of serious CV-ADRs were generally high, ranging from 80% for ventricular tachycardia to 100% for cardiogenic shock, hypotension, AMI, and ventricular fibrillation. Almost all cases were reported as part of clinical care and not clinical trials, and most were additionally reported by health professionals (Tables S2–S9).

Outcomes

The overlaps between identified CV-ADRs are shown in Figure 1 and Table 4. AMI cases were frequently associated with concurrent conditions (Table 4), such as cardiac arrest (33.3%) and, in rare cases, ventricular tachycardia (11.1%). Ventricular fibrillation was often associated with cardiac arrest (42.8%). Most of these eight CV events occurred with other serious ADRs, except for atrial fibrillation.

Remdesivir induced cardiotoxicity on hPSC-CMs in vitro

To examine whether remdesivir could induce cardiotoxicity in the human heart within the range of half maximal effective antiviral concentration (EC50), the culture hPSC-CMs were treated with increasing concentrations of remdesivir, and the cell viability was measured at 24 h and 48 h after treatment using cell proliferation assay. We observed that remdesivir treatment induced substantial cytotoxic effects in CMs derived from both hESCs and hiPSCs (Figure 2). In addition, treatment with remdesivir for a longer time (48 h) demonstrated significantly lower cell viability of hPSCS-CMs as compared to 24 h post-treatment, indicating time- and dose-dependent reaction and potential induced cardiotoxicity by remdesivir. These findings are consistent with previous reports of dose-dependent remdesivir toxicity.[27]

DISCUSSION

On October 22, 2020, the FDA approved remdesivir as the first drug to treat hospitalized patients with COVID-19, and the approval may have rapidly increased remdesivir use worldwide. The large increase in remdesivir demand and associated ADR reports warrant urgent pharmacovigilant evaluations of this drug.[28,29] We conducted a clinical characterization of CV-ADRs disproportionally

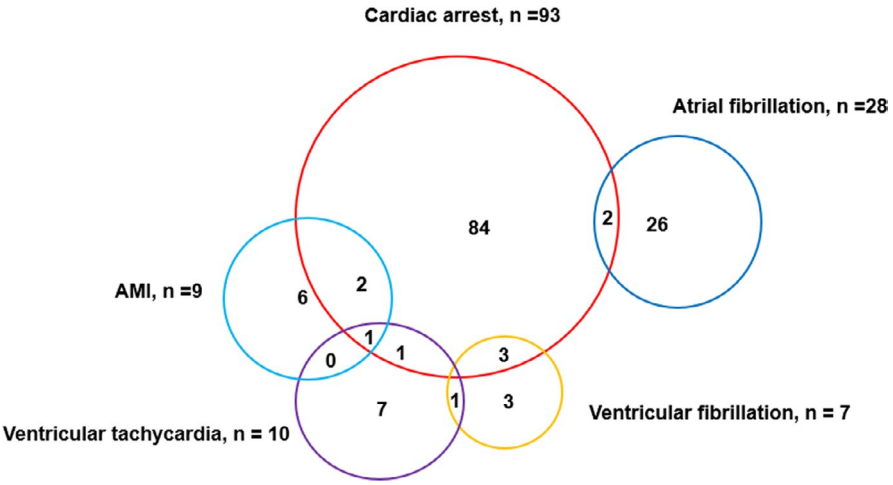

FIGURE 1 Overlap between cardiovascular entities. AMI, acute myocardial infarction

TABLE 4 Overlap of cardiac ADR associated with remdesivir

	Cardiac arrest	Atrial fibrillation	Ventricular tachycardia	Acute myocardial infarction	Ventricular fibrillation
Cardiac arrest ($n = 93$)		2/93 (2.2)	2/93 (2.2)	3/93 (3.2)	3/93 (3.2)
Atrial fibrillation ($n = 28$)	2/28 (7.1)		0/28 (0.0)	0/28 (0.0)	0/28 (0.0)
Ventricular tachycardia ($n = 10$)	**2/10 (20.0)**	0/10 (0.0)		1/10 (10.0)	1/10 (10.0)
Acute myocardial infarction ($n = 9$)	**3/9 (33.3)**	0/9 (0.0)	1/9 (11.1)		0 (0.0)
Ventricular fibrillation ($n = 7$)	**3/7 (42.8)**	0/7 (0.0)	1/7 (14.3)	0/7 (0.0)	

Note: Values are expressed as n/N (%). Although we adopted the overlap rate between cardiac arrest and pulseless activity from the reported data to VigiBase, all pulseless electrical activity is regarded a part of cardiac arrest regardless of proper notification to VigiBase by definition.

In bold, when overlap is ≥20%.

Abbreviation: ADR, adverse drug reaction.

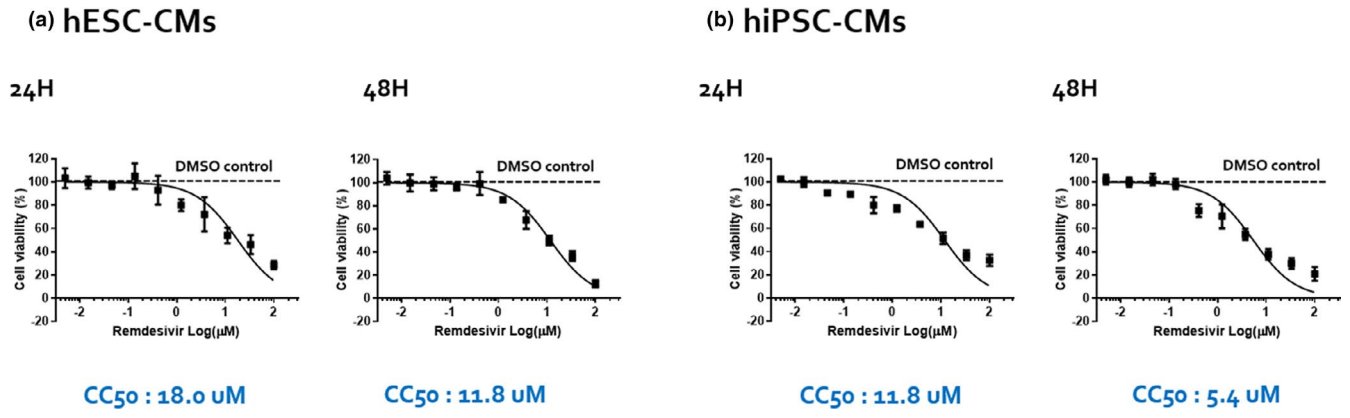

FIGURE 2 Redemsivir elicits cardiotoxic effects in hPSC-CMs (a) and hiPSC-CMs (b). Cardiotoxicity analyses was performed using hPSC-CMs (hESC-CMs and hiPSC-CMs cell lines) in the presence of various concentrations of remdesivir. After 24 and 48 h post-treatment, cell viability was determined by using the CellTiter 96 AQueous One Solution Cell Proliferation Assay (MTS, Promega). The data represent the mean (±SD) of at least two independent experiments performed in triplicate. CC_{50}, 50% cytotoxic concentration; hESC-CMs, cardiomyocyte derived from human embryonic stem cells; hiPSC-CMs, cardiomyocytes derived from human embryonic stem cells

related to remdesivir using the international pharmacovigilance database (VigiBase), which includes information from over 130 countries and 20 million individuals until September 1, 2020. To the best of our knowledge, this is the first population-based pharmacovigilance study on the CV-ADRs of remdesivir. In this study, we comparatively analyzed CV-ADRs reported to be associated with remdesivir treatment and those for the entire dataset, and identified eight CV-ADRs candidates that were disproportionately associated with remdesivir among 37 broad CV

outcomes; these were cardiac arrest, bradycardia, shock, hypotension, atrial fibrillation, ventricular tachycardia, ventricular fibrillation, and AMI (Table 1). To distinguish drug-induced CV-ADRs from COVID-19-induced CV effects,[18,19] we further restricted the analysis to patients with COVID-19 and the results were consistent, except for cardiogenic shock, atrial fibrillation, and ventricular tachycardia. However, the effect sizes (ROR) of all CV-ADRs were smaller than those of the results of the overall population, indicating that the RORs of CV-ADRs derived from the overall database were overestimated, perhaps due to the intrinsic COVID-19 CV deleterious effects (Tables 1 and 2). After further adjustment for potential confounders (i.e., corticosteroid use), cardiac arrest (aOR: 1.88, 95% CI: 1.08–3.29), bradycardia (aOR: 2.09, 95% CI: 1.24–3.53), and hypotension (aOR: 1.67, 95% CI: 1.03–2.73) were significantly associated with the use of remdesivir.

The prevalence in the VigiBase for cardiac arrest, bradycardia, and severe hypotension was reported to be as high as 3.58%, 3.64%, and 3.97%, respectively, in patients with COVID-19 taking remdesivir, whereas they were 0.97%, 1.75%, and 1.25%, respectively, in patients with COVID-19 taking other drugs (Table 2); the rate of cardiac arrest and serious hypotension with remdesivir reported in this study was marginally higher than the pooled incidence rate of cardiac arrest and severe hypotension from clinical trials (1.3% and 1.0%, respectively, as described in Table S10).[7,8,10,30,31] The discrepancies could be explained in part by differences in the included cases. Of note, the total number of remdesivir users in VigiBase (2107 patients) corresponds to a total number of any ADRs reported on remdesivir (e.g., hepatotoxicity) and does not include remdesivir users without any ADRs; therefore, actual ADR rate may be much lower in the general population and the prevalence rates reported in VigiBase should not be taken as absolute prevalence rates in the real-world settings.

Gilead Sciences began developing remdesivir as early as 2009 as an agent against RNA-based viruses with high transmission potential.[32] Early studies mainly focused on the efficacy of remdesivir against SARS and EBOV, because it protected primate kidney epithelial cells from SARS-induced cytotoxicity,[32] and significantly improved the survival of EBOV-infected primate models.[33,34] The effectiveness of remdesivir was preserved to varying degrees against various other viruses, including the human immunodeficiency virus (HIV), MERS-CoV, and deltacoronaviruses.[3,35] Although remdesivir demonstrates effectiveness against several viruses, it was not extensively used in mainstream clinical practice until it was repurposed as a potential therapeutic agent for COVID-19 in 2020, and was subsequently integrated into clinical practice as a specific treatment.[28] In addition, parallel studies evaluating its effectiveness in reducing mortality and time-to-recovery have been conducted.[8,10,30]

Numerous efficacy studies and increased application of remdesivir have not been matched by population-based safety evaluations. As remdesivir is a relatively novel agent in the market, its ADR evaluation is substantially lacking compared to other repurposed drug agents used to manage COVID-19. To date, a few clinical trials have reported major CV-ADRs associated with remdesivir (Tables S10 and S11),[7,8,10,30,31] but these trials have investigated effects only in several hundred patients, which may not capture rare but fatal CV-ADRs and, thus, these findings cannot be extrapolated to large populations. Pharmacovigilance studies using VigiBase, with ICSRs from 20 million individuals, are uniquely poised to identify ADRs that clinical trials may not detect, as demonstrated in previous studies.[13–16,36] The present study represents the first large-case pharmacovigilance evaluation of remdesivir and provides novel insights into remdesivir ADR clinical spectrums.

Given that COVID-19 can cause myocardial injury and challenges the CV system by inflammatory activation and hypoxia,[18,19] it is uncertain if the higher rates of CV events in patients taking remdesivir are caused by adverse reactions of remdesivir or by severe COVID-19. To confirm the biological causation, we designed in vitro experiments using hPSC-CM and found that remdesivir indeed reduced cell viability of hPSC-CMs; the cytotoxic effect of the drug increased with the escalation of dosage. Some of our group previously demonstrated that remdesivir has higher potency for reducing cell viability, whereas less likely to introduce arrhythmogenic risk compared with hydroxychloroquine, albeit both drugs eventually cause cardiotoxicity and arrhythmogenic risk at high concentration[27]; our independent experiments herein replicated the findings denoted by Choi et al. under a mock-infected control setting. Although the experiments were limited to in vitro and the data alone do not guarantee the extrapolation of the results to clinical settings, they provided a biological plausibility for our observational findings. Altogether, our findings at the population-level captured cardiotoxicity associated with remdesivir distinguished from the COVID-19 natural courses, and these findings may help physicians be aware of potential CV adverse consequences following remdesivir.

Study limitations

Our study has some limitations that are worth noting. First, although we conducted a sensitivity analysis with patients with COVID-19 and subsequent multivariable analyses to minimize the confounding effect on CV outcomes by the nature of COVID-19, some degrees of confounding may persist as a bias. Remdesivir trials have demonstrated greatest

efficacy in moderate to severe COVID-19.[22] It is possible that the CV-ADRs from cases that warrant remdesivir treatment reflect more severe underlying infection rather than drug toxicity. Although other drugs used to treat COVID-19 at the time, such as lopinavir-ritonavir,[37] interferon,[37] and dexamethasone,[23] were either used primarily for or most effective in moderate to severe infection, the possibility of this bias could not be entirely eliminated. We further conducted experimental research to understand the genuine effect of the drug on hPSC-CMs, yet the results are primarily limited to in vitro and thus should not be overinterpreted. Second, national drug authorities may have overlooked some drug-induced CV-ADR cases and not included these events in VigiBase, introducing potential reporting biases. In addition, comorbidities were not completely reported to VigiBase and thus adjustment for the baseline characteristics was limited. Disproportionality analyses are primarily used to generate ADR signals in an exploratory manner and cannot be interpreted to quantify the risk of any given ADR. However, the countermeasure of this study lies on the most extensive ADR data to date that include ICSRs from more than 130 nations, which helps classify rare but fatal ADRs. Nevertheless, our results from VigiBase would be better to be validated by important pharmacovigilance dababase as FDA AE reporting system. Third, the dosage of remdesivir used for in vitro experiments may differ from that used for treatment. As such, the experimental dosages should be taken simply as inferences of a dose-response relationship and evidence of causality, and not actual therapeutic effect measures. Last, our study did not begin with total exposure data for remdesivir but, rather, relies on disproportionality analyses between ADRs of remdesivir and the total number of ADRs reported to the database. However, the advantage of VigiBase and the methods used in this study (disproportionate analysis) has been well-established through numerous studies[13–16,36] and may provide reliable and sufficient evidence to support potential safety concerns with the increased administration of remdesivir.

STUDY HIGHLIGHTS

Remdesivir is administered for COVID-19, but CV safety data are limited, conflicting, and derive from a small selection of clinical trials. This study attempts to identify and quantify adverse CV outcomes associated with remdesivir use. We find that remdesivir putatively associated with cardiac arrest, bradycardia, and hypotension, which has been in part validated in vitro as a cytotoxic effect on hPSC-derived cardiomyocytes. Clinicians should be aware of potential CV consequences following remdesivir use, albeit infrequent. Adequate cardiac monitoring should be instituted to maintain a tolerable safety margin when using remdesivir until further matched prospective observational studies confirm the CV safety of remdesivir.

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CONFLICT OF INTEREST

All authors have no conflict of interest.

AUTHOR CONTRIBUTIONS

J.I.S., S.Y.J., M.S.K., H.L., K.H.L., S.C., S.H.H., S.K.C., L.J., J.S., D.K.Y., S.W.L., K.K., A.Y.K., K.B., and L.S. wrote the manuscript. J.I.S., S.Y.J., M.S.K., A.Ko., M.S., A.Kr., R.A.G., N.K.K., L.J., J.S., D.K.Y., S.W.L., K.K., J.W.J., and J.Y.C. designed the research. J.I.S., S.Y.J., M.S.K., H.L., E.D., K.T., S.C., S.T., N.K.K., J.S.S., S.J.P., S.W.C., K.B., S.H.M., Y.Y.G., and L.S. performed the research. J.I.S., S.Y.J., M.S.K., K.H.L., A.Ko., A.Kr., S.H.H., R.A.G., N.K.K., J.S., D.K.Y., S.W.L., and K.B analyzed the data. J.I.S., S.Y.J., M.S.K., H.L., M.S., E.D., J.S., J.S.S., S.J.P., S.W.L., and K.B. contributed new reagents/analytical tools. This manuscript has been reviewed and approved by all authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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