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Neuropsychological adverse drug reactions of Remdesivir: analysis using VigiBase, the WHO global database of individual case safety reports

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Abstract. – OBJECTIVE: Although remdesivir (GS-5734) has recently demonstrated clinical benefits against the pandemic outbreak of coronavirus disease 2019 (COVID-19), neuropsychological adverse reactions (ADRs) remain to be examined in real-world settings. Therefore, we aimed to identify and characterize the neuropsychological ADRs associated with remdesivir use.

MATERIALS AND METHODS: We obtained data for this international pharmacovigilance cohort study from individual case safety reports (ICSRs) in a World Health Organization database (VigiBase) from the first report on remdesivir on February 17, 2020, until August 30, 2020 (n=1,403,532). ADRs reported to be relevant to remdesivir were compared with the full database by using a Bayesian neural network method to calculate the information component (IC).

RESULTS: A total of 2,107 reported cases of neuropsychological ADRs suspected to be associated with remdesivir were identified from among all ICSRs in the database during the observation period. Although 108 neuropsycholog-

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ical ADRs (64 neurologic events and 44 psychologic events) were reported in association with the medication, no statistically significant pharmacovigilance signal could be detected; the IC025 value was negative for all of the neuropsychological dysfunctions (anxiety [n=13, 0.62%], seizures [n=12, 0.57%], lethargy [n=6, 0.28%], agitation [n=5, 0.25%], cerebral infarction [n=3, 0.14%], ischemic stroke [n=3, 0.14%], and hemiparesis [n=3, 0.14%]).

CONCLUSIONS: Our study demonstrates that remdesivir, a novel drug applied to the treatment of COVID-19, does not have a significant association with adverse neurologic or psychiatric reactions in the real-world setting.

Key Words:
Remdesivir, Pharmacovigilance, VigiBase, Neuropsychological toxicities, Adverse drug reactions.

Abbreviations

Adverse Drug Reactions (ADRs); Individual Case Safety Reports (ICSR); Severe Acute RespiratorySyndrome-Coronavirus 2 (SARS-CoV-2); Coronavirus disease 2019 (COVID-19); Medical Dictionary for Regulatory Activities (MedDRA); Information Component (IC); Reporting Odds Ratio (ROR).

Introduction

Remdesivir (GS-5734) is an antiviral prodrug of a nucleotide analogue that is metabolized within cells as a pharmacologically active nucleoside triphosphate metabolite (GS-443902)[1]. After its metabolic conversion within cells, this active metabolite inhibits viral replication and synthesis by sterically interacting with the viral ribonucleic acid (RNA)-dependent RNA polymerase[2,3]. Although it was initially developed to treat Ebola virus and was tested *in vitro* as a broad-spectrum antiviral therapy against RNA viruses of several families, remdesivir has recently demonstrated preclinical efficacy against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2), that leads to coronavirus disease 2019 (COVID-19)[4,5]. Furthermore, several recently conducted clinical studies showed that remdesivir could be an effective treatment option for COVID-19, despite the lack of definite evidence from randomized clinical trials[6-8].

As the use of this medication has increased on a compassionate-use basis, several safety issues have been detected and caused concerns for clinicians. Diverse adverse events have been noted, from mild gastrointestinal symptoms, such as nausea and diarrhea to hepatic enzyme elevation to nephrotoxicity (renal impairment or acute kidney injury) and cardiovascular toxicities (hypotension or atrial fibrillation)[9,10]. However, despite the widely known fact that several other nucleotide analogues used to treat human immunodeficiency virus or hepatitis C virus can cause sensorineural peripheral neuropathy and other neurological toxicities, the potential for remdesivir to cause neuropsychological adverse drug reactions (ADRs) has been identified only in case reports[11-13]. Therefore, whether remdesivir is associated with neuropsychological ADRs remains to be demonstrated.

However, clinical trials can sometimes be insufficient in demonstrating an association between a targeted drug and ADRs because these trials are often conducted in a very restricted environment, and their sample sizes might be too small to detect rare but potentially fatal ADRs. On the other hand, relying on individualized reports of suspected events could mislead clinicians to think that extremely rare cases are common. Therefore, a systemic review of the reports of ADRs could be essential in defining the potential connection between the medication and symptoms. For this study, we investigated the neuropsychological ADRs associated with remdesivir use by examining the individual case safety reports (ICSRs) in the World Health Organization's (WHO) international pharmacovigilance database (VigiBase)[14,15]. Thus, this study provides the first detailed neuropsychological safety information for remdesivir to clinicians and policymakers.

Materials and Methods

Study Design and Data Source

VigiBase originates from the WHO Program for International Drug Monitoring containing more than 18 million deduplicated ICSRs, which was initiated in 1968 and monitored by the Uppsala Monitoring Centre on behalf of WHO[14]. Each report contains administrative data (report date, country of origin, qualification of notifier), patient data (age and sex), ADR data (reported terms including Medical Dictionary for Regulatory Activities [MedDRA] classification terms, onset date, end date, seriousness, and final outcome), medication data (indication for treatment,

administration start and end dates, dose and regimen, route of administration), and additional information[16,17]. This study is based on a disproportionality analysis, a case-non-case analysis, to generate pharmacovigilance signals and evaluate the clinical relevance between remdesivir and suspected neuropsychological ADRs. We searched and included all terms classified as neurological or psychological ADRs by MedDRA, a clinically validated international medical terminology coding system used in VigiBase. Then, we queried VigiBase for all reported neuropsychological cases suspected to be associated with remdesivir. Furthermore, we obtained data on previously reported neuropsychological ADRs from February 2020 when ADRs of remdesivir was first reported to VigiBase as a background. This study protocol was approved by the Institutional Review Board of Yonsei University (4-2020-0868) and ClinicalTrials.gov (NCT04314817).

Statistical Analysis

To assess the clinical relevance between remdesivir and suspected neuropsychological ADRs within the entire database, a disproportionality analysis was applied. All patients reported to VigiBase from February, 17, 2020, the data in which the first remdesivir-associated ADR was reported, to August, 30, 2020, were included in the analysis. A disproportionality analysis compares the proportion of specific ADRs reported for a selected drug (e.g., remdesivir) or group of drugs with that of the same ADRs for a control group of drugs (e.g., full database). Thus, potential ADRs are regarded as a potential safety concern when the proportion between them and the drug of interest exceeds that in the control group.

The analyses used the Bayesian neural network method developed by Uppsala Monitoring Centre[18]. Information component (IC) value, a statistical analysis validated for the comparison of proportions of ADRs between a selected drug and the full database, was calculated by logarithmically comparing the proportions of observed and expected ADRs to find pharmacovigilance signals. The precise statistical formula is $\log_2((Nobserved + 0.5)/(Nexpected + 0.5))$, where *Nobserved* (*Nexpected*) is the actual (expected) number of cases reported between the selected drug and the suspected ADRs. *Nexpected* is calculated as (*Ndrug* * *Neffect*)/*Ntotal*, where *Ndrug* is the number of cases reported for the drug, regardless of effects, and *Neffect* is the number of cases reported for the effect (ADRs), regardless of the drug. It is defined as statistically significant when $IC_{0.25}$, the lower end of a 95% credibility interval for the IC, is positive (>0).

Results

Systematic Review

To identify the possible association between remdesivir and neuropsychological ADRs we reviewed previous studies reporting on such associations. Although no significant relevance between remdesivir and neuropsychological toxicities could be found upon our investigation, few reported cases have been detected suggesting further investigation (Table I).

Table I. Reports on neuropsychological toxicity after treatment with remdesivir.

Author	Suspected neuropsychological toxicity	Publication date	Reference
A. Barlow et al	Upon treatment for Ebola viral infection, one patient showed neurologic complications after receiving remdesivir in a phase 1 study (European Medicines Agency Committee for Medicinal Products for Human Use).	April 2020	Pharmacotherapy
J. Grein et al	Two (3.8%) of 53 patients presented delirious symptoms while on remdesivir.	June 2020	N Engl J Med
C. Bonardel et al	Bilateral occipitotemporal infarction presenting with symptoms of sudden cortical blindness and disorientation 30 min after the fourth injection of remdesivir (loading dose: 200 mg IV, 100 mg IV per day thereafter).	September 2020	J Stroke Cerebrovasc Dis.
C. Carothers et al	Two patients presented remdesivir-associated acute liver failure accompanied by encephalopathy between day 3 and day 10 of remdesivir therapy.	October 2020	Pharmacotherapy
P. Anand et al	A previously healthy 61-year-old patient given remdesivir and anakinra to treat COVID-19 presented with persistent poor mental status and demonstrated posterior reversible encephalopathy syndrome.	November 2020	J Stroke Cerebrovasc Dis

Patient Demographics

We found 2,107 case reports in VigiBase of ADRs suspected to be associated with remdesivir during the study period (between February 2020, when the medication was first used to treat COVID-19, and August 2020), compared with 1,403,532 ICSRs identified in the full database for the same period. Among the reported ADRs associated with remdesivir, 108 events were classified by MedDRA as neuropsychological (64 neurologic events and 44 psychologic events), compared with 234,433 cases (151,184 neurologic events and 83,249 psychological events) reported in the full database. The most frequently identified neuropsychological toxicities to remdesivir were anxiety (n=13, 0.62% of all ADRs to remdesivir in VigiBase), followed by seizures (n=12, 0.57%), lethargy (n=6, 0.28%), agitation (n=5, 0.25%), cerebral infarction (n=3, 0.14%), ischemic stroke (n=3, 0.14%), and hemiparesis (n=3, 0.14%). The remaining neuropsychological ADRs were noted in only a single case report. The most commonly detected neuropsychological ADRs in the full database were dizziness (n=49,389, 3.52%), headache (n=48,477, 3.45%), somnolence (n=14,571, 1.04%), and insomnia (n=13,223, 0.94%) (Table II, Table

Table II. Neurologic ADRs associated with remdesivir in the full VigiBase database since February 2020.

	Remdesivir (since Feb. 2020)	Full database (since Feb. 2020)	IC/IC_{025}
Total number of ICSRs available	2,107	1,403,532	
Cerebral infarction	3(0.14)	321 (0.02)	1.83/-0.22
Cerebral artery occlusion	2 (0.09)	25 (0.00)	2.22/-0.37
Ischemic stroke	3(0.14)	429 (0.03)	1.61/-0.44
Hemiparesis	3 (0.14)	439 (0.03)	1.59/-0.46
Seizure	12 (0.57)	5925 (0.42)	0.41/-0.52
Lethargy	6 (0.28)	2558 (0.18)	0.58/-0.79
Hemorrhagic stroke	2 (0.09)	242 (0.02)	1.53/-1.05
Brain injury	2 (0.09)	308 (0.02)	1.38/-1.21
Intracranial hemorrhage	2 (0.09)	420 (0.03)	1.14/-1.44
Encephalopathy	2 (0.09)	605 (0.04)	0.83/-1.76
Vertebral artery occlusion	1 (0.05)	5 (0.00)	1.56/-2.23
Intention tremor	1 (0.05)	9 (0.00)	1.55/-2.25
Brain midline shift	1 (0.05)	17 (0.00)	1.51/-2.28
Lacunar infarction	1 (0.05)	20 (0.00)	1.50/-2.30
Myasthenia gravis crisis	1 (0.05)	26 (0.00)	1.48/-2.32
Brain herniation	1 (0.05)	43 (0.00)	1.41/-2.39
Slow response to stimuli	1 (0.05)	49 (0.00)	1.39/-2.41
Carotid artery occlusion	1 (0.05)	51 (0.00)	1.38/-2.42
Metabolic encephalopathy	1 (0.05)	70 (0.00)	1.31/-2.49
Toxic encephalopathy	1 (0.05)	100 (0.01)	1.21/-2.59
Brain edema	1 (0.05)	259 (0.02)	0.76/-3.04
Nervous system disorder	1 (0.05)	559 (0.04)	0.16/-3.63
Dystonia	1 (0.05)	562 (0.04)	0.16/-3.64
Generalized tonic-clonic seizures	1 (0.05)	605 (0.04)	0.09/-3.71
Tremor	1 (0.05)	11702 (0.83)	-2.01/-3.74
Transient ischemic attack	1 (0.05)	653 (0.05)	0.02/-3.78
Neuropathy peripheral	2 (0.09)	3870 (0.28)	-1.34/-3.92
Hypotonia	1 (0.05)	1256 (0.09)	-0.67/-4.47
Dysarthria	1 (0.05)	1299 (0.09)	-0.71/-4.51
Cerebral hemorrhage	1 (0.05)	1373 (0.10)	-0.77/-4.57
Headache	1 (0.05)	48477 (3.45)	-3.49/-4.87
Dyskinesia	1 (0.05)	1933 (0.14)	-1.18/-4.98
Syncope	1 (0.05)	4259 (0.30)	-2.20/-6.00
Migraine	1 (0.05)	4468 (0.32)	-2.26/-6.06
Dizziness	1 (0.05)	49389 (3.52)	-4.41/-6.46
Paresthesia	1 (0.05)	8858 (0.63)	-3.20/-7.00

Values are n (%) unless otherwise indicated. First ADR associated with remdesivir was reported in Feb. 2020. The information component (IC) and the lower margin of its 95% confidential interval ($IC_{0.25}$) were compared from Feb. 17, 2020 (when the first ADR to remdesivir was reported to VigiBase) to Aug. 30, 2020. A positive $IC_{0.25}$ value (>0) is the traditional threshold used for statistical signal detection. ADRs, adverse drug reactions.

Table III. Psychiatric ADRs associated with remdesivir in the full VigiBase database since February 2020.

	Remdesivir (since Feb. 2020)	Full database (since Feb. 2020)	IC/IC$_{025}$
Total number of ICSRs available	2,107	1,403,532	
Agitation	5 (0.24)	2694 (0.19)	0.28/-1.25
Anxiety	13 (0.62)	11819 (0.84)	-0.43/-1.32
Confused state	7 (0.33)	5532 (0.39)	-0.23/-1.49
Parosmia	1 (0.05)	33a4 (0.02)	0.58/-3.21
Hallucination, auditory	1 (0.05)	430 (0.03)	0.39/-3.41
Psychomotor hyperactivity	1 (0.05)	650 (0.05)	0.02/-3.77
Hallucination	2 (0.09)	3584 (0.26)	-1.23/-3.82
Psychotic disorder	1 (0.05)	771 (0.05)	-0.14/-3.94
Abnormal dreams	1 (0.05)	833 (0.06)	-0.22/-4.02
Hallucination, visual	1 (0.05)	926 (0.07)	-0.33/-4.13
Disorientation	1 (0.05)	1155 (0.08)	-0.57/-4.37
Delirium	1 (0.05)	1307 (0.09)	-0.71/-4.51
Cognitive disorder	1 (0.05)	1448 (0.10)	-0.83/-4.63
Aggression	1 (0.05)	1560 (0.11)	-0.92/-4.72
Suicidal ideation	1 (0.05)	1978 (0.14)	-1.21/-5.01
Disturbance in attention	1 (0.05)	2033 (0.14)	-1.24/-5.04
Nervousness	1 (0.05)	2645 (0.19)	-1.58/-5.37
Somnolence	1 (0.05)	14571 (1.04)	-3.16/-5.75
Depression	1 (0.05)	6898 (0.49)	-2.86/-6.65
Paresthesia	1 (0.05)	8858 (0.63)	-3.20/-7.00
Insomnia	1 (0.05)	13223 (0.94)	-3.76/-7.56

Values are n (%) unless otherwise indicated. First ADR associated with remdesivir was reported in Feb. 2020. The information component (IC) and the lower margin of its 95% confidential interval (IC$_{0.25}$) were compared from Feb. 17, 2020 (when the first ADR to remdesivir was reported to VigiBase) to Aug. 30, 2020. A positive IC$_{0.25}$ value (>0) is the traditional threshold used for statistical signal detection. ADRs, adverse drug reactions.

III). Additional information on the characteristics of reported ICSRs and the patients are provided in a **Supplementary Table I**.

Relevance of Neuropsychological Toxicities to Remdesivir

Upon reviewing the IC$_{0.25}$ value indicating the proportion of neuropsychological ADRs associated with remdesivir versus the full database, we found no statistically significant pharmacovigilance signal. The IC$_{0.25}$ of all neuropsychological toxicities was negative, indicating that no significant relevance could be demonstrated between remdesivir and neuropsychological ADRs.

Discussion

This study found no evidence to support an association between remdesivir and neuropsychological toxicities, which is contrary to a few recent case reports that have raised concerns about the neuropsychological effects of remdesivir. Because no definitely designated treatment is available for patients diagnosed with COVID-19 and because those patients usually present with complicated past histories, the efficacy and safety of newly developed medications are being examined rigorously[19-21]. Due to several recent reports on the efficacy of remdesivir, its application has been increasing, despite the dearth of available information about potential safety issues[6,7]. Therefore, the finding of this study can assure clinicians possibly about the safety of using this medication, although further prospective studies are warranted, especially in patients with concurrent neuropsychological illnesses, such as epilepsy or in those at high risk of neuropsychological effects.

We used a disproportionality analysis of an international pharmacovigilance database. This method, a way to systemically analyze pharmacovigilance signals, is widely applied to analyze safety issues with medications. Statistical relevance between suspected complications and several medications has been determined and provided clinicians with abundant data for use in clinical settings[16,17,22-25]. Prior to our study, this method was applied to non-neurologic safety issues with remdesivir, and it was found that complications such as renal injury, hepatic disease,

and cardiovascular toxicity could be relevant to the use of this medication, verifying the utility of our method for identifying the relevance of ADRs to selected drugs[15,26,27].

Based on our analysis, it might be logical to assume that the neuropsychological complications of remdesivir reported to this point were caused by multifactorial parameters such as (1) disease factors, (2) patient factors (past history), (3) environmental or other infectious factors, and (4) treatment factors, rather than the remdesivir. Among those factors, several reports and other evidence suggest an association between the natural disease course of COVID-19 and neurological complications[28-30]. SARS-CoV-2, the causal pathogen of COVID-19, is known to bind to the angiotensin converting enzyme 2 receptor, which is widely expressed throughout the body, including the central nervous system (CNS)[31,32]. Other potential routes of neuro-invasion, such as a trans-synaptic pathway and the blood-brain barrier pathway, have been found to cause neuro-inflammation and neurologic manifestations such as headache, altered mental status, anosmia, and encephalopathy[30]. Therefore, it is rational to assume that the neuropsychological symptoms detected in COVID-19 patients are caused by the disease itself rather than by the remdesivir.

In addition, remdesivir demonstrates low CNS penetrance, achieving a less than 5% brain-to-plasma ratio[33]. Likewise, favipiravir, a similar nucleotide analog prodrug used to treat viral infections, shows low CNS penetrance and demonstrates little association with neuropsychiatric complications, whereas other nucleotide analogs such as zalcitabine or clevudine, which are used to treat tumors, show high CNS penetrance and pronounced neurologic toxicity, such as neuropathy or encephalopathy[34,35]. Therefore, even though the efficacy of remdesivir applied to treat CNS inflammation, such as viral encephalopathy, is unknown, its poor CNS penetrance probably explains the low association we found between remdesivir and neuropsychological ADRs.

Several limitations of our study should be noted. First, even though we found no statistically significant pharmacovigilance signals, further analysis of *in vitro* laboratory studies and prospective clinical trials must be done to confirm the actual safety signals. Moreover, under-notification and reporting biases could have occurred. Some adverse events might have been dismissed and not reported to the national healthcare authorities. Also, the authorities might have received incomplete information because the reporting system is voluntary and lacks professionalism; thus, the data could be biased. However, since VigiBase contains ICSRs collected from >130 countries and thus contains abundant data, an absence of rarely identified adverse events is unlikely, and this study is considered generalizable.

Conclusions

Our study demonstrated that remdesivir, a novel drug applied to treat COVID-19, does not show a significant association with adverse neurologic or psychiatric reactions. This finding, together with recent research about the pharmacologic complications of remdesivir, can help clinicians to safely apply this medication in real clinical settings.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Clinical Trial Registration

Clinicaltrial.gov: NCT04314817.

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