**Neuropsychological Adverse Drug Reactions to Remdesivir: Results from the WHO International Pharmacovigilance Database**

Sangbo Lee1\*, Jae Won Yang2\*, Se Yong Jung1\*, Min Seo Kim3, Dong Keon Yon4, Seung Won Lee 5, Hoon-Chul Kang1, Elena Dragioti6, Kalthoum Tizaoui7, Louis Jacob8,9, Ai Koyanagi8,10, Joe-Elie Salem11, Karel Kostev12, Ana Lascu13, Jae Il Shin1+, Ji Hong Kim1+, Lee Smith14

1Department of Pediatrics, Yonsei University College of Medicine, Yonsei-ro 50-1, Seodaemun-gu, Seoul 03722, Republic of Korea; [sangbo14@yuhs.ac](mailto:sangbo14@yuhs.ac) (SB Lee), [jung811111@yuhs.ac](mailto:jung811111@yuhs.ac) (SY Jung), [hipo0207@yuhs.ac](mailto:hipo0207@yuhs.ac) (HC Kang), [kkkjhd@yuhs.ac](mailto:kkkjhd@yuhs.ac) (JH Kim), [shinji@yuhs.ac](mailto:shinji@yuhs.ac) (JI Shin)

2Department of Nephrology, Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; kidney74@yonsei.ac.kr

3Genomics and Digital Health, Samsung Advanced Institute for Health Sciences and Technology (SAIHST), Sungkyunkwan University, Seoul, Republic of Korea; [minseolike@naver.com](mailto:minseolike@naver.com)

4Department of Pediatrics, Seoul National University Children's Hospital, Seoul National University College of Medicine, Seoul, Republic of Korea; [yonkkang@gmail.com](mailto:yonkkang@gmail.com)

5Department of Data Science, Sejong University College of Software Convergence, Seoul, South Korea; lsw2920@gmail.com

6Pain and Rehabilitation Centre, and Department of Health, Medicine and Caring Sciences, Linköping University, SE-581 85 Linköping, Sweden; [elena.dragioti@liu.se](mailto:elena.dragioti@liu.se)

7Laboratory Microorganisms and Active Biomolecules, Sciences Faculty of Tunis, University Tunis El Manar, Tunis, Tunisia.Tunisia; [kalttizaoui@gmail.com](mailto:kalttizaoui@gmail.com)

8Research and Development Unit, Parc Sanitari Sant Joan de Déu, Universitat de Barcelona, Fundació Sant Joan de Déu, CIBERSAM, 08830 Barcelona, Spain; [louis.jacob.contacts@gmail.com](mailto:louis.jacob.contacts@gmail.com); a.koyanagi@pssjd.org

9Faculty of Medicine, University of Versailles Saint-Quentin-en-Yvelines, Montigny-le-Bretonneux, 78180, France

10ICREA, Barcelona, Spain

11Sorbonne 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](mailto:joe-elie.salem@aphp.fr)

12University Clinic of Marburg, Marburg, Germany; [Karel.Kostev@gmx.de](mailto:Karel.Kostev@gmx.de)

13Discipline of Pathophysiology, Department of Functional Sciences, Victor Babeş University of Medicine and Pharmacy, Timişoara, Romania; [analascu@yahoo.com](mailto:analascu@yahoo.com)

14 Centre for Health, Performance, and Wellbeing, Anglia Ruskin University, Cambridge CB1 1PT, UK; lee.smith@aru.ac.uk

\* These three authors contributed equally to this work as 1st authors.

+**Corresponding author information**

Correspondence to Jae Il Shin, MD (E-mail: [SHINJI@yuhs.ac](mailto:SHINJI@yuhs.ac))

Correspondence to Ji Hong Kim, MD (E-mail: [KKKJHD@yuhs.ac](mailto:KKKJHD@yuhs.ac))

**Highlights:**

* A disproportionality analysis of individualized case safety reports from the WHO global pharmacovigilance database, VigiBase, enables an evaluation of the clinical association between a selected medication and suspected adverse events.
* Remdesivir, an antiviral drug recently applied to the treatment of COVID-19, does not show any significant association with neuropsychiatric complications.

**Running Title:** Neuropsychological adverse drug reactions to remdesivir

**Funding Source:** This research was supported by a National Research Foundation of Korea (NRF) grant funded by the Korean government (NRF2019R1G1A109977912).

**Acknowledgements:** None.

**Conflicts of Interest:** The authors have no conflicts of interest to disclose.

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

**Keywords:** Remdesivir, Pharmacovigilance, VigiBase, Neuropsychological toxicities, Adverse drug reactions

**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.

**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).

**Result:** 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 neuropsychological 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%]).

**Conclusion:** 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.

**Clinicaltrial.gov**: NCT04314817

**1. 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 polymerase2,3. 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 trials6-8.

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 reports11-13. 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 policy-makers.

**2. METHODS**

**2.1 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 WHO14. 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 information16,17. 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).

**2.2 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 Centre18. 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 log2((*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 IC0.25, the lower end of a 95% credibility interval for the IC, is positive (>0).

**3. RESULTS**

**3.1 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)**

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

**3.3 Relevance of neuropsychological toxicities to remdesivir**

Upon reviewing the IC0.25 value indicating the proportion of neuropsychological ADRs associated with remdesivir versus the full database, we found no statistically significant pharmacovigilance signal. The IC0.25 of all neuropsychological toxicities was negative, indicating that no significant relevance could be demonstrated between remdesivir and neuropsychological ADRs.

**4. 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 rigorously19-21. Due to several recent reports on the efficacy of remdesivir, its application has been increasing, despite the dearth of available information about potential safety issues6,7. 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 settings16,17,22-25. 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 drugs15,26,27.

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 complications28-30. 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 encephalopathy30. 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 ratio33. 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 encephalopathy34,35. 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, because 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.

**5. CONCLUSION**

In conclusion, 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.

**REFERENCES**

1) Eastman RT, Roth JS, Brimacombe KR, Simeonov A, Shen M, Patnaik S, Hall MD. Remdesivir: A Review of Its Discovery and Development Leading to Emergency Use Authorization for Treatment of COVID-19. ACS Cent Sci 2020; 6: 672-683.

2) Yin W, Mao C, Luan X, Shen DD, Shen Q, Su H, Wang X, Zhou F, Zhao W, Gao M, Chang S, Xie YC, Tian G, Jiang HW, Tao SC, Shen J, Jiang Y, Jiang H, Xu Y, Zhang S, Zhang Y, Xu HE. Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. Science 2020; 368: 1499-1504.

3) Jorgensen SCJ, Kebriaei R, Dresser LD. Remdesivir: Review of Pharmacology, Pre-clinical Data, and Emerging Clinical Experience for COVID-19. Pharmacotherapy 2020; 40: 659-671.

4) Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, Soloveva V, Siegel D, Perron M, Bannister R, Hui HC, Larson N, Strickley R, Wells J, Stuthman KS, Van Tongeren SA, Garza NL, Donnelly G, Shurtleff AC, Retterer CJ, Gharaibeh D, Zamani R, Kenny T, Eaton BP, Grimes E, Welch LS, Gomba L, Wilhelmsen CL, Nichols DK, Nuss JE, Nagle ER, Kugelman JR, Palacios G, Doerffler E, Neville S, Carra E, Clarke MO, Zhang L, Lew W, Ross B, Wang Q, Chun K, Wolfe L, Babusis D, Park Y, Stray KM, Trancheva I, Feng JY, Barauskas O, Xu Y, Wong P, Braun MR, Flint M, McMullan LK, Chen SS, Fearns R, Swaminathan S, Mayers DL, Spiropoulou CF, Lee WA, Nichol ST, Cihlar T, Bavari S. Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. Nature 2016; 531: 381-385.

5) Pardo J, Shukla AM, Chamarthi G, Gupte A. The journey of remdesivir: from Ebola to COVID-19. Drugs Context 2020; 9.

6) Goldman JD, Lye DCB, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn MY, Nahass RG, Chen YS, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. N Engl J Med 2020; 383: 1827-1837.

7) Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, Feldt T, Green G, Green ML, Lescure FX, Nicastri E, Oda R, Yo K, Quiros-Roldan E, Studemeister A, Redinski J, Ahmed S, Bernett J, Chelliah D, Chen D, Chihara S, Cohen SH, Cunningham J, D'Arminio Monforte A, Ismail S, Kato H, Lapadula G, L'Her E, Maeno T, Majumder S, Massari M, Mora-Rillo M, Mutoh Y, Nguyen D, Verweij E, Zoufaly A, Osinusi AO, DeZure A, Zhao Y, Zhong L, Chokkalingam A, Elboudwarej E, Telep L, Timbs L, Henne I, Sellers S, Cao H, Tan SK, Winterbourne L, Desai P, Mera R, Gaggar A, Myers RP, Brainard DM, Childs R, Flanigan T. Compassionate Use of Remdesivir for Patients with Severe Covid-19. N Engl J Med 2020; 382: 2327-2336.

8) Spinner CD, Gottlieb RL, Criner GJ, Arribas López JR, Cattelan AM, Soriano Viladomiu A, Ogbuagu O, Malhotra P, Mullane KM, Castagna A, Chai LYA, Roestenberg M, Tsang OTY, Bernasconi E, Le Turnier P, Chang SC, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wang H, Gaggar A, Brainard DM, McPhail MJ, Bhagani S, Ahn MY, Sanyal AJ, Huhn G, Marty FM. 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.

9) Fan Q, Zhang B, Ma J, Zhang S. Safety profile of the antiviral drug remdesivir: An update. Biomed Pharmacother 2020; 130: 110532.

10) Kim MS, Jung SY, Lee SW, Li H, Koyanagi A, Kronbichler A, Dragioti E, Tizaoui K, Wasuwanich P, Hong SH, Ghayda RA, Yoo HW, Kim H, Jacob L, Salem JE, Kostev K, Shin YH, Kim SY, Gamerith G, Yon DK, Shin JI, Smith L. Hepatobiliary Adverse Drug Reactions Associated With Remdesivir: The WHO International Pharmacovigilance Study. Clin Gastroenterol Hepatol 2021; doi:10.1016/j.cgh.2021.04.039.

11) Cherry CL, McArthur JC, Hoy JF, Wesselingh SL. Nucleoside analogues and neuropathy in the era of HAART. J Clin Virol 2003; 26: 195-207.

12) Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. Drug Saf 1998; 19: 481-494.

13) Kiwuwa-Muyingo S, Kikaire B, Mambule I, Musana H, Musoro G, Gilks CF, Levin JB, Walker AS. Prevalence, incidence and predictors of peripheral neuropathy in African adults with HIV infection within the DART trial. Aids 2014; 28: 2579-2588.

14) Lindquist M. VigiBase, the WHO Global ICSR Database System: Basic Facts. Drug Information Journal 2008; 42: 409-419.

15) Gérard AO, Laurain A, Fresse A, Parassol N, Muzzone M, Rocher F, Esnault VLM, Drici MD. Remdesivir and Acute Renal Failure: A Potential Safety Signal From Disproportionality Analysis of the WHO Safety Database. Clin Pharmacol Ther 2020; doi:10.1002/cpt.2145.

16) Salem JE, Manouchehri A, Moey M, Lebrun-Vignes B, Bastarache L, Pariente A, Gobert A, Spano JP, Balko JM, Bonaca MP, Roden DM, Johnson DB, Moslehi JJ. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. Lancet Oncol 2018; 19: 1579-1589.

17) Johnson DB, Manouchehri A, Haugh AM, Quach HT, Balko JM, Lebrun-Vignes B, Mammen A, Moslehi JJ, Salem JE. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. J Immunother Cancer 2019; 7: 134.

18) Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM. A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 1998; 54: 315-321.

19) Liang C, Tian L, Liu Y, Hui N, Qiao G, Li H, Shi Z, Tang Y, Zhang D, Xie X, Zhao X. A promising antiviral candidate drug for the COVID-19 pandemic: A mini-review of remdesivir. Eur J Med Chem 2020; 201: 112527.

20) Wondmkun YT, Mohammed OA. A Review on Novel Drug Targets and Future Directions for COVID-19 Treatment. Biologics 2020; 14: 77-82.

21) Sternberg A, McKee DL, Naujokat C. Novel Drugs Targeting the SARS-CoV-2/COVID-19 Machinery. Curr Top Med Chem 2020; 20: 1423-1433.

22) Wang DY, Salem JE, Cohen JV, Chandra S, Menzer C, Ye F, Zhao S, Das S, Beckermann KE, Ha L, Rathmell WK, Ancell KK, Balko JM, Bowman C, Davis EJ, Chism DD, Horn L, Long GV, Carlino MS, Lebrun-Vignes B, Eroglu Z, Hassel JC, Menzies AM, Sosman JA, Sullivan RJ, Moslehi JJ, Johnson DB. Fatal Toxic Effects Associated With Immune Checkpoint Inhibitors: A Systematic Review and Meta-analysis. JAMA Oncol 2018; 4: 1721-1728.

23) Arnaud L, Mertz P, Gavand PE, Martin T, Chasset F, Tebacher-Alt M, Lambert A, Muller C, Sibilia J, Lebrun-Vignes B, Salem JE. Drug-induced systemic lupus: revisiting the ever-changing spectrum of the disease using the WHO pharmacovigilance database. Ann Rheum Dis 2019; 78: 504-508.

24) Cornet L, Khouri C, Roustit M, Guignabert C, Chaumais MC, Humbert M, Revol B, Despas F, Montani D, Cracowski JL. Pulmonary arterial hypertension associated with protein kinase inhibitors: a pharmacovigilance-pharmacodynamic study. Eur Respir J 2019; 53.

25) Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Meyboom RH, Egberts TC, Leufkens HG. Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organization VigiBase. Diabetes Care 2011; 34: 369-374.

26) Montastruc F, Thuriot S, Durrieu G. Hepatic Disorders With the Use of Remdesivir for Coronavirus 2019. Clin Gastroenterol Hepatol 2020; 18: 2835-2836.

27) Touafchia A, Bagheri H, Carrié D, Durrieu G, Sommet A, Montastruc F. Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns. Clin Microbiol Infect 2021; doi:10.1016/j.cmi.2021.02.013.

28) Niazkar HR, Zibaee B, Nasimi A, Bahri N. The neurological manifestations of COVID-19: a review article. Neurol Sci 2020; 41: 1667-1671.

29) Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, Kneen R, Defres S, Sejvar J, Solomon T. Neurological associations of COVID-19. Lancet Neurol 2020; 19: 767-783.

30) Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and Neurologic Manifestations of the Coronaviruses in the Age of Coronavirus Disease 2019: A Review. JAMA Neurol 2020; 77: 1018-1027.

31) Yang JM, Moon SY, Lee JY, Agalliu D, Yon DK, Lee SW. COVID-19 morbidity and severity in patients with age-related macular degeneration: a Korean nationwide cohort study. Am J Ophthalmol 2021; doi:10.1016/j.ajo.2021.05.024. 11881.

32) Yang JM, Koh HY, Moon SY, Yoo IK, Ha EK, You S, Kim SY, Yon DK, Lee SW. Allergic disorders and susceptibility to and severity of COVID-19: A nationwide cohort study. J Allergy Clin Immunol 2020; 146: 790-798.

33) Richardson PJ, Ottaviani S, Prelle A, Stebbing J, Casalini G, Corbellino M. CNS penetration of potential anti-COVID-19 drugs. J Neurol 2020; 267: 1880-1882.

34) Feng JY. Addressing the selectivity and toxicity of antiviral nucleosides. Antivir Chem Chemother 2018; 26: 2040206618758524.

35) Borg N, Ståhle L. Pharmacokinetics and distribution over the blood-brain barrier of zalcitabine (2',3'-dideoxycytidine) and BEA005 (2', 3'-dideoxy-3'-hydroxymethylcytidine) in rats, studied by microdialysis. Antimicrob Agents Chemother 1998; 42: 2174-2177.

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 |

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/IC025 |
| **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 (IC0.25) were compared from Feb. 17, 2020 (when the first ADR to remdesivir was reported to VigiBase) to Aug. 30, 2020. A positive IC0.25 value (>0) is the traditional threshold used for statistical signal detection. ADRs, adverse drug reactions

|  |  |  |  |
| --- | --- | --- | --- |
|  | Remdesivir  (since Feb. 2020) | Full database  (since Feb. 2020) | IC/IC025 |
| **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) | 334 (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 |

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

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 (IC0.25) were compared from Feb. 17, 2020 (when the first ADR to remdesivir was reported to VigiBase) to Aug. 30, 2020. A positive IC0.25 value (>0) is the traditional threshold used for statistical signal detection. ADRs, adverse drug reactions

**Supplementary Table.** Characteristics of reported ICSRs with neuropsychiatric ADRs associated with remdesivir in VigiBase (Last accessed Aug. 30, 2020)

|  |  |
| --- | --- |
|  | Neuropsychiatric ADRs (n = 101\*) |
| Regions Reporting | **101 (100.0)** |
| Americas | 90/101 (89.1) |
| Europe | 9/101 (8.9) |
| Australia | 1/101 (1.0) |
| Asia | 1/101 (1.0) |
| Report from Clinical Trials | 5/101 (5.0) |
| Reporter | **96 (95.0)** |
| Health care professional | 96/96 (100.0) |
| Non-health care professional | 0/96 (0.0) |
| Age Groups | **99 (98.0)** |
| < 18 years | 1/99 (1.0) |
| 18 – 44 years | 15/99 (15.2) |
| 45 - 64 years | 39/99 (39.4) |
| 65 – 74 years | 20/99 (20.2) |
| ≥ 75 years | 24/99 (24.2) |
| Sex | **101 (100)** |
| Male | 51/101 (50.5) |
| Female | 50/101 (49.5) |
| Serious ADRs | **101 (100)** |
|  | 89 (88.1) |
| Drug Treatment Duration | **91 (96.3)** |
| Median Days (IQR,  min-max) | 4.0 (2.0-8.0,  0.0-10.0) |

\* A total of 101 patients with neuropsychiatric ADRs after exclusion of overlapping ICSRs were analyzed.

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 a life-threatening ADR causing persistent or significant disability, requiring hospitalization (first or prolonged), or causing death. ADR, adverse drug reaction