Clinical Microbiology and Infection 27 (2021) 791.e5–791.e8

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Research note

Serious bradycardia and remdesivir for coronavirus 2019 (COVID-19): a new safety concerns

Anthony Touafchia [1, 2], Haleh Bagheri [1, 3], Didier Carrié [2], Geneviève Durrieu [1, 3], Agnès Sommet [1, 3], Laurent Chouchana [4], François Montastruc [2, *]

[1)] *Department of Medical and Clinical Pharmacology, Centre of PharmacoVigilance and Pharmacoepidemiology, Toulouse University Hospital (CHU), Faculty of Medicine, Toulouse, France*
[2)] *Department of Cardiology, Toulouse University Hospital (CHU), Faculty of Medicine, Toulouse, France*
[3)] *CIC 1436, Team PEPSS « Pharmacologie En Population cohorteS et biobanqueS », Toulouse University Hospital, France*
[4)] *Department of Pharmacology, Regional Pharmacovigilance Center, Cochin Hospital, AP-HP.Centre – Université de Paris. Paris, France*

ARTICLE INFO

Article history:
Received 3 November 2020
Received in revised form
12 January 2021
Accepted 6 February 2021
Available online 27 February 2021

Editor: W. Couet

Keywords:
Bradycardia
COVID-19
Pharmacovigilance
Remdesivir
RNA-dependent RNA-polymerase inhibitors
Vigibase

ABSTRACT

Objectives: In recent clinical trials some cardiac arrhythmias were reported with use of remdesivir for COVID-19. To address this safety concern, we investigated whether use of remdesivir for COVID-19 is associated with an increased risk of bradycardia.
Methods: Using VigiBase®, the World Health Organization Global Individual Case Safety Reports database, we compared the cases of bradycardia reported in COVID-19 patients exposed to remdesivir with those reported in COVID-19 patients exposed to hydroxychloroquine, lopinavir/ritonavir, tocilizumab or glucocorticoids. All reports of patients with COVID-19 registered up to the 23 September 2020 were included. We conducted disproportionality analyses allowing the estimation of reporting odds ratios (RORs) with 95% CI.
Results: We found 302 cardiac effects including 94 bradycardia (31%) among the 2603 reports with remdesivir prescribed in COVID-19 patients. Most of the 94 reports were serious (75, 80%), and in 16 reports (17%) evolution was fatal. Compared with hydroxychloroquine, lopinavir/ritonavir, tocilizumab or glucocorticoids, the use of remdesivir was associated with an increased risk of reporting bradycardia (ROR 1.65; 95% CI 1.23–2.22). Consistent results were observed in other sensitivity analyses.
Discussion: This post-marketing study in a real-world setting suggests that the use of remdesivir is significantly associated with an increased risk of reporting bradycardia and serious bradycardia when compared with the use of with hydroxychloroquine, lopinavir/ritonavir, tocilizumab or glucocorticoids. This result is in line with the pharmacodynamic properties of remdesivir. **Anthony Touafchia, Clin Microbiol Infect 2021;27:791.e5–791.e8**

Introduction

Remdesivir is a phosphoramidate prodrug. Its triphosphate form is close to adenosine triphosphate (ATP) and inhibits RNA-dependent RNA-polymerases (RdRp) from distinct Coronaviridae such as SARS-CoV-2 [1]. In vitro and animal models demonstrated the antiviral activity of remdesivir. Remdesivir was authorized by the Food and Drug Agency (FDA) for suspected or laboratory-confirmed COVID-19 in hospitalized adult or paediatric patients, irrespective of their severity of disease. While safety signals emerged concerning hepatic disorders, little is known about its cardiac safety [2]. In the clinical trial evaluating the effects of remdesivir on Ebola virus, arterial hypotension and cardiac arrest in one patient in the remdesivir group (among 175) was described [3]. In the first COVID-19 clinical trial, another cardiac arrest was reported in a patient exposed to remdesivir [4]. In this study, a higher proportion of patients with remdesivir treatment discontinued due to an adverse event, including worsened cardiopulmonary status compared with those patients receiving placebo. In the Adaptive Covid-19 Treatment Trial (ACTT-1), more cardiac

* Corresponding author. François Montastruc, Department of Medical and Clinical Pharmacology, 37 Allées Jules Guesde, 31000 Toulouse, France.
E-mail address: francois.montastruc@univ-tlse3.fr (F. Montastruc).
@montastrucf (F. Montastruc)

https://doi.org/10.1016/j.cmi.2021.02.013
1198-743X/

arrhythmias occurred with the use of remdesivir than with placebo (8‰ versus 2‰) [5]. While most trials are powered to detect benefits but not adverse events, there is an urgent need to investigate this safety concern [6]. Using VigiBase®, the World Health Organization Global Individual Case Safety Reports database, we determined whether use of remdesivir is associated with an increased risk of reporting bradycardia and serious bradycardia with in COVID-19 patients.

Materials and methods

wThis pharmacovigilance study was conducted using VigiBase®. The WHO pharmacovigilance database gathers more than 23 million spontaneous reports of suspected adverse drug reactions from more than 130 countries, covering more than 90% of the world's population. Each safety report includes information related to the reporter, the patient, the suspected and concomitant drugs, and the adverse drug reactions. The seriousness of each adverse drug reaction is also recorded. According to the official definition, a serious adverse effect is as any effects leading to death, invalidation, significant incapacity, after-effects, malformations, congenital anomalies, birth defects or requires hospitalization or prolongation of hospital stay. VigiBase® identified duplicate reports which are removed from the database. The Medical Dictionary for Regulatory Activities (MedDRA®) are used to code each adverse drug reaction. According to the clinical research French law, review by an ethics committee is not required for such observational studies. As all data from VigiBase® were deidentified, patient informed consent was not necessary.

All reports of patients with COVID-19 registered up to the 23 September 2020 were included. We performed disproportionality analysis to assess a potential increased risk of reporting bradycardia with remdesivir compared with drugs prescribed in COVID-19 patients. Reporting Odds Ratio (ROR) with 95% CI was calculated to estimate the risk of reporting bradycardia. ROR is a ratio similar in concept to the odds ratio in case–control studies and corresponds to the exposure odds among reported cases of bradycardia over the exposure odds among reported non-cases. To test the robustness of our main analyses, four sensitivity analyses were conducted. First, to limit the potential of confounding by disease severity, we repeated the primary analysis considering only users of tocilizumab or glucocorticoids, drugs recommended in patients with severe COVID-19. Second, we restricted our analysis to only serious bradycardia. Third, we included all reports where COVID-19 drugs were defined as suspected or concomitant by reporters. Fourth, as a recent study suggested a risk of cardiac arrhythmias with hydroxychloroquine, we performed a head-to-head comparison (remdesivir versus hydroxychloroquine) [7]. In addition, to address the effect of age and sex, we used stratification analyses according age groups (≤44 years, 45–64 years and ≥65 years) and sex.

Table 1
Reporting odds ratios for the association between bradycardia and the use of remdesivir for coronavirus disease 2019 in vigibase[a]

	Cases[b]	Non-cases[c]	ROR (95% CI)
Primary analysis			
Other drugs prescribed for COVID-19[d]	88	3883	1 (reference)
Remdesivir	94	2509	1.65 (1.23–2.22)
Restricting to drugs used for severe COVID-19			
Tocilizumab or glucocorticoids	8	751	1 (reference)
Remdesivir	94	2509	3.52 (1.70–7.28)
Restricting to reports of serious adverse effects[e]			
Other drugs prescribed for COVID-19[d]	60	9911	1 (reference)
Remdesivir	75	2528	1.93 (1.37–2.72)
Including reports where drugs was defined as suspected or concomitant[f]			
Other drugs prescribed for COVID-19[d]	124	4928	1 (reference)
Remdesivir	94	2536	1.47 (1.12–1.93)
Head-to-head comparison			
Hydroxychloroquine	61	2810	1 (reference)
Remdesivir	94	2509	1.73 (1.25–2.39)
Age groups[g]			
≤44 years			
Other drugs prescribed for COVID-19[d]	8	1101	1 (reference)
Remdesivir	14	475	4.06 (1.69–9.74)
45–64 years			
Other drugs prescribed for COVID-19[d]	25	1087	1 (reference)
Remdesivir	34	843	4.75 (1.04–2.96)
≥65 years			
Other drugs prescribed for COVID-19[d]	25	1022	1 (reference)
Remdesivir	40	1037	1.58 (0.95–2.62)
Sex groups[h]			
Female			
Other drugs prescribed for COVID-19[d]	17	1381	1 (reference)
Remdesivir	39	930	3.41 (1.92–6.06)
Male			
Other drugs prescribed for COVID-19[d]	40	1935	1 (reference)
Remdesivir	54	1519	4.75 (1.04–2.96)

[a] ROR is a ratio similar in concept to the odds ratio in case–control studies and corresponds to the exposure odds among reported cases of bradycardia over the exposure odds among reported non-case.
[b] Reports containing any terms including the terminology 'Bradycardia' or 'Sinus Bradycardia' found in MedDRA dictionary https://www.meddra.org.
[c] All other adverse events.
[d] Hydroxychloroquine, tocilizumab, lopinavir/ritonavir, dexamethasone, methylprednisolone.
[e] Occurrence of death, a life-threatening adverse event, inpatient hospitalisation or prolongation of hospitalisation, significant disability, congenital anomaly.
[f] Drugs used concurrently but not suspected by the reporter to have caused the adverse effect.
[g] 863 reports with missing age data.
[h] 659 reports with missing sex data.

Results

We identified 6574 reports with remdesivir or other drugs prescribed in COVID-19 patients. Among the 2603 reports with remdesivir, 302 were registered as cardiac effects. Among these cardiac reports, we found 94 bradycardia reports (31%), mainly from the United States (88, 93%). Patients with bradycardia had wide spectrum of age (61.2 ± 18.1 years, 6–90 min–max), were mostly men (53, 56%), with a mean body weight of 93 ± 28.3 kg. Mean treatment duration with remdesivir was 3.5 ± 1.8 days (range 1–9). Remdesivir was the sole suspected drug in 88 patients (94%). Two-thirds of patients (61, 65%) did not received concomitant cardiovascular medications. Most of reports were serious (75, 80%) and in 16 reports (17%) evolution was fatal. Furthermore, concurrent cardiovascular adverse effects occurred in 22 (23%) patients, mostly hypotension (10). The median onset of bradycardia was 2.4 days (range 1–6) (data available for 18 reports). For bradycardia reports with remdesivir, reporters were mostly pharmacists (77 cases 82%) followed by physicians (11 cases, 12%) and other health professional (4 cases, 4%) (two cases reporters were unknown).

Compared with hydroxychloroquine, lopinavir/ritonavir, tocilizumab or glucocorticoids, the use of remdesivir was associated with an increased risk of reporting bradycardia (ROR 1.65; 95% CI 1.23–2.22) (Table 1). The ROR remained significant (3.52, 95% CI 1.70–7.28) when the analysis was retitrated to tocilizumab or glucocorticoid users in the reference group. Consistent results were observed in other sensitivity analyses and according age groups and sex.

Discussion

In this observational study including more than 6500 reports of COVID-19 patients, we found for the first time an association between remdesivir use and reports of bradycardia. Most of bradycardia reports with remdesivir were serious and some were fatal (17%). Our study suggests an increased risk of reporting bradycardia with remdesivir than other drugs. While such analysis could be subject to limitations as reporting bias, our results are in line with previous reports of cardiac events in remdesivir clinical trials [5]. This safety concern reminds us of two other cardiac safety signals with other RNA-dependent RNA-polymerase inhibitors. First, clinical development of the antiviral BMS986094 was discontinued after a phase II study due to serious cardiac events including heart rhythm disorders [8]. Second, in 2015, the FDA warned about serious bradycardia with hepatitis C treatments containing sofosbuvir [9]. The pharmacodynamic mechanism for bradycardia with remdesivir is still unknown. However, similarly to sofosbuvir, an effect on sinoatrial node function might be suggested [10]. Indeed, the active remdesivir metabolite is a nucleotide triphosphate derivative with similarity to ATP, known to slow sinoatrial node automaticity [1]. In the heart, ATP exerts negative chronotropic and dromotropic effects. The cardiac actions of ATP are mediated by adenosine its metabolite and by a vagal reflex triggered by ATP's stimulation of vagal sensory nerve terminals in the left ventricle [11]. Although this evidence is based on data from individual case safety reports, disproportionality analyses in pharmacovigilance databases remain important and provide reproducible information essential for early post-marketing surveillance [12,13]. These cardiac safety concerns should be particularly considered to limit the risk of cardiac adverse effects, particularly in the context of polypharmacy [14]. In addition, pharmacovigilance investigations are still necessary for cardiac risk with remdesivir, as a previous study reported the potential block of *hERG* (human ether-a-go-go gene) and prolongation of cardiac repolarization with remdesivir [15]. Post hoc analyses of trials and additional observational studies are needed to corroborate our findings. Given the increased use of remdesivir and recent FDA recommendations, physicians should be aware of this cardiac safety signal.

Transparency declaration

All authors have no relevant conflicts of interest to disclose. The work was performed during the university research time of the authors using the database which is available without fees in the department of the authors.

Author contributions

All authors conceived and designed the study. F.M. and A.T. acquired the data and did the statistical analyses. All authors analysed and interpreted the data. F.M. wrote the manuscript, and all authors critically revised the manuscript. F.M. supervised the study and is the guarantor. All authors approved the final version of the manuscript and are accountable for its accuracy.

Acknowledgements

The authors acknowledge the Uppsala Monitoring Centre (UMC) who provided and gave permission to use the data analysed in the present study. Access to the World Health Organization global individual case safety report database, VigiBase®, is available without fees to Dr Bagheri, Dr Durrieu and Dr Montastruc. The authors are indebted to the National Pharmacovigilance centres that contributed data. The opinions and conclusions in this study are not necessarily those of the various centres or of the World Health Organization.

References

[1] Gordon CJ, Tchesnokov EP, Woolner E, Perry JK, Feng JY, Porter DP, et al. Remdesivir is a direct-acting antiviral that inhibits RNA-dependent RNA polymerase from severe acute respiratory syndrome coronavirus 2 with high potency. J Biol Chem 2020;295:6785–97. https://doi.org/10.1074/jbc.RA120.013679.

[2] Montastruc F, Thuriot S, Durrieu G. Hepatic disorders with the use of remdesivir for coronavirus 2019. Clin Gastroenterol Hepatol 2020;18:2835–6. https://doi.org/10.1016/j.cgh.2020.07.050.

[3] Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med 2019;381:2293–303. https://doi.org/10.1056/NEJMoa1910993.

[4] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;395:1569–78. https://doi.org/10.1016/S0140-6736(20)31022-9.

[5] Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalil AC, et al. Remdesivir for the treatment of covid-19 – final report. N Engl J Med 2020;383:1813–26. https://doi.org/10.1056/NEJMoa2007764.

[6] Onakpoya IJ. Rare adverse events in clinical trials: understanding the rule of three. BMJ Evid Based Med 2018;23:6. https://doi.org/10.1136/ebmed-2017-110885.

[7] Goldman A, Bomze D, Dankner R, Hod H, Meirson T, Boursi B, et al. Cardiovascular adverse events associated with hydroxychloroquine and chloroquine: a comprehensive pharmacovigilance analysis of pre-COVID-19 reports. Br J Clin Pharmacol 2020. https://doi.org/10.1111/bcp.14546. In press.

[8] Ahmad T, Yin P, Saffitz J, Pockros PJ, Lalezari J, Shiffman M, et al. Cardiac dysfunction associated with a nucleotide polymerase inhibitor for treatment of hepatitis C. Hepatology 2015;62:409–16. https://doi.org/10.1002/hep.27488.

[9] Fontaine H, Lazarus A, Pol S, Pecriaux C, Bagate F, Sultanik P, et al. Bradyarrhythmias associated with sofosbuvir treatment. N Engl J Med 2015;373:1886–8. https://doi.org/10.1056/NEJMc1505967.

[10] Regan CP, Morissette P, Regan HK, Travis JJ, Gerenser P, Wen J, et al. Assessment of the clinical cardiac drug-drug interaction associated with the combination of hepatitis C virus nucleotide inhibitors and amiodarone in Guinea pigs and rhesus monkeys. Hepatology 2016;64:1430–41. https://doi.org/10.1002/hep.28752.

[11] Pelleg A, Belhassen B. The mechanism of the negative chronotropic and dromotropic actions of adenosine 5'-triphosphate in the heart: an update. J Cardiovasc Pharmacol 2010;56:106–9. https://doi.org/10.1097/FJC.0b013e3181e0f8b2.

[12] Coloma PM, Trifirò G, Patadia V, Sturkenboom M. Postmarketing safety surveillance: where does signal detection using electronic healthcare records fit into the big picture? Drug Saf 2013;36:183–97. https://doi.org/10.1007/s40264-013-0018-x.

[13] Gagne JJ. Finding meaningful patterns in adverse drug event reports. JAMA Intern Med 2014;174:1934–5. https://doi.org/10.1001/jamainternmed.2014.3270.
[14] Al Rihani SB, Smith MK, Bikmetov R, Deodhar M, Dow P, Turgeon J, et al. Risk of adverse drug events following the virtual addition of covid-19 repurposed drugs to drug regimens of frail older adults with polypharmacy. J Clin Med 2020;9:2591. https://doi.org/10.3390/jcm9082591.
[15] Michaud V, Dow P, Al Rihani SB, Deodhar M, Arwood M, Cicali B, et al. Risk assessment of drug-induced long QT syndrome for some COVID-19 repurposed drugs. Clin Transl Sci 2020;14:20–8. https://doi.org/10.1111/cts.12882.