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Hepatic Disorders With the Use of Remdesivir for Coronavirus 2019

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Remdesivir is a nucleotide analog prodrug with antiviral activity against a broad spectrum of human coronavirus in cell cultures and mouse models including severe acute respiratory syndrome–associated coronavirus 2. Recently, the Food and Drug Agency (FDA) and the European Medicines Agency (EMA) recommended remdesivir for the treatment of patients hospitalized with severe coronavirus disease 2019 (COVID-19) infection.[1,2] In the remdesivir clinical development program, some cases have raised concerns regarding potential hepatobiliary disorders associated with remdesivir, including in healthy volunteers and patients with COVID-19.[3] In cohort studies of patients hospitalized for severe COVID-19 who were treated with compassionate-use remdesivir, elevated hepatic enzymes were the most frequent adverse drug reaction reported.[4,5] In the first randomized, double-blind, placebo-controlled clinical trial assessing the effect of intravenous remdesivir in adults admitted to hospital with severe COVID-19 (n = 237), a higher proportion of remdesivir recipients than placebo recipients had dosing prematurely stopped by the investigators because of adverse events including aminotransferase or bilirubin increases (3 versus 0).[6] Although there is no signal from the available data of severe hepatotoxicity or drug-induced liver injury in clinical trials, the number of patients exposed to remdesivir was too limited. Therefore, there is an urgent need to investigate the hepatic safety profile associated with remdesivir in COVID-19 patients.

Methods

Here, we performed a pharmacovigilance analysis of VigiBase, the World Health Organization's individual case safety reports database, to describe hepatic impairment reports with remdesivir.[7] VigiBase contains more than 22 million spontaneous generated adverse drug reactions from 136 countries covering more than 90% of the world's population. VigiBase includes information on patient, medical history, country, and drugs taken with their initiation and stop dates. We considered only reports of patients with COVID-19 registered up to June 15, 2020. Disproportionality analysis was performed to assess a potential increased risk of reporting hepatic disorders with remdesivir compared with drugs prescribed in COVID-19 patients.[8] The risk of hepatic disorders was calculated by using the reporting odds ratios (ROR) with their 95% confidence interval (CI), a ratio similar in concept to the odds ratio in case-control studies. To minimize the potential of confounding by disease severity (hepatic disorders could be associated with the severity of COVID-19 infection), we repeated the primary analysis considering only users of tocilizumab, a drug recommended in severe COVID-19 cases.

Results

We found 387 reports with remdesivir registered in VigiBase, and among them 130 hepatic adverse effects (34%) were reported. Reports originated from United States (87) and Europe (43), involving mostly men (81, 62%), with a mean age of 54.9 years (minimum 2, maximum 92). Treatment duration with remdesivir varied between 1 day (15 discontinuations for serious adverse effects) and 11 days, with a mean duration of 3.8 days. In the majority of cases (122, 94%), remdesivir was the sole suspected drug. Most cases were serious (94, 72%) (ie, resulting in hospitalization or prolongation of hospital stay). The mean time to onset of hepatic disorders was 5.4 days. Increased hepatic enzymes were the most frequent adverse drug reactions reported (114, 88%), involving the liver transaminases (aspartate transaminase and alanine transaminase) in 79 cases (61%) and bilirubin in 4 cases (3%). Other cases were reported as hepatic failure or hepatitis. Compared with hydroxychloroquine, lopinavir/ritonavir, or tocilizumab, the use of remdesivir was associated with an increased risk of reporting hepatic disorders (ROR, 1.94; 95% CI, 1.54–2.45) (Table 1). When we restricted the analysis to tocilizumab users (reference group), the ROR remained significant (1.60; 95% CI, 1.13–2.27).

Abbreviations used in this paper: CI, confidence interval; COVID-19, coronavirus disease 2019; EMA, European Medicines Agency; FDA, Food and Drug Administration; ROR, reporting odds ratios.

Most current article

1542-3565/$36.00
https://doi.org/10.1016/j.cgh.2020.07.050

Table 1. Reporting Odds Ratios for Association Between Hepatic Disorders and Use of Remdesivir for Coronavirus Disease 2019 in Vigibase[a]

Exposures	Cases[b]	Non-cases[c]	ROR (95% CI)
Other drugs prescribed for COVID-19[d]	524	2010	1 (reference)
Remdesivir	130	257	1.94 (1.54–2.45)

CI, confidence interval; COVID-19, coronavirus disease 2019; ROR, reporting odds ratio.
[a]We used the case non-case method, which is similar to case-control studies but adapted for pharmacovigilance studies. We used reporting odds ratios (ROR) and their 95% confidence interval (95% CI) to calculate disproportionality. 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 hepatic disorders over the exposure odds among reported non-case.
[b]Cases were individual case safety reports containing any terms including the terminology "Hepatobiliary disorders" in the System Organ Class (SOC) view found in MedDRA dictionary https://www.meddra.org/.
[c]Non-cases were individual case safety reports containing all other adverse events reported linked with the respective drug.
[d]Hydroxychloroquine, tocilizumab, and lopinavir/ritonavir prescribed for COVID-19 patients.

Discussion

This is the first investigation of the association between remdesivir use for COVID-19 patients and hepatic disorders. Although the pharmacovigilance analysis could be subject to limitations such as reporting bias, our results corroborate in a real-world setting observations that were made in remdesivir clinical program development. Regardless of the association of COVID-19 infection with liver abnormalities, our study suggests an increased risk of liver impairment with remdesivir compared with other drugs. Although values of aspartate aminotransferase, alanine aminotransferase, and bilirubin elevations were not fully available in VigiBase, we found that hepatic disorders were generally serious (in 3 cases out of 4). In most cases remdesivir was the only suspected drug. To mitigate confounding factors, we used as a group reference COVID-19 patients exposed to hydroxychloroquine, tocilizumab, or lopinavir/ritonavir. The result was consistent when we restricted the analysis to tocilizumab users. Owing to the limitations of this study, our results warrant replication in further population-based studies. However, because of the recent FDA and EMA recommendations to use remdesivir for COVID-19 patients, physicians should be aware of this possible association and perform hepatic monitoring when prescribing remdesivir.

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

Conflicts of interest
The authors disclose no conflicts.