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Research Correspondence

Hepatic disorders with the use of remdesivir for coronavirus 2019 (COVID-19)

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Declaration of interests

All authors have no relevant conflicts of interest to disclose.

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Introduction

Remdesivir is a nucleotide analog prodrug with antiviral activity against a broad spectrum of human coronavirus in cell cultures and mouse models including SARS-CoV-2. Recently, the Food and Drug Agency (FDA) and the European Medicines Agency (EMA) recommended remdesivir for the treatment of patients hospitalized with severe COVID-19 infection.^{1,2} In the remdesivir clinical development program, some cases have raised concerns regarding a potential hepato-biliary 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, hepatic enzyme elevated 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 (DILI) 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, drugs taken with their initiation and stop date. We considered only reports of patients with COVID-19 registered up to the 15th of June 2020. Disproportionality analysis was performed to assess a potential increased risk of reporting hepatic disorders with remdesivir compared to drugs prescribed in COVID-19 patients.⁸ The risk of hepatic disorders was calculated 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 were reported (34%). Reports originated from US (87) and Europe (43), involving mostly men (81, 62%), with a mean age of 54.9 years (min 2, max 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 of cases were serious (94, 72%) (i.e. resulting in hospitalization or prolongation of hospital stay). The mean time to onset hepatic disorders was 5.4 days. Hepatic enzymes increased 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**). When we restricted the analysis to tocilizumab users (reference group), the ROR remained significant (1.60, 95% CI 1.13-2.27).

Discussion

This is the first investigation of the association between remdesivir use for COVID-19 patients and hepatic disorders. While the pharmacovigilance analysis could be subject to limitations as reporting bias, our results corroborate in a real-world setting, observations made in remdesivir clinical program development. Regardless of the association of COVID-19 infection with liver abnormalities, our study suggest an increased risk of liver impairment with remdesivir compared to other drugs. While values of AST, ALT 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 of cases remdesivir was the only one suspected drug. To mitigate confounding factors, we used as a group reference COVID-19 patients exposed to hydroxychloroquine or 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, given 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.

Article information

CONTRIBUTIONS

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

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Table . Reporting Odds Ratios for the Association Between Hepatic Disorders and the 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)

Abbreviations: 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, lopinavir/ritonavir prescribed for COVID-19 patients