Remdesivir and Acute Renal Failure: A Potential Safety Signal From Disproportionality Analysis of the WHO Safety Database

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Remdesivir is approved for emergency use by the US Food and Drug Administration (FDA) and authorized conditionally by the European Medicines Agency (EMA) for patients with coronavirus disease 2019 (COVID-19). Its benefit-risk ratio is still being explored because data in the field are rather scant. A decrease of the creatinine clearance associated with remdesivir has been inconstantly reported in clinical trials with unclear relevance. Despite these uncertainties, we searched for a potential signal of acute renal failure (ARF) in pharmacovigilance postmarketing data. An analysis of the international pharmacovigilance postmarketing databases (VigiBase) of the World Health Organization (WHO) was performed, using two disproportionality methods. Reporting odds ratio (ROR) compared the number of ARF cases reported with remdesivir, with those reported with other drugs prescribed in comparable situations of COVID-19 (hydroxychloroquine, tocilizumab, and lopinavir/ritonavir). The combination of the terms "acute renal failure" and "remdesivir" yielded a statistically significant disproportionality signal with 138 observed cases instead of the 9 expected. ROR of ARF with remdesivir was 20-fold (20.3; confidence interval 0.95 [15.7–26.3], $P < 0.0001$]) that of comparative drugs. Based on ARF cases reported in VigiBase, and despite the caveats inherent to COVID-19 circumstances, we detected a statistically significant pharmacovigilance signal of nephrotoxicity associated with remdesivir, deserving a thorough qualitative assessment of all available data. Meanwhile, as recommended in its Summary of Product Characteristics, assessment of patients with COVID-19 renal function should prevail before and during treatment with remdesivir in COVID-19.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ Remdesivir is a nucleoside analog recently approved by the US Food and Drug Administration (FDA) for emergency use and conditionally authorized by the European Medicines Agency (EMA) in patients with coronavirus disease 2019 (COVID-19), although data pertaining to its effectiveness and safety are scant. A decrease of the creatinine clearance has been reported inconstantly in clinical trials.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ Is there a potential signal of a risk of acute renal failure associated with remdesivir in pharmacovigilance postmarketing databases?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ There is a statistically suggestive disproportionality signal regarding the association of acute renal failure and remdesivir. This possible signal stood out when calculating the reporting odds ratio compared with 3 drugs used in patients with COVID-19. However, many confounding factors persist.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ These results raise awareness about a possible pharmacovigilance signal regarding the risk of acute renal failure associated with remdesivir, currently being qualitatively explored by regulatory agencies. Meanwhile, close serum creatinine monitoring seems warranted in patients treated with remdesivir.

Remdesivir is an antiviral prodrug belonging to the adenosine nucleoside analog family, which is hydrolyzed into GS-441524 and further phosphorylated to its active metabolite.[1] GS-441524, the main circulating drug, has a half-life of 24 hours.[1] Remdesivir is injected with a sulfobutylether-β-cyclodextrin (SBECD) carrier. Originally developed as a possible treatment for hepatitis C and Ebola virus diseases,[2] remdesivir has shown promising efficacy against severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2).[3] Its use in coronavirus disease 2019 (COVID-19) has been authorized by the US Food

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and Drug Administration (FDA) for emergency use,[4] and by the European Medicines Agency (EMA) under conditional marketing authorization[5]: the marketing authorization holder is committed to provide further clinical and safety data. A Risk Management Plan has been agreed, including hypersensitivity as an important identified risk, hepatotoxicity and nephrotoxicity as important potential risks, and safety in patients with hepatic or severe renal impairment and in pregnant/lactating women as missing information.

Alongside evidence of a possible efficacy,[6] potential adverse drug reactions (ADRs) with remdesivir are currently being investigated.[7] Renal tubular damage had been observed experimentally, pertaining to the drug itself, its metabolite,[8] and/or its excipient.[9,10] The clinical relevance of these preclinical findings is still being questioned. Assessment of drug-induced nephrotoxicity is particularly challenging as COVID-19 also bears frequent renal complications.[11] In a clinical trial (CT) of remdesivir used during 10 days in severe forms of COVID-19, a grade 3 or 4 decrease of the creatinine clearance occurred in 19% of patients (36/386 patients) with unclear relevance due to the lack of controls.[12] In another open-label CT, acute kidney injury occurred in 22.8% of the patients (8/35 patients) and proved the most frequent cause of treatment discontinuation.[13] Yet, randomized CT yielded comparable incidence of acute renal failure (ARF) with remdesivir and placebo.[14,15]

Real conditions of use add further uncertainties on those discrepancies about the benefit-risk ratio of remdesivir because of the limited number of patients exposed in CT. Therefore, postmarketing data are paramount to detect a signal for potential ADRs. We aimed to evaluate if an ARF signal could be identified with the use of remdesivir in COVID-19 based on data obtained from international pharmacovigilance databases.

METHODS

Since 1978, Uppsala Monitoring Centre (UMC) monitors drug safety on the behalf of the World Health Organization (WHO).[16] UMC gathers pharmacovigilance data from the national pharmacovigilance networks (130 member states). Each local pharmacovigilance organization relies on spontaneous notifications then collected into VigiBase, respecting the anonymity of patients and notifiers. Individual patient data collected included sociodemographic characteristics (age, sex, and notifier's country), and the reported effect (suspected and concomitant drugs, ADRs, date of occurrence, and seriousness). We queried VigiBase for notified cases of ARF with remdesivir suspected and sought a potential pharmacovigilance signal relying on two different disproportionality approaches.

Comparison of observed and expected notifications with remdesivir

We used the Information Component (IC), a statistical disproportionality measure based on the observed and expected number of notifications for a drug-ADR combination.[17] The expected number of notifications is based on the number of case reports for the active ingredient and reaction in question, calculated with the following formula: $N_{expected} = (N_{drug} * N_{reaction})/N_{total}$. N_{drug} is the number of notifications for the drug, regardless of effects, and $N_{reaction}$ is the number of notifications for the effect, regardless of drug. IC value is calculated with the formula: $IC = \log_2((N_{observed} + 0.5)/(N_{expected} + 0.5))$. $N_{observed}$ is the observed number of notifications for the drug-effect combination. A positive IC value means higher reporting than expected. IC_{025} is the lower endpoint of the 95% credibility interval for the IC. A positive IC_{025} value is the statistical basis for drug safety signal detection in VigiBase. When a drug-effect combination is reported more often than expected, IC highlights a potential signal of interest.

We queried the disproportionality values for the combination of remdesivir "active ingredient" as "suspect" (and not merely "concomitant") in the occurrence of the effect "acute renal failure" ("broad") according to the Standardized MedDRA version 23.0 Query (SMQ). This SMQ is an exhaustive, validated, predetermined set of MedDRA terms intended to help regulatory agencies and pharmaceutical companies to address issues pertaining to drug safety.[18]

Comparison of remdesivir with other drugs used in COVID-19

Because COVID-19 may also cause ARF, we compared remdesivir with other drugs used similarly during the same period in hospital COVID-19 units: hydroxychloroquine, tocilizumab, and lopinavir/ritonavir. We queried VigiBase for all cases with the SMQ "acute renal failure" ("broad") between February 1, 2020, and August 7, 2020, associated with either remdesivir "active ingredient" or other drugs used in COVID-19 (hydroxychloroquine, tocilizumab, and lopinavir/ritonavir) also "active ingredients."

The risk of ARF notified with remdesivir was evaluated with a disproportionality method specific to "case-non-case" studies.[19] We calculated the reporting odds ratio (ROR; which calculation is similar to that of the odd-ratio of case-control studies) to estimate the extent to which a given ADR is associated with a specific drug, relative to patients using reference drugs. An ROR of 1 translates as no signal (the ADR is reported similarly with the drug of interest and the comparator). Conversely, an ROR > 1 suggests an ADR more frequently reported with the drug of interest. The higher the ROR, the more statistically relevant is the pharmacovigilance signal.

For this purpose, we used the total number of ADRs reported with remdesivir and with the comparator drugs over the study period. The ROR was calculated as (a/c)/(b/d): "a" is the number of cases of ARF notified with remdesivir, "c" the number of cases of ARF notified with the comparator drugs, "b" the number of extra-renal ADR notified with remdesivir, and "d" the number of extra-renal ADR notified with the comparator drugs. The ROR was expressed as a point estimate with a 95% confidence interval (Woolf's method).

RESULTS

Between February 1, 2020, and August 7, 2020, 138 cases of the broad SMQ "acute renal failure" associated with remdesivir were reported in VigiBase. Healthcare professionals notified 134 of 138 (97.1%) cases. The most represented age group was the 65–74-year-old group (50 reports, 36.2%) and 96 patients were men (69.6%). The United States contributed 99 reports (71.7%). The most often specifically reported effects were acute kidney injury (67 reports, 48.6%), blood creatinine increased (45, 32.6%), renal impairment (16, 11.6%), glomerular filtration rate (GFR) decreased (15, 10.9%), renal failure (13, 9.4%), dialysis (7, 5.1%), and renal tubular necrosis (5, 3.6%). Co-suspect or interacting drugs reported in more than 1 case were furosemide and piperacillin/tazobactam in, respectively, 4 (2.9%) and 2 cases (1.4%). The most often nonsuspected co-reported active ingredients were norepinephrine (43 reports, 31.2%), enoxaparin (43, 31.2%), propofol (43, 31.2%), fentanyl (38, 27.5%), and midazolam (32, 23.2%). The main co-reported ADR concomitant to ARF (**Table 1**) was respiratory failure (11 reports, 8.0%). ARF was serious in 129 reports (93.5%), including 29 fatal reports (21.0%) and 15 cases of life-threatening ARF (10.9%).

Comparison of observed and expected notifications with remdesivir

The combination of the SMQ "acute renal failure" ("broad") and remdesivir yielded an IC of 3.9 with an IC_{025} of 3.7, with 138 notifications being observed instead of the 9 expected. The different terms of the SMQ yielded a suggestive quantitative signal for increased blood creatinine (IC_{025} 4.4), acute kidney injury (4.0), GFR decreased (3.8), renal impairment (2.3), dialysis (2.2), renal failure (1.6), renal tubular necrosis (1.6), blood urea increased (0.6), and hemodialysis (0.5).

Comparison of remdesivir with other drugs used in COVID-19

The 138 cases of ARF notified with remdesivir were compared with the 138 cases of ARF notified (same numbers coincidentally) with the use of the comparator drugs (hydroxychloroquine, tocilizumab, and lopinavir/ritonavir) over that same period based and according to the same "acute renal failure broad" SMQ. The total number of cases reported with remdesivir, regardless of the effect, was 363. ARF accounted for 38.0% (138/363) of all effects notified with remdesivir as suspected drug. The total number of cases reported with hydroxychloroquine, tocilizumab, and lopinavir/ritonavir, regardless of the effect, was 7,385 (**Table 2**). Consequently, the ROR of ARF with remdesivir was 20.3 (95% confidence interval: 15.7–26.3, $P < 0.0001$).

DISCUSSION

This analysis based on international pharmacovigilance reporting from February to August 2020 highlights a statistically suggestive disproportionality signal of a potential nephrotoxicity associated with remdesivir in COVID-19. Compared with three common drugs used in COVID-19 and unexpected to be significantly nephrotoxic, remdesivir appears to be associated with an ~ 20-fold increased risk of ARF reporting. Although COVID-19 is associated with acute renal failure *per se*, the prescription of remdesivir and its comparators fall under a comparable use strategy. However, this safety signal should be considered with caution because it is an indicator arising from spontaneous reports and only suggests a potential association requiring further investigations, which are being explored by the EMA.[20]

Table 1 Most frequently co-reported terms in the 138 reports of acute renal failure associated with remdesivir

Effect	Number of reports	Percentage
Respiratory failure	11	8.0% (11/138)
Aspartate aminotransferase increased	8	5.8% (8/138)
Acidosis	7	5.1% (7/138)
Alanine aminotransferase increased	7	5.1% (7/138)
Acute respiratory distress syndrome	6	4.3% (6/138)
Hypotension	6	4.3% (6/138)
Hypoxia	6	4.3% (6/138)
Multiple organ dysfunction syndrome	6	4.3% (6/138)

The IC comparing observed and expected ARF reports with remdesivir may be confounded by the inner risk of ARF induced by COVID-19[11] or its hemodynamic complications. SARS-CoV-2 has been detected in multiple organs, including the kidneys,[21] and ARF has been described as a frequent complication of COVID-19. However, the disproportionality signal stood out when comparing remdesivir with 3 comparators used in patients with COVID-19, during a timeframe corresponding to the initial spread of the COVID-19 pandemic in Europe and the United States. A similar methodological approach has been used recently to suggest a safety signal of remdesivir-associated hepatic adverse events.[22]

The occurrence of ARF may likely be multifactorial in these patients. Anesthetic drugs were the most co-reported active ingredients in reports of ARF, suggesting that numerous reports concerned patients admitted in intensive care units. Moreover, 21% of cases reported a fatal outcome, illustrating the severity of illness in this population. Nonetheless, few cotreatments were reported as suspect in several cases of our analysis except furosemide and piperacillin/tazobactam (respectively, 4 and 2 cases).

Experimental studies of remdesivir in murine and mammalian models identified the kidneys as toxicity dose-dependent target organs. Microscopic changes in the kidneys suggested a regenerative process following sustained low-level cortical tubules injury with tubular atrophy, basophilia, karyomegaly, casts, and fibrosis.[8] In rats, a mechanism of OAT3-dependent cytotoxicity has been suggested even if the suspected metabolite (GS-704277) is not a substrate for human OAT.[8] Nephrotoxicity may also arise from its metabolite GS-441524, or its SBECD carrier rather than remdesivir itself.[9] Uncertainties also remain regarding the safety of remdesivir beyond its intended plasma range (i.e., in case of kidney failure).[8] Other nucleoside analogues are also characterized by their nephrotoxicity,[23] which underlying mechanism may tend to lead to mitochondrial and/or direct proximal tubule injury.[24]

Our study has several limitations to consider. This signal, triggered by the statistical analysis of quantitative data, needs further assessment based on a detailed qualitative analysis of all available data related to this issue. Important confounding factors are infection of the kidneys by SARS-CoV-2 and the severity of COVID-19 in patients treated with remdesivir: multi-organ failure can deteriorate renal function. Although few co-prescriptions of nephrotoxic drugs were notified, it still remains a possibility because ADR reporting is not the main priority of healthcare practitioners in these circumstances.

Table 2 ROR for the SMQ ARF (broad) associated with remdesivir

Exposure	Cases of ARF	Non-cases	ROR [95% confidence interval]
Comparator drugs[a]	138	7,385	/
Remdesivir	138	363	20.3 [15.7–26.3] ($P < 0.0001$)

ARF, acute renal failure; ROR, reporting odds ratio; SMQ, Standardized MedDRA version 23.0 Query.
[a]Hydroxychloroquine, tocilizumab, and lopinavir/ritonavir.

Pharmacovigilance studies are also known for under-notification and reporting biases. Indeed, clinicians might be prone to attribute ARF with remdesivir (formulated with SBECD) than with long known drugs perceived as "safer." Hence, physicians more willingly suspect new drugs when an ADR occurs, especially in compassionate use programs where all events are reported, regardless of their degree of causality. Spontaneous notifications are not intended to be representative of all patients treated with remdesivir. They may concern patients not included in CT, such as patients with pre-existing kidney disease. Characteristics about kidney injury are often briefly described and histologic characteristics often missing, hindering the assessment of a precise causality between remdesivir and the ADR notified, especially in patients prone to multifactorial ARF.

Last, data were collected from international pharmacovigilance postmarketing databases[25] and many cases originated from the United States, which have coding practices differing from other countries, possibly contributing to the disproportionality signal observed.[26]

Despite these caveats, our result raises awareness about a potential signal regarding the risk of ARF in patients treated with remdesivir. Such a signal has been recently picked up by the EMA and is currently explored.[20] Awaiting the results of detailed qualitative inquiries, and as already recommended in the European Summary of Product Characteristics of remdesivir,[8] all patients should have an estimation of their GFR determined before starting and during the course of treatment with remdesivir. Remdesivir should not be used in patients with an estimated GFR < 30 mL/min. Prospective qualitative assessment and larger studies are needed to identify whether this pharmacovigilance signal translates in a confirmed causal association.

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CONFLICT OF INTEREST
All authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS
A.G., A.L., A.F., N.P., M.M., F.R., V.L.M.E., and M.-D.D. wrote the manuscript. A.G., F.R., and M.-D.D. designed the research. A.G., F.R., and M.-D.D. performed the research. A.G., A.L., and F.R. analyzed the data.

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