Exhibit 360

Kidney disorders as serious adverse drug reactions of remdesivir in coronavirus disease 2019: a retrospective case–noncase study

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7907730/pdf/main.pdf

Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

protecting immune-compromised patients. In the presence of scarce resources, equitable and effective risk–benefit allocation will be vital, prioritizing vulnerable patients. Timing immunotherapy with vaccination and determining vaccination response will be crucial. Concurrent SARS-CoV-2 infection should not prevent delivery of effective immunomodulatory therapy in patients with severe autoimmune diseases, essential for the protection and recovery of vital organ function.

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Kidney disorders as serious adverse drug reactions of remdesivir in coronavirus disease 2019: a retrospective case–noncase study

To the editor Remdesivir is a novel adenosine-like nucleotide analogue, representing the first drug approved for coronavirus disease 2019 (COVID-19), albeit an uncertain clinical relevance. In clinical trials and case series, acute kidney injury (AKI), including renal replacement, has been frequently reported.[1,2] Although causality is debatable, kidney injuries, especially proximal tubular epithelial cell necrosis, have also been observed in animal studies during remdesivir development.

To provide additional data, we performed a pharmacovigilance analysis on the World Health Organization global database of individual case safety reports, VigiBase (https://www.who-umc.org/vigibase/vigibase/). This database gathers spontaneous reports of suspected adverse drug reactions from >130 countries, which makes it a powerful tool to perform disproportionality analyses.[3] This approach, based on a case–noncase method, estimates whether an adverse event is differentially reported for a specific drug compared with other drugs.

Among 1,565,117 reports registered from January 1st until August 30th, 2020, 5532 concerned COVID-19 patients and have been included in this study. Of them, 434 (7.8%) cases were related to kidney disorders, including 327 (5.9%) reported with remdesivir. In remdesivir kidney disorder cases, 217 (66.3%) patients were male, with a median age of 65 (interquartile range, 55–73) years (Supplementary Table S1). Remdesivir was discontinued early after kidney disorder onset, with a median treatment duration of 3 (interquartile range, 1–4) days. In the vast majority of cases (316 [96.6%]), no other drug was suspected in the onset of

Table 1 | Reporting of kidney disorders in remdesivir users among COVID-19 patients, and their RORs within the WHO global pharmacovigilance database

Type of analysis	Kidney disorder cases[a]	Noncases[b]	ROR (95% CI)
Primary analysis			
Remdesivir users	327	1526	7.2 (5.7–9.0)
Other drug users	107	3572	1 (Reference)
Sensitivity analysis restricted to severe to critical COVID-19 patients			
Remdesivir users	327	1526	3.7 (2.6–5.4)
Dexamethasone, sarilumab, or tocilizumab users	34	591	1 (Reference)
Sensitivity analysis restricted to serious kidney disorders[c]			
Remdesivir users	301	1552	6.9 (5.4–8.7)
Other drug users	101	3578	1 (Reference)
Sensitivity analysis restricted to kidney disorders not including concomitant nephrotoxic drugs[d]			
Remdesivir users	242	1611	6.1 (4.8–7.9)
Other drug users	88	3591	1 (Reference)

CI, confidence interval; COVID-19, coronavirus disease 2019; ROR, reporting odds ratio; WHO, World Health Organization.

The case–noncase approach is similar to case-control method but for purpose of pharmacovigilance studies. Disproportionality in adverse drug reaction reporting between groups is expressed using RORs and their 95% CIs. 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 kidney disorders over the exposure odds among reported noncases. An ROR >1 suggests that kidney disorders are more frequently reported in remdesivir users compared with other drug users (i.e., chloroquine, hydroxychloroquine, dexamethasone, lopinavir/ritonavir, sarilumab, or tocilizumab users) among patients with COVID-19 (list of terms is provided in the Supplementary Data). Reports with remdesivir that also included any other drug mentioned above were further excluded (corresponding to 806 reports). To assess the robustness of the main analysis, we performed several sensitivity analyses. First, to take into account clinical patient status and intensive care unit settings, we further restricted the analysis to drugs specifically used in severe to critical COVID-19 patients (i.e., dexamethasone, sarilumab, or tocilizumab). Second, we restricted the analysis to (i) serious kidney disorder cases only and (ii) kidney disorder cases that did not include known concomitant nephrotoxic drugs. In sensitivity analyses, nonserious cases and cases including concomitant nephrotoxic drugs were considered as noncases.

[a]Kidney disorder cases were individual case safety reports containing any reaction belonging to the kidney system as system organ class, according to the Medical Dictionary for Regulatory Activities (https://www.meddra.org/).

[b]Noncases were reports containing any other reaction.

[c]Serious cases were defined, according to the WHO, as the occurrence of death, life-threatening adverse event, inpatient hospitalization or prolongation of an existing hospitalization, significant disability, or requirement of intervention to prevent any of these.

[d]List of concomitant or suspected nephrotoxic drugs is in the Supplementary Data.

kidney disorders. Reactions were serious in 301 (92.0%) cases, with a fatal outcome for 15 (4.6%) patients. They were mainly AKI in 295 (90.2%) cases and tubular necrosis in 8 (2.4%) cases.

Compared with the use of chloroquine, hydroxychloroquine, dexamethasone, sarilumab, or tocilizumab, the use of remdesivir was associated with an increased reporting of kidney disorders (reporting odds ratio, 7.2; 95% confidence interval, 5.7–9.0) (Table 1).

The retrospective design of our pharmacovigilance analysis has several limitations, especially underreporting and residual confounders, including the role of COVID-19 in AKI occurrence. Nevertheless, sensitivity analyses showed similar results, especially when excluding other nephrotoxic drugs or when comparing with only drugs used in severe to critical COVID-19.

Our findings, based on postmarketing real-life data from >5000 COVID-19 patients, support that kidney disorders, almost exclusively AKI, represent a serious, early, and potentially fatal adverse drug reaction of remdesivir. These results are consistent with findings from another group.[4] Physicians should be aware of this potential risk and perform close kidney monitoring when prescribing remdesivir. Further data are needed to confirm that safety signal.

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Information from VigiBase comes from a variety of sources, and the probability that the suspected adverse effect is drug related is not the same in all cases. The information does not represent the opinion of the Uppsala Monitoring Center or the World Health Organization and only reflects the authors' opinion.

VigiBase is a fully deidentified database maintained by the Uppsala Monitoring Center. According to VigiBase access rules, no specific ethical approval is needed. VigiBase access is granted to national and regional pharmacovigilance centers, such our teams. Data sharing: aggregated data of spontaneous reports are available at http://www.vigiaccess.org/.

The corresponding author attests that this article is an honest, accurate, and transparent account of the study being reported; and that no important aspects of the study have been omitted.

AUTHOR CONTRIBUTIONS

LC and FM designed the study and drafted the article. LC performed data extraction and statistical analysis. LHP, MT, BT, and JMT critically reviewed the article. All the authors approved the final version of the article. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Characteristics of kidney disorder cases reported with remdesivir in COVID-19 patients within the WHO global safety database.

Supplementary Data S2. List of MedDRA terms used to identify COVID-19 patients in drug indication.

Supplementary Data S3. Concomitant or suspected nephrotoxic drugs identified in kidney disorders cases reported with remdesivir.

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Zero health care–associated respiratory viral infections: impact of enhanced infection prevention on a renal unit during the coronavirus disease 2019 pandemic

To the editor We read with interest the study by Thaunat *et al.* that identified significant excess mortality attributed to coronavirus disease 2019 (COVID-19) among dialysis patients.[1] Indeed, the COVID-19 pandemic has provided the impetus for the introduction of strategies to optimize protection of hemodialysis patients from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[2] Outside the pandemic setting, however, patients with chronic kidney disease have significantly higher risk of nosocomial acquisition of other common respiratory-viral infections (RVIs), with increased mortality and length-of-stay.[3] Implementation of protective strategies against COVID-19 on renal units may reduce health care–associated-RVI (HA-RVI) as a positive consequence.

From January to December 2020, a COVID-19 containment strategy was implemented at the largest tertiary hospital