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ORIGINAL RESEARCH

Rapid review of suspected adverse drug events due to remdesivir in the WHO database; findings and implications

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ABSTRACT

Objectives: Remdesivir has shown promise in the management of patients with COVID-19 although recent studies have shown concerns with its effectiveness in practice. Despite this there is a need to document potential adverse drug events (ADEs) to guide future decisions as limited ADE data available before the COVID-19 pandemic.

Methods: Interrogation of WHO VigiBase® from 2015 to 2020 coupled with published studies of ADEs in COVID-19 patients. The main outcome measures are the extent of ADEs broken down by factors including age, seriousness, region and organ.

Results: A total 1086 ADEs were reported from the 439 individual case reports up to July 19, 2020, in the VigiBase®, reduced to 1004 once duplicates were excluded. Almost all ADEs concerned COVID-19 patients (92.5%), with an appreciable number from the Americas (67.7%). The majority of ADEs were from males > 45 years and were serious (82.5%). An increase in hepatic enzymes (32.1%), renal injury (14.4%), rise in creatinine levels (11.2%), and respiratory failure (6.4%) were the most frequently reported ADEs.

Conclusions: Deterioration of liver and kidney function are frequently observed ADEs with remdesivir; consequently, patients should be monitored for these ADEs. The findings are in line with ADEs included in regulatory authority documents.

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Remdesivir; adverse drug events; COVID-19; Vigibase®; hepatic enzyme changes; renal injury

1. Introduction

A number of medicines now have been proposed and researched for managing patients with COVID-19 [1–4]. However, to date, there appears to be no cure although dexamethasone is showing the most promise in well-constructed studies [5–7]. The earlier randomized, placebo-controlled trial in China with remdesivir involving 240 hospitalized patients with severe COVID-19 found no significantly improved clinical benefit [8]. However, it was recognized this trial was underpowered [9]. The more recent study with Beigel *et al*. (2020) found that among patients hospitalized with severe COVID-19, a 10-day course of remdesivir was associated with a faster time to recovery, with the findings significant among patients who received oxygen. The mortality rate was 7.1% with remdesivir compared with 11.9% with placebo, although this difference was not statistically significant [10]. More recently, Goldman *et al*. (2020) showed no significant difference in outcomes between patients with severe disease prescribed either a 5 or 10-day course of remdesivir; however, this study was not placebo-controlled [11]. Spinner et al (2020) have also recently shown that remdesivir has variable clinical benefit in patients with moderate COVID-19 [12], with the recent interim analysis of the WHO Solidarity study suggesting no benefit from remdesivir in reducing initiation of ventilation, duration of hospitalization or mortality [7,13]. Consequently, further studies may still be needed to fully assess the place of remdesivir in the management of patients with COVID-19 [14].

In view of this, it is important to continue to collect safety data on the re-purposed use of remdesivir for the treatment of patients with COVID-19 alongside the collection of additional data regarding its effectiveness in patients with moderate to severe disease [15]. This is because there have been reports of serious adverse effects with remdesivir including hepatotoxicity [16], with the ability of SARS-CoV-2 to induce alterations in hepatic function potentially a particular concern when prescribing remdesivir [15,17]. This includes routine clinical care in addition to randomized studies since we are aware for instance that in the study of Beigel et al. (2020) that there

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Supplemental data for this article can be accessed here.

Article highlights

- Remdesivir is one of the proposed medicines for the treatment of the COVID – 19; however, there is paucity of data regarding its safety.
- We analyzed all the ADEs suspected to be caused by remdesivir reported in the WHO database durimg the last five years.
- Rise in hepatic enzymes, as well as renal injury, rises in blood creatinine, respiratory failure, tachy or bradyarrhythmia, hypotension, and rashes were the most frequent ADEs reported in the WHO database. Similar reporting was observed in data reported from clinical trials.
- Majority of these ADEs were of a serious nature and many of the serious ADEs were fatal but in the absence of causality assessment these cannot be attributed to remdesivir with certainty.
- Overall, reported ADEs are in line with the adverse drug reactions reported from the clinical trials.

were substantial exclusion criteria, e.g. AST or ALT (Alanine Aminotransferase) 5 times the upper limit of normal (ULN) and those with impaired renal function [10,17]. Renal impairment is included since urine is found to contain 49% of remdesivir's metabolite GS-441,524 [18]. Similar exclusion criteria existed in the UK with respect to ALT levels and impaired renal function in the prescribing guidance issued from NHS England working with the devolved administrations, with treatment stopped if there was ALT elevation accompanied by signs or symptoms of liver inflammation or increasing alkaline phosphatase, conjugated bilirubin or international-normalized ratios, as well as with the European Medicine Agency's authorization of compassionate use for remdesivir [19,20].

We are aware from data supplied by Gilead in their application to the EMA for compassionate use in patients with COVID-19 that in pooled studies adverse drug reactions (ADRs) were observed in < 5% of the subjects [20]. The most common ADRs in these studies, and in a controlled trial with patients with Ebola virus disease, were phlebitis, constipation, headache, ecchymosis, nausea and pain in extremities, and a transient increase in liver enzymes [20,21]. Prior to this, remdesivir was found to reversibly increase liver enzymes in healthy volunteers during early drug development studies. However, there was also a rise in liver enzymes in patients administered remdesivir in the compassionate use programme [22].

Consequently, we believed it was important to rapidly review the current status of adverse drug events (ADEs) associated with remdesivir including those emanating from published studies in patients with COVID-19. We believe this is important since even ADEs that were rare before the widespread use of remdesivir become important for patients who are hospitalized on COVID-19, especially those requiring oxygen. Further, drug–disease interactions may differ given the differences in the populations with patients with COVID-19 generally older and with co-morbidities. In view of this, we believe it is critical to characterize specific ADEs that arise from the repurposed use of remdesivir for COVID-19. The findings can further guide physicians and others in the management of patients with COVID-19 with remdesivir given some of the controversies surrounding its use. This builds on physicians in the US and wider still being encouraged to report any adverse events relating to remdesivir to the FDA's MedWatch Safety Information and Adverse Event Reporting Program to accrue more safety data especially with more clinical trials needed to fully assess the place of remdesivir in the management of patients with COVID-19 [14,23].

2. Patients and methods

This principally involved interrogating the VigiBase®, which is the global pharmacovigilance database maintained by the WHO, and previously used to evaluate ADEs associated with hydroxychloroquine [24,25]. VigiBase® contains all individual case safety reports (ICSRs) of adverse events collected by the national pharmacovigilance centers from over 130 countries [26–28]. An ICSR is an anonymized report for a single individual (patient) who was given suspected drug, who experienced single or multiple ADEs.

VigiBase® contains reports in a structured form containing information regarding patient demographics, drugs (route of administration, indication for use, start, end date), suspected ADEs (date of onset, outcome, seriousness, and causality), and administrative data (type of report and source). Medicines are coded according to the WHO Drug Dictionary Enhanced, including the ATC (Anatomical Therapeutic Chemical) classification [29]. Adverse events are coded according to the WHO Adverse Reaction Terminology and the Medical Dictionary for Regulatory Authorities (MedDRA) [25,30]. The MedDRA dictionary is organized by System Organ Class (SOC), divided into Preferred Terms (PT), and Lowest-Level Terms (LLT).

2.1. Data and analysis

This study included the analysis of all suspected adverse events related to remdesivir notified in last 5 years to VigiBase®, i.e. from January 1, 2015 to July 19, 2020. Each report in VigiBase® referred to a single individual who may have encountered one or several adverse events simultaneously. Consequently, the number of reported adverse events is typically higher than the number of patients for whom the case reports were recorded. ADEs were again classified following the Medical Dictionary for Regulatory Authorities (MedDRA); grouped at the System Organ Classification (SOC) level and at the individual preferred term (PT) level. The System Organ Classification, i.e., the SOC, is a grouping of individual ADEs coded in pre fix preferred terms into the different headings based on etiology, e.g. infections and infestations, manifestation site, e.g. hepatobiliary disorders, purpose, e.g. surgical and medical procedures, product issues and social circumstances.

The reports were analyzed on the basis of age, gender, region of reporting, organ classification (SOC) level, and at the individual preferred term (PT) level category of adverse event, seriousness, outcome, dechallenge–rechallenge action and outcome. With respect to age, we chose before and after 64 years of age as mortality with COVID-19 rises with age [31–33]. The seriousness of the ADE was decided based on ICH E2B criteria in which ADEs leading to the following conditions are categorized as serious ADEs – Death, life threatening, require hospitalization, prolongation of hospitalization

leading to disability or congenital anomaly [34,35]. Data cleaning was performed manually and same ADEs reported in different terminology from the same case information reports were removed to prevent multiple counting. Reporting of the same ADE by different terms happens due to multiple reporting of the same ADEs by different stakeholders, i.e., physicians, nursing professionals, and pharmacists.

Reporting of death was not clear in the database that was shared with us. We subsequently inquired about this from the database administrators. Following the guidance received from them, death reported in any of the heading 'seriousness', 'outcome' and 'preferred term' were considered for the calculation of death.

Descriptive statistics was reported in the form of frequency and percentages. The Statistical Package for Social Science (SPSS) Version 21 was used for the analysis.

2.2. Published and other studies regarding adverse events seen with remdesivir

Alongside documenting the ADEs seen with remdesivir in the VigiBase®, we also sought to document ADEs contained within published studies as well as submissions by Gilead to the regulatory authorities to compare and contrast the findings.

We are aware that age and other factors can play a role in the extent of ADEs [36–38], which is a concern if such factors have not been included in trial design or analysis. There is also a concern with new medicines generally as clinical trials tend to include carefully selected patients, who are generally younger and less co-morbid than those treated in routine clinical care [39,40]. Consequently, we believe it is critical to analyze both spontaneous reports with remdesivir alongside data from the clinical trials to provide future guidance given current concerns.

3. Results

We will first summarize reported ADEs in the published studies as well as summaries provided by Gilead to the regulatory authorities before documenting the ADEs reported to VigiBase®.

3.1. Summary of reported ADEs in published and other documents

Table 1 summarizes the findings form published and other sources including submissions to the various regulatory authorities.

3.2. Summary of findings from VigiBase®

There were a total 1087 ADEs reported from the 439 case information reports. Each case information report represents one person who was given remdesivir. After removal of duplicate ADEs (same ADE reported in different terminologies) from each case information report, 1004 unique ADEs were available for the analysis (Table 2). As multiple ADEs were often reported for each patient, the number of ADEs were appreciably more than number of persons. Overall, 1004 ADEs were reported from 439 people, giving an average 2.28 ADEs per person. Out of these 439 Individuals, 145 (33%) were from Europe, 288 (65%) from the region of Americas and 6 (1.3%) from the western pacific region. 267 (61%) were males and 163 (37.1%) were females, with gender not reported for 9 (2%) individuals. However, the majority of ADEs came from persons in the Americas (680–67.7%)

Table 2 represents the characteristics of 1004 ADEs reported in the WHO database. All these are unique ADEs reported from 439 individuals. It was noted that around half of the ADEs were reported from the age group 18 to 64. More ADEs were reported from males than females (58.9%) and the majority of the ADEs were serious. Indications for the use of remdesivir for almost all cases was COVID – 19 infection (92.6%), with 5.8% ADEs fatal. Parameters to assess the causality, i.e., dechallenge action, dechallenge outcome, rechallenge action and rechallenge outcome was reported for a minority of the ADEs. However, as complete data was typically lacking assessment of causality was not possible.

An increase in liver enzymes was the most frequent ADEs suspected to be caused by remdesivir. Overall, approximately one-third of the patients who were given remdesivir reported an increase in liver enzymes (Table 3). However, it was not possible to pinpoint which liver enzyme was most frequently increased due to the unavailability of such data in many of the case information reports. Kidney-related ADEs were also frequent as there were many reports of renal injury (14.4%), rise in blood creatinine (11.2%), renal impairment, and a decrease in glomerular filtration rate (3.2%). Respiratory failure, arrhythmia, hypotension, and rash were also commonly reported ADEs (Table 2). All 1004 ADEs reported from the 439 individuals are mentioned in Appendix 1.

On comparing some important characteristic of ADEs of persons between ages < 64 and > 64, it was observed that serious and fatal ADEs were more often reported in the older age group. ADEs related to investigations were more common in the younger age group, i.e., age < 64 in comparison to the age group > 64 (34% vs. 21%). ADEs related to renal and urinary disorders were more often seen in the older age group, i.e., > 64 as compared to the younger age group, i.e. < 64 (14% vs. 7%) (Table 4).

Serious ADEs were more often seen in males in comparison to the females (59% Vs 40%). Cardiac, renal and respiratory ADEs were more frequently reported as serious as compared to other ADEs (Table 5).

87 deaths were reported. The majority of these were in people aged > 64 and male gender. The most common immediate reasons for death were multiple organ dysfunction, cardiac, cardio-respiratory and respiratory arrest (Table 6).

4. Discussion

We believe this is one of the first studies post-COVID-19 pandemic to appraise the nature and extent of remdesivir ADEs in the WHO database following its repurposing for COVID-19, building on the published studies (Table 1). We believe this is important given some of the controversies surrounding treatments for patients with COVID-19 including remdesivir

Table 1. Summary of ADEs seen with remdesivir.

Source and year	Patient categories	Findings
Mulangu et al (2019) [21]	Randomized trial of 681 patients testing positive for Ebola virus the on reverse-transcriptase–polymerase-chain-reaction assay	• 29 serious AEs were determined by trial investigators to be potentially related to the trial drugs • After adjudication by an independent panel, 4 events in 3 patients, all resulting in death, were possibly related to trial drugs. This included one patient in the remdesivir group who had hypotension that resulted in cessation of a loading dose of remdesivir followed rapidly by cardiac arrest – however, could not be readily distinguishable from underlying Ebola • Typically, the safety profile was generally consistent with Phase 1 data
EMA summary for compassionate use (2020) [20]	AE data from 131 patients in Gilead sponsored studies	The following was found to occur in 5 or more subjects: • Phlebitis – 8 patients • Constipation – 7 patients • Headache – 6 patients • Ecchymosis, nausea, and pain in extremities – 5 patients each
Grein et al (2020) [41]	Analysis of data from 53 patients with severe COVID-19 enrolled into a compassionate use programme	32 patients (60%) reported ADEs. These included: • Hepatic enzyme increases – 23% of patients • Diarrhea – 9% of patients • Renal impairment, rash, hypotension – 8% of patients • Acute kidney injury, multiple organ dysfunction syndrome, hypernatremia, DVT – 6% of patients • Serious ADEs occurred in 23% of patients with 8% discontinuing remdesivir due to side effects
Wang et al (2020) [8]	237 patients with severe COVID-19 enrolled and randomly assigned to remdesivir (158 patients) or placebo (79 patients)	• ADEs were reported in 66% of patients in the remdesivir group and 64% in the control • The most common ADEs in the remdesivir group were constipation (14%), hypoalbuminaemia (13% – nonsevere), hypokalaemia (12% – 1% severe), anemia (12% – 1% severe), thrombocytopenia (19% – 3% severe), and increased total bilirubin (10% – 1% severe) • 28 patients in the remdesivir group (18%) had serious ADEs with more patients in the remdesivir group discontinuing treatment due to ADEs • All deaths during the observation period were judged to be unrelated to the intervention
Goldman et al (2020) [11]	397 patients with severe COVID-19 randomized to either 5 days treatment (200 patients) or 10 days treatment (197 patients)	• 70% of patients in the 5-day group and 74% in the 10-day group experienced ADEs, with 21% in the 5-day group and 35% in the 10-day group experiencing serious ADEs The most common ADEs were: • Nausea – 10% in the 5-day group and 9% in the 10-day group • Acute respiratory failure – 6% in the 5-day group and 11% in the 10-day group • Increased ALT – 6% in the 5-day group and 8% in the 10-day group • Constipation – 7% in both groups • 4% in the 5-day group discontinued treatment owing to ADEs versus 10% in the 10-day group
Biegel et al (2020) [10]	1062 hospitalized patients with COVID-19 randomized either to remdesivir or placebo	• Serious ADEs occurred in 24.6% of patients in the remdesivir group vs. 31.6% in the placebo group • 8.8% of patients in the remdesivir group had serious respiratory failure AEs including acute respiratory failure and the need for endotracheal intubation • No deaths were considered by the investigators to be related to treatment assignment • The most common nonserious ADEs occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin levels and lymphocyte counts, respiratory failure, anemia, pyrexia, and hyperglycemia as well as increased blood creatinine levels and blood glucose levels. The incidence of AEs was generally similar between the remdesivir and placebo groups
Spinner et al (2020) [12]	Study of 596 patients with moderate COVID-19 randomized to either 5 or 10 days of treatment with remdesivir vs. standard care	• AEs were experienced by 51% of patients in the 5-day remdesivir group vs. 59% in the 10-day remdesivir group and 47% in the standard care group • Differences between the 5-day remdesivir group and standard care was not statistically significant but the difference between the 10-day remdesivir group and standard care were • AEs more common in the remdesivir groups vs. standard care included nausea (10% 5-day and 9% 10-day groups), hypokalemia (5% 5-day and 7% 10-day), and headaches (5% both groups). Diarrhea also occurred but 6% in 5-day group, 5% in 10-day group and 7% in standard care group • Serious AEs were less common in the remdesivir groups (5% in both) vs. standard care (9%) • Deaths occurred in the remdesivir group (but also standard care group) but none were attributed to remdesivir

Table 2. Characteristics of adverse drug events (N = 1004 ADEs) reported from 439 individuals reported for remdesivir in WHO database.

Parameter		Frequency (%)
Age	< 18 Years	21 (2.1)
	18–64 Years	469 (46.7)
	≥ 65 Years	417 (41.5)
	Not reported	97 (9.7)
Gender	Female	399 (39.7)
	Male	591 (58.9)
	Not reported	14 (1.4)
Continents	Americas	680 (67.7)
	Asia	7 (0.7)
	Europe	314 (31.3)
	Oceania	3 (0.3)
Report Type	Report from study	249 (24.8)
	Spontaneous	755 (75.2)
Seriousness of Adverse Event	Serious	828 (82.5)
	Non-Serious	176 (17.5)
Route of Administration	Intravenous	805 (80.2)
	Iontophoresis	8 (0.8)
	Respiratory (inhalation)	3 (0.3)
	Other	1 (0.1)
	Unknown	53 (5.3)
	Not reported	134 (13.4)
Indication for use	Covid-19 treatment	930 (92.6)
	Acinetobacter infection	2 (0.2)
	ARDS	1 (0.1)
	Drug use for unknown indication	5 (0.5)
	Not reported	66 (6.5)
Outcome	Fatal	58 (5.8)
	Not recovered/not resolved	122 (12.2)
	Recovered/resolved	101 (10.1)
	Recovered/resolved with sequelae	1 (0.1)
	Recovering/resolving	30 (3.0)
	Unknown	93 (9.7)
	Not reported	599 (59.7)
Dechallenge Action	Dose not changed	122 (12.2)
	Drug withdrawn	221 (22.0)
	Not applicable	25 (2.5)
	Unknown	35 (3.5)
	Not reported	601 (59.9)
Dechallenge Outcome	Fatal	57 (5.7)
	No effect observed	120 (12.0)
	Reaction abated	132 (13.2)
	Effect unknown	93 (9.3)
	Not Reported	602 (60.0)
Rechallenge Action	Rechallenge	133 (13.2)
	Not Reported	871 (86.8)
Rechallenge Outcome	Effect unknown	106 (10.6)
	No recurrence	27 (2.7)
	Not Reported	871 (86.8)

[6,7,12,42]. In additon, the differences in the nature of the COVID-19 population compared to those patients typically receiving remdesivir before the COVID-19 pandemic.

It was observed that the majority of ADEs were reported from male subjects and those aged 45 years or greater (Table 2). The majority of events were reported from the American continent and were spontaneously reported by health professionals (Table 2). This may reflect the fact that almost all ADEs were for the management of patents with COVID-19 (92.6%), the high profile NIH study with remdesivir, endorsement of remdesivir by the US FDA, and moves by the USA government to stockpile supplies limiting their availability initially to other countries [43–45]. Just under a third of the reports were from Europe, perhaps again reflecting initial endorsement from the European Medicine Agency and others for compassionate use [19,46,47]. However, further research is needed before we can make any definitive statements. We are aware though that there have been concerns with the extent of ADE reporting in a number of countries, especially lower- and middle-income countries (LMICs) in recent years, which may have impacted on the extent of reports outside of Europe and the US [48–52]. Improvements in ADE and ADR reporting are needed across countries generally and especially with new medicines, with educational and other initiatives known to be successful [53–55].

The majority of the ADEs were related to investigations followed by renal, urinary, and respiratory disorders (Tables 3 and 4). An increase in hepatic enzymes and kidney injury were the principal individual ADEs (Table 2) reflecting findings in the published studies, with more non-serious ADEs found in the younger age group, i.e. < 64 (Tables 4 and 5). Serious ADEs were found more in males (Table 5) and, as expected, fatal and not recovered/resolved events were found more in those patients with serious ADEs (Tables 5 and 6). The main individual reasons for the death was multiple organ failure and cardiac arrest (Table 6), again reflecting some of the published literature.

An increase in hepatic enzymes is a concern with the administration of remdesivir. To address this, the product information for remdesivir suggests that liver function tests should be performed before starting remdesivir and that remdesivir should not be given to patients having ALT levels more than 5 times normal levels, ALT increases associated with signs and symptoms of liver inflammation or with an increase in other liver enzymes [22]. Consequently, we believe it is important for physicians to keep tracking patient's liver function during treatment with remdesivir as suggested in the product summary information. However, we are currently unaware of any guidance regarding the need for dose adjustments of remdesivir in patients with hepatic impairment. Consequently, physicians will need to decide to initiate or continue the use of remdesivir in such patients based on their perceived risk-benefit ratio.

Kidney injury and dysfunction is seen as another major ADE associated with remdesivir (Tables 3 and 5, Appendix). However, we are aware that kidney dysfunctions have been observed in the control arm of the clinical trials indicating that the disease process itself may be associated with these ADEs. We believe that up to now remdesivir has not been systematically assessed in patients with severe renal impairment or end stage renal failure, which is a concern that needs to be addressed with more widespread use. However, before initiating remdesivir the GFR should be measured in adults, and > 28 days old pediatric patients, and this should be > 30 ml/min. In the case of pediatric patients age < 28 days, serum creatinine should be measured, and this should be more than 1 mg/dl [22]. The remdesivir formulation also has the excipient sulfobutylether β cyclodextrin (SBECD), which is cleared in the kidneys, and accumulates when GFR is low. Consequently, we recommend that the renal function of patients with COVID-19 is assessed before initiation of remdesivir to prevent any toxicity due to SBECD affecting treatment decisions [56,57]. Overall, renal function is a concern with remdesivir, and should be

Table 3. Top 25 ADEs suspected to be caused by remdesivir reported in 439 individuals in WHO database (N = 439).

Sl. No.	ADEs	Frequency (%)
1	Hepatic enzyme increased	141 (32.11)
2	Renal Injury	63 (14.4)
3	Blood creatinine increased	49 (11.2)
4	Medication Error	34 (7.7)
5	Product Use in Unapproved Condition	29 (6.6)
6	Respiratory failure	28 (6.4)
7	Tachy or Bradyarrythmia	26 (5.9)
8	Hypotension	24 (5.5)
9	Rash	22 (5.0)
10	Therapy cessation	22 (5.0)
11	Condition Aggravated/Disease Progression	19 (4.3)
12	Sepsis and Septic Shock	18 (4.1)
13	Cardiac and Cardiorespiratory Arrest	17 (3.9)
14	Nausea/Vomiting	15 (3.4)
15	Glomerular filtration rate decreased	14 (3.2)
16	Renal impairment	14 (3.2)
17	Abnormal Hemogram	13 (3.0)
18	Renal failure	13 (3.0)
19	Death	12 (2.7)
20	Multiorgan Disorder/Organ Failure	11 (2.5)
21	Pyrexia	11 (2.5)
22	Hypoxia	11 (2.5)
23	Dialysis	11 (2.5)
24	Diarrhea	10 (2.3)
25	Acidosis	10 (2.3)

closely monitored with limited improvement following withdrawal [22,23].

Overall, there is a need to continually monitor ADEs arising from remdesivir to provide future guidance. There is a role for Drug and Therapeitic Committess (DTCs) in hospitals to enhance ADE reporting as well as continue to promote evidence-based medicine (EBM) to optimize treatment for patients with COVID-19 and other diseases [53,58–60]. This includes updating physicians on the effectiveness and safety of remdesivir as new information becomes available in line with activities and recommendations for managing the entry of new medicines into clinical care as seen with new oral anticoagulants and new medicines for patients with hepatitis C [61–64].

We are aware of a number of limitations with this study. Firstly, this study is based on VigiBase®, which is a global database of individual case safety reports. The individual case safety reports in this database come from different sources and information emanating from this database should not be taken as the opinion of the Uppsala Monitoring Center or the World Health Organization. Secondly, there may be ADEs that are less frequent that can only be observed in large datasets. Thirdly, there is also no absolute certainty about the causality for the reported ADEs especially as many characteristics of COVID-19 are still unknown and the disease itself is associated with considerable morbidity and mortality in some patients. In addition, data obtained from the VigiBase® does not typically include an overall judgment about the causality of ADEs but does report a few components deciding about causality, i.e., dechallenge action, dechallenge out, rechallange action, and rechallenge outcomes as depicted in our analysis. However, if at least one component for these data is missing, which was the case in almost all the reports in our study, such data cannot be incorporated into the analysis.

Table 4. Comparison of ADEs of remdesivir between the age groups less and more than 64 years of age (N = 1004).

Parameters		Age < 64 (N = 485)	Age 64 & Above (N = 417)	Age Unknown (N = 97)
Seriousness				
	Serious (N = 828)	384 (79.2)	373 (89.4)	71 (73.2)
	Non serious (N = 176)	106 (21.8)	44 (10.6)	26 (26.8)
ADR organ system				
	Blood and lymphatic system disorders (N = 20)	8 (1.6)	7 (1.7)	5 (5.2)
	Cardiac disorders (N = 51)	22 (4.5)	27 (6.5)	2 (2.1)
	Ear and labyrinth disorders (N = 1)	1 (0.2)	0	0
	Eye disorders (N = 6)	2 (0.4)	0	4 (4.1)
	Gastrointestinal disorders (N = 42)	22 (4.5)	16 (3.8)	4 (4.1)
	General disorders and administration site conditions (N = 84)	39 (8.0)	40 (9.6)	5 (5.2)
	Hepatobiliary disorders (N = 23)	10 (2.1)	8 (1.9)	5 (5.2)
	Immune system disorders (N = 1)	1 (0.2)	0	0
	Infections and infestations (N = 36)	16 (3.3)	16 (3.8)	4 (4.1)
	Injury, poisoning and procedural complications (N = 73)	36 (7.4)	28 (6.7)	9 (9.3)
	Investigations (N = 283)	165 (34.0)	88 (21.1)	30 (30.9)
	Metabolism and nutrition disorders (N = 22)	11 (2.3)	8 (1.9)	3 (3.1)
	Musculoskeletal and connective tissue disorders (N = 5)	0	3 (0.7)	2 (2.1)
	Nervous system disorders (N = 34)	11 (2.3)	21 (5.0)	2 (2.1)
	Psychiatric disorders (N = 10)	3 (0.6)	7 (1.7)	0
	Renal and urinary disorders (N = 102)	35 (7.2)	58 (13.9)	9 (9.3)
	Reproductive system and breast disorders (N = 1)	1 (0.2)	0	0
	Respiratory, thoracic and mediastinal disorders (N = 89)	35 (7.2)	49 (11.8)	5 (5.2)
	Skin and subcutaneous tissue disorders (N = 36)	24 (4.9)	7 (1.7)	5 (5.2)
	Social circumstances (N = 1)	0	1 (0.2)	0
	Surgical and medical procedures (N = 41)	23 (4.7)	17 (4.1)	1 (1.0)
	Vascular disorders (N = 43)	25 (5.2)	16 (3.8)	2 (2.1)
Outcome	Fatal (N = 58)	9 (1.9)	42 (10.1)	7 (7.2)
	Not recovered/Not resolved (N = 122)	67 (13.8)	19 (4.6)	36 (37.1)
	Recovered/Resolved (N = 101)	62 (12.8)	15 (3.6)	24 (24.7)
	Recovered/Resolved with sequelae (N = 1)	0	0	1 (1.0)
	Recovering/Resolving (N = 30)	11 (2.3)	10 (2.4)	9 (9.3)
	Unknown (N = 93)	50 (10.3)	25 (6.0)	18 (18.6)
	Not Reported (N = 599)	291 (6)	306 (73.4)	2 (2.1)

NB: Values in parenthesis are percentages. The denominator for the percentages are people in each age category.

We have also not undertaken any comparisons based on statistical tests to prevent bias arising from missing/unavailable data for any variable. We are also aware it would have been worthwhile to compare the ADEs reported for remdesivir before and after COVID – 19 especially given likely differences in the patient characteristics; however, this was not possible

Table 5. Comparison of serious and non-serious ADEs for various characteristics (N = 1004).

Parameters		Serious (N = 828)	Non-Serious (N = 176)
Gender	Male (N = 591)	490 (59.2)	101 (57.4)
	Female (N = 399)	332 (40.1)	67 (38.1)
	Gender Not mentioned (N = 14)	6 (0.7)	8 (4.5)
System involved in ADR	Blood and lymphatic system disorders (N = 20)	16 (1.9)	4 (2.3)
	Cardiac disorders (N = 51)	48 (5.8)	3 (1.7)
	Ear and labyrinth disorders (N = 1)	1 (0.1)	0
	Eye disorders (N = 6)	2 (0.2)	4 (2.3)
	Gastrointestinal disorders (N = 42)	33 (4.0)	9 (5.1)
	General disorders and administration site conditions (N = 84)	71 (8.6)	13 (7.2)
	Hepatobiliary disorders (N = 23)	19 (2.3)	4 (2.3)
	Immune system disorders (N = 1)	1 (0.1)	0
	Infections and infestations (N = 36)	32 (3.9)	4 (2.3)
	Injury, poisoning and procedural complications (N = 73)	41 (5.0)	32 (18.2)
	Investigations (N = 283)	221 (26.7)	62 (35.2)
	Metabolism and nutrition disorders (N = 22)	17 (2.1)	5 (2.8)
	Musculoskeletal and connective tissue disorders (N = 5)	5 (0.6)	0
	Nervous system disorders (N = 34)	32 (3.9)	2 (1.1)
	Psychiatric disorders (N = 10)	4 (0.5)	6 (3.4)
	Renal and urinary disorders (N = 102)	99 (12.0)	3 (1.7)
	Reproductive system and breast disorders (N = 1)	1 (0.1)	0
	Respiratory, thoracic and mediastinal disorders (N = 89)	85 (10.3)	4 (2.3)
	Skin and subcutaneous tissue disorders (N = 36)	25 (3.0)	11 (6.3)
	Social circumstances (N = 1)	1 (0.1)	0
	Surgical and medical procedure (N = 41)	35 (4.23)	6 (3.4)
	Vascular disorders (N = 43)	39 (4.7)	4 (2.3)
Outcome	Fatal (N = 58)	58 (7.0)	0
	Not recovered/not resolved (N = 122)	98 (11.8)	24 (13.6)
	Recovered/resolved (N = 101)	66 (8.0)	35 (19.9)
	Recovered/resolved with sequelae (N = 1)	0	1 (0.6)
	Recovering/resolving (N = 30)	23 (2.3)	7 (4.0)
	Unknown (N = 93)	80 (9.7)	13 (7.2)
	Not Mentioned (N = 599)	502 (60.6)	96 (54.6)

NB: Values in parenthesis are percentages. The denominator for the percentages are the frequency of serious and non-serious ADEs.

Table 6. Characteristics of deaths reported for remdesivir in WHO database (N = 87).

PARAMETER		FREQUENCY (%)
Age	Age below 64	25 (28.7)
	Above 64	56 (64.4)
	Unknown	6 (6.9)
WHO Region	Region of America	60 (69.0)
	Europe	26 (29.9)
	Western Pacific Region	1 (1.2)
Gender	Female	30 (34.5)
	Male	57 (65.5)
Adverse Drug Event System Involved (Top 5)	General disorders and administration site conditions	23 (26.4)
	Cardiac disorders	20 (23.0)
	Respiratory, thoracic and mediastinal disorders	11 (12.6)
	Infections and infestations	11 (12.6)
	Blood and lymphatic system disorders	4 (4.6)
Adverse Drug Event (Top 5)	Multiple organ dysfunction syndrome	8 (9.2)
	Cardiac arrest	8 (9.2)
	Cardio-respiratory arrest	6 (6.9)
	Respiratory failure	5 (5.8)
	Condition aggravated	4 (4.6)

because no ADE was reported to Vigibase® between 2015 and 2019 possibly due to infrequent use before the COVID-19 pandemic. There may have been some ADEs reported before 2015; however, this was outside the scope of this study. All the ADEs included in the analysis were those in which remdesivir was suspected. We have not incorporated in our analysis any ADEs where remdesivir was concomitantly given but was not suspected. We are aware the WHO receives information on ICSRs from numerous sources; consequently, there is a probability that suspected adverse effects is drug-related is not the same in all cases. However, despite these limitations, we believe it is helpful to consolidate current knowledge regarding potential ADEs from remdesivir and possible ways to address these. The findings and their interpretation can be added to as more data become available.

5. Conclusion

This study was an attempt to descriptively analyze ADEs reported to date for remdesivir to add to the information about the safety of remdesivir reported to date from published clinical trials in patients with COVID-19 given potential concerns. The most important ADEs were elevation of liver enzymes and those arising from kidney injury, which is in line with the product information given by the FDA. These findings call for greater monitoring of liver enzymes during treatment, building on existing guidance, with the potential for dose adjustments, as well as monitoring renal function before and during treatment with remdesivir. Greater guidance can also be given by the authorities as more knowledge becomes available including

potential doses of remdesivir in patients with COVID-19 with existing hepatic impairment or poor renal function.

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