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SHORT RESEARCH REPORT

Remdesivir for COVID-19 and acute kidney injury: disproportionality analysis of data from the U.S. Food and Drug Administration Adverse Event Reporting System

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Abstract

Background Evidence about remdesivir-associated acute kidney injury (AKI) among patients with novel coronavirus disease 2019 (COVID-19) was controversial.

Aim To investigate the signal of disproportionate reporting of remdesivir-related AKI in COVID-19 patients over time with data from US Food and Drug Administration Adverse Event Reporting System.

Method Adverse events in COVID-19 patients reported between April 2020 and September 2022 were included. Reporting odds ratios (RORs) of AKI and renal disorders (a more sensitive definition for AKI) were estimated to compare remdesivir with other medications prescribed in comparable situations of COVID-19.

Results During the entire study period, significant signals were identified for remdesivir-related AKI (ROR 2.00, 95% CI: 1.83–2.18) and renal disorder (ROR 2.35, 95% CI: 2.17–2.54) when compared to all comparable drugs. However, in the third quarter of 2022 (the most recent quarter) signals disappeared as the ROR of AKI was 1.50 (95% CI 0.91–2.45) and ROR of renal disorder was 1.69 (95% CI 1.06–2.70). Number of signals in sensitivity analyses and the proportion of AKI in remdesivir-associated events decreased over time.

Conclusion In COVID-19 patients, we observed diminishing signals of remdesivir-associated AKI over time and no significant signal in the most recent quarter, suggesting remdesivir might not be nephrotoxic.

Keywords Acute kidney injury · COVID-19 · Disproportionality analysis · Remdesivir

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Impact statements

- Our results reinforce the evidence that there is no association between remdesivir and AKI, suggesting remdesivir needs not to be avoided based on the concerns about AKI.
- This study shows that pharmacovigilance signals of a new drug can diminish and even disappear as time lapses, suggesting we should be more cautious in interpreting disproportionality signals of new medications and the importance of time-trend analysis for disproportionality analysis.

Introduction

As of December 14, 2022, there have been more than 646 million confirmed cases of COVID-19, including more than 6 million COVID-related deaths. In clinical trials, remdesivir substantially reduced the risk of hospitalization or death among non-hospitalized COVID-19 patients who were at high risk for progression [1], and significantly reduced the risk of death or progression to ventilation in hospitalized but not ventilated patients [2]. Therefore, remdesivir is recommended by guidelines of Infectious Disease Society of America [3] and the World Health Organization [4] for these patients. In addition to high baseline risk (about 40%) of acute kidney injury (AKI) in hospitalized COVID-19 patients [5, 6], there are concerns that remdesivir may further increase risk of AKI [7]. Previous trials were underpowered to address this potential safety concern for remdesivir in COVID-19 patients since renal adverse events were not predefined outcomes in some trials [1, 2, 8, 9]. AKI might be a relatively rare adverse event, and vulnerable patients (e.g., those with liver disease or serious heart disease[1, 2, 8, 9]) were often excluded.

Previous disproportionality analysis [10–14] have reported significant signals for nephrotoxicity associated with remdesivir. However, these signals might be influenced by the Weber effect (a peak in adverse event reporting right after regulatory approval following by a continuous decline thereafter) as the emergence use authorization for remdesivir was issued in May 2020. Such analyses might also be affected by "notoriety bias"—a selection bias in which cases are more likely to be reported if the patient is exposed to a medication that is suspected to cause a specific adverse event [15]. This is relevant because remdesivir was suspected to be nephrotoxic in in vitro and animal experiments [16, 17] and was thus not recommended in patients with severe renal impairment [3].

To our knowledge, three observational studies have assessed the association of remdesivir use and AKI in hospitalized COVID patients and all have suggested remdesivir was not associated with increased risk of AKI [18, 19], or reported the decreased risk of AKI in remdesivir users [20]. These results might not reflect the truth because of selection bias (patients with better kidney function might have higher probability of receiving remdesivir) and limited sample size (245 [18], 932 [19] and 1999 [20] patients were included, respectively), which can make studies more prone to false negative findings. The association between remdesivir and AKI remains controversial.

Aim

To investigate the pharmacovigilance signal of remdesivir-related AKI in COVID-19 patients over time using data from US Food and Drug Administration Adverse Event Reporting System (FAERS).

Ethics approval

This study used de-identified open-source data and involved no human participants, hence no ethics approval was required.

Method

We queried FAERS for COVID-19 cases reported from April 1, 2020 to September 30, 2022, with COVID-19 related terms provided by the Medical Dictionary for Regulatory Activities (MedDRA, version 23.1) (Table S1). The primary outcome AKI was defined with a narrow Standardized MedDRA Query (SMQ) of acute renal failure (ARF), the specific list of terms for identifying AKI [21]. The secondary outcome, renal disorders, was defined by a broader SMQ of ARF, which includes the primary outcome and is more sensitive in searching AKI [21].

All other drugs thought comparable to remdesivir in managing COVID-19, including hydroxychloroquine/chloroquine, lopinavir-ritonavir, azithromycin, tocilizumab, sarilumab and tofacitinib, were combined as the comparator in the primary analysis. Nirmatrelvir-ritonavir and molnupiravir were not included in comparator since they are only recommended for non-hospitalized patients [3, 4] while remdesivir, which is only for injection, was mainly used in hospitalized patients. Brand and generic names (Table S2) were used to identify these drugs for COVID-19.

In sensitivity analyses, remdesivir was compared with each individual comparator. To assess whether signals had changed over time, signals were assessed by quarters, and remdesivir-related reports reported in each quarter before the third quarter (Q3) of 2022 were compared with remdesivir-associated cases reported in 2022 Q3.

We conducted a disproportionality analysis to estimate the reporting odds ratio (ROR) using two-by-two contingency tables (Table S3) to detect signals. We defined a signal of increased risk using an ROR ≥ 2, the lower limit of the 95% CI of ROR > 1 and three or more cases. We analyzed data using SAS 9.4 (SAS Institute Inc., Cary, NC).

Results

During the study period from April 2020 through September 2022, a total of 86,277 reports associated with COVID-19 were reported to FAERS. Among 8,581 cases related to remdesivir, there were 957 reports with AKI (11.2%), in which the median age was 66 years and 34.7% were female (Table 1). Regarding AKI cases, remdesivir users had a smaller proportion of hospitalization (10.2% vs 21.6%) but a larger proportion of deaths (12.5% vs 5.1%) compared to non-users of remdesivir (Table 1).

In this entire period, COVID-19 treatment with remdesivir was associated with increased odds of being reported with AKI (ROR 2.00, 95% CI 1.83–2.18) and renal disorder (ROR 2.35, 95% CI 2.17–2.54), compared to all other medications used in similar strategies. We observed signals of both remdesivir-associated AKI and renal disorder when HCQ/CQ, tocilizumab and tofacitinib were used as individual comparators, and signal of renal disorder when azithromycin was the comparator. We did not observe a signal of AKI when remdesivir was compared to individual azithromycin, lopinavir-ritonavir or sarilumab, nor signal of renal disorders when compared with lopinavir-ritonavir and sarilumab, respectively (Table 2).

Table 3 shows that RORs generally declined as time lapsed. In 2022 Q3 (the most recent quarter) there was no signal when comparing remdesivir to all other medications for AKI (ROR 1.50, 95% CI 0.91–2.45) or renal disorders (ROR 1.69, 95% CI 1.06–2.70). In 2022 Q3 there was no significant signal in sensitivity analyses for both outcomes except for the comparison between remdesivir and HCQ/CQ, while in the second quarter of 2020 all sensitivity analyses for renal disorders showed significant signals and three comparisons showed signals for AKI. Comparing remdesivir-associated reports in every other quarter to remdesivir-associated reports in 2022 Q3, all four trimesters between 2020 Q2 and 2021 Q1 showed significant signals (Table 3). Comparing 2020 Q2 to 2022 Q3, the odds of reporting AKI in remdesivir-associated events was 5.56 times higher (95% CI 3.57–8.33) and the odds of reporting renal disorders was 7.14 times higher (95% CI 5.00–11.11).

Table 1 Descriptive characteristics of COVID-19 cases with AKI* reported to FAERS from 1 April 2020 to 30 September 2022

Characteristics	Remdesivir N = 957	Without Remdesivir n = 1638
Age, years		
Median (IQR)	66 (56, 76)	64 (49, 73)
Sex		
Female	319 (34.7)[a]	544 (38.0)[b]
Male	601 (65.3)[a]	889 (62.0)[b]
Weight, kg		
Median (IQR)	90.0 (78.0, 109.0)	82.8 (66.0, 98.3)
Concurrent medications may induce AKI[c]		
Acetaminophen	126 (13.2)	97 (5.9)
Aminoglycosides	14 (1.5)	27 (1.6)
Amphotericin B	15 (1.6)	16 (1.0)
ACEI	45 (4.7)	94 (5.7)
ARB	117 (12.2)	153 (9.3)
Clopidogrel	29 (3.0)	22 (1.3)
Furosemide	169 (17.7)	129 (7.9)
Interferon-Alfa	0	0
Lansoprazole	16 (1.7)	19 (1.2)
Omeprazole	75 (7.8)	79 (4.8)
Quinolones	4 (0.4)	20 (1.2)
Statins	129 (13.5)	153 (9.3)
Vancomycin	0	0
Lopinavir/Ritonavir	2 (0.2)	119 (7.3)
Serious outcomes		
Hospitalization	98 (10.2)	353 (21.6)
Life-threatening	66 (6.9)	83 (5.1)
Disability	6 (0.6)	0
Death	120 (12.5)	84 (5.1)

Data are n (%) unless otherwise indicated

AKI acute kidney injury, *IQR* interquartile range, *ACEI* angiotensin-converting enzyme inhibitor, *ARB* angiotensin receptor blocker

[a]In remdesivir users there were 37 (3.9%) AKI reports with missing age

[b]In remdesivir non-users there were 205 (12.5%) AKI reports with missing age

[c]AKI in this table is the primary outcome in this study, which was defined with a narrow Standardized MedDRA Query of acute renal failure

Discussion

Our analysis indicates that from 2020 Q2 to 2022 Q3 there was a diminishing trend on pharmacovigilance signals of remdesivir-associated AKI and renal disorders when compared with other medications prescribed in comparable

Table 2 Reporting odds ratio for the remdesivir compared to other drugs in COVID-19 patients

Comparison	No. of event of interest/no. of other ADEs		Reporting odds ratio (95% CI)
	Remdesivir	Comparator	
Acute kidney injury			
Remdesivir vs. all comparators[a]	931/7892	1328/22496	2.00 (1.83, 2.18)
Remdesivir vs HCQ/CQ	931/7892	450/8495	2.23 (1.98, 2.50)
Remdesivir vs Azithromycin	931/7892	428/6446	1.78 (1.58, 2.00)
Remdesivir vs Tocilizumab	931/7892	299/5721	2.26 (1.97, 2.58)
Remdesivir vs Lopinavir-Ritonavir	931/7892	116/969	0.99 (0.80, 1.21)
Remdesivir vs Sarilumab	931/7892	22/332	1.78 (1.15, 2.76)
Remdesivir vs Tofacitinib	931/7892	13/533	4.84 (2.78, 8.42)
Renal disorders			
Remdesivir vs all comparators[a]	1238/7585	1549/22275	2.35 (2.17, 2.54)
Remdesivir vs HCQ/CQ	1238/7585	530/8415	2.59 (2.33, 2.88)
Remdesivir vs Azithromycin	1238/7585	497/6377	2.09 (1.88, 2.34)
Remdesivir vs Tocilizumab	1238/7585	357/5663	2.59 (2.29, 2.93)
Remdesivir vs Lopinavir-Ritonavir	1238/7585	122/963	1.29 (1.06, 1.57)
Remdesivir vs Sarilumab	1238/7585	28/326	1.90 (1.29, 2.81)
Remdesivir vs Tofacitinib	1238/7585	15/531	5.78 (3.45, 9.69)

The primary outcome was acute kidney injury defined by a narrow Standardized MedDRA Query (SMQ) of acute renal failure (ARF). The secondary outcome, renal disorders, was defined with a broad SMQ of ARF, including the primary outcome. The way to calculate reporting odds ratio was showed in Table S3

ADEs, adverse drug events; HCQ, hydroxychloroquine; CQ, chloroquine

[a]All comparators means all other six medications listed in the table

situations of COVID-19. There was a significant decrease in the proportion of AKI and renal disorders in remdesivir-related events. To the best of our knowledge, this is the first disproportionality analysis revealing this trend overtime.

The incidence of AKI in hospitalized COVID-19 patients was reported to be about 49% between March and July 2020, and about 40% from July 2020 through Jan 2022, suggesting about a 20% reduction [5]. This can partly explain the higher proportions of AKI and renal disorders in remdesivir-related reports in 2020 compared to those in 2022. These proportions were more than 5 times higher in 2020 Q2 compared with 2022 Q3, suggesting a more than 80% reduction from 2020 Q2 to 2022 Q3 (Table 3). Therefore, it is likely that as knowledge about COVID-19 and medications for COVID-19 increased, people became more confident that AKI was induced by COVID-19 rather than medications in many cases. This is also probably the cause for diminishing signals of remdesivir-associated nephrotoxicity.

Five previously published disproportionality analyses all used spontaneously reported data received before June 2021 [10–14]. Pharmacovigilance signals were observed in all primary analyses and most sensitivity analyses in these studies. Our overall analyses using data reported in the entire study period, and most of our sensitivity analyses using data reported by 2021 Q2 also indicated signals, but these signals diminished over time. Hence, it is likely that these published studies were affected by Weber effect [22] and notoriety bias [15], considering remdesivir was a new treatment for COVID-19 with much uncertainty about its safety, especially within the first year of its approval, and preclinical studies suggested potential risk of AKI [23]. This study indicates that time-trend analysis has the potential in address the Weber effect and notoriety bias.

Thus, our findings support no association between remdesivir and AKI, being consistent with published cohort studies [18–20] and the case-series study [24] that suggested no increased risk of AKI in remdesivir users.

Limitations of this study arise mainly from the inherent weakness of FAERS database: (1) the unavailability of important potential confounders that makes it impossible to control for them; (2) reporting bias that can underestimate or overestimate the signal; (3) inconsistent measurement of the adverse events; (4) delayed reporting. However, in this study we mitigated Weber effect [22] and notoriety bias [15] by time-trend analysis. To ameliorate indication bias, we compared remdesivir with a combination of drugs that have comparable uses.

Table 3 Reporting odds ratio for the remdesivir compared to other drugs in COVID-19 patients by quarter

Comparison	Reporting odds ratio (95% CI)									
	2020 Q2	2020 Q3	2020 Q4	2021 Q1	2021 Q2	2021 Q3	2021 Q4	2022 Q1	2022 Q2	2022 Q3
Acute kidney injury										
Remdesivir vs all comparators[a]	1.94 (1.60, 2.36)	1.63 (1.36, 1.95)	1.70 (1.38, 2.10)	1.89 (1.45, 2.46)	2.63 (1.89, 3.66)	1.35 (0.88, 2.07)	1.55 (1.09, 2.20)	1.25 (0.82, 1.93)	2.66 (1.62, 4.39)	1.50 (0.91, 2.45)
Remdesivir vs HCQ/CQ	1.80 (1.37, 2.37)	2.22 (1.74, 2.85)	1.88 (1.46, 2.44)	2.20 (1.60, 3.03)	3.30 (2.15, 5.06)	1.27 (0.77, 2.11)	1.49 (0.93, 2.40)	1.28 (0.70, 2.35)	2.37 (1.15, 4.88)	2.69 (1.16, 6.21)
Remdesivir vs Azithromycin	1.59 (1.21, 2.10)	1.30 (1.04, 1.63)	1.55 (1.18, 2.05)	2.03 (1.43, 2.87)	2.49 (1.59, 3.90)	2.17 (1.16, 4.07)	2.38 (1.36, 4.19)	1.10 (0.62, 1.95)	2.75 (1.25, 6.03)	0.90 (0.47, 1.74)
Remdesivir vs Tocilizumab	2.94 (2.07, 4.17)	1.70 (1.24, 2.35)	1.85 (1.30, 2.63)	1.27 (0.87, 1.85)	2.92 (1.85, 4.62)	1.22 (0.70, 2.11)	1.60 (1.02, 2.52)	1.20 (0.72, 2.01)	2.87 (1.40, 5.90)	1.84 (0.88, 3.83)
Remdesivir vs Lopinavir/Ritonavir	2.00 (1.27, 3.13)	0.72 (0.47, 1.11)	1.46 (0.77, 2.76)	1.75 (0.41, 7.48)	0.35 (0.16, 0.73)	0.21 (0.10, 0.45)	0.52 (0.30, 0.89)	2.06 (0.62, 6.84)	1.94 (0.58, 6.44)	0.47 (0.21, 1.06)
Remdesivir vs Sarilumab	1.63 (0.91, 2.93)	2.44 (1.06, 5.63)	0.90 (0.49, 1.64)	2.25 (0.30, 17.08)	1.60 (0.21, 12.21)	NA	NA	NA	NA	NA
Remdesivir vs Tofacitinib	NA	NA	3.04 (0.41, 22.59)	0.63 (0.18, 2.20)	1.60 (0.56, 4.54)	NA	6.73 (0.92, 49.31)	1.60 (0.48, 5.36)	4.56 (0.61, 33.80)	NA
Previous remdesivir vs 2022 Q3 remdesivir[b]	5.56 (3.57, 8.33)	3.23 (2.17, 4.76)	2.5 (1.64, 3.7)	2.56 (1.64, 4)	1.82 (1.14, 2.86)	0.98 (0.58, 1.67)	1.49 (0.93, 2.38)	1.15 (0.68, 1.96)	1.16 (0.69, 1.96)	NA
Renal disorders										
Remdesivir vs all comparators[a]	2.61 (2.18, 3.12)	1.94 (1.66, 2.27)	1.87 (1.54, 2.27)	2.29 (1.79, 2.94)	2.76 (2.03, 3.74)	1.46 (0.99, 2.16)	1.57 (1.12, 2.19)	1.25 (0.83, 1.87)	2.52 (1.57, 4.05)	1.69 (1.06, 2.70)
Remdesivir vs HCQ/CQ	2.62 (2.02, 3.39)	2.57 (2.07, 3.20)	2.14 (1.68, 2.72)	2.67 (1.98, 3.61)	2.78 (1.92, 4.04)	1.37 (0.86, 2.18)	1.42 (0.91, 2.22)	1.23 (0.70, 2.16)	2.17 (1.11, 4.22)	2.79 (1.27, 6.10)
Remdesivir vs Azithromycin	2.07 (1.61, 2.68)	1.56 (1.28, 1.91)	1.69 (1.31, 2.19)	2.45 (1.76, 3.42)	2.97 (1.93, 4.58)	2.25 (1.27, 3.99)	2.70 (1.55, 4.70)	1.14 (0.66, 1.96)	2.68 (1.27, 5.64)	1.07 (0.56, 2.03)
Remdesivir vs Tocilizumab	3.25 (2.40, 4.39)	1.83 (1.39, 2.40)	1.84 (1.33, 2.52)	1.62 (1.13, 2.34)	3.37 (2.18, 5.20)	1.40 (0.84, 2.34)	1.65 (1.07, 2.55)	1.28 (0.78, 2.09)	2.86 (1.44, 5.70)	1.98 (0.99, 3.97)
Remdesivir vs Lopinavir/Ritonavir	3.24 (2.08, 5.05)	1.13 (0.74, 1.71)	1.86 (0.99, 3.50)	2.24 (0.53, 9.55)	0.43 (0.20, 0.89)	0.26 (0.12, 0.56)	0.50 (0.30, 0.84)	1.38 (0.53, 3.59)	1.58 (0.55, 4.54)	0.56 (0.25, 1.25)
Remdesivir vs Sarilumab	2.45 (1.39, 4.30)	3.22 (1.48, 7.01)	0.97 (0.55, 1.71)	0.85 (0.25, 2.98)	1.97 (0.26, 15.02)	1.81 (0.24, 13.63)	NA	NA	NA	NA
Remdesivir vs Tofacitinib	NA	NA	3.87 (0.52, 28.74)	0.80 (0.23, 2.81)	1.97 (0.70, 5.57)	4.16 (0.56, 30.78)	7.62 (1.04, 55.73)	1.35 (0.47, 3.90)	5.01 (0.68, 37.07)	NA
Previous remdesivir vs 2022 Q3 remdesivir[b]	7.14 (5.00, 11.11)	4.17 (2.94, 6.25)	2.63 (1.82, 3.85)	2.70 (1.82, 4.17)	1.89 (1.22, 2.86)	1.03 (0.64, 1.67)	1.41 (0.91, 2.22)	1.1 (0.68, 1.79)	1.08 (0.65, 1.75)	NA

The primary outcome was acute kidney injury defined by a narrow Standardized MedDRA Query (SMQ) of acute renal failure (ARF). The secondary outcome, renal disorders, was defined with a broad SMQ of ARF, including the primary outcome. The way to calculate reporting odds ratio (ROR) was showed in Table S3. In this table, RORs were estimated with events reported in each quarter separately

HCQ hydroxychloroquine, *CQ* chloroquine

[a]All comparators means all other six medications listed in the table

[b]In this comparison, number of remdesivir-associated AKI events in each quarter before 2022 Q3 is a, while this number in 2022 Q3 was b. The number of all other remdesivir-related events in in each quarter before 2022 Q3 is c while this number in 2022 Q3 was d. ROR $= \frac{(a/c)}{(b/d)} = \frac{ad}{bc}$

Conclusion

In conclusion, we observed diminishing signals of remdesivir-associated AKI over time in COVID-19 patients and no signal in the most recent quarters, indicating remdesivir might not be nephrotoxic.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11096-023-01554-4.

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Conflicts of interest The authors have no conflicts of interest to declare.

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