BRIEF REPORT

Is remdesivir safe in patients with renal impairment? Experience at a large tertiary urban medical center

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Abstract

Purpose Remdesivir is FDA-approved for treatment of patients hospitalized with COVID-19 pneumonia, but not recommended in patients with severe renal failure. This study aims to evaluate the safety of remdesivir in this patient population.

Methods This was a single-center, retrospective cohort study including patients ≥ 18 years old, admitted between May 1, 2020 and April 30, 2021 who received remdesivir. Patients were divided into two groups: estimated creatinine clearance (eCrCl) < 30 mL/min and eCrCl ≥ 30 ml/min. Primary outcomes were development of acute kidney injury (AKI) after remdesivir initiation and hepatotoxicity (alanine aminotransferase [ALT] or aspartate aminotransferase [AST] > 5 × upper limit of normal) both at end of treatment (EOT) or 5 days after EOT. Secondary outcomes were length of stay (days) and mortality.

Results 513 patients were assessed with 416 patients included in the study (eCrCl < 30 mL/min, $n = 55$; eCrCl ≥ 30 mL/min $n = 361$). Incidence of AKI (eCrCl < 30 mL/min 11% vs eCrCl ≥ 30 mL/min 7%, OR 1.57, 95% CI 0.57, 4.3) and hepatotoxicity (ALT: 2% vs 4%, OR 0.47, 95% CI 0.05, 3.7 and AST: 2% vs 2%, OR 1.26, 95% CI 0.14, 11.04) were similar between the two groups. Length of stay was longer in the eCrCl < 30 mL/min group (mean 18.6 vs 11.9, difference 6.7, 95% CI 3.8, 9.6), and no difference in mortality was observed (21.8% vs 18.8%, OR 1.2, 95% CI 0.6, 2.4).

Conclusion Remdesivir was not associated with development of AKI or hepatotoxicity in patients with eCrCl < 30 mL/min compared to patients with eCrCl ≥ 30 mL/min, and warrants further investigation.

Keywords Remdesivir · Renal impairment · COVID-19 · Safety

Background

Remdesivir is an inhibitor of the SARS-CoV-2 RNA-dependent polymerase, which is essential for viral replication [1]. In clinical trials, remdesivir has been shown to shorten time to recovery in adults hospitalized with COVID-19, however, patients with eGFR < 30 mL/min were typically excluded [2]. As a result, when remdesivir was granted an emergency use authorization by the Food and Drug Administration (FDA) on May 1, 2020, it was recommended to avoid use in patients with eGFR < 30 mL/min "unless benefit outweighs the risk." Subsequently, remdesivir was granted FDA approval, under the brand name Veklury® on October 22, 2020. The labeling for the use in patients with eGFR < 30 mL/min was changed to "not recommended" [1].

Based on the pharmacokinetic profile of remdesivir, renal toxicity from remdesivir itself would be unexpected, but there is a warning for possible hepatotoxicity. Remdesivir is about 88–96% protein bound with an elimination half-life ($t^{1/2}$) of about 1 h. It is primarily metabolized in the liver, which is the major route of elimination as only 10% of the dose is excreted in urine. The primary metabolite of remdesivir, GS-441524, has a half-life of about 27 h, is excreted through glomerular filtration and active tubular secretion however it is unknown if increased levels of this metabolite are correlated with toxicity. The rationale for the warning in patients with renal impairment is due to the concern for the accumulation of its sulfobutylether-β-cyclodextrin (SBECD) carrier. The SBECD vehicle is required due to the limited water solubility of remdesivir. The vehicle is excreted through glomerular filtration, with a $t^{1/2}$ of elimination of < 2 h in patients with normal kidney function. Accumulation of SBECD has been associated with liver necrosis

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and renal tubule obstruction in animal studies, however, this occurs at doses 50–100-fold higher than expected with a course of remdesivir [3]. Remdesivir formulations contain 3 g and 6 g of SBECD in the 100 mg doses of remdesivir in the lyophilized powder and solution, respectively [1].

Intravenous (IV) voriconazole is also formulated with SBECD and has a similar warning for use in patients with renal impairment [3]. Clinical studies have been conducted to evaluate the safety of this formulation in patients with AKI and requiring renal replacement therapy (RRT) and found no associated adverse events [4–6]. The SBECD concentration for a typical regimen of IV voriconazole (200 mg IV q12h) is 6.4 g per day, which is greater than the amount contained in remdesivir formulations. The amount of SBECD in both the remdesivir concentrations and in IV voriconazole is significantly lower than the maximum recommended safety threshold dose of 250 mg/kg/day as recommended by the European medicines agency [3].

Given the few treatment options currently available for patients with COVID-19, it is important to assess the safety of remdesivir in patients with severe renal failure, as this may comprise an important patient population who may in fact benefit from treatment. There is limited data on the use of remdesivir in patients with severe renal failure. The results of currently available studies in this population have shown no increase in hepatic or renal toxicity in patients with renal impairment, including those requiring RRT [7–10].

Criteria for use of remdesivir at our institution included a positive SARS-CoV-2 PCR or suspected COVID-19 infection, initiation within 10 day of the onset of symptoms, infiltrates on imaging and/or oxygen saturation < 94%. Remdesivir was allowed for use in patients with eCrCl < 30 mL/min in patients who may benefit from treatment at the discretion of the attending physicians. In this report we describe the safety of remdesivir in terms of nephrotoxicity and hepatotoxicity, as well as clinical outcomes in patients with severe renal failure at the time of remdesivir initiation compared to those without renal impairment.

Methods

This was a single-center, retrospective cohort study conducted at Kings County Hospital Center, an academic medical facility in Brooklyn, NY that treats a predominantly low socio-economic and underserved population. The study population included patients aged 18 years and older who were admitted between May 1, 2020 and April 30, 2021 and received remdesivir for the treatment of COVID-19 during the admission. Patients were excluded if they received less than 3 doses of remdesivir, did not have laboratory data

after initiation of remdesivir, or expired during the treatment course.

Data was collected via retrospective chart review. Baseline characteristics collected included age, gender, race/ethnicity, comorbidities, body mass index (BMI), concomitant nephrotoxic agents at the time of remdesivir initiation, level of care, oxygen requirements at initiation of treatment, serum creatinine (SCr), calculated creatinine clearance (CrCl) using the Cockroft–Gault equation, history of chronic kidney disease (CKD) or end stage renal disease (ESRD) on RRT, aspartate aminotransferase (AST), alanine aminotransferase (ALT), duration of symptoms prior to initiation of remdesivir, duration of remdesivir treatment, concomitant use of steroids and vasopressor use during treatment. Outcome data collected were SCr, ALT and AST at end of treatment of 5 days post-treatment, length of stay measured in days, and in-hospital mortality.

For data analysis, patients were divided into two groups: eCrCl < 30 mL/min and eCrCl ≥ 30 mL/min. The eCrCl was calculated at the time of remdesivir initiation to determine which group patients would be categorized to. The Cockroft–Gault formula was used to calculate eCrCl using the most recent SCr value on the day of or prior to the first dose of remdesivir. The primary outcomes were AKI (defined by Acute Kidney Injury Network [AKIN] stages with values at time of remdesivir initiation used as baseline) and hepatotoxicity (defined by AST or ALT greater than 5 times the ULN) either at EOT or 5 days post-treatment [11]. Preexisting AKI at the time of remdesivir initiation was determined by at least a 0.3 mg/dL increase in SCr from baseline. Secondary outcomes included length of stay and mortality.

Statistical analysis

Categorical data was summarized using percentages and statistical differences analyzed using the Chi-Square test. Odds ratios with 95% confidence intervals were reported for outcomes. Continuous data were summarized as means with standard deviations and differences analyzed using the Student's t-test with 95% confidence intervals reported. A 2-sided alpha of 0.05 was used to be considered statistically significant.

Results

A total of 513 who met inclusion criteria were reviewed. Upon chart review, 97 patients were excluded (63 patients received less than 3 doses of remdesivir, 28 patients had no outcome data available and 6 patients expired during remdesivir treatment). 416 patients were included in the final data analysis: 55 in the eCrCl < 30 mL/min and 361 in the eCrCl ≥ 30 mL/min. Patients with ESRD on RRT at

baseline were excluded from the renal outcome analysis (nine patients) and patients without EOT or 5 days post-EOT AST and/or ALT were excluded from the hepatotoxicity outcome analysis (53 in eCrCl ≥ 30 mL/min group, 6 in the eCrCl < 30 mL/min group).

Baseline characteristics are summarized in Table 1. Patients in the eCrCl < 30 mL/min group were older, more likely to have diabetes mellitus, hypertension and cardiovascular disease. This group was also more likely to be admitted to the ICU at the time of remdesivir initiation, receive vasopressors during treatment, have a higher baseline SCr, lower CrCl, have baseline CKD, and AKI at the time of remdesivir initiation. Patients in the eCrCl ≥ 30 mL/min group had a higher BMI, higher baseline ALT values and were more likely to receive concomitant steroids.

Both groups were predominantly Black/African American and about 29% of patients in each group received concomitant nephrotoxins. Oxygen requirements at time of remdesivir initiation were most commonly nasal cannula and high flow nasal cannula in both groups. The average duration of symptoms was about 5.6 days in both groups and average duration of remdesivir treatment was about 5 days.

Renal and hepatotoxicity outcomes are summarized in Table 2, as well as secondary outcomes. No difference was found in percentage of patients with AKI (either at EOT or 5 days post EOT compared to SCr at time of remdesivir initiation) between the two groups (11% vs 7%, $p = 0.377$). Most patients with AKI in each group were classified as Stage 1 per the AKIN criteria. In regard to the hepatotoxicity outcomes, no difference was found for either ALT and AST increases (2% vs 4%, $p = 0.465$ and 2% vs 2%, $p = 0.833$, respectively). Length of stay was significantly longer in the eCrCl < 30 mL/min group (mean 18.6 days vs 11.9 days, $p < 0.0001$) however there was no difference in mortality at discharge (21.8% vs 18.8%, $p = 0.601$).

Discussion

Given the lack of effective treatment options available for COVID-19, it is vital to have these treatments available to as many patients as possible. The incidence of AKI has been reported to be increased in patients with COVID-19. One study reported AKI occurrence in 46% of patients hospitalized with COVID-19, with 19% of these patients requiring dialysis as well as a higher mortality rate in patients with AKI compared to those without AKI (50% vs 8%) [12]. Remdesivir is currently the only FDA-approved medication for the treatment of COVID-19, however the recommendation against the use in patients with eGFR less than 30 mL/min may prevent the use of this medication in this patient population who can potentially benefit from this treatment.

To date, there is a sparse amount of data for the use of remdesivir in patient with severe renal failure. To our knowledge, this is the largest study in a primarily low-socioeconomic population to evaluate the use of remdesivir in patients with renal impairment. We observed no significant difference in rates of AKI or hepatotoxicity between patients with eCrCl < 30 mL/min and eCrCl ≥ 30 mL/min who were treated with remdesivir. Despite the fact that patients with eCrCl < 30 mL/min were more likely to be older, have more comorbidities that may predispose renal dysfunction (hypertension, diabetes mellitus) and were more likely to be admitted to the ICU and receive vasopressors, the incidence of AKI being similar between the two groups may indicate that remdesivir use is safe in this subset of patients. In addition, most patients were requiring either nasal cannula or high flow nasal cannula at the time of remdesivir initiation indicating an overall high severity of illness in the study population. Although more patients in the eCrCl ≥ 30 mL/min group received corticosteroids, this is unlikely to have an effect on either the renal or hepatic outcomes.

The average length of hospital stay was significantly longer in the eCrCl < 30 mL/min group, however this can likely be explained by the higher severity of illness in this group. Patients were more likely to be admitted to the ICU and receive vasopressors during remdesivir treatment indicating more critically ill patients in this group. Moreover, patients were more likely to have AKI in this group as expected, however the use of eCrCl to define AKI may not accurately differentiate between AKI from pre-existing renal impairment versus renal toxicity from remdesivir. All these factors likely contributed to the prolonged length of stay seen in this group as a prolonged time to recovery may be anticipated. While the length of stay was longer, there was no significant difference seen in mortality between the two groups.

Our study has several limitations. It was a single-center study with a small patient population in the eCrCl < 30 mL/min group which may limit the applicability of these results to other patient populations. Moreover, with only 5 patients meeting criteria for AKI in the eCrCl < 30 mL/min group, we cannot draw definite conclusions and the results need to be interpreted with caution given the small patient population in this group. The retrospective nature of this study limits the ability to control for variables that may have affected the study outcomes. There was also only a small number of patients who were on RRT at baseline limiting the results of the hepatotoxicity outcome in these patients, however, there have been reports that hemodialysis can remove SEBCD and one study showed that remdesivir was well-tolerated and safe in hemodialysis patients [13, 14].

When compared to patients with eCrCl > 30 mL/min there was no increase in rates of AKI or hepatotoxicity observed with the use of remdesivir in patients with eCrCl < 30 mL/

Table 1 Baseline characteristics of patients receiving remdesivir with and without renal impairment

	eCrCl < 30 mL/min (n = 55)	eCrCl ≥ 30 mL/min (n = 361)	Difference (95% CI)	*P* value
Baseline characteristics				
Age (years, mean (SD))	74 (14)	61 (14.8)	**13 (8.8–17.2)**	**< 0.0001**
Gender (female, *n* (%))	29 (52.7)	172 (47.6)		0.482
Race/ethnicity				
Black/African American (*n* (%))	49 (89.1)	289 (80.1)		0.110
Hispanic (*n* (%))	2 (3.6)	26 (7.2)		0.326
Other/unknown (*n* (%))	4 (7.3)	46 (12.7)		0.245
BMI (kg/m^2, mean (SD))	28.4 (6.4)	31.8 (8.2)	**− 3.4 (− 5.7 to − 1.1)**	**0.004**
Comorbidities				
Diabetes mellitus (*n* (%))	33 (60)	165 (45.7)		**0.048**
Hypertension (*n* (%))	46 (83.6)	227 (62.9)		**0.003**
Cardiovascular disease (*n* (%))	12 (21.8)	34 (9.4)		**0.006**
Autoimmune/connective tissue disorder (*n* (%))	2 (3.6)	10 (2.8)		0.721
Concomitant nephrotoxins (*n* (%))	16 (29.1)	106 (29.4)		0.967
Vancomycin (*n*)	7	10		
Diuretic (*n*)	7	10		
IV Contrast (*n*)	4	57		
ACEi/ARB (*n*)	3	28		
Acyclovir (*n*)	2	1		
NSAIDs (*n*)	0	20		
Aminoglycosides (*n*)	0	1		
Level of care				
Medical/surgical floor (*n* (%))	38 (69.1)	294 (81.4)		
Intensive care unit (*n* (%))	17 (30.9)	67 (18.6)		**0.034**
Oxygen requirement				
RA (*n* (%))	6 (10.9)	41 (11.4)		0.922
NC (*n* (%))	21 (38.2)	177 (49)		0.133
FM (*n* (%))	4 (7.3)	25 (6.9)		0.925
HFNC (*n* (%))	12 (21.8)	75 (20.8)		0.859
BiPAP (*n* (%))	6 (10.9)	22 (6.1)		0.184
MV (*n* (%))	6 (10.9)	19 (5.3)		0.101
ALT (U/L, mean (SD))	30 (20.8)	41 (33)	**− 11 (− 20 to − 2)**	**0.017**
ALT > 5 × ULN (*n* (%))	0	1 (0.3)		
AST (U/L, mean (SD))	51 (33)	56 (40.5)	− 5 (− 16.3 to 6.3)	0.384
AST > 5 × ULN (*n* (%)	0	6 (2.7)		
SCr (mg/dL, mean (SD))	2.9 (1.8)	1.3 (5.1)	**1.6 (0.2 to 3)**	**0.022**
CrCl (mL/min, mean (SD))	21 (5.6)	89 (48.1)	**− 68 (− 80.8 to − 55.2)**	**< 0.0001**
Baseline CKD (*n* (%))	36 (65.5)	16 (4.4)		**< 0.0001**
Acute kidney injury (*n* (%))	36 (65.5)	85 (23.5)		**< 0.0001**
ESRD (*n* (%))	9 (16.4)	N/A		
Duration of symptoms (days, mean (SD))	5.6 (8.3)	5.6 (3.4)	0 (− 1.2 to 1.2)	1.00
Duration of RDV treatment (days, mean (SD))	4.8 (0.6)	5 (1)	− 0.2 (− 0.5 to 0.1)	0.15
Concomitant Steroids (*n* (%))	52 (94.5)	358 (99.2)		**0.007**
Vasopressors during RDV treatment (*n*(%))	6 (10.9)	15 (4.2)		**0.033**

BMI body mass index, *ACEi* angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *NSAIDs* nonsteroidal anti-inflammatory drugs, *RA* room air, *NC* nasal cannula, *FM* facemask, *HFNC* high flow nasal cannula, *BiPAP* bilevel positive airway pressure, *MV* mechanical ventilation, *RDV* remdesivir

Bold values indicate a statistically significant difference between the two groups

Table 2 Renal, hepatic, and clinical outcomes of patients with or without baseline renal impairment

	eCrCl < 30 mL/min ($n = 46$)	eCrCl ≥ 30 mL/min ($n = 361$)	Odds ratio/difference (95% CI)	P-value
Renal outcome				
Acute kidney injury (n (%))	5 (11)	26 (7)	1.57 (0.57–4.3)	0.377
Stage 1 (n)	3	13		
Stage 2 (n)	0	3		
Stage 3 (n)	2	10		
Hepatotoxicity outcomes				
	eCrCl < 30 mL/min ($n = 49$)	eCrCl ≥ 30 mL/min ($n = 308$)		
ALT > 5 × ULN (n (%))	1 (2)	13 (4)	0.47 (0.05–3.7)	0.465
AST > 5 × ULN (n (%))	1 (2)	5 (2)	1.26 (0.14–11.04)	0.833
Secondary Outcomes				
	eCrCl < 30 mL/min ($n = 55$)	eCrCl ≥ 30 mL/min ($n = 361$)		
LOS (days, mean (SD))	18.6 (15.4)	11.9 (8.3)	**6.7 (3.8–9.6)**	**< 0.0001**
Mortality (n(%))	12 (21.8)	68 (18.8)	1.2 (0.6–2.4)	0.601

ULN upper limit of normal, *LOS* length of stay

Bold values indicate a statistically significant difference between the two groups

min. Based on these results, remdesivir should be considered as a therapeutic option in patients with severe renal failure, however larger, controlled trials are warranted to further investigate the use of remdesivir in this patient population.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This is a retrospective study that was reviewed and deemed exempt by our Institutional Review Board at SUNY-Downstate Medical Center and the System to Track and Approve Research at NYC Health and Hospitals.

Consent to participate This retrospective study was deemed exempt by our Institutional Review Board at SUNY-Downstate Medical Center and the System to Track and Approve Research at NYC Health and Hospitals and consent was not required.

Consent to publish This retrospective study was deemed exempt by our Institutional Review Board at SUNY-Downstate Medical Center and the System to Track and Approve Research at NYC Health and Hospitals and consent was not required.

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