Remdesivir Use in the Setting of Severe Renal Impairment: A Theoretical Concern or Real Risk?

Natasha N. Pettit[1]

Jennifer Pisano[2]

Cynthia T. Nguyen[1]

Alison K. Lew[1]

Aniruddha Hazra[2]

Renslow Sherer[2]

Kathleen Mullane[2]

[1]Department of Pharmacy, University of Chicago Medicine, Chicago, IL

[2]Department of Medicine, Section of Infectious Diseases and Global Health, University of Chicago Medicine, Chicago, IL

Corresponding Author

Natasha N. Pettit, PharmD, BCIDP, BCPS

5841 S Maryland Ave MC0010

Chicago, IL 60637

Office: 773-834-7853

Fax: 773-702-8998

Email: Natasha.Pettit@uchospitals.edu

Summary:

Minimal data is available on the use of remdesivir in the setting of severe renal impairment. While we observed numerically higher rates of potential toxicities, the differences were non-significant. Observed increases in LFTs and SCr were explained by other etiologies.

Abstract:

Introduction: Remdesivir (RDV) is FDA approved for COVID-19, but not recommended for patients with severe renal impairment (SRI, i.e. creatinine clearance < 30ml/min). Few studies have evaluated RDV in patients with SRI due to theoretical toxicity concerns.

Methods: Hospitalized patients receiving RDV for COVID-19 between 5/1/2020-10/31/2020 were analyzed in a retrospective chart review. We compared incident adverse events (AEs) following RDV in patients with and without SRI, including hepatotoxicity, nephrotoxicity, any reported AE, mortality and length of stay.

Results: A total of 135 patients received RDV, 20 patients had SRI. Patients with SRI were significantly older (70 vs. 54 years, p=0.0001). The incidence of possible AEs following RDV was 20% among those with SRI versus 11% without (p=0.26). LFT elevations occurred in 10% vs. 4% (p=0.28), and SCr elevations occurred in 20% vs. 6% (p=0.06) of patients with SRI versus those without, respectively. The LFT and SCr elevations were not attributed to RDV in either group.

Mortality and length of stay were comparable and consistent with historical controls.

Conclusion: RDV AEs occurred infrequently with low severity and were not significantly different between those with and without SRI. While a higher percentage of patients with SRI experienced SCr elevations, 3 (75%) patients were in AKI prior to RDV. Overall, the use of RDV in this small series of patients with SRI appeared to be relatively safe, and the potential benefit outweighed the theoretical risk of liver or renal toxicity; however, additional studies are needed to confirm this finding.

Keywords: COVID-19, remdesivir, renal impairment

Introduction:

Remdesivir (RDV) has become the mainstay of anti-viral therapy in the management of patients with COVID-19, the viral illness caused by the novel SARS-CoV-2 virus.[1] RDV has been shown to reduce time to recovery and potentially provide additional benefits depending on the severity of illness.[2] On October 22, 2020 RDV received FDA approval for the management of hospitalized adult and pediatric patients aged 12 - 17 years (weighing >=40kg) with COVID-19.[3] Prior to this, RDV was available through emergency use authorization (EUA) since May 1, 2020.

Recommendations regarding the use of RDV in the setting of severe renal insufficiency (SRI) have changed following FDA approval. Under EUA, it was recommended to avoid use if estimated glomerular filtration rate (eGFR) was less than 30 ml/min, unless benefit outweighed risk. Following FDA approval, the recommendation was updated to avoid use at the same eGFR threshold, however does not allow the exception of 'unless benefit outweighs risk.'[3] The cited reason for avoidance of RDV in the setting of SRI is the concern for accumulation of the excipient betadex sulfobutyl ether sodium, commonly known as sulfo-butyl-ether beta-cyclodextrin-sodium (SBECD). Accumulation of SBECD in animals at doses 50-fold greater than typically administered in humans has been associated with liver necrosis and obstruction of the renal tubules; however, these effects have not been observed in humans.[4] Furthermore, there are limited data on the use of RDV among patients with SRI including those requiring renal replacement therapy. One recently published study evaluated the use of RDV in patients with acute kidney injury (AKI) (n=30) or end stage renal disease (ESRD) (n=16) with the majority of patients (n=36) receiving hemodialysis at a single center.[5] They observed liver function test (LFT) elevations in 3 (6.5%) patients, however no patients experienced an LFT increase by >5 times upper limit normal (ULN) and no patients had renal function abnormalities following RDV. The observed mortality rate in this study was 30.4%. Another recently published analysis evaluated RDV pharmacokinetics in a patient receiving hemodialysis and did not

observe significant accumulation of RDV or its metabolites and noted that there were no signs of drug related toxicity.[6]

Aside from RDV and corticosteroids, few medications have proven beneficial and are available for use outside of clinical trials for patients with COVID-19 thus far. The inability to use RDV in the setting of SRI limits treatment options and prevents a considerable subset of patients from receiving potentially beneficial therapy. Several studies have identified a high incidence of chronic kidney disease (CKD) (24%) and acute kidney injury (AKI) (>40%) among hospitalized COVID-19 patients.[7,8] Twenty percent of deaths among COVID-19 patients occurred in patients with CKD in one series from the Italian Health Institute, and patients with AKI are reported to have a 13 times higher risk of death.[9,10]

At our medical center, our protocol for RDV allowed for use in patients with SRI in whom the potential benefit was deemed to outweigh the risk. Herein we report the liver and renal toxicities and clinical outcomes observed among patients with and without SRI that received RDV.

Methods:

This study was performed at single academic medical center in Chicago, IL. All patients admitted to the hospital between May 1, 2020 to October 31, 2020 that received RDV for the management of COVID-19 were included. Patients were excluded if they expired prior to completing RDV therapy. Patients with SRI at the time of RDV initiation were compared to those without SRI. SRI was defined as CrCl (calculated using the Cockroft-Gault equation) less than 30ml/min, or receipt of renal replacement with hemodialysis, peritoneal dialysis, or continuous renal replacement therapy. We

used CrCl as this is more relevant to dosing of medications in clinical practice, rather than eGFR used in product labeling to set the threshold for when to avoid RDV.

Outcomes evaluated included adverse events related to RDV, hepatotoxicity, and nephrotoxicity. RDV-related adverse events were defined as any adverse event report or documentation of an adverse event related to RDV in the electronic medical record. We tracked all patients receiving RDV on a daily basis, and consistent with the EUA, monitored for any toxicities and noted in our protocol that any adverse events thought to be related to RDV should be reported to the FDA and through our internal adverse event reporting system. Hepatotoxicity was defined as an increase in liver function tests (LFTs) to greater than 5 times ULN following RDV initiation. Nephrotoxicity was defined as an increase in serum creatinine by >/= 1.5 times baseline.

Criteria per our hospital protocol for RDV required all of the following: (1) documented hypoxia defined as oxygen saturation of less than or equal to 94% on room air or requirement of oxygen supplementation, mechanical ventilation or extracorporeal membrane oxygenation (ECMO) (2) chest imaging suggestive of viral pneumonia (3) having tested positive for SARS-CoV-2 within the prior 10 days (with the caveat that we may still consider RDV initiation outside of 10 days depending upon immune-compromised status or there is suspicion for re-infection). During the included time frame, our hospital protocol recommended that all patients meeting criteria for RDV receive 5 days of RDV with the option to consider extending to 10 days if poor response at day 5. Some patients did not complete a full 5 day duration if discharged home prior to the end of therapy. Use of RDV was also contraindicated if LFTs were > 5 times ULN during the included time-frame, however the threshold has since been modified to an ALT > 10 times ULN or ALT elevation is accompanied by signs or symptoms of liver inflammation, consistent the FDA labeling.[3] Our protocol also allows for

use of remdesivir regardless of CrCl. Of note, patients in this analysis received primarily the IV solution formulation, which contains 6g/100mg SBECD. The lyophilized formulation was reserved for pediatric patients <12 yo and pregnant patients.

From the electronic medical record the following data was collected retrospectively on all patients: age, gender, race/ethnicity, SARS-CoV-2 positivity date, date of admission, RDV duration, baseline oxygen status and oxygen status at time of RDV initiation if not started on day of admission, requirement of mechanical ventilation or ECMO at time of RDV initiation, decreased CrCl to <30 ml/min following RDV initiation, increases in SCr by >/= 1.5x baseline (SCr at the start of RDV), increases in LFTs to > 5 times ULN following RDV initiation, any report or notation in a progress note of an adverse event related to RDV, hospital length of stay, and mortality. Data collection was performed by three reviewers on the basis of a shared review protocol.

This project received a formal Determination of Quality Improvement status according to University of Chicago Medicine institutional policy. As such, this initiative was not considered human subjects research and was therefore not reviewed by the Institutional Review Board.

Statistical analysis:

Categorical data were analyzed with a Fisher's exact test or a Chi-Square test. Continuous data were analyzed by the Shapiro-Wilk test to determine if the data were normally distributed. Continuous data were analyzed with Student's t-test for parametric data or a Mann-Whitney U Test for non-parametric data. The significance level for all tests were set at alpha = 0.05. All statistical analyses were performed with STATA®, version 16, College Station, TX.

Results:

One-hundred and thirty-seven patients received a course of RDV between May 1, 2020 and October 31, 2020. Two patients were excluded who expired prior to the completion of RDV therapy, and neither patient had SRI. Among the included patients, 20 (14.6%) had either a CrCl of <30 ml/min (15, 75%) or had ESRD (5, 25%) requiring either intermittent hemodialysis or peritoneal dialysis at the time of RDV initiation. Of the 15 patients with a CrCl <30 ml/min, 13 presented with AKI on CKD, 1 AKI, and 1 CKD. Three of these 15 patients required renal replacement therapy (RRT) (2 CVVHD, 1 HD) during or within 24 hours from the end of RDV course. The two patients requiring CVVHD remained on RRT until they expired, and the patient requiring HD required two sessions 1 day apart, then no further dialysis was indicated. Baseline characteristics are shown in Table 1. Patients with SRI were older (70 years vs. 54 years, p=0.0001). The majority of patients in both groups were Black/African American. The median CrCl in the SRI group was 26 ml/min compared to 88 ml/min in the no SRI group (p<0.0001). The median baseline SCr was 2.6 (IQR 1.75-3.1) in the SRI group (of those not receiving RRT) compared to 0.9 (IQR 0.75-1.2) in patients without SRI. The median SCr at the end of RDV therapy was 1.8 (IQR 1.45-4.2) in patients with SRI (not receiving RRT) compared to 0.8 (IQR 0.7-1.1) among patients without SRI. Concomitant dexamethasone was given to 13 (65%) patients with SRI and 59 (51%) patients without, p=0.26.

Table 2 includes information on any adverse drug events that occurred after initiating RDV therapy in addition to observed clinical outcomes. No progress notes or adverse event reports implicated RDV as the direct cause of any adverse events. One adverse drug event report was filed, reporting LFT elevations following RDV during the dates included. Overall, a potential adverse drug event following RDV was present in 6 (30%) with SRI and 13 (11%) without, p=0.26. Two patients (10%) in

the SRI group had hepatotoxicity following the initiation of RDV. However, both were attributed to acute liver injury in the setting of septic and cardiogenic shock. In both cases LFTs peaked to AST/ALT 228/128 and 2403/393 on day 5 of RDV therapy. Five patients (4.3%) without SRI developed hepatotoxicity following RDV. In 4 of the 5 cases of LFT elevations following RDV, peak increases occurred at day 5 of therapy. In one patient, LFTs continued to increase 4 days after the end of RDV. In all cases regardless of SRI, LFT elevations were not attributed specifically to RDV , rather to a broad differential including COVID-19 itself. One patient without SRI also experienced LFT elevations post-RDV, also receiving furosemide and azithromycin, had complaints of bilateral hearing loss. Otolaryngology was consulted, however an audiogram and further evaluation was deferred given the patients COVID infection and clinical status at the time. No further follow-up was completed as the patient later expired. Elevations in SCr to >/= 1.5x baseline occurred in 4 (27%) patient with SRI (based on 15 patients not requiring RRT at baseline), and in 7 (6%) patients without, p=0.02. Among the 4 patients with SRI that experienced an elevation in SCr, 3 had acute kidney injury prior starting RDV. The 1 remaining patient experienced an increase in SCr on day 4 of therapy, and was noted to be secondary to clinical decompensation requiring vasopressor support. The median time from RDV initiation to an elevation in SCr to >/=1.5x baseline among those with SRI was 5 days, and 5 days among those without SRI.

Median length of stay was 8.5 days among those with SRI and 7 days in those without, p=0.01. Significantly more patients in the SRI group died compared to the no SRI group (5 (25%) vs. 4 (3.5%), p=0.004). Autopsy results and noted cause of death among those with SRI that expired following RDV are noted in Table 3. The remaining 15 (75%) patients in the SRI group were discharged, and 101 (87%) without SRI have been discharged with 10 patients still admitted to the hospital as of October 31, 2020.

Discussion:

In our cohort of 20 patients with SRI, 2 (10%) of the patients experienced LFT elevations possibly related to RDV, and 4 (20%) had SCr elevations following RDV. However, the LFT abnormalities were not attributed to RDV as the primary cause in either case and 3 of 4 patients with SCr elevations while on therapy were in AKI prior to the initiation of RDV. These data are consistent with observed incidence of ALT elevation in 2-7% and AST elevation in 3-6% of patients who received RDV in investigational trials and the overall incidence of LFT abnormalities of 11.7% in patients who received RDV through expanded access.[3,11] Our observed rate of SCr elevations (27%) in those with SRI is higher than clinical trial data, that identified an incidence of 10-15%, however clinical trials primarily excluded patients with CrCl <30-50 ml/min.[2,3] Compared to the 115 patients that received RDV without SRI, the overall rate of possible adverse events secondary to RDV was not significantly different (30% vs. 11%, p=0.26). Importantly, it should be noted that COVID-19 itself is also known to be associated with increases in LFTs as well as AKI.[7,12,13] Therefore the ability to differentiate if the observed LFT or SCr elevations were related to COVID-19 versus RDV is difficult.

The mortality rate in the SRI group was higher than among those without SRI (25% vs. 3.5%, p=0.004). A higher mortality among COVID-19 patients with SRI has been reported by numerous investigators.[14,15] As such, the higher mortality may be more likely related to SRI and ESRD themselves. AKI and ESRD have also been associated with higher incidence of cardiac toxicity, venous thromboembolism, and bacterial coinfections in our cohort and in other studies.[7,13] It is possible that worse outcomes among those with AKI or ESRD are related to these additional complications. The higher mortality among people with COVID-19 and ESRD argues for greater urgency in the use of RDV to reduce the time to recovery. It also suggests SBECD toxicity should only

prevent the use of RDV if the evidence for its additional toxicity are a more compelling threat to patient's morbidity and mortality than COVID-19 itself. It is also evident from the autopsy and cause of death information in Table 3 that the patients in the SRI group that expired had other reasons for the poor outcome.

The primary concern regarding the use of RDV in the setting of CrCl <30 ml/min as mentioned is the concern for SBECD accumulation. Several clinical studies have evaluated the use of intravenous (IV) voriconazole in setting of AKI and in patients requiring renal replacement therapy, which also is formulated with SBECD, and have found no association with adverse events or untoward outcomes.[16-19] A 200mg voriconazole IV dose contains 3.2 grams SBECD, therefore patients, for example, receiving 200mg q12hrs (a commonly employed maintenance dose) each day is receiving 6.4 grams per day.[20] Comparatively, the lyophilized formulation of RDV contains 3 grams and IV solution formulation contains 6 grams of SBECD, per 100mg.[3] In this study, all patients in the SRI group received the IV solution formulation.

If a dose of 6.4 grams SBECD per day with use voriconazole has not been associated with enhanced adverse events due to accumulation of the diluent, it stands to reason that a dose of 6 grams daily with RDV will not result in untoward SBECD associated toxicity.

Ultimately, the amount of SBECD in IV voriconazole and RDV is well below the maximum recommended daily dose of approximately 250mg/kg, based on European Medicines Agency recommendations.[21]

It should be noted that while RDV has only minor renal excretion (<10%), that 49% of GS-441524 the RDV metabolite, is found in the urine. SRI could result in increased plasma concentrations of this metabolite, however the implications of this are unknown.[22] No studies to date have evaluated the

pharmacokinetics of RDV in the setting of SRI and clinical trials published to-date excluded patients with CrCl <30 to <50 ml/min.[2,23,24] Only one study, previously mentioned, has been published regarding the pharmacokinetics of RDV in the setting hemodialysis as observed in a single patient.[6]

There are several limitations to this analysis. The small sample size limits interpretation of the overall rate of potential toxicities and clinical outcomes observed. Retrospective data collection can also introduce the potential for bias and may be limited based on documentation in the electronic medical record. Additionally, identifying whether the observed increases in LFTs or SCr were an artifact of COVID-19 versus RDV is difficult to differentiate, as we know the disease state itself is associated with hepatotoxicity and nephrotoxicity. Patients were also not matched according to severity of illness or other markers for poor prognosis among patients with COVID-19 which could introduce bias. However, we did follow our inpatient protocol outlining criteria for RDV use consistently, as all RDV required review by an Infectious Diseases physician or pharmacist. Therefore all patients met, at a minimum, the definition for moderate disease. At present, the ID Consult Service continues to recommend RDV in patients with SRI in whom the benefit is deemed to outweigh the risk based on these findings and emerging reports in the literature.[5]

At best, the concern for RDV use in the setting of SRI appears theoretical, and should not in our opinion, preclude the consideration to give RDV to hospitalized patients with COVID-19. Our study provides some evidence that RDV-related toxicities in patients with COVID-19 and SRI are similar to those seen in COVID-19 patients without SRI, and that a signal of increased or unexpected toxicities due to SBECD was not observed. In the setting of the COVID-19 pandemic where we have few therapeutic options, we must be able to weigh the benefits versus risks when considering whether to give RDV in patients with SRI as these individuals are at greater risk for severe disease and poor

outcomes. We recommend shared decision making in these settings, where the potential risk of using RDV is discussed with the patient and/or caregiver and an informed decision is made regarding whether the potential risk is outweighed by the potential benefit. Studies evaluating the safety of RDV in the setting of impaired renal function are urgently needed to better define the risk.

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Table 1: Baseline Characteristics

	SRI (N=20)	No SRI (N=115)	p-value
Age, mean ± standard deviation	70 ± 15.8	54 ± 16	0.0001
Gender, M (%)	8 (40)	57 (50)	0.43
Race/Ethnicity (%)			--
Black/African American	17 (85)	81 (70)	0.18
Hispanic/Latino	2 (10)	9 (8)	0.67
White	0 (0)	14 (12)	0.13
Other/unknown	1 (5)	11 (10)	>0.99
O2 requirement (%)*			--
RA <=94%	1 (5)	11 (10)	0.70
1-3L NC	10 (50)	50 (43)	0.80
4-6L NC	5 (25)	27 (23)	0.90
BiPAP	0 (0)	2 (2)	>0.99
HFNC	2 (10)	17 (15)	0.74
Mechanical Ventilation	2 (10)	8 (7)	0.64
CrCl (ml/min), median	26 (21, 28)	88 (63, 100)	<0.0001
ESRD (iHD or PD) (%)	5 (25)	0 (0)	0.0001
AST (U/L), median	53 (34, 64)	44 (29, 55)	0.25
ALT (U/L), median	29 (22, 37)	38 (19, 46)	0.60
RDV duration, median (IQR)	5 (5, 5)	5 (5, 5)	0.97
Concomitant Dexamethasone (%)	13 (65)	59 (51)	0.26

*O2 requirement at time of Remdesivir initiation

Table 2: Adverse Events and Clinical Outcomes

	SRI (N=20)	No SRI (N=115)	p-value
Any adverse drug event	6 (30)	13 (11)	0.26
Transaminitis	2 (10)	5 (4)	0.28
Hearing loss	0 (0)	1 (0.9)*	>0.99
Serum Creatinine (SCr) elevation†	4 (27)‡	7 (6)	0.02
Length of stay, median (IQR)	8.5 (8, 13)	7 (5, 10)	0.01
Mortality (%)	5 (25)	4 (3.5)	0.004

* One patient had both LFT elevation and hearing loss

† SCr elevation of >/=1.5 times baseline

‡ 3 of 4 patients in AKI prior to starting RDV, the remaining 1 patient had AKI secondary to clinical decompensation resulting in vasopressor administration, excluding patients on RRT at baseline, n=15

Table 3: Autopsy results and reported cause of death among patients with SRI who received RDV

Patient		CrCl at start of RDV course (ml/min)	AST/ALT at start of RDV course (U/L)	Time from EOT RDV to Death
		CrCl at RDV EOT (ml/min)	AST/ALT at RDV EOT (U/L)	
1*	No autopsy done. Cardiac (PEA) arrest in setting of acute right heart failure and PEA arrest.LFTs within normal limits prior to arrest	16	71/36	2 days
		24	228/128	
2*	No autopsy done. Evidence of hypoxic brain injury on arrival. Sustained tachyarrythmias which required multiple synchronized cardioversions. Ultimately developed mixed shock (cardiogenic and distributive) refractory to six vasoactive agents. LFTs within normal limits prior to multi-organ system failure.	ESRD, iHD	43/34	1 day
		CRRT	2402/393	
3	Autopsy completed. Cause of death determined as cardiac and respiratory failure secondary to COVID-19 pneumonia. Chronic kidney disease, hypertension, and obesity may have been contributing or predisposing factors. No evidence of hepatic necrosis or renal tubular obstruction were noted on autopsy.	18	45/16	3 days
		8.6	122/34	
4	No autopsy done. Acute hypoxic respiratory failure secondary to COVID-19 pneumonia. Patient made comfort care after oxygen status worsened after completing RDV and patient could not tolerate noninvasive oxygen supplementation	10	53/24	7 days
		8	61/32	
5	No autopsy done.	19	77/48	1 day

	Acute respiratory failure and severe ARDS secondary to COVID-19 pneumonia.Suffered multiple cardiac arrests in setting of profound hypoxemia before expiring.	12	98/48	

EOT: End of therapy, RDV: Remdesivir, ARDS: Acute Respiratory Distress Syndrome

* Patients 1 and 2 had LFT elevations to >5 x ULN following initiation of RDV, patient #1 peak AST and ALT (228 and 128) and patient #2 peak AST and ALT (2403 and 393).