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Original Article

Renal and Hepatic Outcomes after Remdesivir Therapy in Coronavirus Disease-2019-Positive Patients with Renal Dysfunction at Baseline or after Starting Therapy

Ahmad Shakir, Nikhil Bhasin, Rudramani Swami, Kalpana Mehta, Smriti Sinha, Sayed Salman Ali, Jyoti Bansode

Department of Nephrology, Topiwala Nair Medical College and BYL Nair Hospital, Mumbai, Maharashtra, India

ABSTRACT. We aimed to study the effect of remdesivir therapy on renal and hepatic function in coronavirus disease-2019 (COVID-19) patients with renal dysfunction at baseline or after starting therapy and identify the factors, if any, related to the efficacy of remdesivir therapy on patient outcome. Patients included in the study were those who met all the following criteria irrespective of baseline glomerular filtration rate [including those already on maintenance hemodialysis (HD)] or baseline deranged liver function test. (1) Age >18 years, (2) COVID-19 reverse transcriptase-polymerase chain reaction positive, (3) Meeting criteria for administration of remdesivir – [any one of the following: (a) COVID-19 pneumonia with respiratory rate >30/min or SPO_2<94% on room air, (b) Acute respiratory distress syndrome (ARDS)]. (4) Renal dysfunction at baseline, during or within 48 h of completion of therapy. Thirty-four patients had renal dysfunction at baseline or developed it after remdesivir therapy – 16 were acute kidney injury (AKI), 10 chronic kidney diseases (CKD), four CKD stage 5D, and four were postrenal transplant. The overall mortality was 18/34 (52.9%). Eight out of 30 (26.66%) needed HD during or after therapy and of these, 15 died and among 15 survivors, 14 returned to their baseline renal function after cessation of therapy, one patient is still dialysis dependent. In the dialysis-dependent CKD (n = 4) subgroup, three died and one was discharged. In the postrenal transplant (n = 4) group, all developed AKI during or after the completion of therapy. None required HD, two returned to their baseline renal function, and two died. Only five had alanine aminotransferase elevation (×1 upper limit of normal) during or within 48 h of completion of therapy – three died and two returned to baseline. Lower PaO_2/FiO_2 (severe ARDS) (P = 0.0001), higher C-reactive protein (P = 0.022), higher serum lactate dehydrogenase (P = 0.038), and duration of symptoms before starting therapy (P = 0.05) were statistically significant variables at baseline associated with higher mortality. Remdesivir can be tried

Correspondence to:

Dr. Kalpana Mehta,
Department of Nephrology, Topiwala Nair Medical College and BYL Nair Hospital, Mumbai, Maharashtra, India.
E-mail: kalpana.drs@gmail.com

in moderate-to-severe COVID-19 cases with renal dysfunction as a complete recovery of renal function was noted in survivors. However, larger and well-controlled studies evaluating its safety and efficacy in patients with AKI and CKD are needed.

Introduction

The presence of acute kidney injury (AKI) and chronic kidney diseases (CKD) has been shown to have a higher morbidity and mortality in patients infected with the novel coronavirus.[1,2] Various drugs have been tried since the pandemic broke out, but only a few have shown benefit in clinical trials. Remdesivir is a nucleotide analog that inhibits viral RNA-dependent RNA polymerase and was given an emergency use authorization by the United States Food and Drug Administration (USFDA) in May 2020.[3] Active metabolite of remdesivir is eliminated by kidney and can accumulate in patients with reduced estimated glomerular filtration rate (eGFR); moreover, the sulfobutylether-β-cyclodextrin (SBECD) carrier is also known to accumulate in these patients. The drug's potential toxicity in patients with kidney disease relates both to remdesivir's actions and to the potential accumulation of SBECD. Animal studies have associated SBECD accumulation with liver necrosis and renal tubule obstruction.[4] Increased aminotransferase levels and AKI with remdesivir have been noted in animal studies and human clinical trials.[4] Under the emergency use authorization, liver function tests (LFTs) must be monitored daily, and remdesivir is discontinued in patients with alanine aminotransferase more than five times the upper limit of normal (ULN).[5]

The Adaptive COVID-19 Treatment Trial (ACTT-1), a study sponsored by the US National Institutes of Health, found a significant benefit in time to recovery evaluating the use of this agent in coronavirus disease-2019 (COVID-19). However, it excluded patients with stage 4 CKD or those requiring dialysis (i.e., eGFR <30).[6] Ours was the first dedicated COVID-19 hospital (with attached medical college) in a large metropolitan city. Large inflow of moderate-to-severe COVID-19 patients in early phase of the pandemic with dynamic guidelines for this novel disease and nonavailability of drugs resulted in high morbidity and mortality. As per Adamsick et al,[5] conclusive data on the safety of remdesivir among individuals with eGFR <30 mL/min/1.73 m^2 are lacking. Nevertheless, the limited duration of treatment (5–10 days) and relatively low concentration of SBECD carrier suggest that its benefits may outweigh risk in selected patients with eGFR <30 mL/min/1.73 m^2. We used remdesivir in our COVID-19 patients with renal dysfunction after approval from our hospital COVID-19 protocol committee as it was a life-saving option in the pandemic situation with very few other treatment options available. Through this small study, we report our findings of remdesivir therapy on renal and hepatic function, in patients with AKI or CKD at baseline or after starting therapy.

Aims of the Study

Our research aimed to study the effect of remdesivir on renal and hepatic function in COVID-19-positive patients with renal dysfunction at baseline or after starting therapy and to identify factors, if any, related to efficacy of remdesivir therapy on patient outcome.

Materials and Method

Study design

It is a prospective interventional study conducted at the Topiwala Nair Medical College and BYL Nair Hospital in Mumbai, India, from July 30 to November 7, 2020. The study was started after obtaining permission from the Institution's Ethics Committee. All patients admitted during this period and passed the inclusion criteria were studied. Baseline characteristics of all patients including demographic variables, comorbidities, laboratory investigations, serum lactate dehydrogenase (LDH), inflammatory markers such as C-reactive protein (CRP), interleukin-6, serum

ferritin, and D-Dimer and mode of oxygenation were noted. High-resolution computed tomography (CT) of the thorax was done in all, and CT staging (CORADS staging with severity index) was also noted. All patients meeting criteria for administration of remdesivir were given the drug as per the GFR protocol of our department (see remdesivir dosing below). Written informed consent was obtained in all patients, with risks explained, especially in patients with deranged renal and/or hepatic function at baseline. Patients were observed for their renal and hepatic function after completion of remdesivir therapy, and till the period of admission including requirement of hemodialysis (HD), if any. The final patient outcome was also recorded.

Remdesivir

Remdesivir available as DESREM – as lyophilized vial (100 mg/vial) manufactured by MYLAN Ltd, under license from Gilead Sciences, Inc. USA]. Patients with eGFR >30 mL/min were given 200 mg on Day 1, followed by 100 mg per day, daily, for four days. Those with eGFR <30 mL/min, but not on dialysis, were given 200 mg on day 1, followed by 100 mg alternate day for four doses (in CKD patients with eGFR <30 mL/min not on dialysis, we decided to give remdesivir on alternate days to see if there is any further worsening of renal function on the day the drug was not given), while those on dialysis were given 200 mg on day 1, followed by 100 mg per day, daily for four days.

Inclusion criteria

Patients who met all the criteria listed below were included in the study:

1. Age ≥18 years
2. COVID-19 reverse transcriptase–polymerase chain reactionpositive
3. Meeting criteria for administration of remdesivir (any one of the following)
   a. COVID-19 pneumonia with respiratory rate >30/min or SPO2<94% on room air
   b. Acute respiratory distress syndrome (ARDS).
4. All patients having renal dysfunction at baseline or during remdesivir therapy or within 48 h of completion of therapy.

Exclusion criteria

The following patients were excluded from the study:

1. Those who are below 18 years old
2. Patients not having any renal dysfunction at baseline or during remdesivir therapy or within 48 h of completion of therapy
3. Alanine aminotransferase (ALT)/aspartate aminotransferase (AST) more than 5 times the ULN
4. Mild COVID-19 cases not meeting the criteria for administration of remdesivir.

Statistical Analysis

Data were expressed as mean ± standard deviation for continuous variable and median (interquartile range) for categorical variable. The correlation of two groups was performed using Spearman's correlation test. P <0.05 was taken as significant. Statistical analyses were performed using IBM SPSS Statistics for Windows version 21.0 (IBM Corp., Armonk, NY, USA).

Results

A total of 3485 COVID-19 patients were admitted to our hospital from July 30 to November 7, 2020. Out of these, 1514 patients received remdesivir. Out of these, 34 patients had renal dysfunction at baseline or developed it after remdesivir therapy. The mean age was 58.65 ± 12.59 years (27–90 years) with 23 (67.6%) males. Out of these, 16 patients were AKI, 10 were CKD (stage 3-5), four were CKD stage 5D, and four were postrenal transplant. The baseline patient characteristics were hypertension – 27 (79.4%), diabetes – 19 (55.9%), coronary artery disease – five (14.74%), and hepatitis C in one patient. Mean baseline serum creatinine (SCr) in the cohort group before remdesivir therapy was 2.23 ± 1.64 mg/dL (0.7–7 mg/dL). Mean baseline AST was 28.52 ± 13.10U/L (13–78 U/L) and

ALT was 28.08 ± 12.60 U/L (10–80 U/L). The mean neutrophil-to-lymphocyte ratio was 16.24 ± 12.82 (0.96–51). The mean LDH was 887.68 ± 471.17 U/L (1423–2013 U/L), M = mean D-Dimer was 269.72 ± 605.96 ug/mL (0.13–2092 ug/mL), mean CRP was 74.95 ± 64.26 mg/L (43–316 mg/L), mean ferritin was 1739.03 ± 1980.57 ng/mL (152-10968 ng/mL), and mean IL-6 was 1079.64 ± 1585.28 pg/mL (63–6515 pg/mL). Before remdesivir therapy, ARDS severity was mild – four (11.76%), moderate – 14 (41.17%), and severe – 16 (47.05%). Eleven (32.35%) patients were on BMV, 13 (38.23%) were on continuous positive airway pressure, and 10 (29.41%) were on invasive ventilation. The mean duration of symptom onset before starting remdesivir therapy was 6.79 ± 2.23 days (13–12 days). Remdesivir dose (600 mg) was completed in all except five patients who expired before completion of therapy. None of the patients experienced infusion reactions. Patients were discharged after they were clinically stable (no oxygen requirement) with clearance documented on chest X-ray. The mean follow-up was 15.2 days (3–42 days). Repeat inflammatory markers could not be done in all, more so when improvement was seen.

The overall mortality was 18/34 (52.9%) (Table 1).

Renal Outcome

Eight out of 30 (26.66%) patients needed HD during or after remdesivir therapy, four were already on HD before therapy (all were CKD stage 5D). Fourteen out 30 (46.66%) patients returned to their baseline renal function after cessation of remdesivir therapy, one patient is still dialysis dependent, and 15 died. In the AKI (n = 16) subgroup, two (12.50%) were Kidney Disease Improving Global Outcomes (KDIGO) stage 1 AKI, five (31.25 %) were KDIGO stage 2, and nine (56.25%) were KDIGO stage 3. The mean baseline SCr was 1.52 ± 1.50 mg/dL (0.7–7 mg/dL), mean peak SCr during or after completion of remdesivir therapy was 3.45 ± 1.87 mg/dL (1.7–9.2 mg/dL). Four of 16 (25%) patients needed HD. Nine (56.25%) patients died, of which three died while on HD. All the seven survivors returned to their baseline renal function and were discharged (Figure 1). In the nondialysis-dependent CKD (n = 10) subgroup, two were KDIGO stage 3, six were KDIGO stage 4, and two were KDIGO stage 5. The mean baseline SCr was 3.49 ± 1.4 mg/dL (1.5–5.4 mg/dL), mean peak SCr during or after completion of remdesivir therapy was 5.44 ± 2.05 mg/dL (2.3–9.2 mg/dL). Four of 10 (40%) patients needed HD. Six patients (60%) survived and four (40%) died. Of four who died, two died while on HD. Five out of the six survivors returned to their baseline renal function and only one patient is dialysis dependent at present (Figure 2). In the dialysis-dependent CKD (n = 4) subgroup, three patients died and one was discharged. In the postrenal transplant (n = 4) group, two patients were on tacrolimus, mycophenolate mofetil (MMF), and prednisolone; one was on everolimus, MMF, and prednisolone; and one was on sirolimus, MMF, and prednisolone. None had cytomegalovirus infection; other opportunistic investigations were not done. All developed AKI during or after completion after remdesivir therapy. None required HD, two returned to their baseline renal function after completion of therapy, while the other two patients died.

Hepatic outcome

Two patients had hepatic dysfunction at baseline (ALT elevation ×1 ULN), both were CKD stage 5D and both died. Five patients had hepatic dysfunction (ALT elevation ×1 ULN) during or within 48 h of completion of remdesivir therapy – three were AKI and two were CKD. Of these, three died and two returned to baseline. No patient had a severe rise in AST/ALT (>5 times ULN); hence, therapy was not required to be discontinued for this reason in any of the patients (Table 2).

Baseline factors influencing final patient outcome

On comparing the deceased versus the survivors, lower PaO_2/FiO_2 (severe ARDS)

Table 1. Mean baseline demographic characteristics and factors influencing final patient outcome.

Variables	Name of subgroup	Total (*n*=34)	Died (*n*=18)	Survivors (*n*=16)	Correlation	*P*
Age (years)		58.65±12.59	62.00±12.98	54.88±11.34	−0.226	0.20
Gender	Female	11 (32.4%)	7 (38.9%)	4 (25.0%)	0.148	0.403
	Male	23 (67.6%)	11 (61.1%)	12 (75.0%)		
Hypertension	Yes	27 (79.4%)	14 (77.8%)	13 (81.3%)	−0.043	0.810
	No	7 (20.6%)	4 (22.2%)	3 (18.8%)		
Diabetes mellitus	Yes	19 (55.9%)	8 (44.4%)	11 (68.8%)	−0.244	0.164
	No	15 (44.1%)	10 (55.6%)	5 (31.3%)		
Coronary artery disease	Yes	5 (14.7%)	4 (22.2%)	1 (6.3%)	0.225	0.201
	No	29 (85.3%)	14 (77.8%)	15 (93.8%)		
Renal dysfunction	AKI	16 (47.1%)	9 (50.0%)	7 (43.8%)	0.060	0.738
	CKD	14 (41.2%)	7 (38.9%)	7 (43.8%)		
	Transplant	4 (11.8%)	2 (11.1%)	2 (12.5%)		
Severity of ARDS	Mild	4 (11.8%)	0 (0.0%)	4 (25.0%)	−0.575	**0.0001**
	Moderate	14 (41.2%)	5 (27.8%)	9 (56.3%)		
	Severe	16 (47.1%)	13 (72.2%)	3 (18.8%)		
	Pao2/Fio2	133.95±71.31	98.72±51.86	173.60±70.52	0.505	**0.002**
Mode of oxygenation	BMV	11 (32.4%)	2 (11.1%)	9 (56.3%)	−0.565	**0.001**
	CPAP	13 (38.2%)	7 (38.9%)	6 (37.5%)		
	Invasive	10 (29.4%)	9 (50.0%)	1 (6.3%)		
Inflammatory markers	NLR	16.24±12.82	18.23±14.19	14.00±11.10	−0.132	0.456
	D-Dimer (ug/mL)	269.72±605.96	287.11±571.85	250.15±660.64	−0.045	0.80
	CRP (mg/L)	74.95±64.26	89.94±64.58	58.07±61.52	−0.391	**0.022**
	LDH (U/L)	887.68±471.17	1046.72±447.09	708.75±303.05	−0.358	**0.038**
	IL-6 (pg/mL)	1079.64±1585.28	1345.33±1963.99	780.74±988.58	−0.159	0.369
	Ferritin (ng/mL)	1739.03±1980.57	1810±1131.14	1659.13±2677.12	−0.321	0.064
Duration of symptoms before remdesivir (Days)		6.79±2.23	7.56±2.31	5.94±1.84	−0.337	**0.051**
Renal function	SCr before initiation of remdesivir (mg/dL)	2.23±1.64	2.39±1.79	2.07±1.53	−0.104	0.584
Hepatic function	Baseline AST before initiation of remdesivir (U/L)	28.52±13.10	30.60±17.32	25.06±8.13	−0.127	0.475
	Baseline ALT before initiation of remdesivir (U/L)	28.08±12.60	29.94±20.72	26.00±7.71	0.024	0.892

AKI: Acute kidney injury, CKD: Chronic kidney disease, ARDS: Acute respiratory distress syndrome, CPAP: Continuous positive airway pressure, NLR: Neutrophil-to-lymphocyte ratio; IL-6: Inteleukin-6, CRP: C-reactive protein, LDH: Lactate dehydrogenase, SCr: serum creatinine.

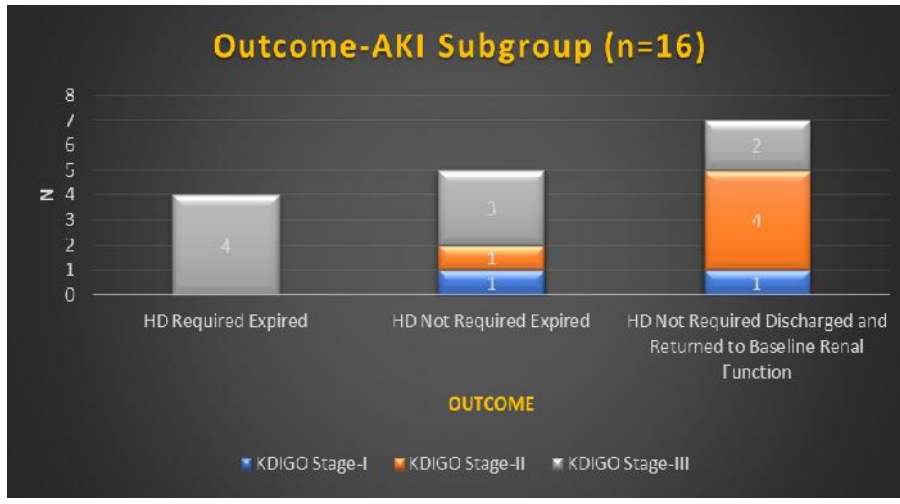

Figure 1. Renal outcome – acute kidney injury subgroup.

AKI: Acute kidney injury, HD: Hemodialysis, KDIGO: Kidney Disease Improving Global Outcomes.

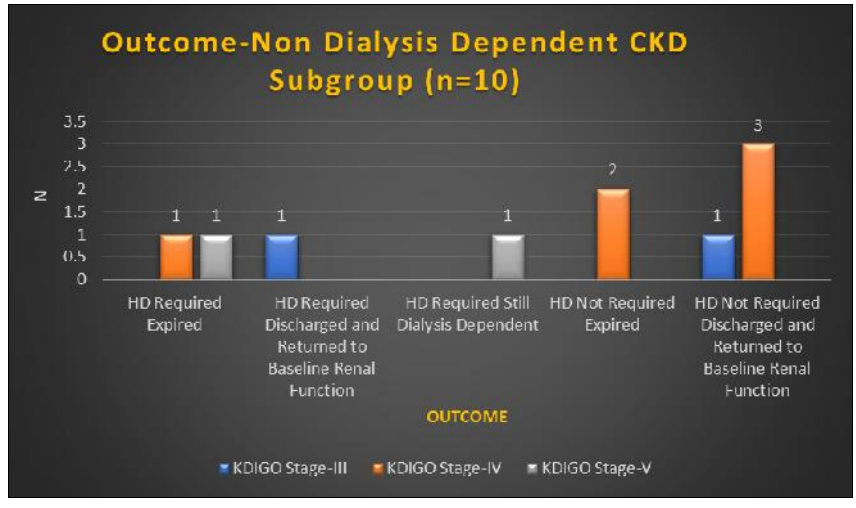

Figure 2. Renal outcome-nondialysis-dependent CKD subgroup

CKD: Chronic kidney disease, HD: Hemodialysis, KDIGO: Kidney Disease Improving Global Outcomes.

Table 2. Hepatic outcome after remdesivir therapy.

Variable/Subgroup	Hepatic dysfunction at baseline	Hepatic dysfunction after remdesivir therapy
Number	2	5
Acute kidney injury		3
Chronic kidney disease	2	2
Chronic kidney disease stage 5D	2	0
Hemodialysis required		1
Outcome		
Expired	2	3
Discharged		2
Returned to baseline		2

(P = 0.0001), higher CRP (P = 0.022), higher serum LDH (P = 0.038), and duration of symptoms before starting remdesivir therapy (P = 0.05) were statistically significant variables at baseline associated with higher mortality (Table 1).

Discussion

Remdesivir, first developed by Gilead pharmaceuticals, has been used to treat a wide range of viruses, such as severe acute respiratory syndrome, Middle East respiratory syndrome, and also the recent Ebola virus epidemic in West Africa.[7] The FDA has authorized the emergency administration of remdesivir to treat hospitalized patients with COVID-19 in the United States based on the results of the ACTT-1 study which showed that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection. However, it excluded patients with stage 4 CKD or those requiring dialysis (i.e., eGFR <30).[6] Remdesivir is administered intravenously. It has limited water solubility and is given with a cyclodextrin carrier. Each 100 mg of remdesivir powder contains 3 g of cyclodextrin and the solution contains 6 g. In addition, based on the experience with voriconazole, both dialysis and continuous renal replacement therapy should effectively remove cyclodextrin.[5] This carrier is filtered solely by the glomeruli; hence, patients with normal renal function eliminate it quickly. However, patients with AKI or CKD are at risk of cyclodextrin accumulation.

Since remdesivir has limited aqueous solubility, SBECD is applied in the formulation process as a solubilizing agent. However, SBECD has a route of renal excretion and patients with moderate-or-severe renal impairment can have significant exposure to SBECD. Hence, close eGFR monitoring is needed at the time of administration of remdesivir, especially in patients with renal dysfunction. Remdesivir has been contraindicated in patients with severe renal impairment (eGFR less than 30 mL/min).[8] According to the Gilead company product declaration, laboratory abnormalities during the phase 1 trials were increased liver enzymes, coagulopathy, and blood sugar in <5% of the patients. In addition, serious adverse events were septic shock and AKI in 23% of cases, in such a way that 8% of the patients discontinued because of the side effects after the use of remdesivir.[9]

Very few studies have evaluated the effect of remdesivir therapy in patients with renal dysfunction (AKI or CKD) at baseline. In an early study, Wang et al[10] showed that out of the 61 subjects who received remdesivir, renal impairment developed only in seven patients, and all required invasive ventilation. In a systematic review and meta-analysis "Whether Remdesivir Increases the Risk of AKI in Patients with COVID-19" published online in Research Square,[11] two RCTs[12,13] were analyzed. Meta-analysis showed that compared with COVID-19 patients without remdesivir treatment, the remdesivir treatment did not increase the risk of AKI in COVID-19 patients showing OR 0.80 (95%CI: 0.44–1.46, P >0.05) and these two studies showed no significant heterogeneity in their study populations. In a recent study carried out in Mumbai, Thakare et al[14] showed that out of the 46 patients with renal dysfunction who received remdesivir, no renal function abnormalities attributable to drug were observed, and only three patients were found to have newly occurring grade 1 elevations of AST/ALT during therapy. However, a limitation of this study was that most of the patients were already on HD prior to administration of remdesivir. In another recent study by Estiverne et al,[15] 18 patients with eGFR <30 mL/min/1.73 m^2 or on renal replacement therapy received remdesivir – none had high-grade ALT elevations attributed to remdesivir. The majority of patients had improving kidney function, though in one case, worsening Cr was attributed as likely related to remdesivir by a study investigator. In another study from India by Aiswarya et al,[16] remdesivir given in 48 patients on HD resulted in no alteration in LFTs and when initiated within 48 h of

hospitalization showed reduction in the mean duration of hospitalization by 5.5 days; however, no mortality benefit was observed.

In our study, the overall mortality was52.9% (18/34), which is comparable to that reported for inpatients with COVID-19 and stage 3 AKI (54%–60%) or baseline end-stage renal disease (ESRD) (31%).[1,17,19] Although AKI could have been multifactorial in nature and just not attributed to remdesivir therapy, in the AKI subgroup, all seven survivors recovered to their baseline renal function after completion of therapy. Similarly, in the CKD subgroup, five out of the six survivors returned to their baseline renal function and only one became dialysis dependent. In the transplant subgroup, though all four patients developed AKI, both the survivors recovered to their baseline renal function without requiring dialysis support. So even our experience is consistent with the available reports mentioned above suggesting considerable safety of remdesivir in patients with renal dysfunction. However, still larger studies are required to make a strong recommendation. As far as hepatic safety is concerned, in our study, only five patients had mild hepatic dysfunction (ALT elevation ×1 ULN) during or within 48 h of completion of remdesivir therapy – of which both survivors returned to their baseline. No patient had a severe rise in AST/ALT (>5 times ULN); hence, therapy was not required to be discontinued for this reason in any of the patients. This is also comparable to the hepatic outcomes in the studies mentioned above.

Furthermore, comparing the deceased versus the survivors, lower PaO2/FiO2 (severe ARDS) (P = 0.0001), higher CRP (P = 0.022), higher serum LDH (P = 0.038), and duration of symptoms before starting remdesivir therapy (P = 0.05) were statistically significant variables at baseline associated with higher mortality.

Conclusion

The overall mortality was 52.9% (18/34), with nonsurvivors having statistically significant poor prognostic indicators: severe ARDS, higher inflammatory markers, and duration of symptoms before remdesivir therapy. All AKI survivors showed complete recovery of renal function. All, except one, among CKD survivors showed return of SCr to baseline. Only five patients developed mild hepatic dysfunction. Remdesivir can be tried in moderate-to-severe COVID 19 cases with renal dysfunction, as complete recovery of renal function was noted in survivors. However, larger, well-controlled studies evaluating its safety and efficacy in patients with AKI and CKD are needed.

Limitations of Study

Our study though had several limitations. The study population was small – 34 cases, a single-center study, and there was no control group taken. Renal biopsy could not be performed in any of the cases. However, it included patients with AKI, CKD, and ESRD on dialysis as well as transplant patients. A multicenter blinded randomized control trial with a larger sample size would be ideal to make a strong recommendation. However, through our study, we still hope to provide some help to treating clinicians who are faced with the dilemma whether or not to initiate remdesivir therapy in patients with renal dysfunction.

Conflict of interest: None declared.

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