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"SAFETY AND TOLERABILITY OF REMDESIVIR IN PATIENTS WITH ACUTE OR CHRONIC KIDNEY DISEASE-A RETROSPECTIVE STUDY"

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ABSTRACT **BACKGROUND** Remdesivir has been recommended for hospitalized patients with COVID-19 pneumonia. Due to lack of safety data, it is not used in patients with severe renal impairment. Our objective was to assess its safety in patients with renal dysfunction and to describe clinical outcome. **METHODOLOGY** Here we present retrospectively collected data of covid 19 positive admitted patients who received remdesivir from March to December 2020 with evident renal dysfunction (Group 2) and without renal dysfunction (Group 1) prior to drug initiation**RESULT** We found 104 and 150 patients in group 1 and 2 respectively. Mean age of patients was 62.5 ±14.3 and 60.4 ±13.4 years respectively. Median charlson comorbidity index was 2.66 and 3.07 respectively. Mean(±SD) baseline oxygen saturation was 86.54%(±12.55) and 88%(±11.65) respectively. Total 25% patients developed AKI in group 1 with requirement of renal replacement therapy in 7.7% patients while in group 2, total 103 patients had AKI prior to remdesivir use with 40.78% had worsening renal function while 59.22% improved to normal after remdesivir use. Requirement of RRT was in 19% of patients. Only 6% patients had significant elevations in liver enzymes. Mortality was seen in 33.65% and 38% in group 1 and 2 respectively. **CONCLUSION** Use of remdesivir in impaired renal function group lead to increased creatinine and more requirement of dialysis **(p= 0.018 and 0.019 -statistically significant)** but without increased risk of hepatotoxicity. AKI in covid is multifactorial, related more with disease severity, prothrombotic phase, underlying CKD and not solely due to drug use. Mildly raised liver enzymes should not be contraindication for its initiation. Use of Remdesivir in CKD patients on maintenance hemodialysis and in patients with mild AKI should not be precluded. However, it should be used only if benefit outweigh risk in presence of moderate to severe renal impairment not on hemodialysis.

KEYWORDS : Acute kidney injury, Covid 19, End stage renal disease, Remdesivir

INTRODUCTION

Patients with chronic kidney disease(CKD), especially those with end-stage renal disease (ESRD), are highly susceptible to the development of severe COVID-19 which is associated with high mortality [1]. Similarly, incidence of acute kidney injury(AKI) in hospitalized patients with severe covid 19 infection is high and it is associated with grave prognosis.[2,3,4]

Till date so many drugs have been tried in various trials for the treatment of covid 19 infection. Even after 15 months since inception of pandemic, no single agent except steroid found to have substantial role in severe covid 19 disease management. Remdesivir (GS-5734), a prodrug of adenosine analogues, has been shown to have antiviral activity against several RNA viruses, including MERS-CoV, Ebola virus and SARS-CoV-2.[5]. In a study by J.H. Beige et al, remdesivir was superior to placebo (11 versus 15 days; hazard ratio, 1.31; 95% confidence interval, 1.12 to 1.54; **p-0.001**) in shortening the time to recovery in patients with COVID-19 and evidence of lower respiratory tract infection.[6] Overall mortality among patients treated with remdesivir was 8.0% compared with 11.6% among those treated with placebo (P=0.59). [7]

BACKGROUND / RATIONALE

On May 1, 2020, after review of various published and unpublished data from available clinical trials, the US Food and Drug Administration (US FDA) issued an emergency use authorization (EUA) to permit the use of remdesivir that inhibits viral RNA-dependent RNA polymerase (RDRP), for treatment of severe coronavirus disease 2019 (COVID-19). Later on October 22, 2020, FDA approved its use in adults and pediatric patients (12 years of age and older and weighing at least 40 kg) for the treatment of COVID-19 requiring hospitalization.[8]

On 1 December 2020, the European Medicines Agency also recommended only remdesivir (RDV) and dexamethazone for the treatment of COVID-19 in patients with pneumonia who require supplemental oxygen [9]. Notably, patients with severe AKI and ESKD were excluded from this and all other remdesivir trials on the basis of eGFR cut-offs (either 50 or 30 ml/min per 1.73m2). [8] So there is no data on its efficacy and safety in renal failure. The Indian national clinical management protocol states that the use of remdesivir is contraindicated in patients with eGFR <30ml/min/m2 or when there is a need for haemodialysis in view of unavailability of safety data in this group.[10] Policy of withholding its use in patients with kidney diseases due to lack of safety data can deprive these patients of one of the only available therapeutic options. It has been suggested that remdesivir can be used with close monitoring in patients with renal impairment based on one published Indian study [11].In another recently published study, pharmacokinetics of remdesivir was studied in a patient receiving hemodialysis; significant accumulation of remdesivir or its metabolites was not noted, and there were no signs of drug-related toxicity [12].Apart from remdesivir and corticosteroids, not many drugs are available for use outside of clinical trials for patients with COVID-19 to date. There is already documented substantially high mortality rate in patients with CKD or AKI who were infected with COVID-19 infection The inability to use remdesivir in the setting of severe kidney injury (AKI or advanced CKD) limits treatment options and prevents a considerable subset of patients from receiving potentially beneficial therapy. [13,14]

Based on initial observation, our institute designed protocol for remdesivir use.

According to that, remdesivir use was allowed for those presenting with severe and critically ill disease and advanced CKD or AKI in

whom potential benefit outweigh risk after taking informed written consent from patient's keen. Here, we describe hepatic or renal toxicities observed among patients with and without baseline renal dysfunction who received remdesivir and their outcome.

OBJECTIVES

- To assess safety of drug remdesivir in patients with renal dysfunction either acute or chronic kidney injury.
- To describe clinical outcomes of the patients infected with covid 19 who received remdesivir
- To find out predictors for mortality

MATERIALS AND METHODOLOGY

Study design

It was retrospective, observational, analytical single center study

Study setting

All covid 19 positive patients admitted in Shree Krishna Hospital who had evident renal dysfunction based on their presenting creatinine report or who had oliguria/anuria on first 24 hours and who also received remdesivir during hospital stay were included in this study. Shree Krishna hospital is government designated center for management of covid19 infected patients since the beginning of pandemic. Ours is the only center in Anand and Kheda districts of central Gujarat state which is providing maintenance hemodialysis and hemodialysis for acute kidney injury patients with covid 19 infection. So covid positive patients who require dialysis support have been referred from other covid designated facilities of this and surrounding districts.

INCLUSION CRITERIA

All covid positive (Rapid antigen test or RT PCR) patients admitted in shree Krishna hospital from March 2020 to December 2020 whose presenting creatinine was more than 1.4 mg/dl in Male or 1.2 mg/dl in Female or who were having oliguria /anuria (urine output less than 0.3 ml/kg/hour in first 24 hours –stage 3 AKI as per Standard KDIGO criteria) and who also received remdesivir short or prolonged course during hospital stay were included.

EXCLUSION CRITERIA

Those covid positive patients with renal dysfunction who did not complete the course of remdesivir suggested by clinician or died before completion of remdesivir course were excluded from study. Patients who received remdesivir but whose documented data was incomplete were also excluded.

CASE DEFINITION:

Diagnosis of COVID-19 was made based on clinical history (presence of fever, cough, shortness of breath or presence of anosmia, ageusia/dysgeusia-any one symptom), radiological findings compatible with covid 19 and laboratory confirmation of positive rapid antigen test or positive severe acute respiratory syndrome corona virus 2 nucleic acid by PCR testing on clinical specimen (nasopharyngeal and oropharyngeal swabs, bronchoalveolar lavage) as per Indian council of medical research advisory on testing.

EXPLANATION

Every patient admitted with clinical suspicion of covid 19 infection was subjected to rapid antigen test. If rapid antigen test came negative, one was subjected to RT PCR of nasopharyngeal and oropharyngeal swab. On the instances of first negative RTPCR result, second test was ordered. On few occasions, where rapid antigen and two RTPCR swabs were negative, but clinical and radiological suspicion was high, they were considered positive cases and treated accordingly. All patients were subjected to laboratory tests like CBC, renal function test, electrolytes, liver function test, inflammatory markers (ferritin, LDH, D dimer, CRP, IL-6) and radiological tests like chest radiogram. Lab parameters including inflammatory markers were repeated every 48-72 hours. All patients admitted in covid isolation wards or critical care were treated with azithromycin, zinc, vitamin C, other multivitamins and other supportive treatment. Anticoagulant (conventional unfractionated heparin) was given to all admitted patients either prophylactic or therapeutic dose as per recommendation by European society of cardiology for general population with covid infection.[15]

Remdesivir injection (powder form) was offered to those who had persistent high spiking fever more than 72 hours with rising CRP and/or other inflammatory markers and lung infiltrates (even without hypoxia), hypoxia requiring oxygen supplementation and/or severe radiological findings (lung infiltrates >50%) in symptomatic patients with rising CRP, D Dimer or ferritin after taking informed written consent from patient's kin where benefits outweighed risk. [16,17,18]

Remdesivir was not offered to those who had elevated liver enzymes more than 5 times or were pregnant/lactating women or had known hypersensitivity to drug.

All were supplemented with oxygen whenever saturation dropped below 92% by nasal prongs, ventury mask, nonrebreathing mask(NRBM), high flow nasal cannula(HFNC), biPAP (Bilevel positive airway pressure) or noninvasive ventilatory support(NIV) and invasive ventilation(IV) in that order to maintain adequate oxygenation. Those patients who were already on maintenance hemodialysis were subjected to intermittent hemodialysis every alternate day to avoid any adverse impact of hyperkalemia and volume overload on over all outcome. Patients with acute kidney injury and some ESRD patients who had hemodynamic instability were offered prolonged intermittent renal replacement therapy/sustained low efficiency dialysis (PIRRT/SLED). Those who were afebrile for 72 hours and those who were maintaining adequate oxygen saturation for more than 24 hours and had declining inflammatory markers were deemed fit for discharge.

DATA SOURCE:

Demographic data, clinical data, details of their hospital course, details of treatment modalities and adverse drug reaction charts were obtained from the medical record of those patients who received remdesivir and also had abnormal renal function (AKI/CKD). We also noted data of those patients who received remdesivir and had normal renal function on presentation within same time frame as a control arm. Worst values of inflammatory markers along with change in liver enzymes and serum creatinine values were noted of both groups. Those patients who died before completion of remdesivir course were exclude from study. All methods were carried out in accordance with relevant guidelines and regulations. We used the STROBE checklist while writing our report[19].

ETHICS APPROVAL:

This study was approved by the Institutional ethics committee-2, H M Patel centre for medical care and education, Karamsad, Anand and also registered under clinical trial registry of India. As study involved collection of data retrospectively from electronic medical record of the hospital with maintenance of privacy and confidentiality, waiver of informed consent was granted from above mentioned ethics committee.

STATISTICAL ANALYSIS-

Statistical analysis was done using STATA software version 14. Quantitative variables are described with their mean ± SD for unskewed distribution of data or median and interquartile range for skewed distribution. Qualitative variables are summarized with their frequency distribution. Baseline characteristics of patients who received remdesivir with abnormal renal function on admission versus those who receive it with normal renal function on presentation were compared using independent t test. Univariate analysis for Lab parameters/continuous variables were done using independent t test if the distribution of values was unskewed and median test if the distribution was found to be skewed. To explore the independent predictor of mortality a binary logistic regression model with backward likelihood method was used.

RESULTS

We screened total 550 patients' records who received remdesivir between march 2020 to December 2020.We found 104 patients who had normal renal function before starting remdesivir treatment (Group 1) and 150 patients who had abnormal renal function before starting remdesivir (Group 2) fulfilling inclusion-exclusion criteria of our study. Mean age of patients was 62.5 ±14.3 and 60.4 ±13.4 years in Group 1 and 2 respectively. Males constitute 85.6% and 80.7% in Group 1 and 2 respectively. Table 1 shows the details of the characteristics of the two groups across the basic demographic and clinical parameters while Table 2 reveals baseline as well as change in renal and liver function test.

Table 1: Comparison between Normal renal function group and altered renal function group with respect to their characteristics

Sr no.	Parameter		Group 1 Normal baseline renalfunction before initiation of RDV(n=104)	Group 2 Altered renal function before initiation of RDV (n=150)	P value

1.	Age*		62.5(14.3)	60.4(13.4)	0.224
2.	Gender	Male	89(85.57%)	121(80.6%)	0.399
3.	Charlson comorbidity index*		2.66(1.5)	3.07(1.3)	**0.030**
4.	Covid Test	Rapid antigen test	79	78	-
		RT PCR	24	68	
5	Baseline O2 saturation at start of RDV*		86.94(12.55)	88.09(11.66)	0.455
6.	Median s.creatinine before RDV use		1.3(0.13)	1.95(1.36)	**<0.0001**
7.	Median s.creatinine after RDV course		1.17(1.00)	2.11(3)	**<0.0001**
	Median difference S. Creatinine		-0.165(73)	-0.19(1.59)	0.750
8.	Median SGPT before RDV initiation		45(32)	32(27)	0.001
9.	Median SGPT after 48 hours of RDV completion		49(38)	49(55)	0.523
	Median difference SGPT		1.0(34)	11(41)	0.276
10.	Median SGOT before RDV initiation		51.50(41)	45(40)	0.003
11.	Median SGOT after 48 hours of RDV completion		51.50(55)	54(65)	0.372
	Median difference SGOT		0(34)	7(35)	0.147
12	Mean(SD) day of illness on which Remdesivir was given		5(3.1)	4.5(3.08)	0.205
13.	Mortality		36/104	57/150	0.599
14.	Median Duration of hospital stay		11(6)	9(5)	**0.086**
15	Mode ofventilation	Room air	25	29	0.837
		Nasal Prong	8	19	
		Face mask	14	17	
		NRBM	20	27	
		NRBM + Nasal Prong			
		HFNC	1	3	
		NIV	8	11	
		Invasive	28	44	
16.	Severity of covid illness a.Moderate b.Severe c.Critically ill		 0 44 60	 0 61 89	0.797

*Mean(SD) Median accompanied with Interquartile range (IQR)

Table 2: baseline as well as change in renal and liver function test

Sr no.	Parameter	Group 1 Normal baseline renal function before initiation of RDV n=104	Group 2 Altered renal function before initiation of RDV n=150	P value
1.	AKI KDIGO Stage 1 Stage 2 Stage 3	26(25%) 12(11.54%) 3(2.88%) 11(10.58%)	75(50%) 50(33.33 %) 14(9.33%) 11(7.33 %)	-
2.	AKI on CKD	NA	28(18.66%)	-
3.	CKD KDIGO stage 3 Stage 4 Stage 5	NA	47(31.33%) 15(10%) 02(1.33%) 30(20%)	-
4.	Rise in creatinine £ after RDV use	26/104(25%)	42/103 #(40.78%)	**0.018**
5.	Requirement of RRT *	8/104(7.7%)	23/121 (19%)	**0.019**
6	Improvement in s. creatinine after RDV use	None	61/103(59.22 %)	
7.	Significant rise in SGPT after RDV -3-5 TIMES UNL ->5 times UNL	3(2.88%) 2 1	6(4%) 5 1	-
8.	Significant rise in SGOT After RDV use -3-5 TIMES UNL -5 times UNL	6(5.76%) 5 1	5(3.33%) 5 0	-
9.	Improvement in liver enzymes after RDV discontinuation	100%	100%	
10	Mortality	**36/104(33.65%)**	**57/150(38%)** AKI- 36(24%) AKI on CKD-5(3.33%) CKD-3 & 4-6(4%) CKD 5-10/30 (6.66%)	0.59

£ significant rise in creatinine as per KDIGO AKI criteria i.e. at least 1.5 times baseline or ≥ 0.3 mg/dl rise in last 48 hours

103 patients are all AKI and AKI on CKD patients in group 2 in which 61 patients had improvement in creatinine after remdesivir use during hospital course

*This excluded those patients who were already on maintenance hemodialysis in group 2.

In Group1, 48(46.15%) patients had diabetes mellitus, 68(65.38%) patients had hypertension, 16(15.38%) patients had cardiac disease (Ischemic heart disease with preserved ejection fraction or reduced ejection fraction), 5(4.81%) patients had chronic lung disease and 2 (1.92%) patients had chronic liver disease while in Group 2, 66 (44%)patients had diabetes mellitus , 115(76.66%) patients had hypertension, 24(16%) patients had cardiac disease (Ischemic heart disease with preserved ejection fraction or reduced ejection fraction), 8(5.33%) patients had chronic lung disease and 2(1.33%) patients had chronic liver disease.

Mean(±SD) oxygen saturation at admission or before starting remdesivir was 86.94(±12.55)% and 88.09(±11.65)% in Group 1 and 2 respectively. Mean (±SD) day of illness on which remdesivir started were day 5(±3.1) and 4.5(±3.08) in Group 1 and 2 respectively. In Group 1, total 44 patients (42.31%) had severe covid illness while 60 patients (57.69%) had critically ill disease. In Group 2, total 60 patients (40%) had severe disease and 90 patients (60%) were critically ill.[20] The two groups were found to be comparable in all these aspects (p >0.05)

In Group 1, total 26 patients developed acute kidney injury. Peak stages of AKI (KDIGO)[21] were stage 1 in 12 patients (11.54%), stage 2 in 3 patients (2.88%)and stage 3 in 11 patients (10.58%). In this group, 8 patients (7.7%) from stage 3 AKI required any form of renal replacement therapy. (Slow Low Efficiency Dialysis-SLED/ Intermittent hemodialysis-IHD)

In group 2, total 75 patients (50%) had acute kidney injury,28 patients (18.66%) had acute on chronic kidney disease and 47 patients (31.33%) had chronic kidney disease. Out of all 75 patients with acute kidney injury(AKI),50(33.33%),14(9.33%) and 11(7.33%) patients were having KDIGO AKI stage 1,2 and 3 respectively. Out of 47 patients of chronic kidney disease,15 patients (10 %)were belonged to stage 3 CKD (KDIGO STAGING) while 2 patients (1.33 %)were in

stage 4 CKD and 30 patients (20 %) were of stage 5 CKD. Among 30 patients of advanced CKD/stage 5 CKD,29 were already on maintenance hemodialysis. In Group 2, 61 patients, those had already raised creatinine before starting remdesivir treatment improved to baseline post treatment although 15 such patients died despite of improvement in renal function. Remaining 43 patient's creatinine did not improve post remdesivir. Total 23 patients (19%) out of those 103 patients (from AKI/AKI On CKD group -103 patients) required renal replacement therapy during hospital stay. Median(IQR) hospital stay was 10.31(4.21) and 9.35(2.91) days in Group 1 and 2 respectively. We did not observe any patients with change in behavior post remdesivir transfusion while we witnessed 1 and 2 patients with infusion reaction in Group 1 and 2 respectively. Total 36 patients (34.61%) in Group 1 succumbed while 57 out of 150 patients of Group 2(38%) could not make it eventually. In Group 1, 10 patients had raised SGPT/ALT and 13 patients had raised SGOT /AST (albeit < 5 times upper normal limit) before remdesivir treatment but improved to baseline or at least started showing improving trend post remdesivir.(Table-2) In Group 2, total 4 and 10 patients had elevated SGPT and SGOT(< 5 times upper normal limit) respectively before remdesivir treatment and later showed improving trend post treatment. Out of 104 patients in Group 1,2.88% and 5.76% patients had elevated SGPT and SGOT more than grade 2.[22] Similarly, in Group 2, 4% and 3.33% patients had elevated SGPT/ALT and elevated SGOT/AST more than grade 2. All these patients had improved enzymes after stopping remdesivir.

The distribution of most of the continuous variables was found to be not normal and hence nonparametric Median test was applied to compare the medians across the two groups. Comparing the Lab parameters by Median test, it was observed that the D Dimer and ferritin values of the altered renal function group (Group 2) was significantly raised than the normal renal function group.(Group 1) (Table 3). The median D Dimer value for Group 1 was in the normal range while the value for Group 2 was way beyond the normal. (≤ 500) The median ferritin reading in the Group 1 is seen to be although statistically significantly lesser than the Group 2, the reading is well above the required normal value of ≤ 250. (Table 3)

At univariate level, the analysis of median comparisons of different variables with mortality as the outcome suggested that the median age, SGOT, Oxygen saturation, CRP, LDH, DDIMER, Ferritin, TC was significantly different between discharged and dead patients. (Table 4)

Table 3: Comparison of the median(IQR) values of Lab parameters across the normal renal function group and the Altered renal function group before the initiation of Remdesivir

Lab parameter	Group 1 Normal baseline renal function	Group 2Altered renal function	P value
CRP	102.1(137.95)	101.6(128.5)	0.880
LDH	415(250)	391(282)	0.660
D DIMER	450(885)	809(2675)	**0.030***
Ferritin	599(683)	884(1316)	**0.005***
TC	7650(4800)	9150(7575)	0.160
Absolute Lymphocyte count	1010(740)	960(758)	0.486

*Statistically significant

Table 4: Univariate median comparison of surviving and dead patients

Parameter	Discharged	Dead	P value
Age	60(19)	66.5(12)	**<0.001**
SGOT	42.5(35)	58.5(44)	**0.002**
Oxygen saturation	96(9)	81(22)	**<0.001**
CRP	72.4(103)	140.7(109.6)	**<0.001**
LDH	346(171)	536(280)	**<0.001**
DDIMER	380(1065)	943(3027)	**0.001**
Ferritin	557(687)	1078(1215)	**0.034**
TC	7150(4500)	10200(7625)	<0.001
Mean(SD) day of illness on which Remdesivir was given	4.54(2.99)	4.98(3.26)	0.284

Table 5: Binary Logistic regression findings to predict mortality

Significant variable	Odds Ratio (CI)	P value
Charlson comorbidity Index	**1.952 (1.286,2.965)**	**0.002**
Mode of Oxygen Room Air (Ref)		
Nasal prong	0.670(0.056,8.036)	0.752
Face mask	0.57(0.047,6.915)	0.659
NRBM	2.213(0.383,12.777)	0.375
HFNC	12.090(0.924,158.201)	0.057
NIV	**22.146(3.763,130.318)**	**0.001**
IV	**2652.020(198.908,35359.042)**	**<0.0001**

To explore the independent predictor of mortality a Binary Logistic regression model with backward likelihood method was developed considering death or survival as the outcome and group(whether baseline renal dysfunction or baseline normal renal function), Charlson comorbidity index, severity of disease(severe/critically ill), oxygen saturation on arrival, mode of oxygen administration(room air, nasal prong, face mask, NRBM, HFNC,NIV and IV), mean day of illness on which remdesivir given, CRP, D-DIMER, Total Leucocyte Count and absolute Lymphocyte count as predictor variables.

The model so developed has a Nagelkarke R square value of 0.827 with 94% correct classification. The final model suggested mode of oxygen administration and Charlson comorbidity index to be significant predictor for mortality in this specific population. The model suggests that the odds of death increases by 1.952 times with unit increase in the Charlson comorbidity index score. The odds of death is 22.146 times higher in a person who needed NIV compared to a person on room air while odds of death is 2652.02 times higher in patients on IV compared to those on room air. (Table 5)

DISCUSSION

Each and every trials of various drugs for treatment of covid 19 illness excluded patients with renal dysfunction either AKI or CKD(e GFR <50 and < 30 respectively)despite their maximum vulnerability to adverse outcome of covid 19. According to product monograph, remdesivir is not recommended in this high risk group with eGFR <30 ml/min/1.73 m2 unless benefit outweigh risk. [23] Based on our own experience, our institution designed our own protocol for remdesivir use. Here we report our experience of use of remdesivir in covid 19 affected patients with renal dysfunction either acute or chronic.

In group 1, with use of remdesivir 25% patients had risen creatinine(AKI). Similar incidence of acute kidney injury has been described in ADQI work group consensus report irrespective of remdesivir use. [24] Moreover, these all patients are of severe or critically ill disease which could have shown worse incidence of AKI. In this group 7.76% patients required any form of renal replacement therapy which is lesser than study by Hirsch JS from New York [25]

In group 2,61 patients' (59.22%) creatinine improved to normal after initiating remdesivir treatment while 40.78% had worsening creatinine (true AKI incidence post remdesivir) that is more than group 1(**p value-0.018 statistically significant**). But people with baseline renal dysfunction are already at high risk of acute kidney injury with any bacterial/viral infection. Hence it cannot be solely attributed to remdesivir use. In this group 23 patients (19%) patients required any form of renal replacement therapy which is more than group 1(**p 0.019 statistically significant**).

Improvement in creatinine can be explained by correction of pre renal factors with volume repletion and treatment of viremia with antiviral agent that lead to less direct cytopathic effects on tubulointerstitial compartment and simultaneous use of steroid. Rise in creatinine in both group can be multifactorial. Covid 19 can cause acute kidney injury by following mechanism :(a.)direct effect of SARS-CoV-2 on glomeruli or tubulointerstitial compartment (b.) adverse hemodynamic complication /or as a part of multiorgan dysfunction mediated by various inflammatory cytokines (c). co-prescription of some known /unknown nephrotoxic drugs like furosemide, norepinephrine, enoxaparin, fentanyl, midazolam, piperacillin tazobactum etc. (d.) metabolites of remdesivir GS-441524 and GS-704272 (e.) SBECD (Sulfobutylether-b-cyclodextrin) carrier of remdesivir. (f.) prothrombotic phase of disease itself [26].

As remdesivir triphosphate is a weak inhibitor of mammalian RNA polymerases, it is considered to have very low potential for mitochondrial toxicity. Although other nucleotide/nucleoside antivirals (i.e., tenofovir) can cause mitochondrial injury in renal tubular epithelial cells albeit after prolonged exposure and therefore, would be extremely rare to occur within a 5- or 10-day therapy course of remdesivir.[27,28] Studies in murine and mammalian models showed kidney injury and casts at doses of 5, 10, and 20 mg/kg for 7 days, way

higher than the recommended dose.[8] Significant renal adverse events were not observed when remdesivir was used in a clinical trial for Ebola virus.[29]

SBECD, a cyclic oligosaccharide that is used as a carrier in intravenous preparation like voriconazole is predominantly excreted through glomerular filtration. Animal studies have shown liver necrosis and renal tubule obstruction with SBECD at doses 50- to 100-fold higher than expected for a 5- to 10-day RDV course [30]. Each 100 mg of lyophilized powder and solution of RDV contains 3 and 6 g of SBECD, respectively, which is quite lesser than the maximum recommended safety threshold dose of 250 mg/kg/day. Additionally, SBECD is effectively removed by dialysis modality to the level generally considered safe [31]. Accumulation of SBCED may occur in patients who are not on dialysis or discontinue dialysis without renal improvement. Still significant hepatotoxicity in patient with severe renal impairment due to accumulation and high blood conc. is rare. Much of the pharmacokinetics and clinical effects of SBECD in kidney failure is known from literature of intravenous voriconazole. Intravenous therapy may be necessary in patients with invasive fungal infections who are critically ill with poor gut perfusion that limits oral absorption even in presence of severe renal failure. In this scenario, short courses are generally well tolerated, without significant adverse renal/hepatic events noted despite documented accumulation of SBECD well above levels in patients with normal kidney function. [32,33] We suggest shorter course of 5 days and not prolonged course of 10 days to be used in patients with severe renal impairment especially if they are not on dialysis.

We report only 2.88% and 4% incidence of SGPT elevation and 5.76 % and 3.33% incidence of SGOT elevation in group 1 and 2 respectively. This is similar to observed incidence in investigational trials.[23] None had increased SGPT/OT more than 20 times in both group.

None required discontinuation of treatment. We didn't report even single case of acute liver failure following RDV.

We reported mortality rate apx.33.65% in group 1 while 38% in group 2. This is almost identical to mortality rate of 35% in a study of AKI patients affected with covid 19 infection form New York and 30.1% in a study from Mexico.[25,34] Advanced age, higher total leucocyte count. lower oxygen saturation on admission or just before remdesivir, higher CRP, LDH, D-Dimer, ferritin were associated with increased risk of mortality (statistically significant) in univariate analysis. Every single unit increase in charlson comorbidity score would lead to increased risk of death. (Adjusted Odds ratio 1.952,95% C.I. (1.286-2.965)) Requirement of noninvasive and invasive ventilator support would increase risk of dying significantly as compare to patients who were on room air. (Adjusted Odds ratio 22.146 ,95% C.I.(3.763-130.318) and 2652.020 ,95% C.I. (198.908-35359.042) respectively.) Here we could not find out effect of remdesivir on mortality as we don't have control group comprised of subjects without remdesivir use

CONCLUSION

Remdesivir can increase serum creatinine especially in patients with baseline renal impairment and may result in increased requirement of RRT. But it is not associated with significant hepatotoxicity which is theoretically expected due to increased plasma concentration of its metabolite or SBCED carrier. Slightly elevated liver enzymes before initiation should not be of great concern Remdesivir use is also not associated with any infusion reaction or change in behavior. AKI in covid is multifactorial. Patients with preexisting renal impairment are already at increased risk of acute kidney injury. So it can't be attributed to drug use rather it is disease severity, prothrombotic state, concomitant known/unknown nephrotoxic drugs and concomitant respiratory failure which are strongly associated with AKI. Use of remdesivir in this group should be done only if benefit outweigh risk. However, patients with mild /transient AKI (KDIGO stage 1 and 2) and patients on maintenance hemodialysis are suitable candidate for use of remdesivir in standard recommended dose preferably lyophilized powder form with close liver function test and renal function test monitoring. Severely altered renal function should not be contraindication for remdesivir. Patients with CKD not on dialysis (CKD stage 3 and 4) require special attention while using remdesivir as there is risk of worsening creatinine and requirement of dialysis.

LIMITATION

Its single center, record based, retrospective study hence the study design has inherent biases such as selection and confounding biases. We haven't measured blood concentration of SBCED or active metabolites of drug. We could not gather information regarding concomitant use of dexamethasone or other drugs along with remdesivir which could have potential effect on renal or liver function as well as impact on disease outcome We suggest more controlled studies with larger group as well as multicenter study to confirm our findings.

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Conflict of interest
None

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