ORIGINAL ARTICLE

Safety and Tolerability of Remdesivir in Patients with End-stage Renal Disease on Maintenance Hemodialysis

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Abstract

Introduction: The use of remdesivir is not recommended in patients with end-stage renal disease (ESRD) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection unless potential advantage offset disadvantage due to limited safety data. Our objective was to assess the safety of remdesivir in patients with end-stage renal failure and evaluate the outcome of this vulnerable group.

Methodology: We carried out a retrospective observational study in dialysis-dependent ESRD patients with SARS-CoV-2 infection who received a standard 5-day course of remdesivir (powder form) from June 2020 to December 2020. Oxygen requirement, hemogram, inflammatory markers, and liver function tests before and after remdesivir treatment were compared.

Result: We found thirty-nine such patients with mean age of patients 58.79 ± 12.13 years. Diabetes mellitus, hypertension, and cardiac diseases were present in 58.97, 87.17, and 23.07% of patients, respectively. Mean oxygen saturation on admission was 85.41% (±7.73). There were no events of hepatotoxicity, altered behavior, or infusion reaction. There was statistically significant improvement in total leukocyte count, absolute lymphocyte counts, and C-reactive protein (*p* value <0.001, 0.01, and 0.02, respectively) post remdesivir treatment. A total of 60% of patients had improved oxygenation while 13% of patients had no change in oxygen requirement after completion of remdesivir course. Mortality in our study was 28.21%. We did not find any significant benefit of early remdesivir administration (3–6 days of illness) on mortality or days of hospitalization.

Conclusion: The use of remdesivir in end-stage kidney disease is safe. Improvement in oxygenation was significant when baseline oxygen requirement was less. It requires prospective controlled trials with larger population to assess its impact on mortality.

Keywords: End-stage renal disease, Hemodialysis, Remdesivir, SARS-CoV-2.

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Highlights

The use of remdesivir is not recommended in advanced renal failure patients. But nephrology community is suggesting its use in this scenario based on personal experience. Still not enough studies either from India or Abroad are available. This study will provide some insight regarding its use in this group.

Introduction

Dialysis-dependent ESRD patients are highly susceptible to the development of severe SARS-CoV-2 infection.[1] Many pharmaceutical agents have been tried in various trials for the management of SARS-CoV-2 infection till date. One of such drugs is antiviral drug, remdesivir. It is a prodrug of adenosine analogue originally developed for the management of Ebola virus.[2] Its use for the treatment of coronavirus disease-19 (COVID-19) infection requiring hospitalization has been approved lately by the US Food and Drug Administration (US FDA) and the European Medicines Agency.[3,4] Sadly, patients with ESRD status were excluded from these trials due to safety concerns.[3] The Indian national clinical management protocol also recommends against its use in patients with CKD stage 4 and beyond in view of sparse safety data in this group.[5]

Recently, it has been evident that remdesivir can be used cautiously with close monitoring in patients who are on maintenance hemodialysis.[6,7]

In another recently published pharmacokinetic study, there was no clinically significant accumulation of remdesivir or its metabolites in dialysis patients without residual renal function and there was no evidence of any drug-related toxicity.[8] Till date, only few drugs other than corticosteroids and remdesivir are available for use outside of clinical trials for dialysis-dependent patients with

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COVID-19 infection. That is why this group has already registered remarkably high mortality rate when they confronted with COVID-19 infection. The inability to use remdesivir in dialysis-dependent patients just due to lack of approval from regulatory agencies curtails therapeutic armamentarium and impedes a substantial subset of patients from getting likely advantageous therapy.[9,10] After viewing promising early results, our institute prepared protocol for remdesivir use. In accordance with that, remdesivir use was permitted for those who are on maintenance hemodialysis in whom advantage outweigh disadvantage after getting informed written consent from the patient or patient's caretaker. Here, we delineate its adverse reactions in term of effects on liver enzymes or behavior or any other unknown effects observed among patients with advanced renal failure along with the outcome of these patients.

Objectives

- To assess the safety of drug remdesivir in patients with end-stage kidney disease
- To report clinical outcomes of the ESRD patients infected with SARS-CoV-2 virus who received remdesivir

Methods

This retrospective, observational study was carried out at Shree Krishna hospital, the university hospital which is the only tertiary care institute that provided maintenance hemodialysis even for COVID-19 infected patients

Inclusion Criteria

All COVID-19 positive end-stage kidney disease patients [rapid antigen test or reverse transcription–polymerase chain reaction (RT-PCR) positive as per Indian council of medical research] who are on maintenance hemodialysis admitted to Shree Krishna Hospital from March 2020 to December 2020 and who also received remdesivir (at least more than one dose) during hospital stay were included in this study.

Exclusion Criteria

Patients who received remdesivir but whose data were missing in records were excluded.

Institutional Protocol

Each patient admitted with clinical suspicion of COVID-19 infection was subjected to confirmatory molecular tests (bedside rapid antigen test and qualitative RT-PCR test if former was negative of nasopharyngeal and oropharyngeal swab), blood investigations (hemogram, creatinine, urea, electrolytes, liver function test, inflammatory parameters), and radiological tests (chest X-ray). On few instances when despite very high clinical and radiological suspicion of COVID, consecutive confirmatory molecular tests were negative; they were considered positive cases and managed in accordance with that. Blood tests including inflammatory parameters [ferritin, C-reactive protein (CRP), D-dimer, and/or interleukin (IL)-6] were repeated every 48–72 hours.

Mild disease is defined as patients who have any of the various symptoms and signs of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, nausea, vomiting, diarrhea, and loss of taste and smell) but who do not have shortness of breath or abnormal chest imaging. Moderate disease is defined as individuals who have shortness of breath or whose respiratory rate >24/minute and/or oxygen saturation (SpO_2) ≥94% on room air at sea level and who show evidence of lower respiratory disease on imaging but lung infiltrates <50%. Severe disease is defined as individuals who have respiratory rate >30 breaths/minute, SpO_2 <94% on room air at sea level, or lung infiltrates >50%. Critical illness is defined as individuals who have respiratory failure, septic shock, and/or multiple organ dysfunctions.

Criteria for Remdesivir Treatment

Remdesivir injection (powder form) was recommended to those

- Who had persistent high spiking fever more than 3 days with steeply rising CRP and/or other inflammatory parameters and lung opacities (even without hypoxia),
- Hypoxia requiring oxygen supplementation, and/or
- Severe radiological findings (lung opacities >50%) in symptomatic patients with leapfrogging CRP, D-dimer or ferritin after taking informed written consent from patient's kin where advantage offset disadvantage.[11–13]

All these patients were having either severe or critical disease hence they all were treated with remdesivir, anticoagulant (conventional heparin prophylactic or therapeutic dose depending upon D-dimer level), and methylprednisolone 40 mg once a day for 5 days (extended for 10 days if critical disease).[14,15]

Remdesivir was not advised to those who had altered hepatic function (liver enzymes more than five times) or were pregnant/lactating women or had known hypersensitivity to the drug.

All were administered with oxygen whenever saturation dropped below 92% by nasal prongs (NP), face mask (FM)/ventury mask, nonrebreathing mask (NRBM), high-flow nasal cannula (HFNC), bilevel positive airway pressure (biPAP), and invasive ventilation (IV) in that order to maintain adequate oxygenation. These patients were advised for hemodialysis every alternate day to ward off any adverse effect of electrolyte imbalance, uremia, and volume overload on overall outcomes. Hypotensive patients were advised for prolonged intermittent renal replacement therapy/sustained low-efficiency dialysis (PIRRT/SLED). Those who were afebrile for 3 days and those who were maintaining adequate oxygen saturation without any supplemental oxygen for more than 1 day and had declining inflammatory parameters were regarded as appropriate for discharge. RT-PCR test was sent every week even after discharge till it becomes negative.

Data Source

Demographic data, clinical data, details of their hospital course, details of treatment modalities, and adverse drug reaction charts were obtained from the electronic medical record of eligible patients. Values of total leukocyte count, absolute lymphocyte count, CRP, lactate dehydrogenase (LDH), D-dimer, ferritin, serum glutamic pyruvic transaminase (SGPT), and serum glutamic-oxaloacetic transaminase (SGOT) before and after remdesivir course were collected. All methods were carried out in accordance with relevant guidelines and regulations. We followed the STROBE checklist while writing our report.[16]

Ethics Approval

This study was approved by the Institutional ethics committee-2, HM Patel Center for Medical Care and Education, Karamsad, Anand and also registered under the clinical trial registry of India (CTRI/2020/12/030046). As the study involved collection of data

retrospectively from electronic medical records 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 ± standard deviation (SD) for unskewed distribution of data or median and interquartile range (IQR) for skewed distribution. Qualitative variables are summarized with their frequency distribution. Univariate analysis was done applying the Chi-square test for finding association between the categorical variables. Independent sample *t*-test was done to compare means and median test was applied for quantitative skewed data for which median was calculated.

Result

A total of seventy-seven patients with ESRD on maintenance hemodialysis were admitted with COVID-19 infection between June and December 2020. Out of these, thirty-nine patients received remdesivir during hospital admission as per criteria laid down by our hospital. Mean age of patients was 58.79 ± 12.13 years. Males constitute 76.92% of total patients. Diabetes mellitus, hypertension, and cardiac diseases were present in 58.97, 87.17, and 23.07% of patients, respectively. Patients presented to our hospital with a median duration of symptoms of 4.6 days with (IQR 1.82). Median duration of hospital stay was 9.59 days (IQR 3.89). Mean oxygen saturation on admission was 85.41% (±7.73). Total twenty-three patients received remdesivir during 3–6 days of illness while sixteen patients received it between day 7 and day 10 of illness. Thirty-five patients completed full course of remdesivir (5 days). One patient received two doses and three patients received three doses of remdesivir. The Table 1 gives the distribution and comparison of the baseline demographic and laboratory characteristics of the patients.

Mean total leukocyte count and absolute lymphocyte count of all patients were 7828 ± 4007/mm^3 and 1041 ± 430/mm^3, respectively. Mean CRP, LDH, and IL-6 were 113.51 (±89.59), 388.34 ± 177, and 91.40 ± 142.71, respectively (Table 1). Two patients had elevated liver enzymes [alanine aminotransferase (ALT)/aspartate aminotransferase (AST)] on admission (albeit <5 times), which subsequently improved to normal even after remdesivir use. Three patients (7.69%) had elevated ALT while four patients (10.25%) had elevated AST post remdesivir administration. But all these patients had grade I elevation only. Eleven patients (28.21%) died including one patient who died at home after being discharged from the hospital.

Clinical and Laboratory Parameters across Disease Severity

Among all, twenty-seven patients had severe COVID-19 while 12 had critical disease with multi-organ dysfunction. (Table 2) Mean age of patients with critical disease was 61.5 years (±8.67), which was more than those with severe disease (57.48 ± 13.32). In the critically ill patient's group, 75% of patients had diabetes

Table 1: Comparison of the baseline demographic and laboratory characteristics of the patients

Parameter	*Baseline characteristics overall (n = 39)*	*Discharged (N = 28)*	*Death (N = 11)*	*p value*
Age (years)	58.79 (±12.13)	59.43 (±12.54)	57.18 (±11.42)	0.609
Gender (Male)	30 (76.92%)	20 (71.42%)	10 (90.90%)	0.399
DM	23 (58.97%)	16	7	0.993
HTN	34 (87.17%)	26	8	0.246
Cardiac disease	9 (23.07%)	7	2	0.974
Duration of symptoms before hospitalization (in days)	4.67 (±1.82)	4.36 (±1.68)	5.45 (±2.02)	0.091
Day of illness on which RDV administered	5.85 (±2.45)	5.57 (±2.45)	6.55 (±2.42)	0.271
Days of hospitalization	9.59 (±3.89)	10.71 (±3.61)	6.73 (±3.16)	**0.003**
TC	7828 (±4007)	7378 (±3396)	8973 (±5280)	0.269
ALC	1041 (±430)	1096 (±432)	900 (±409)	0.204
SGPT	29.28 (±30.12)	30.5 (±35)	26.18 (±11.25)	0.693
SGOT	36.59 (±40.30)	36.86 (±47)	35.91 (±13.18)	0.948
CRP	113.51 (±89.59)	93 (±76)	166 (±103)	**0.020**
LDH	388.34 (±177)	371 (±151)	437 (±238)	0.318
D-dimer	1495.22 (±2385)	1222 (±2132)	2259 (±2977)	0.243
Ferritin	1296.56 (±545)	1344 (±525)	1175 (±602)	0.390
IL-6	91.40 (±142.71)	64.75 (±67.82)	158.03 (±247.22)	0.182
Baseline oxygen saturation	85.41 (±7.73)	86.75 (±6.28)	82.00 (±10.12)	0.084
Severity of disease				
Severe disease	27	24	3	0.001
Critically ill	12	4	8	
Infusion reaction	None	None	None	
Change in behavior	None	None	None	

Bold values are statistically significant thus important observations

Table 2: Comparison of parameters across disease severity

Parameter	*Severe disease (N = 27)*	*Critically ill (N = 12)*	*p value*
Age (years) Mean (SD)	57.48 (±13.32)	61.75 (±8.67)	0.317
Gender (Male)	19 (70.37%)	11 (91.66%)	0.228
DM present	14 (51.85%)	9 (75%)	0.291
HTN present	24 (88.88%)	10 (83.33%)	0.634
Cardiac disease present	6 (22.22%)	3 (25%)	1.00
Duration of symptoms before hospitalization	4.48 (±1.84)	5.08 (±1.78)	0.349
Day of illness on which RDV administered	5.59 (±2.33)	6.42 (±2.75)	0.340
Days of hospitalization	10.48 (±3.92)	7.58 (±3.14)	0.030
TC	7037 (±2963)	9608 (±5453)	0.147
ALC	1073 (±434)	970 (±434)	0.501
SGPT	24.70 (±28.71)	39.58 (±31.92)	0.157
SGOT	35.11 (±48.10)	39.92 (±11.18)	0.736
CRP	89.78 (±65.49)	166.91 (±114.45)	**0.046**
LDH	376.85 (±167.61)	416.55 (±204.10)	0.538
D-dimer	1227.74 (±2203)	2151.78 (±2786)	0.285
Ferritin	1324.67 (±543.84)	1233.30 (±566.42)	0.635
IL-6	53.33 (±56.48)	167.56 (±225.44)	0.232
Baseline oxygen saturation	87.56 (±5.59)	80.58 (±9.765)	**0.036**
Death	3 (11.11%)	8 (66.66%)	**0.001**

Bold values are statistically significant thus important observations

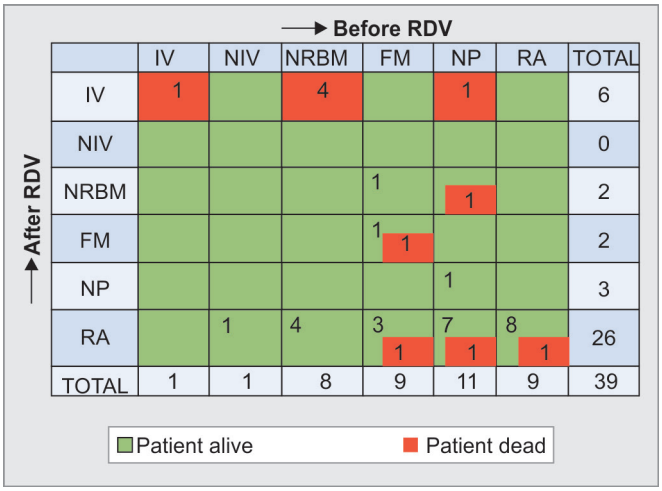

Fig. 1: Respiratory support of the patients before and immediately after completion of remdesivir treatment and their eventual outcome

mellitus as compared to 52% of patients with severe disease. The prevalence of hypertension and cardiac diseases were almost similar between two groups. Oxygen saturation on admission was 80.58% in patients with critical disease which was significantly lower than patients with severe disease ($p = 0.036$). C-reactive protein at the time of admission was higher in patients with critical disease ($p = 0.046$). Patients with critical disease had lower lymphocyte count, higher LDH, D-dimer, and IL-6 level than patients with severe disease although it was not statistically significant. Eight out of 12 critically ill patients (66.66%) died as compared to three patients (11.11%) among patients with severe disease ($p = 0.001$).

Oxygen Requirement before and after Remdesivir (Fig. 1)

Out of thirty-nine patients, nine patients were on room air, eleven patients were on nasal prongs, nine patients were on face mask, eight patients were on NRBM, one patient was on biPAP, and one patient was requiring mechanical ventilator prior to remdesivir use. After completing a 5-day course of remdesivir, eight out of eleven patients on nasal prong improved, one patient was still on nasal prong, one patient was on NRBM, and one patient was on invasive mechanical ventilator support. Three out of nine patients on face mask were on room air, two patients were on nasal prong, three patients were on face mask, and one patient was on NRBM. Four out of eight NRBM patients were on room air while four patients were on invasive mechanical ventilator support. One patient on biPAP improved after remdesivir and was on room air while one patient who was on invasive mechanical ventilator had worsening oxygen requirement after remdesivir completion.

By comparing laboratory parameters before and after remdesivir administration, there was improvement in total leukocyte count, lymphocyte count, and CRP. There was also a rise in SGPT/ALT post remdesivir (Table 3).

Timing of Initiation of Remdesivir and Its Impact on Outcome

Twenty-three patients received remdesivir between day 3 and day 6 of illness while sixteen patients received it between day 7 and day 10 of illness. Mean day of hospitalization was lesser for the early remdesivir (RDV) initiation group than those who received it in the second week (8.83 vs 10.69 days) although it was not statistically significant. The distribution of severe and critical diseases was comparable in both groups. There was no statistically significant

difference in change in CRP, D-dimer, and LDH values between two groups. There was no benefit in terms of mortality or days to become negative whether remdesivir initiated early or late (Table 4).

Discussion

Remdesivir is not recommended in patients with estimated glomerular filtration rate (eGFR) <30 mL/minute/1.73 m^2 by the US FDA as well as the European medicine agency due to lack of data. Theoretical concerns are for adverse reactions because of accumulation of remdesivir metabolites or its carrier sulfobutylether-beta-cyclodextrin (SBECD). Petit et al. studied the incidence of adverse effects of remdesivir in patients with severe renal impairment in a retrospective study and found it relatively safe. The author recommended shared decision-making after discussing all possible adverse effects of remdesivir with the patient or caregiver and informed decision to be taken whether potential benefit outweighs the risk or not.[17]

Aishwarya et al. and Thakare et al. from India also found it safe to use in ESRD patients.[6,7]

In this retrospective study, a total of thirty-nine ESRD patients were analyzed who received remdesivir during their hospitalization. Out of thirty-nine patients, twelve patients (30.72%) had dialysis vintage less than 1 year. Among patients who died, 63.63% of patients had dialysis vintage of less than 1 year. Our dialysis patients were relatively younger with mean age of patients 58.79 ± 12.13 years as compared to their counterpart in the Spain (mean age 71 ± 12 year) and the United States [median age 63 years (56–78)].[1,18] This difference in age could possibly be explained by the fact that the Indian dialysis patients' group is comprised of younger patients as compared to those from western countries.[19]

All patients who were not hypoxic before remdesivir initiation remained so even after completion of 5-day course of remdesivir. Among those who were on nasal prong before remdesivir initiation, 72% of patients improved or weaned, 9% of patients had the same oxygen requirement, and 18% of patients had worsening oxygen requirement after completion of 5-day course of remdesivir. Of those who were on face mask, 56% improved or weaned, 33% status quo, and only 11% of patients had worsening oxygen requirement. Of those who were on NRBM and biPAP, 50% improved while 50% worsened. One-hundred percent of patients who were on invasive ventilator worsened clinically even after completion of remdesivir. Total thirty patients required oxygen support by various modalities during the hospital stay. Out of those, eighteen patients (60%) had improvement in their oxygenation at the end of remdesivir treatment while four patients (13.33%) had same oxygen requirement even after completion of remdesivir (Fig. 1—ordinal scale). This is similar to a study by Aishwarya et al. from south India.[7] Improvement with remdesivir was evident when it was used while patients were on lower oxygen requirement (nasal prong, face mask). Once patients' oxygen requirement is more, i.e., nonrebreathing masks, invasive ventilator, the likelihood of improvement with remdesivir is less. One patient on biPAP improved and was on room air after completing remdesivir but that patient had underlying chronic obstructive lung disease.

Table 3: Comparison of lab parameters before and after Remdesivir (RDV)

Parameter (n)	*Before RDV*	*After RDV*	*p value*
TC (*n* = 37)	7708 (±3905)	10770 (±5270)	<0.0001
ALC (*n* = 37)	1060 (±416)	1338 (±474)	0.01
CRP (*n* = 34)	102 (±85)	56 (±77)	**0.002**
LDH (*n* = 33)	376 (±156)	357 (±190)	0.582
D-dimer (*n* = 33)	1213 (±2050)	1253 (±2113)	0.938
Ferritin (*n* = 33)	1351 (±502)	1298 (±472)	0.537
IL-6 (*n* = 33)	60 (±64)	27 (±47)	0.075
SGPT/ALT (*n* = 33)	28 (3±2)	40 (±28)	**0.022**
SGOT/AST (*n* = 33)	36 (±43)	40 (±27)	0.565

Bold values are statistically significant thus important observations

Safety, Efficacy, and Tolerability of Remdesivir

There was statistically significant rise in total leukocyte count and lymphocyte count while statistically significant reduction in CRP (whether severe or critical disease) was noted. There was also statistically significant increment in mean SGPT/ALT value but absolute rise was not more than grade II or five times the UNL. Changes in LDH, D-dimer, ferritin, and IL-6 values were not statistically significant after remdesivir administration (*p* value 0.582, 0.938, 0.537, and 0.075, respectively). Not a single patient developed infusion reaction immediately after drug administration. Similarly, there was not any instance for altered behavior due to remdesivir use.

Out of total eleven patients who died, eight patients were having worsening oxygen requirement at the time of death while three patients died despite improvement in oxygenation possibly due to thromboembolic phenomenon. Mortality in our study cohort was 28.21% compared with 21.74% in ESRD patients with COVID-19 infection being dialyzed at our center (unpublished

Table 4: Comparison between patients who received RDV in week 1 or early week 2

	RDV initiation between 3 and 6 days (n = 23)	*RDV initiation between 7 and 10 days (n = 16)*	*p value*
Mean (SD) Days of hospitalization	8.83 (±3.13)	10.69 (±4.68)	0.145
Severe disease	17 (73.91%)	10 (62.5%)	0.498
Critically ill disease	6 (26.08%)	6 (37.5%)	
Median (IQR) change in CRP after RDV	−29.4 (32.4)	−43.6 (50)	0.720
Median (IQR) change in D-dimer after RDV	20 (500)	−153.0 (848.4)	0.137
Median (IQR) change in LDH after RDV	−9 (151.5)	−96 (200)	0.818
Death	6	5	0.725
Days to become negative	23.29 (8.61)	23.64 (4.72)	0.905

data). It is higher than mortality reported in ERA–EDTA registry (23.8%)[20] and that reported from the study by Yiqiong et al. in Chinese group (16.2%)[21] while similar to study from USA (31%).[1] There was no difference in mortality whether remdesivir was given early or late.

Remdesivir triphosphate is a weak inhibitor of mammalian RNA polymerases.[22,23] Studies in animal models showed tubular casts at remdesivir doses of 5, 10, and 20 mg/kg/day for 7 days, which is much higher than the recommended dose.[3] Significant adverse kidney events were not observed in clinical trials of remdesivir for Ebola virus.[24] SBECD, a cyclic oligosaccharide that is used as a carrier is primarily eliminated through glomerular filtration. SBECD can cause liver necrosis and renal tubular obstruction at very high doses. Its cumulative dose with a 5-day course of remdesivir is just 18 g which is quite less than its dose at which adverse hepatic and renal events could happen.[25] Additionally, SBECD is efficiently removed by the 4-hour session of hemodialysis to the safe level.[26] Blood concentration of SBECD may rise in advanced kidney disease patients who are not on dialysis or skipped dialysis without renal improvement. Still adverse hepatic events due to high blood concentration are rare. Pharmacokinetics of SBECD in kidney failure is evident from studies of intravenous voriconazole that also carries it as a carrier. Oral voriconazole therapy is usually preferred over intravenous in the presence of severe renal impairment. But most of these critically ill patients have poor gut perfusion that necessitates intravenous treatment. In these scenarios, short courses of intravenous voriconazole are generally safe and well tolerated despite the documented accumulation of SBECD well above levels in patients with normal kidney function.[26,27]

This is probably one of few published studies regarding remdesivir use in the ESRD group. We continued with a loading dose of 200 mg and administered drug for short course (5 days) without modifying its standard protocol.

Conclusion

Short course of remdesivir use (in lyophilized powder form) in patients with ESRD is safe. It is not associated with significant hepatotoxicity. Administration of remdesivir reduced oxygen requirement and CRP significantly although reduction of other inflammatory markers (LDH, ferritin, IL-6) was not statistically significant. Improvement in oxygenation was significant when baseline oxygen requirement was less. This reduction in oxygenation and CRP is not translated into any mortality benefit. Early or late remdesivir did not result in any significant benefit in terms of hospitalization, days to become negative, or mortality.

Limitation

This study is a single-center study involving small target population. Observational nature of study design itself has its own inherent biases. We could not measure the blood concentration of SBECD or its active metabolites. Additionally, information regarding concomitant use of corticosteroid, biological agents along with remdesivir that could have a potential role in disease management is also not available. We suggest more controlled prospective multicentric studies with a larger group to confirm our findings.

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