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Feasibility and safety of remdesivir in SARS-CoV2 infected renal transplant recipients: A retrospective cohort from a developing nation

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Abstract

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection has drastically impacted the transplant communities. Remdesivir (RDV) has shown some promising results in coronavirus disease (COVID-19) albeit with low certainty. Data in kidney transplant recipients (KTR) are still lacking.

Methods: This was a retrospective cohort of 57 moderate to severe COVID-19 positive KTR in a single center who received RDV as a part of COVID-19 management. No dose adjustments were done. The outcomes were measured as acute kidney injury (AKI) recovery; liver function tests abnormalities; other side effects; graft loss and death.

Results: The median (inter-quartile range) age of presentation was 44 (31-51) years. The duration from onset of symptoms to RDV initiation was 6 (5-7) days. Thirty-two (56%) cases received RDV on the day of admission. Forty-six (81%) cases were on oxygen support upon initiation of RDV. Thirty-eight (66.6%) cases had acute kidney injury on admission. The median baseline, admission, and 28-day follow-up serum creatinine of the cohort were 1.59 (1.1-2.1), 2.13 (1.3-3.1), and 1.58 (1.05-2.1) mg/dl, respectively. A total of 8(14%) cases died in the study with 1 (1.7%) graft loss. All those cases that died were on oxygen therapy at the time of initiation of RDV. No liver function derangements or any other major adverse events with the drug were reported.

Conclusion: RDV therapy is safe and clinically feasible in renal transplant recipients as seen in our cohort. Larger clinical registries and randomized clinical trials should be conducted to further explore the efficacy in transplant recipients.

KEYWORDS

COVID-19, graft dysfunction, liver dysfunction, remdesivir

1 | BACKGROUND

SARS-CoV2 pandemic has medically, economically and psychosocially upended the world. Globally as of 11 April 2021, there have been 134,957,021 confirmed cases of COVID-19, including 2,918,752 deaths, reported to the WHO.[1] India ranks second in the number of COVID-19 cases worldwide as updated by the WHO. As per the Ministry of health and family welfare India (MOHF), COVID-19 has a 90.44% recovery rate and 1.27% mortality.[2] SARS-CoV2 in the transplant community poses itself as a unique challenge. The clinical course and the therapy guidelines as validated for the general population cannot be followed completely for the transplant population. The United States Centre for disease control and prevention (US CDC) enlists organ transplant recipients under high risk for developing severe COVID-19 disease.[3] Since the outbreak, many therapies have been tested but only steroids have shown mortality benefit. Remdesivir (RDV) appears to hold promise as an anti-viral agent that could be effective against SARS-CoV2. RDV is an intravenous (IV) drug that acts by inhibiting viral RNA polymerase and has shown broad-spectrum activity against viruses like Ebola, severe acute respiratory syndrome virus (SARS) and in animal models of SARS-CoV2.[4-6] Few studies in the general population have also shown encouraging results.[7-10] Recently, a few studies have shown that RDV can be used in hemodialysis, acute kidney injury and chronic kidney disease.[11-13] However, we still have limited data regarding the effectiveness of RDV in the setting of transplant recipients. Till date, this remains the largest cohort of KTR who have received RDV therapy.

2 | MATERIALS AND METHODS

2.1 | Design and settings

The study was designed as a retrospective observational study. The research methodology was done in accordance with strengthening the reporting of observational studies in epidemiology (STROBE) statement. Data were extracted from the Institute of Kidney Diseases and Research Centre, Dr H L Trivedi Institute of Transplantation Sciences, Ahmedabad, Gujarat, India, which is an organ transplantation center and functioned as a dedicated COVID-19 center to combat the COVID-19 surge in the country. A total of 57 KTR with moderate to severe SARS-CoV2 received RDV from 4 July 2020 to 14 November 2020.

2.2 | Study participants

KTR who had a positive SARS-CoV2 polymerase chain reaction (PCR) from a nasopharyngeal or oropharyngeal swab and moderate to severe illness were eligible for the study. Moderate SARS-CoV2 was defined as radiological or clinical evidence of pneumonia and oxygen saturation ≥94%; while severe had saturation below <94% or lung infiltrates >50% or respiratory rate >30 breaths/minute.[14]

KTR were managed as per the availability of resources and the national guidelines.[15] RDV was used in all severe cases and moderate cases having a high risk of progression based on clinical and laboratory profile. RDV was administered in a dose of 200 mg OD on the first day, followed by 100 mg OD for the subsequent 10 days. RDV was stopped early on a case-to-case basis as per the treating clinician's discretion. Exclusion criteria included an elevation of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) >5 times the upper limit of normal range (ULN) or a history of liver disease. Low estimated glomerular filtration rate (eGFR) and AKI were not considered as an exclusion criterion in the study. Intravenous methylprednisolone at a dosage of 1mg/kg was used in all cases requiring oxygen therapy; subcutaneous unfractionated heparin 5000 IU or low molecular weight heparin was used in all cases with raised inflammatory markers. Immunosuppression was curtailed by cessation of antimetabolite in all moderate and severe cases. Calcineurin inhibitors (CNI) were reduced or stopped on a case-to-case basis. Other investigational therapies like tocilizumab and COVID-19 convalescent plasma therapy were advised as per the local availability and severity of COVID-19.

2.3 | Data collection

Demographic and clinical characteristics of KTR were recorded which included age, sex, comorbidities, duration of symptoms, blood group and transplant date. Clinical status was recorded daily which comprised of the heart rate, respiratory rate, blood pressure, temperature, oxygen saturation and the daily modified WHO ordinal scale.[16] The 7-point ordinal scale was as follows: (7) Death; (6) KTR on invasive mechanical ventilation; (5) KTR on noninvasive ventilation or high flow oxygen devices; (4) KTR on supplemental oxygen; (3) Hospitalized KTR but on room air; (2) Not hospitalized, limitation on activities; (1) Not hospitalized, no limitations on activities. Serial routine laboratory parameters were planned every third day and repeat RT-PCR was sent depending on the clinical status. Time to viral resolution cannot be interpreted as the timing of repeat RTPCR was not uniform in all of the cases. Other than the routine blood chemistries inflammatory markers including Lactate dehydrogenase (LDH), Interleukin 6 (IL-6), Ferritin, D-dimer levels and high-sensitivity C-reactive protein (hs-CRP) were followed for serial trends.

The cutoff for the measurement of inflammatory markers implying severity was obtained from previously published larger studies.[17,18]

All the blood reports were electronically retrieved from the online hospital database. Baseline eGFR on admission was calculated as per the CKD-EPI 2009.

2.4 | Outcome measurement

The outcomes were measured in terms of AKI recovery at discharge or on 28-day follow-up; graft loss; aspartate transaminase (AST),

alanine transaminase (ALT) levels >5times the ULN and any other adverse events. AKI was defined as an increase in serum creatinine by 0.3 mg/dl or more within 48 hours or an increase to 1.5 times or more from baseline based on the Kidney Disease: Improving Global Outcomes (KDIGO) definition. Complete AKI recovery was defined as serum creatinine reaching the baseline status at 28-day follow-up and partial recovery was defined as serum creatinine declining but remaining above the baseline values. No recovery was defined as graft loss that caused initiation of renal replacement therapy. Outcome was also measured in terms of improvement in the modified WHO ordinal scale.

Improvement was defined as a reduction of a 2-point or 1-point in the scale from baseline levels to 28-day or discharge from the hospital.

2.5 | Ethical statement

The study was approved by the institutional review board: IKDRC-ITS, Ahmedabad, Gujarat, India (Registration number ECR/I43/Inst/GJ/2013/RR-19). The complete process of the study was conducted in compliance with the declaration of Helsinki, declaration of Istanbul, and Good clinical practice guidelines. Informed consent about the risks and benefits of the investigational therapies was taken from individual patients and their privacy and confidentiality were maintained throughout the research.

2.6 | Statistical analysis

This was an open-label study of an investigational drug and hence no predefined sample size was calculated. Variables were expressed in number, percentage, median, inter-quartile range (IQR) as appropriate. All analysis was done by SPSS software version 1.

3 | RESULTS

A total of 92 post-transplant COVID-19 cases were admitted from 4 July 2020 to 14 November 2020 in the institute of which 57 moderate to severe COVID-19 cases received RDV therapy.

3.1 | Baseline characteristics of the cohort

Table 1 shows the demographic characteristics of the recipients. The median (inter-quartile range) age of presentation was 44(31-51) years. The most common age group affected was 18-50 years (39, 68%). Forty-seven (82%) cases were males in the cohort. The blood group distribution of the cohort was A (10, 18%), B (22, 38.5%), AB (3, 5%) and O (22, 38.5%). Fourteen (24.5%) cases were deceased donor transplants while the majority were living-related transplants (43, 75.5%). Fifteen (26%) of the 57 KTR tested COVID-19 positive

TABLE 1 Baseline characteristics of the remdesivir cohort

Baseline characteristics[a]	n = 57
Age[b]	44 (31-51)
Age group in years	
<18	2 (3.5)
18-50	39 (68)
50-65	14 (25)
>65	2 (3.5)
Sex	
Male	47 (82)
Female	10 (18)
Blood group distribution	
A	10 (18)
B	22 (38.5)
O	22 (38.5)
AB	3 (5)
Type of transplant	
LRKT	20 (34)
SKT	14 (24.5)
KPD	9 (16)
DKT	14 (24.5)
Time from transplant to COVID-19	
<1 year	15 (26)
>1 year	42 (74)
Comorbidities	
Hypertension	39 (68)
Diabetes	10 (17)
Heart disease	2 (3.5)
Obesity	21 (37)
Others	8 (14)
Baseline immunosuppression	
Triple regimen	48 (82)
Dual regimen	10 (18)
Radiological abnormalities on admission	
Yes	57(100)
No	0 (0)
COVID-19 severity on hospital admission	
Moderate	34 (59)
Severe	23 (41)
Days from admission to RDV initiation	
0	32 (56)
1-2	21 (37)
3-4	2 (3.5)
>5	2 (3.5)
Modified WHO Ordinal scale on RDV initiation[c]	
3	11 (19)
4	21 (37)

(Continues)

TABLE 1 (Continued)

Baseline characteristics[a]	n = 57
5	25 (44)
6	0 (0)
Days from onset of symptoms to RDV initiation[b]	6 (5-7)
Remdesivir course	
5 days	18 (31)
10 days	39 (69)

Note: Abbreviations: DKT, deceased donor transplant; KPD, kidney paired donation; LRKT, living related kidney transplant; SKT, spousal kidney donation.

[a]Data expressed as numbers(percentage).

[b]Data expressed as median(interquartile range).

[c]The 7-point modified WHO ordinal scale used was as follows: (7) Death, (6) KTR on invasive mechanical ventilation, (5) KTR on noninvasive ventilation or high flow oxygen devices, (4) KTR on supplemental oxygen, (3) hospitalized KTR but on room air, (2) not hospitalized, limitation on activities, (1) not hospitalized, no limitations on activities.

within one year of transplant. The cohort had multiple comorbidities that included hypertension (39.68%), obesity (21, 37%), diabetes (10, 17%), heart disease (2, 3.5%) and others (8, 14%). On admission, radiological abnormalities were present in all the cases. Thirty-four (59%) cases did not require oxygen support on admission while 23(41%) cases had oxygen requirements on admission. Forty-seven (82%) patients were on a triple regimen of immunosuppression at baseline while 10 patients were on a dual regimen.

3.2 | Laboratory profile of the cohort

Table S1 shows the detailed laboratory profile of the cohort. The median (IQR) hemoglobin of the cohort was 11.5 (9.9-13.3) g/dl, white blood cell count was 6085 (3845-8815) per mm^3, neutrophil percentage was 75 (68-84), lymphocyte percentage was 20 (12-27), absolute lymphocyte count was 1217 (461-2380) per mm^3, platelet count was 207(162-266) $\times 10^9$ per liter, highly sensitive C reactive protein was 51.9 (24-104) mg/dl, Interleukin-6 was 28.5 (3-120) pg/ml, Ferritin was 439 (229-994) microgram/L, D-dimer was 1705 (620-2935) ng/ml, lactate dehydrogenase was 326 (268-431) IU/L, AST was 30 (18-41) IU/L and serum albumin was 3.3 (3-3.7) mg/dl. Table 2 summarizes the laboratory profile of the cohort.

3.3 | The outcome in the cohort

Tables 2 and S3 show the outcome of the cohort. The median baseline serum creatinine of the cohort was 1.59 (1.1-2.1) mg/dl. Cases 54 and 57 were lost to institutional follow-up for more than a year and had been evaluated for their respective renal function a year ago. Case 53 was undergoing treatment for biopsy-proven acute thrombotic

TABLE 2 Graft status, laboratory profile, and outcome of the remdesivir cohort

Characteristics[a]	n = 57 (100)
Graft status	
Baseline serum creatinine(mg/dl) before COVID-19	1.59 (1.1-2.1)
Serum creatinine (mg/dl) on admission	2.13 (1.3-3.1)
Acute kidney injury on admission	38 (66.6)
eGFR on admission	
>60	12 (21)
45-59	12 (21)
31-44	12 (21)
15-30	14 (25)
<15	7 (13)
Graft outcome	
Complete recovery	50 (87.7)
Partial recovery	6 (10.6)
Graft loss	1 (1.7)
Follow-up 28-day creatinine (mg/dl)	1.58 (1.05-2.1)
Peak laboratory profile of the cohort	
Lowest hemoglobin, g/dl	11.5 (9.9-13.3)
Lowest white blood cell counts, per mm^3	6085 (3845-8815)
Lowest absolute lymphocyte counts, per mm^3	1217 (461-2380)
Lowest platelet count, $\times 10^9$ per liter	207 (162-266)
Highest C-reactive protein, mg/dl	51.9 (24-104)
Highest D-Dimer levels, ng/ml	1705 (620-2935)
Highest serum ferritin, microgram/L	439 (229-994)
Highest Aspartate transferase, IU/L	30 (18-41)
Highest Lactate dehydrogenase, IU/L	326 (268-431)
Highest Interleukin-6, pg/ml	28.5 (3-120)
Decline in Modified WHO Ordinal scale at 28-day follow-up[b]	
1-point	4 (7)
2-point	45 (79)
No decline	8 (14)

Note: Abbreviation: eFGR, estimated glomerular filtration rate (ml/min/1.73 m^2).

[a]Data expressed as numbers(percentage) or median (interquartile range).

[b]The 7-point modified WHO ordinal scale used was as follows: (7) Death, (6) KTR on invasive mechanical ventilation, (5) KTR on noninvasive ventilation or high flow oxygen devices, (4) KTR on supplemental oxygen, (3) Hospitalized KTR but on room air, (2) Not hospitalized, limitation on activities, (1) Not hospitalized, no limitations on activities.

microangiopathy when he acquired COVID-19. The median (IQR) eGFR on admission was 36 (21-59) ml/min/1.73 m^2. The eGFR distribution of the cohort included values less than 15 (7, 12%), 16 to 30 (14, 25%), 30 to 44 (12, 21%), 45 to 59 (12, 21%) and greater than 60(12, 21%). The median admission serum creatinine was 2.13 (1.3-3.1) mg/dl. Thirty-eight (66.6%) cases had acute kidney injury on admission. Index case 55 with baseline creatinine of 5.2 mg/dl was the only graft loss in the study. Eight (14%) cases died in the cohort. Two cases (index case 55 and 57) required hemodialysis. The median serum creatinine (mg/dl) at 28-day follow-up was 1.58 (1.05-2.1). Table S2 exhibits the detailed characteristics of patients with death or graft loss. Index cases 12, 17, 18, 29, 32, 37, 48, 57 died and case 55 had graft loss. A total of 8 (14%) cases died in the study with 1 (1.7%) graft loss. The 1-point decline in modified ordinal scale was seen in 4 (7%) while 2-point decline was reported in 45 (79%) cases. No decline in scale was reported in 8(14%) cases who succumbed to their illness.

4 | DISCUSSION

4.1 | Road to RDV

The world still hopes and fights for the definitive therapy of SARS-CoV2. After dismal performances by various promising therapies,[19,20] RDV emerged with some hope in May 2020. RDV is an adenosine nucleotide pro-drug that is metabolized intracellularly to form the pharmacologically active substrate RDV triphosphate. RDV inhibits the SARS-CoV2 RNA polymerase and thus stops the viral replication. This drug was used for the first time in the USA on 9th January 2020 for the treatment of COVID-19.[21] Currently many international guidelines have recommended RDV in moderate to severe COVID-19 cases.[15,22] The incorporation of RDV in these guidelines was based on the result of initial trials.[8,9] The trial by Wang et al[7] failed to reach specific endpoints subsequently ACCT 1 trial[9] and GS-US-540-5774 trial[8] showed an early recovery rate but no benefit in terms of mortality. GS-US-540-5773 trial[23] demonstrated that a 10-day versus 5-day course of RDV offered no additional benefit. In May 2020 the FDA allowed the use of RDV on an emergency basis and the drug was given the US Food and Drug Administration approval in October 2020. In December 2020, the WHO SOLIDARITY trial[24] which assigned 2750 COVID-19 patients to RDV were published which suggested no mortality benefit with RDV. WHO guideline development group[25] issued a conditional recommendation against the use of RDV for patients with COVID-19, but the evidence was of low certainty. The role of RDV is still being explored and it might have a potential role in the immunosuppressed patients. The timing, duration, and the disease severity in which RDV should be used still remains unclear.

4.2 | Safety profile

The pharmacokinetics, pharmacodynamics and safety profile of RDV is less well studied in the transplant settings. Due to concomitant immunosuppression and chances of drug-drug interaction the potential issue of tolerability and efficacy also remain incompletely answered. RDV is a CYP3A inhibitor and should be avoided with chloroquine and hydroxychloroquine. Previously reported side effect profile of RDV include hypersensitivity, infusion reactions, behavioral disturbances, hypertensive urgency, acute coronary syndromes, septic shock and unexplained death.[31,32] There are also concerns of liver function abnormalities like raised AST, ALT, INR, or bilirubin elevation. Sulfobutylether-β-cyclodextrin (SBECD) is a metabolite of RDV which is majorly excreted in the urine and is considered to have a potential for causing adverse events. It has a half-life of 2 h with intermediates having an extended half-life of up to 24 h. Animal studies have shown concern about the liver and renal injuries with SBECD accumulation.[33] The ministry of health and family welfare (MOHF) guidelines consider RDV use to be contraindicated in patients with eGFR <30 ml/min/1.73 m^2.[15] Our cohort had a baseline median eGFR of 36 (59-21) ml/minutes with 66.6% having baseline acute kidney injury and RDV was started in all these patients. The fact that our cohort had a wide range of renal functions allowed us for a better assessment of the safety of RDV in the setting of deteriorating renal function. Overall, one graft loss was reported in a patient with baseline chronic graft dysfunction and most of the other KTR had a complete recovery (n = 48, 84%) at 28-day follow-up. There were no CNI dose adjustments required in our cohort. Moreover, none of the patients were found to have any liver function derangements. According to the published literature over half of the KTR have allograft dysfunction in SARS-CoV2 and AKI in itself is not an absolute contraindication for initiation of RDV or its continuation. Recently a few recent studies have shown the safety of RDV in kidney diseases as well.[11–13] Overall our cohort had no major adverse events as has been previously described in the literature. In our cohort a total of 8 patients died all of whom had severe COVID-19 pneumonia at the time of initiation of RDV. All deaths were reported in mechanically ventilated patients and were contributed to the progression of respiratory failure in severe COVID-19. There were no unexplained mortalities in our study.

4.3 | RDV in renal and transplant patients

All the trials of RDV have excluded patients with eGFR < 30 or eGFR < 50, so a definitive conclusion about the impact of RDV is lacking in renal patients. There are a few reports of RDV use in AKI and CKD population.[11–13] SARS-CoV2 has shown varying clinical profile and mortality in transplant communities across the world.[24–30] The literature for the use of RDV in transplant patients come in small numbers from cohort studies. A recent meta-analysis comprising 2772 organ transplants including 1500 kidney transplants had around 36 cases who received RDV and the details of the drug regimen used were also not available. The optimal duration of the drug is unknown in transplant settings. In our cohort, patients were started on a 5-day course which was extended to a 10-day course depending on the response. The timing of the initiation of RDV in COVID-19

is unknown. While some of the patients with moderate COVID-19 are known to progress to severe disease and suffer mortality, none of the patients with moderate COIVD-19 at the time of RDV initiation in our cohort died. It has been postulated and some of the published studies also support this hypothesis that early initiation of RDV in COVID-19 is associated with a better outcome. A definitive conclusion cannot be drawn about the efficacy of RDV from our observation. Nevertheless, RDV could be a feasible therapeutic option with promising evidence of safety, improving clinical symptoms and mortality in KTRs with moderate to severe COVID-19.

4.4 | Limitations

This was a retrospectively designed study, and the control group for outcome measurement was not possible. Only two of the KTR in the cohort were over 65 years, and advanced age is considered a major risk factor for mortality in COVID-19. Also, other investigational therapies like plasma and tocilizumab were given which also could confound results. It is also noteworthy that no patient was on a ventilator or extracorporeal membrane oxygenation at the start of the therapy, so our findings cannot be applied to these groups of patients. Viral load measurement would have further supported the improvement in clinical status observed in our study. Even though the sample size was small, still an overall 84% survival rate achieved in RDV receiving moderate to severe SARS-CoV2 post-transplants is a good outcome compared to previous reports where mortality in moderate to severe cases was reported high.[24,25] Accordingly, larger clinical registries and randomized clinical trials involving patients from the immunosuppressed group will further provide evidence for the drug.

5 | CONCLUSION

RDV was a feasible and safe therapeutic option in our cohort which comprised of a wide spectrum of renal functions. In scenarios where resource limitations are not an issue and the benefit of the drug outweighs the risk, RDV is an option to explore as an anti-COVID therapy. Further studies on a large scale are needed in the transplant population to explore the efficacy of the drug.

AUTHOR CONTRIBUTIONS

All authors have made substantial contribution in research design, performance of the research, data collection, data analysis, writing and approval of final version the paper.

DATA AVAILABILITY STATEMENT

Data is available from the corresponding author on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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