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Efficacy and Safety of Remdesivir in Renal Transplant Recipients with Covid-19 Infection – An Initial Experience at Jaslok Hospital, Mumbai, India

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Abstract

Solid organ transplant recipients are at increased risk of COVID-19. Remdesivir has shown clinical benefit in COVID19. However, there is paucity of data on Remdesivir in solid organ transplant recipients. In this non-randomized interventional study on 12 renal transplant recipients admitted in our institute with COVID 19 infection. Eight patients gave consent for Remdesivir and remaining 4 patients who declined consent for Remdesivir were categorised to control (only standard of care given). Mean hospital stay (10.38 ± 2.62 days) was significantly less in Remdesivir group as compared to mean 18.5 ± 2.08 in control group (p<0.001). Mean duration of oxygen support (in days) was 6.98 ± 2.63 and 12.85 ± 0.91 in the Remdesivir and control groups respectively (p= 0.002) suggesting significantly fewer days of oxygen requirement in Remdesivir group. Magnitude of reduction in CRP was significant (p 0.029) in Remdesivir group. Likewise, LDH reduced significantly in Remdesivir group as compared to controls (p 0.047). There was significant improvement in creatinine (p=0.006) and ferritin (p=0.043) on day 5 in patients who received Remdesivir. No side-effects were observed with Remdesivir. Our small data show that Remdesivir was efficacious and safe in renal transplant recipients with Covid19.

Keywords: COVID-19, Remdesivir, Renal Transplant

Introduction

The outbreak of the novel severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) in Wuhan, China, in December 2019 has evolved into a global pandemic, formal announcement of which was made by the World Health Organization on March 11, 2020. Though the pathogenesis of Coronavirus disease 2019 (COVID-19) is still evolving, the spectrum of clinical manifestations ranges from asymptomatic disease to acute respiratory distress syndrome with septic shock and multiorgan failure[1,2]. Several therapeutic options including anti-viral drugs are currently emerging but none has universal consensus or proven efficacy. Only low dose dexamethasone has so far demonstrated mortality benefit compared with usual practice [3].

Solid organ transplant recipients are perceived to be at increased risk of severe COVID-19 because of their chronic immunosuppressed status [4]. Currently, little is known about risk, presentation and outcomes of SARS-CoV-2 (COVID-19) infection in kidney transplantation recipients. The optimal treatment for this patient group is unknown. Consequently, the treatment of Covid-19 in kidney transplant recipients is determined individually, considering patient age and comorbidities. Also, there is very little data on use of Remdesivir in kidney transplant recipients with Covid19.

Remdesivir, a nucleotide analogue prodrug that inhibits viral RNA polymerases, has shown clinical benefit against SARS-CoV-2 in humans[5]. Those who received Remdesivir had a median recovery time of 10 day as compared with 15 days among those who received placebo.The initial length of hospital stay was shorter in the Remdesivir group than in the placebo group[4]. Treatment with Remdesivir was associated with fewer days of subsequent oxygen use for patients receiving oxygen on enrolment[5]. In an open-label, randomized study of Remdesivir in hospitalized patients with moderate severity Covid-19, patients who received Remdesivir for 5 days had higher odds of clinical improvement than those who

received standard care .This benefit was not seen with the 10-day course[6].

A study of 47 solid organ transplant recipients, when compared to a matched group of non-transplant recipients with COVID-19, showed that transplant status itself was not associated with increased mortality[7]. Nevertheless, other studies from Europe and North America have indicated worse outcomes in this population [8,9]. There is little data on the use of anti-viral drug Remdesivir in renal transplant recipients. Therefore, the present study was undertaken to evaluate efficacy and safety of 5 days course of Remdesivir in renal transplant recipients and compare with those who did not receive Remdesivir.

METHODS

This is a non-randomised interventional study carried out in the period June to October 2020, in which Remdesivir was given to renal transplant recipient adults admitted at our institute with COVID 19 infection. The protocol was approved by the institutional review board and written informed consent was obtained from each patient or from the patient's legally authorized representative if the patient was unable to provide consent. Total 12 patients were recruited for the study. Eight patients gave consent for Remdesivir and were put in Remdesivir group (200 mg intravenous first day & then 100 mg intravenous for 4 days) and remaining 4 patients who did not consent for Remdesivir were put in control group (only standard of care given). Efficacy and safety of Remdesivir were monitored and compared with control group.

INCLUSION CRITERIA

Those patients who fulfilled the following criteria were considered eligible for recruitment:

1. Renal transplant recipient (living/cadaver/compatible/incompatible)
2. Covid RT-PCR positive
3. Requiring oxygen support
4. eGFR >30 ml/min
5. Liver functions - ALT/AST < 5 times the normal and total Bilirubin < 1.5 mg/dl
6. Giving consent for Remdesivir and consent for participation in study were included in Remdesivir group and those who did not give consent for Remdesivir but agreed to participate in the study were placed in control group.

EXCLUSION CRITERIA

1. eGFR less than 30 ml/min,
2. Deranged liver functions
3. Required renal replacement therapy
4. Did not give consent for participation in the study.

STANDARD OF CARE

This care was given to both the groups and was started on the day of admission. It included the following: Vitamin C 500mg once daily, Zinc 50mg twice daily, Doxycycline 100mg twice daily (5 days), Ivermectin 12mg once daily (3 days), Injection Dalteparin 2500 U s/c once a day and steroids (Injection Methylprednisolone 40 mg daily or equivalent oral prednisolone).

Remdesivir was given to patients in case group. Dose used was 200 mg intravenously first day and then 100 mg once a day for 4 days. Daily monitoring of liver and renal functions were done during the 5 days course of the drug therapy. Biomarkers of inflammation and coagulopathy (CRP, LDH, Ferritin, D-Dimer) were done on the day of admission (day 0) and after day 5 of Remdesivir.

High resolution computed tomography (HRCT) chest was done for each patient on the day of admission. Immunosuppressive medications were modified on the day of admission i.e Mycofenolate/Azathioprine (anti-metabolites) were stopped, Calcineurin inhibitors (CNI) were continued and levels were monitored.

OUTCOMES

The primary outcomes were period of hospitalization and duration of oxygen dependency. The secondary outcomes included change in liver and renal biochemistries and in biomarkers of inflammation and coagulopathy (D-Dimer, CRP, LDH, and Ferritin).

STATISTICAL ANALYSIS

In descriptive analysis, linear variables were presented as mean, standard deviation, median and range and nominal / categorical variables were presented as number (%). Within group, analysis of linear variables was done by using Paired't' test whereas between groups, difference in difference analysis was done with Unpaired't' test. $P < 0.05$ was taken as significant. SPSS 22 version was used for all statistical calculations.

RESULTS

Out of 8 cases in Remdesivir group, 7 (87.5%) were males whereas there were 3 males (75%) in the control group (n=4). Mean age (years) in Remdesivir group was 47.63 ± 5.37 and 45 ± 7.75 in control group, suggesting no significant difference (p= 0.503). All except one in Remdesivir group (87.5%) had Diabetes whereas 3 (75%) had Diabetes in control group. All patients in Remdesivir (n=8) & control groups (n-4) had hypertension (Table No. 1)

Table 1: Co-morbidities in kidney transplant recipients

	Case(n=8)	Control(n-4)	'p' value*
Male	7	3	1.000
Diabetes Mellitus	7	3	1.000
Hypertension	8	4	NA

* Fisher Exact Test

CT severity score mean value in Remdesivir group was 14.25 ± 2.87 and 14.50 ± 1.29 in control group. No significant difference was noted among both groups (p= 0.874). Patients in the Remdesivir group had significantly shorter hospital stay (Mean, 10.38 ± 2.62) days) as compared to mean duration of 18.5 ± 2.08 days in the control group (p<0.001) (Table No. 2)

Table 2: Baseline Demographic and Clinical characteristics

Parameter	Group	N	Mean	SD	Median	Min.	Max.	'p' value*
Age	Case	8	47.63	5.37	47	40	57	0.503
	Control	4	45.00	7.75	47	34	52	
CT score	Case	8	14.25	2.87	14	11	20	0.874
	Control	4	14.50	1.29	14.5	13	16	
Hospital stay (days)	Case	8	10.38	2.62	10	8	16	<0.001
	Control	4	18.50	2.08	18.5	16	21	
Duration of Oxygen support (days)	Case	8	6.98	2.63	6.4	4	12.4	0.002
	Control	4	12.85	0.91	12.8	11.8	14	

*Unpaired t-test

Table 3: Biomarkers and Biochemistry Profile

Parameter	Group	Day	N	Mean	SD	Median	Min.	Max.	'p' value*
D-DIMER (ng/ml)	Case	Day 0	8	670.00	215.84	678.5	362	944	0.314
		Day 5	8	570.13	380.40	385	150	1301	
	Control	Day 0	4	796.00	127.93	808	632	936	0.115
		Day 5	4	583.50	267.96	599	284	852	
CRP (mg/dL)	Case	Day 0	8	69.75	23.22	65	38	106	0.029
		Day 5	8	36.23	35.48	16.9	6.5	104	
	Control	Day 0	4	80.75	12.45	81.5	65	95	0.011
		Day 5	4	92.50	10.75	91	82	106	
FERRITIN (ng/dL)	Case	Day 0	8	346.00	128.51	339	172	574	0.043
		Day 5	8	272.00	98.15	293	150	444	
	Control	Day 0	4	811.75	169.10	803.5	620	1020	0.268
		Day 5	4	727.00	175.73	715	542	936	
LDH (U/L)	Case	Day 0	8	396.38	111.55	396.5	244	558	<0.001
		Day 5	8	247.25	83.56	215	182	423	
	Control	Day 0	4	417.50	103.06	389	336	556	0.739
		Day 5	4	395.50	142.14	400	220	562	
Creatinine (mg/dL)	Case	Day 0	8	2.18	0.74	2.01	1.03	3.27	0.006
		Day 5	8	1.41	0.34	1.3	1.12	2.2	
	Control	Day 0	4	1.58	0.20	1.525	1.4	1.86	0.059
		Day 5	4	1.33	0.17	1.31	1.15	1.54	
SGOT (U/L)	Case	Day 0	8	42.63	16.99	35.5	26	70	0.093
		Day 5	8	29.75	4.68	30	23	36	
	Control	Day 0	4	38.50	14.06	33.5	28	59	0.114
		Day 5	4	30.25	8.18	29	23	40	
SGPT (U/L)	Case	Day 0	8	49.25	33.06	33	26	113	0.068
		Day 5	8	32.50	11.77	29.5	21	55	
	Control	Day 0	4	45.00	27.63	33	28	86	0.421
		Day 5	4	32.50	1.91	33	30	34	

*Paired t-test

Those patients who received Remdesivir were on oxygen support for lesser period (Mean,6.98 ± 2.63 days) as compared to those in the control group (Mean, 12.85 ± 0.91, p=0.002)

Table 4: Difference analysis between cases and controls

Decrease in Parameters (0-5 day)	Group	N	Mean	SD	Median	Min.	Max.	'p' value*
D-DIMER (ng/ml)	Case	8	99.88	260.53	173	-502	315	0.465
	Control	4	212.50	192.65	140	80	490	
CRP (mg/dL)	Case	8	33.53	34.56	37.25	-43	79	0.029
	Control	4	-11.75	4.11	-11.5	-17	-7	
FERRITIN (ng/dL)	Case	8	74.00	85.02	100.5	-102	156	0.862
	Control	4	84.75	124.89	99.5	-80	220	
LDH (U/L)	Case	8	149.13	75.86	166	24	234	0.047
	Control	4	22.00	120.34	45	-126	124	
Creatinine (mg/dL)	Case	8	0.77	0.57	0.75	-0.31	1.5	0.111
	Control	4	0.25	0.17	0.295	0.01	0.4	
SGOT (U/L)	Case	8	12.88	18.77	4	-2	47	0.651
	Control	4	8.25	7.46	6	2	19	
SGPT (U/L)	Case	8	16.75	21.94	6	2	58	0.774
	Control	4	12.50	26.89	1.5	-5	52	

*Unpaired t-test

Within group analysis, D- dimer values on day 0 & 5 showed reduction in both Remdesivir and control groups. There was mean reduction of 99.88 ± 260.53 in Remdesivir group and 212.5 ± 192.65 in control group which was not significant on difference analysis (p=0.465).

Mean value of CRP on Day 0 was 69.75 ± 23.22 and on Day 5, 36.23 ± 35.48 in Remdesivir group suggesting statistically significant reduction following Remdesivir therapy (p=0.029). Mean value of CRP on Day 0 was 80.75 ± 12.45 compared to 92.50 ± 10.75 on Day 5 in control group which showed a significant increase (p= 0.011). There was an increase in CRP values in control group denoted by a negative value in difference analysis. A mean increase of 11.75 ± 4.11 was seen in control group as compared to mean reduction of 33.53 ± 34.56 in Remdesivir group, which was statistically significant (p=0.029). There was a reduction in ferritin values in both groups, but it was significant (p=0.043) in Remdesivir group only (Mean, 346 ± 128.51 on day 0 and 272 ± 98.15 on day 5). But comparing the magnitude of decrease in ferritin over a period of 5 days was not significant (p=0.862) between the two groups. There was a significant difference in LDH values day 0 & 5 in Remdesivir group (p<0.001). Mean reduction of LDH was 149.3 ± 75.86 in Remdesivir group compared to 22.00 ± 120.34 in control group, suggesting a significant change with Remdesivir treatment (p=0.047).

Creatinine decreased significantly in Remdesivir group with a mean value at Day 0 being 2.18 ± 0.74 and 1.41 ± 0.34 on day 5 (p =0.006). But on difference analysis, no significant reduction was noted over 5 day's period in either group (p=0.11).

AST was reduced in both groups (mean decrease 12.88 ± 18.77 in Remdesivir group and 8.24 ± 7.46) in the control group). But no statistically significant reduction was seen in either group (p=0.651). Likewise, ALT reduced in both groups over a period of 5 days but again, it was insignificant on difference analysis (p=0.774). No in-hospital deaths were reported in either group.

DISCUSSION

This non-randomized interventional study has shown benefits of Remdesivir in kidney transplant recipients with Covid-19. Those patients who received Remdesivir had shorter hospital stay (primary outcome) as compared to those who did not receive Remdesivir (mean, 10.38 days vs 18.50, p<0.001). In a landmark study, Beigel et al[5] showed that the initial length of hospital stay was shorter in the Remdesivir group than in the placebo group[4] (median, 12 days vs. 17 days); though this study was done in non-transplant patients. The duration of oxygen supplementation (another primary outcome) was significantly less in the Remdesivir group as compared to the control (Mean, 6.98 vs 12.85 days, p=0.002). Beigel et al also have shown that treatment with Remdesivir was associated with fewer days of subsequent oxygen use for patients receiving oxygen at enrollment[5].

C-reactive protein has been shown as a robust marker of inflammation in Covid19. In our study, there was significant reduction in CRP levels in the Remdesivir group on day 5 as compared to the baseline value at day 0 (Mean,36.23 vs 69.75, p=0.029). However, in the control group, there was significant increase of CRP on day 5 from the baseline (Mean, 92.50 vs 80.75, p=0.011). This data suggests that

Remdesivir possibly attenuate inflammation induced by Covid19 and frequent monitoring can assess the biochemical efficacy (secondary outcome) of Remdesivir.

D-Dimer is a diagnostic marker of coagulopathy in Covid19. In our study, there was no significant serial change (p=0.465) in D- dimer values in either group. No patient in either group had deep vein thrombosis. Even though acute renal failure improved in Remdesivir group, there was no significant change in D-Dimer suggesting that elevated Creatinine values were due to Covid19. Ferritin, an acute phase reactant, is elevated in Covid19. Although, there was significant reduction in ferritin following Remdesivir therapy (Mean, 272 vs 346, p=0.043), the magnitude of reduction compared between these two groups was not statistically significant (p=0.862). Thus, ferritin is not a reliable marker to monitor biochemical efficacy of Remdesivir. There was significant reduction in LDH on day 5 from the baseline in Remdesivir group (Mean, 247.25 vs 396.38, p<0.001) as compared to controls. Magnitude of reduction compared between the two groups was also significant in Remdesivir group (p=0.047). Since LDH is present in lung tissues, patients with moderate to severe Covid19 can be expected to release greater amounts of LDH in the circulation. Significant reduction in LDH following Remdesivir in our study suggests that lung inflammation is markedly attenuated by Remdesivir which is further corroborated by significant reduction in CRP values.

Our study data suggests that serial CRP and LDH (reflecting lung inflammation) are useful markers to assess the biochemical efficacy (secondary outcome) of Remdesivir in kidney transplant recipients with Covid19.

Yorg Azzi et al [10] have shown that CRP level was >10 mg/dl in 48 % patients, ferritin level >900 mg/ml in 63%, 84% patients had D-dimer level >0.5 mg/ml and 67% patients had LDH level >1.5 times the upper range of normal in kidney transplant recipients with Covid19 in New York city. In another study by Akalin et al [11], inflammatory markers were measured, and 36% patients had ferritin levels higher than 900 mg per milliliter, 46% had CRP levels higher than5 mg per deciliter and 57% had d-dimer levels higher than 0.5 µg per milliliter in renal transplant recipients. However, investigators in both these studies did not give Remdesivir to transplant recipients with Covid19.

We demonstrated beneficial effect of Remdesivir on creatinine levels. Creatinine levels decreased significantly in Remdesivir group on day 5 as compared to baseline value on day 0 (mean, 1.41 vs 2.18, p=0.006). Acute kidney injury has been seen in several studies[12]. Acute kidney injury is not uncommon in COVID-19, and its pathophysiology remains uncertain, but direct parenchymal infection and microangiopathy mediated by complex inflammatory processes have been suggested [13].

Transplant patients are at a high risk of Covid19 infection due to multiple risk factors, including immunosuppression, underlying CKD, and associated comorbidities, especially hypertension and diabetes[14]. Many studies have shown adverse outcome of such comorbidities in COVID-19 patients [15,16]. However, no in-hospital mortality was observed in our study in either group. In the largest multicenter series, Cravedi et al[17] reported 32% mortality in 144 inpatients. Kates et al [18] reported 28-day mortality as 18% from its dataset in which 254 of 318 patients were hospitalized.

Our study did not observe derangement in liver function tests in either group on day 0 & 5. Remdesivir was well tolerated by kidney transplant recipients.

The major limitations of this study are its small size and non-randomization for Remdesivir therapy. However, larger randomized control studies are required to substantiate our findings.

CONCLUSION

This small study has demonstrated possible beneficial role of Remdesivir in kidney transplant recipient patients with Covid19 with respect to primary outcomes- hospital stay and duration of oxygen support. Serial CRP and LDH (reflecting lung inflammation) are reliable markers to assess biochemical efficacy (secondary outcome) of Remdesivir. Also, Remdesivir is safe in kidney transplant recipients.

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ABBREVIATIONS

CRP: C Reactive Protein

LDH: Lactate Dehydrogenase

RT-PCR: Real-Time Polymerase Chain Reaction

eGFR: Glomerular Filtration Rate

AST/ALT: Aspartate Aminotransferases/ Alanine Transaminase

References

1 Hu Z, Song C, Xu C, et al. Clinical characteristics of 24 asymptomatic infections with COVID-19 screened among close contacts in Nanjing, China. Sci China Life Sci. 2020;63(5):706–11. https://doi. org/10.1007/s11427-020-1661-4.

2 Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. JAMA Published online April 22, 2020. https://doi.org/10.1001/jama.2020.6775.

3 RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19: Preliminary Report. N Engl J Med https://doi.org/10.1056/nejmoa2021436.

4 Alberici F, Delbarba E, Manenti C, et al. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney Int. 2020;97(6):1083–8. https://

doi.org/10.1016/j.kint. 2020.04.002.

5 Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, Kalilal AC et al. Remdesivir for the Treatment of Covid-19- Final Report. N Engl J Med 2020; 383:1813-1826. DOI: 10.1056/NEJMoa2007764.

6 Spinner CD, Gottlieb RL, Criner GJ et al. Effect of Remdesivir versus standard care on clinical status at 11 days in patients with moderate COVID-19: a randomized clinical trial. JAMA 2020; 324: 1048-57.

7 Chaudhry ZS, Williams JD, Vahia A, et al. Clinical characteristics and outcomes of COVID-19 in solid organ transplant recipients: a case-control study. Am J Transplant. Published online July 12, 2020:ajt.16188. https://doi.org/10.1111/ajt.16188.

8 Pereira MR, Mohan S, Cohen DJ, et al. COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transplant. 2020;20(7):1800–8. https://doi.org/10.1111/ajt.15941.

9 Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. N Engl J Med. 2020;382(25):2475–7. https://doi.org/10. 1056/NEJMc2011117.

10 Azzi Y, Parides M, Alani O, Loarte-Campos P, Bartash R, Forest S, et al. COVID-19 infection in kidney transplant recipients at the epicenter of pandemics Kidney International (2020) 98,1559-1567;https://doi.org/10.1016/j.kint.2020.10.004).

11 Akalin E, Azzi Y, Bartash R, Seethamraju H, Parides M, Hemmige V, et al. Covid-19 and KidneyTransplantation.DOI:10.1056/NEJMc2011117.

12 Mahalingasivam V, Craik A, Tomlinson L, Ge L, Hou L, Wang Q, Yanget K et al. A Systematic Review of COVID-19 and Kidney Transplantation. Kidney Int Rep (2021) 6, 24–45; https://doi.org/10.1016/j.ekir.2020.10.023).

13 Batlle D, Soler MJ, Sparks MA, et al. Acute kidney injury in COVID-19: emerging evidence of a distinct pathophysiology.J Am Soc Nephrol. 2020;31:1380–1383).

14 Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult in-patients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet.2020 Mar 28; 395(10229): 1054–62.

15 Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med.2020 April 30; 382(18): 1708–20.

16 Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Feb 15; 395(10223): 497–506.

17 Cravedi P, Mothi SS, Azzi Y, et al. COVID-19 and kidney transplantation: results from the TANGO International Transplant Consortium. Am J Transplant 2020;20:3140–3148.

18 Kates OS, Haydel BM, Florman SS, et al. COVID-19 in solid organ transplant: a multi-center cohort study. Clin Infect Dis. doi:https://doi.org/10.1093/cid/ciaa1097.