6. Sourial MY, Sourial MH, Dalsan R, et al. Urgent peritoneal dialysis in patients with COVID-19 and acute kidney injury: a single-center experience in a time of crisis in the United States. *Am J Kidney Dis*. 2020;76:401–406.
7. El Shamy O, Patel N, Abdelbaset MH, et al. Acute start peritoneal dialysis during the COVID-19 pandemic: outcomes and experiences. *J Am Soc Nephrol*. 2020;2:377–380.
8. Burgner A, Ikizler TA, Dwyer JP. COVID-19 and the inpatient dialysis unit: managing resources during contingency planning pre-crisis. *Clin J Am Soc Nephrol*. 2020;15:720–722.
9. Cleveland Clinic. An in-house solution to address a national shortage of dialysate [video]. Available at: https://consultqd.clevelandclinic.org/an-in-house-solution-to-address-a-national-shortage-of-dialysate-video. Accessed September 17, 2020.

Safety of Remdesivir in Patients With Acute Kidney Injury or CKD

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Patients with chronic kidney disease (CKD), especially those with end-stage renal disease (ESRD), are susceptible to the development of severe coronavirus disease 2019 (COVID-19), which is associated with high mortality.[1] Apart from respiratory support depending upon the severity of the respiratory involvement, management of COVID-19 is largely supportive. Remdesivir is a nucleotide analog that inhibits viral RNA-dependent RNA polymerase (RdRp) and that was issued an emergency use authorization by the U.S. Food and Drug Administration in May 2020. The active metabolite of remdesivir is eliminated by the kidneys and can accumulate in patients with reduced estimated glomerular filtration rate (eGFR); moreover, the sulfobutylether-β-cyclodextrin (SBECD) carrier is known to accumulate in these patients. The largest clinical trial evaluating the use of this agent in COVID-19 excluded patients with stage 4 CKD or those requiring dialysis (i.e., eGFR <30 ml/min/1.73 m^2).[2] We aimed to report our single-center experience using remdesivir in patients with COVID-19 who had acute kidney injury (AKI) and CKD.

RESULTS

One hundred fifty-seven patients with COVID-19 who were admitted to the intensive care unit or our nephrology high dependency unit between July 7 and September 22, 2020 had either AKI or CKD. Forty-six of 157 (29.3%) cases were treated with remdesivir. The median age of these patients was 53.1 years (range 15–84 years) and 30 (65.2%) were male. Renal diagnoses were ESRD in 16 (34.7%) and AKI in 30 (65.2%%) patients. Eight (17.4%) of 46 patients were recipients of live donor kidney transplants. Of 30 patients with AKI, 3 (6.5%), 2 (4.3%), and 25 (83.3%) patients had Kidney Disease: Improving Global Outcomes AKI stages 1, 2, and 3, respectively. Notably, all patients with stage 1 and 2 AKI were kidney transplant recipients. Table 1 shows the baseline characteristics of these cases. Comorbidities included hypertension in 35 (76%) patients, diabetes in 26 (56.5%) patients, coronary artery disease in 4 (8.7%) patients, nephrolithiasis in 3 (6.5%) patients, and HIV in 1 (2.2%) patient. Twelve (26%) patients were treated in the intensive care unit. At the time of initiation of remdesivir, oxygen requirements were as follows: noninvasive ventilation ($n = 7$), high flow nasal canula ($n = 1$), nonrebreathing mask ($n = 11$), face mask ($n = 15$), and nasal prongs ($n = 12$). Further in the course of illness, 9 (19.5%) patients required invasive mechanical ventilation.

Remdesivir (COVIFOR, Hetero Labs Limited [Hyderabad, India], under license from Gilead Sciences, Inc [Foster City, CA]) was administered as a total dose of 600 mg (200 mg on day 1, followed by 100 mg/day), which was extended in 2 patients to 1200 mg because satisfactory clinical improvement was not observed. The median number of days from hospital admission to starting remdesivir was 5 days (range 1–26 days). The

Table 1. Baseline characteristics and patient response to remdesivir therapy

Case no.	Age/ sex	Kidney disease (if AKI- KDIGO staging)	Co-morbidities	Duration of symptoms before remdesivir, days	O_2 need before starting remdesivir	Serum AST/ALT, IU/L		Dose of remdesivir, mg	Patient outcome if still admitted (WHO ordinal score change)
						Before starting remdesivir	Peak (if present)/within 48 hrs of cessation of therapy		
1	56/ M	ESRD	HTN, DM	11	NRBM, 6 L/min	118/81	26/25 (improved)	600	Died
2	65/ M	ESRD	HTN, DM	1	HFNC	24/14	20/10	600	Died
3	62/F	AKI 3	HTN, DM, CKD, nephrolithiasis	3	NIV	13/16	Death[a]	500	Died
4	42/ M	AKI 3	HTN, CKD	10	NRBM, 6 L/min	39/14	Day 5: 57/33, day 9: 19/21 (grade 1 AST elevation)	600	Discharged
5	55/ M	ESRD	HTN	4	FM, 4 L/min	20/20	23/16	1200	Discharged
6	50/F	AKI 3	HTN, DM	4	FM, 8 L/min	133/101	14/30 (improved)	600	Discharged
7	68/ M	AKI 3	HTN, DM, CAD, CKD	2	NRBM, 6 L/min	76/56	43/36 (improved)	500	Died
8	50/F	AKI 3	HTN, DM, CKD	2	FM, 10 L/min	41/27	36/23	200	Died
9	50/ M	ESRD	DM	3	NRBM, 8 L/min	69/67	41/62 (persistent grade 1 ALT elevation)	400	Died
10	52/ M	AKI 3	None	7	NIV	101/66	25/31 (improved)	300	Died
11	27/ M	AKI 3	KTR, HTN, Beta thalassemia trait	12	NP, 4 L/min	40/27	Day 5: 39/57, day 9: 15/30 (grade 1 ALT elevation, improved at day 9)	600	Discharged
12	38/ M	AKI 3	None	4	NIV	35/41	20/9	600	Discharged
13	49/ M	ESRD	HTN, DM, CAD	5	FM, 4 L/min	33/22	30/20	600	Discharged
14	44/F	AKI 3	HTN, CKD	8	NRBM, 6 L/min	28/14	27/11	600	Discharged
15	65/ M	AKI 3	HTN, DM, CKD	10	NRBM 12 L/min	20/12	Day 3: 65/18 (grade 1 AST elevation), death[a]	600	Died
16	50/ M	AKI 3	KTR, DM	7	NP, 4 L/min	20/11	32/8	600	Discharged
17	75/F	ESRD	HTN, DM	10	NP, 6 L/min	21/9	27/9	600	Admitted (4 to 3)
18	50/F	AKI 2	KTR, beta thalassemia trait	10	NP, 2 L/min	21/9	48/39	600	Discharged
19	39/ M	AKI 3	KTR, HTN, DM	8	NP, 2 L/min	24/9	20/11	600	Discharged
20	43/F	AKI 3	HTN, CKD	7	NP, 4 L/min	16/11	20/13	600	Discharged
21	52/F	ESRD	HIV, PTB	4	FM, 4 L/min	116/77	44/39 (improved)	600	Discharged
22	48/F	AKI 1	KTR	3	NRBM, 8 L/min	23/13	34/17	1100	Discharged
23	60/ M	AKI 3	HTN, DM, CKD	8	NIV	34/23	44/20	600	Died
24	15/F	AKI 3	CKD	15	NRBM, 8 L/min	164/219	48/113 (improved)	500	Discharged
25	38/F	ESRD	HTN, CKD, PTB	2	FM, 4 L/min	105/27	59/19 (improved)	600	Discharged
26	46/F	AKI 1	KTR, HTN, DM	8	NP, 2 L/min	27/33	24/16	600	Discharged
27	84/ M	AKI 3	HTN, DM, CKD	15	NP, 4 L/min	22/31	25/28	600	Discharged
28	53/ M	ESRD	HTN, DM	1	NIV	56/62	22/15 (improved)	600	Discharged
29	68/ M	ESRD	HTN, DM, CAD	7	NP, 4 L/min	22/10	23/18	600	Discharged
30	36/F	AKI 3	HTN, CKD, PTB	6	FM, 6 L/min	36/17	19/8	600	Discharged
31	48/ M	ESRD	HTN, CAD	4	NRBM 8 L/min	96/40	37/25 (improved)	600	Died
32	58/ M	AKI 2	HTN, DM, KTR	4	FM, 4 L/min	49/22	25/24	600	Discharged
33	50/ M	AKI 3	HTN, DM, PTB	4	FM, 6 L/min	27/25	19/18	600	Died

(Continued on following page)

Table 1. (Continued) Baseline characteristics and patient response to remdesivir therapy

Case no.	Age/ sex	Kidney disease (if AKI- KDIGO staging)	Co-morbidities	Duration of symptoms before remdesivir, days	O_2 need before starting remdesivir	Serum AST/ALT, IU/L		Dose of remdesivir, mg	Patient outcome if still admitted (WHO ordinal score change)
						Before starting remdesivir	Peak (if present)/within 48 hrs of cessation of therapy		
34	58/ M	AKI 3	CKD, nephrolithiasis	18	NIV	12/12	18/10	500	Died
35	71/F	AKI 3	HTN, DM, CKD	7	FM, 4 L/min	17/11	19/11	600	Discharged
36	60/ M	ESRD	HTN, DM	10	FM, 8 L/min	52/25	35/21 (improved)	600	Died
37	80/ M	ESRD	HTN, CKD, nephrolithiasis	15	NRBM, 15 L/ min	55/10	26/24 (improved)	600	Discharged
38	70/ M	AKI 3	HTN, DM, CKD	5	NP, 2 L/min	25/19	25/24	600	Admitted (4)
39	52/ M	AKI 3	HTN, DM, CKD	14	NP, 2 L/min	31/18	19/20	600	Discharged
40	73/ M	ESRD	HTN, DM	15	FM, 6 L/min	42/29	34/23	600	Admitted (4)
41	30/F	AKI 3	SLE, CKD	4	FM, 6 L/min	41/16	39/18	600	Died
42	25/ M	AKI 1	HTN, DM, KTR	3	NP, 4 L/min	57/50	Day 5: 41/108 (persistent grade 1 ALT elevation), day 6: 37/140, day 9: 28/99 (improving)	600	Admitted (4-3)
43	82/ M	ESRD	HTN	1	FM, 4 L/min	25/10	24/14	600	Admitted (4)
44	57/F	AKI 3	RHD	3	NRBM, 15 L/ min	32/54	(Ongoing) day 3: 24/28 (improving)	400	Admitted (5)
45	64/ M	AKI 3	HTN, DM, CKD	5	NIV	23/17	47/21	600	Admitted (6)
46	36/F	ESRD	HTN, CKD, PTB	10	FM, 4 L/min	12/14	(Ongoing) day 2: 11/14	200	Admitted (4)

CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; ESRD, end-stage renal disease; F, female; FM, face mask; HFNC, high flow nasal cannula; HTN, hypertension; KDIGO, Kidney Disease: Improving Global Outcomes; KTR, kidney transplant recipient; M, male; NIV, noninvasive ventilation; NP, nasal prongs; NRBM, non-rebreathing mask; PTB, pulmonary tuberculosis; RHD, rheumatic heart disease; SLE, systemic lupus erythematosus; WHO, World Health Organization.
Reference upper limit of normal for men and women: ALT ≤ 40 IU/L, AST ≤ 40 IU/L.
[a]Further trend of AST/ALT not available.

median duration of follow-up was 15.5 days (range 6–81 days). Thirty-six (78.2%) patients were on dialysis (ESRD [$n = 16$] and AKI [$n = 20$]) at the time of initiation of therapy. Therapy could not be completed in 6 patients who died. Remdesivir was discontinued early because of clinical improvement in 2 patients, and therapy is ongoing in 2 patients.

Most patients tolerated the infusion well except for patient 43 who had an infusion reaction with hypertension, breathlessness, and a drop in oxygen saturation, and the patient responded immediately to steroids and antihistamine treatment. Transient behavioral changes were noted in 5 cases and acute gout was observed in 1 patient while they were undergoing therapy (World Health Organization–Uppsala Monitoring Center causality category: possible) (Supplementary Methods). Baseline liver function test abnormalities (elevated aspartate aminotransferase [AST]/alanine aminotransferase [ALT] levels) were noted in 14 (30.4%) cases before starting remdesivir—grade 1 elevation in 13 patients (AST in 4, ALT in 1, and both AST and ALT in 8) and grade 2 elevation in 1 patient, which improved by the end of therapy in 12 cases. Liver function remained stable in 28 (60.9%) cases. Three (6.5%) patients were found to have newly occurring grade 1 elevations of AST/ALT during therapy. No patient had a severe rise in AST/ALT >5 times the upper limit of normal, therefore therapy was not required to be discontinued for this reason in any of the patients. No renal function abnormalities attributable to drug were observed (Table 2). Fourteen (30.4%) patients died, 24 (52.2%) patients were discharged from the hospital after recovery, and 8 (17.3%) cases are still admitted, of which 2 are still undergoing treatment.

DISCUSSION

We observed no clinically significant ALT elevations and no patients needed early discontinuation of therapy because of side effects. Twenty-four treated patients were discharged from the hospital. No significant abnormalities of renal function attributable to the drug were noted in any of the patients.

Apart from dexamethasone,[3] remdesivir is the only other pharmaceutical agent approved for use in COVID-19. Trials evaluating this agent have excluded patients with impaired kidney function, so there are no data on its efficacy and safety in renal failure. The national clinical management protocol[4] states that the use of remdesivir is contraindicated in patients with eGFR <30 ml/min/1.73 m^2 or when there is a need for hemodialysis. A policy of withholding its use in patients with kidney diseases because of lack of safety data can deprive these patients of one of the only

Table 2. Renal function during remdesivir therapy in patients with AKI

Case	Serum creatinine at admission, mg/dl	KDIGO AKI stage	Serum creatinine before initiation of remdesivir, mg/dl	Peak serum creatinine on remdesivir therapy, mg/dl	Serum creatinine at completion/within 48 hrs of therapy, mg/dl
3	6.6	3	On dialysis	On dialysis	Death[a]
4	15.6	3	On dialysis	On dialysis	On dialysis
6	7.7	3	On dialysis	On dialysis	On dialysis[b]
7	8.0	3	On dialysis	On dialysis	Death[a]
8	7.9	3	On dialysis	Death[a]	Death[a]
10	6.1	3	On dialysis	Death[a]	Death[a]
11	3.5	3	4.5	3.7	2
12	7.3	3	2.9	2.7	2.5
14	5.5	3	4	3.7	3.2
15	8.2	3	On dialysis	On dialysis[c]	Death[a]
16	5.7	3	5.9	5.5	4
18	2.1	2	2.3	2.1	1.7
19	4.72	3	6.0	4	2.2
20	7.0	3	On dialysis	On dialysis	Death[a]
22	2.32	1	2.2	2.3	2.1
23	11.8	3	On dialysis	On dialysis	Death[a]
24	6.7	3	On dialysis	On dialysis	On dialysis
26	1.6	1	1.6	1.6	1.4
27	9.0	3	On dialysis	On dialysis	On dialysis
30	8.7	3	On dialysis	On dialysis	On dialysis
32	2.0	2	2.0	1.7	1.4
33	6.0	3	On dialysis	On dialysis	On dialysis
34	9.8	3	On dialysis	On dialysis	On dialysis
35	4.1	3	6.8[b]	6.6	6.1
38	11.0	3	On dialysis	On dialysis	On dialysis
39	9.8	3	On dialysis	On dialysis	On dialysis
41	7.3	3	On dialysis	On dialysis	On dialysis
42	1.4	1	1.79	1.9	1.5
44	4.7	3	On dialysis	On dialysis	On dialysis
45	11.5	3	On dialysis	On dialysis	On dialysis

AKI, acute kidney injury; KDIGO, Kidney Disease: Improving Global Outcomes.
All patients with end-stage renal disease were receiving hemodialysis or slow, low efficacy dialysis as a modality of renal replacement.
[a]Serum creatinine values not available.
[b]Patient 6 achieved dialysis independence 5 days after the completion of therapy (creatinine at discharge 2.5 mg/dl). Patient 35 received 2 sessions of dialysis before remdesivir therapy, after which creatinine showed a dropping trend.
[c]Patient 15 received 1 session of hemodialysis followed by peritoneal dialysis for 28 hrs. All other patients requiring dialysis were undergoing hemodialysis.

available therapeutic options. Although remdesivir has not been shown to reduce mortality, its use decreased the time to recovery in patients with moderate and severe COVID-19. It has been suggested that remdesivir can be used with close monitoring in patients with renal impairment.[5]

Unmodified alpha- and beta-cyclodextrins are typically reabsorbed and concentrated in renal tubules and interact with cellular structures affecting cell integrity. SBECD was designed to address this problem; it remains in an ionized state after glomerular filtration and does not undergo significant tubular reabsorption. Although SBECD accumulates in patients with decreased eGFR, elevation in the serum creatinine did not correlate with SBECD levels.[6] Moreover, SBECD carrier is effectively removed by dialysis; a 4-hour session removes almost half of the accumulated SBECD.[7]

This is the first report of the use of remdesivir in patients with severely reduced kidney function, and our findings suggest that it is tolerated well. Mild derangement in the liver function tests at baseline improved post-treatment. Although it is not possible to attribute such improvement to drug use, it suggests that mild elevations in transaminases should not be considered as a contraindication.

Our study has several limitations. Most of our patients were on hemodialysis, so we cannot comment on its safety in patients with severe renal impairment but not yet on dialysis. We did not measure serum concentration of the SBECD, so the extent of its accumulation in our patients is not known. However, accumulation of SBECD does not correlate with rise in creatinine. We used the aqueous formulation of remdesivir which has double (6 g vs. 3 g) the concentration of SBECD than powdered form, which can be preferentially used in patients with renal impairment. Although our patients tolerated the drug well, the safety and efficacy of remdesivir cannot be determined without control subjects.

In conclusion, remdesivir was well tolerated in patients with AKI and CKD including those on hemodialysis. Larger, well-controlled studies evaluating its safety and efficacy in patients with kidney diseases are needed.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

REFERENCES

1. Valeri AM, Robbins-Juarez SY, Stevens JS, et al. Presentation and outcomes of patients with ESKD and COVID-19. *J Am Soc Nephrol*. 2020;31:1409–1415.
2. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19 – final report. *N Engl J Med*. 2020;383:1813–1826.
3. RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in hospitalized patients with Covid-19 – preliminary report [e-pub ahead of print]. *N Engl J Med*. https://doi.org/10.1056/NEJMoa2021436. Accessed November 1, 2020.
4. Director General of Health Services, Ministry of Health and Family Welfare, Government of India. Clinical management

protocol: COVID-19 (version-5). New Delhi: EMR Division. Available at: https://www.mohfw.gov.in/pdf/UpdatedClinicalManagementProtocolforCOVID19dated03072020.pdf. Accessed August 8, 2020.

5. Adamsick ML, Gandhi RG, Bidell MR, et al. Remdesivir in patients with acute or chronic kidney disease and COVID-19. *J Am Soc Nephrol*. 2020;31:1384–1386.

6. Luke DR, Tomaszewski K, Damale B, Schlamm HT. Review of the basic and clinical pharmacology of sulfobutylether-beta-cyclodextrin (SBECD). *J Pharm Sci*. 2020;99:3291–3301.

7. Luke DR, Wood ND, Tomaszewski KE, Damle B. Pharmacokinetics of sulfobutylether-β-cyclodextrin (SBECD) in subjects on hemodialysis. *Nephrol Dial Transplant*. 2012;27:1207–1212.

CKD of Unknown Origin in Supebeda, Chhattisgarh, India

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Chronic kidney disease (CKD) is predominantly caused by diabetes, hypertension, and glomerular diseases. Nephrotoxic drugs, herbal medications, toxins, and infection are other causes of CKD in developing countries.

A clustered increase in prevalence of CKD has been observed in select geographic areas in several countries over the past 2 decades.[1] The etiology of CKD cannot be attributed to the known or traditional risk factors or causes, and the term chronic kidney disease of unknown etiology (CKDu) has been used to describe this entity.[2] Young males belonging to agricultural communities comprise the most common affected demographic. In India, this condition has been described from coastal villages of Srikakulam district in Andhra Pradesh and parts of Odisha.[3,S1] A variety of hypotheses including prolonged dehydration leading to heat stress, heavy metal toxicity, pesticide exposure, snake bite and genetics have been proposed.[1]

Recent media reports have highlighted an unusually high number of the deaths due to kidney disease in the tribal village or Supebeda in the Indian state of Chhattisgarh (Supplementary Figure S1).[4] Twelve patients from this village with kidney dysfunction were referred to 2 hospitals in Raipur between November 2019 and March 2020. In this report, we describe the clinical presentation of these patients and present results of select toxicological analyses (Supplementary Methods).

CASE SERIES

The 12 patients in this series (Table 1) came from 9 families (Figure 1), and 8 (66.7%) were males. The median age was 46 (interquartile range: 16.5) years. A majority presented with weakness, body aches, and decreased appetite. None gave a history of edema, hypertension, diabetes, snakebite, or acute kidney injury. All the patients were or had been farmworkers and regularly used pesticides and fertilizers without protective equipment. Six (50%) were regular consumers of locally brewed alcohol, and 7 (58.8%) were tobacco users. All had used herbal and ayurvedic medications. Most patients were poor and uneducated. The predominant cereal used by these patients was rice, and the primary source of drinking water was communal shallow wells and hand pumps. The blood pressure was <140/90 mm Hg in 11 (91.7%) patients.

Table 2 shows the laboratory findings. Three (25%) patients each presented in stages 4 and 5 CKD, whereas 6 (50%) had stage 3 disease. The serum potassium level was low in 5 (41.7%) subjects, and 8 (66.6%) had hyperuricemia. Only 2 patients (16.7%) had