Material and methods

Remdesivir became available in our hospital from 5th July 2020. Patients admitted with severe COVID-19 and renal impairment due to either End Stage Renal Disease (ESRD) or Acute Kidney Injury (AKI) were evaluated for its use. ESRD was defined as patients with irreversible loss of renal function requiring dialysis for >3 months. AKI was defined as per clinical practice guidelines (2012) by Kidney Disease Improving Global Outcomes (KDIGO). Patients with all stages of AKI admitted to the intensive care unit and the nephrology high dependency unit till 22nd September 2020 were included. Primary outcome was studying the safety of remdesivir by evaluating clinical and laboratory parameters in these patients. Secondary outcomes were duration of hospital stay, mortality. Patients underwent clinical evaluation with recording of heart rate, respiratory rate, blood pressure, orthostasis and focused systemic examination. Laboratory evaluation included complete blood counts, renal and liver chemistries, serum electrolytes, arterial blood gas, C reactive protein, lactate dehydrogenase, interleukin 6, D dimer, and serum ferritin. A chest radiograph and high resolution CT scan of chest was done.

Patients were treated as per standard protocol which included respiratory support depending upon the degree of hypoxemia, antibiotics, prophylactic anticoagulation, and steroids (methylprednisolone or dexamethasone). Patients with severe COVID-19 (defined by room air oxygen saturation less than 94% or those requiring oxygen), after informed consent, were treated with intravenous remdesivir 200mg on day 1, followed by 100 mg daily for four consecutive days with therapy extended up to 10 days if indicated as per judgment of treating physician . Depending upon the severity of hypoxia, O2 by nasal prongs, face mask, rebreathing bag, High Flow Nasal Oxygen (HFNO) and Non Invasive Ventilation (NIV) was used. Patients were monitored clinically for vital parameters, fluid balance, pulse oximetry and cardiac monitoring. Renal and liver chemistries were obtained on days 0, 3, 5 and 7 day of remdesivir therapy in all, and daily in those with baseline AST/ALT abnormalities. AIDS- Clinical Trial Group (CTG) grading system for AST/ALT elevations was used. Relatedness of adverse events was judged by patient interview, clinical examination, laboratory corelation while considering the timing of the adverse event in relation to the timing of therapy. Patients were evaluated twice daily by nephrologists (authors DB, ST, AP) focusing on these aspects. This was followed by a discussion of patients' status with author TJ, during which adverse event adjudication was carried out. WHO-UMC scale was used for reporting adverse events. WHO- Ordinal scale was used to denote clinical status of patients who were still admitted.

Criteria for initiation of dialysis in patients with AKI were refractory fluid overload, hyperkalemia, metabolic acidosis, altered mental status attributed to uraemia or need of blood or blood product transfusions in the presence of oligo-anuria. Dialysis was provided either by intermittent haemodialysis or Slow Low Efficiency Dialysis (SLED) depending upon hemodynamic stability. Patients with ESRD were continued on intermittent haemodialysis, as per their schedule.

Reference grading criteria

AIDS Clinical Trials Group- Grading of liver injury[1]

Feature	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT	<1.25	1.25- 2.5	>2.5- 5.0	>5.0- 10	>10
AST	<1.25	1.25- 2.5	>2.5- 5.0	>5.0- 10	>10
ALP	<1.25	1.25- 2.5	>2.5- 5.0	>5.0- 10	>10
GGT	<1.25	1.25- 2.5	>2.5- 5.0	>5.0- 10	>10
Bilirubin	Normal	>1.0- 1.5	>1.5- 2.5	>2.5- 5	>5

Values expressed as multiples of the upper limit of the normal range (ULN)

WHO- UMC Causality Categories[2]

Causality term	**Assessment criteria***
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable / Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible)

	• Disease or other drugs provide plausible explanations
Conditional / Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable / Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Supplementary references

1. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Severity Grading In Drug Induced Liver Injury. [Updated 2019 May 4]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548241/

2. The use of the WHO-UMC system for standardised case causality assessment. [Last accessed on 2020 Sept 22]. Available from: http://www.WHO-UMC.org/graphics/4409.pdf .