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REMDESIVIR IN PATIENTS WITH ACUTE OR CHRONIC KIDNEY DISEASE IN COVID-19 AND IMPACT ON LIVER AND KIDNEY FUNCTION

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ABSTRACT

Introduction: Acute Kidney Injury is commonly present in Covid-19 hospitalised patients whereas chronic kidney disease and end-stage renal disease are also common comorbidities in patients who develop severe COVID-19. These patients require antiviral medication as early as possible but there is no current guidelines for use of Remdesivir therapy in these patents and drug is not used initially in these patients. Antiviral strategies are desperately needed in this population to treat these patients as early as possible. **Material And Methods:** We conducted an observational, retrospective cohort study of adults with COVID-19 confirmed by RT-PCR who had eGFR < 30mL/min/1.73m2 or received RRT prior to receiving at least one dose of Remdesivir. eGFR was estimated from the serum creatinine value just prior to the first dose of Remdesivir using the Chronic Kidney Disease Epidemiology Collaboration calculator. The majority of patients requiring supplemental oxygen were offered Remdesivir; eGFR cut-offs were not used as a strict exclusion criteria. All patients with eGFR < 30mL/min/1.73m2 who received at least one dose of Remdesivir in hospital were included in the study. AKI was defined as at least a 1.5-fold rise in creatinine from baseline per KDIGO criteria. CKD was defined as eGFR < 60mL/min/1.73m2 between 7-365 days prior to admission. Patients with "stable CKD" did not meet criteria for AKI at the time of starting Remdesivir. ESRD was defined as requiring RRT > 3 months prior to hospitalization. The primary objectives were to describe changes in ALT, AST, and Bilirubin and serum creatinine during Remdesivir therapy, and to report adverse effects attributed to Remdesivir. **Results:** A total of 41 patients with eGFR <30 ml/min per 1.73 m2 at the time of Remdesivir initiation were included in the study. 27 patients were in intensive care, and 14 patients were mechanically ventilated at the time of Remdesivir initiation. At the time of Remdesivir initiation, 30 patients were receiving RRT. 11 patients with eGFR <30 ml/min per 1.73 m2 were not on RRT at the time of starting Remdesivir. Four patients developed ALT more than the upper limit of normal and only two patients developed ALT more than 5 times, that may be contributory to other factor also. **Conclusion:** In general, limited information is available on the impact of SARS-CoV-2 infection in patients with eGFR less than 30. Impact of Remdesivir on these patients and their liver and kidney functions are not well studied. Although the available clinical data are limited, but it shows that impact of Remdesivir on liver and kidney function in patients of eGFR less than 30 is limited. However further studies are needed.

KEYWORDS :

INTRODUCTION

Acute Kidney Injury is commonly present in Covid-19 hospitalised patients whereas chronic kidney disease and end-stage renal disease are also common comorbidities in patients who develop severe COVID-19. These patients require antiviral medication as early as possible but there are no current guidelines for use of Remdesivir therapy in these patients and drug is not used initially in these patients. Antiviral strategies are desperately needed in this population to treat these patients as early as possible. Novel Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infection results predominantly in pulmonary involvement (Coronavirus disease 2019, COVID-19), but a direct, SARS-CoV-2-induced liver damage has also been described[1].

Numerous mechanisms have been hypothesized to explain the pathogenesis of liver injury associated with COVID-19, such as direct cytotoxicity due to virus replication in the liver, immune-mediated inflammatory response, hypoxia and ischemia due to severe sepsis, drug toxicity, and worsening of pre-existing liver disease due to systemic illness. SARS-CoV-2 gains entry into host cells by binding of the SARS-CoV-2 spike protein to the angiotensin-converting enzyme 2 (ACE2) receptors[2]. However, the expression of ACE2 receptor in hepatocytes is limited. A recent study involving single-cell RNA sequential data analysis demonstrated the binding of the virus to ACE2 receptors in the cholangiocytes but not hepatocytes. There was also significantly higher ACE2 expression in the cell clusters of cholangiocytes (59.7%) than hepatocytes (2.6%). Contrary to the viral binding to the cholangiocytes, the liver injury in COVID-19 is primarily hepatocellular as opposed to a cholestatic, as evidenced by elevation in aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Viral hepatitis classically manifests with a hepatocellular injury that is ALT predominant; however, hepatocellular injury in COVID-19 appears to be AST predominant[3].

Data regarding the potential hepatotoxicity of remdesivir is currently limited, and there are no specific studies conducted with its use in patients with hepatic impairment. On cellular level, remdesivir has been demonstrated to be toxic to human hepatocytes, and the FDA has cautioned about the incidence of elevated liver enzymes in patients treated with remdesivir, indicating potential drug-induced liver injury. Given the increase in the frequency of liver dysfunction in patients with COVID-19, the attribution of hepatotoxicity to remdesivir is indeed challenging. Mild (Grade 1) to moderate (Grade 2) transaminasemia was observed in healthy volunteers who received remdesivir, with resolution upon discontinuation of remdesivir[4].

Thus, it is important to monitor liver function and evaluate hepatic safety of drugs administered to COVID-19 patients. Remdesivir (RDV), a nucleotide analogue RNA polymerase inhibitor, originally developed and tested for Ebola virus disease, showed in vitro efficacy against SARS-CoV-2, and experience on its efficacy and safety for COVID-19 is accumulating. However, hepatic safety of RDV in COVID-19 has not been the focus of detailed investigation. Here, we studied patterns of liver toxicity in 41 COVID-19 patients of acute or chronic kidney injury treated with RDV in the intensive care unit (ICU) of our hospital[5].

AIM AND OBJECTIVE

The objectives were to describe changes in ALT, AST, and Bilirubin and serum creatinine during Remdesivir therapy, and to report adverse effects attributed to Remdesivir.

MATERIAL AND METHODS

We conducted an observational, retrospective cohort study of adults with COVID-19 confirmed by RT-PCR who had eGFR < 30mL/min/1.73m2 or received RRT prior to receiving at least one dose of Remdesivir. eGFR was estimated from the serum creatinine value just prior to the first dose of Remdesivir using the Chronic Kidney Disease Epidemiology Collaboration calculator. The majority of patients requiring supplemental oxygen were offered Remdesivir; eGFR cut-offs were not used as a strict exclusion criteria. All patients with eGFR < 30mL/min/1.73m2 who received at least one dose of Remdesivir in hospital were included in the study. AKI was defined as at least a 1.5-fold rise in creatinine from baseline per KDIGO criteria. CKD was defined as eGFR < 60mL/min/1.73m2 between 7-365 days prior to admission. Patients with "stable CKD" did not meet criteria for

AKI at the time of starting Remdesivir. ESRD was defined as requiring RRT > 3 months prior to hospitalization. The primary objectives were to describe changes in ALT, AST, and Bilirubin and serum creatinine during Remdesivir therapy, and to report adverse effects attributed to Remdesivir.

RESULTS

A total of 41 patients with eGFR <30 ml/min per 1.73 m^2 at the time of Remdesivir initiation were included in the study. In our present study the mean age of the study subjects was 62.46±9.63 yrs. with range 40-82 yrs., with male preponderance (73.17%). 27 patients were in intensive care, and 14 patients were mechanically ventilated at the time of Remdesivir initiation. At the time of Remdesivir initiation, 30 patients were receiving RRT. 11 patients with eGFR <30 ml/min per 1.73 m^2 were not on RRT at the time of starting Remdesivir.

The Vitals of the study subjects were normal at the time of admission with mean systolic BP was 129.66±9.46, diastolic BP 75.68±6.34, Respiratory rate 22.61±3.36, and pulse rate 92.34±14.95. The mean oxygen saturation of study subjects was 94.54±2.80.

Table 1: The Renal function test of the study subjects before and after treatment with Remdesivir

	group	N	Mean	Std. Deviation	Std. Error Mean	P value
Blood Urea	Before trt	41	143.5048	51.71076	8.07586	.156
	Aftr trt	41	159.4318	48.84422	7.62819	
Creatinine	Before trt	41	4.6590	1.95698	.30563	.443
	Aftr trt	41	5.0016	2.06526	.32254	
Sodium	Before trt	41	137.7126	5.54770	.86641	.66
	Aftr trt	41	138.24	5.46	69.38635	
Potassium	Before trt	41	4.6653	.64974	.10147	.137
	Aftr trt	41	4.9232	.88498	.13821	

In our study the important renal component changes after treatment but these changes are not statistically significant. The mean blood urea of the study subjects before treatment in our study was 143.51±51.71, which increases to 159.43±48.84, with p value 0.156, serum creatinine before treatment was 4.66±1.96 which increases to 5.00±2.06, with statistically non-significant having p value 0.44, In our study serum sodium before treatment was 137.71±5.55 which increases to 138.24±5.46, with non-statistically significant having p value 0.66. Potassium is also non-significantly changed from 4.66±0.65 to 4.92±0.88 with p value 0.14.

Table 2: The Liver function test of the study subjects before and after treatment with Remdesivir

	group	N	Mean	Std. Deviation	Std. Error Mean	P value
Bilirubin (Total)	Before trt	41	.5802	.75365	.11770	.000
	Aftr trt	41	1.2680	.55790	.08713	
Bilirubin (Direct)	Before trt	41	.4293	.64894	.10135	.042
	Aftr trt	41	.6599	.29976	.04682	
SGOT	Before trt	41	44.4760	24.41863	3.81355	.000
	Aftr trt	41	65.8512	23.88642	3.73043	
SGPT	Before trt	41	33.09	22.202	3.467	.000
	Aftr trt	41	60.94	32.482	5.073	

Table 2 shows The Liver function test of the study subjects before and after treatment with Remdesivir. The mean Total bilirubin before treatment was 0.58±0.75, which increases to 1.26±0.56, with statistically significant difference having p value 0.0, The direct bilirubin before treatment was 0.43±0.65, which increases to 0.66±0.30, with p value 0.042, The mean SGOT level before treatment was 44.48±24.41, which increases to 65.85±23.88, with statistically significant difference having p value 0.0, The SGPT level before treatment was 33.09±22.20 which increases to 60.94±32.48 , with statistically significant difference, having p value-0.0. However, the rise in components of Liver function test mainly limited to only few subjects which causes overall mean level to rise, four patients developed ALT more than the upper limit of normal and only two patients developed ALT more than 5 times, that may be contributory to other factor also. The liver function test among majority of study subjects were non-significantly different in majority of the study subjects.

DISCUSSION

In our study Overall, in 41 hospitalized Covid-19 patients who received remdesivir in their treatment for covid-19 included, In our study The mean blood urea of the study subjects before treatment in our study was 143.51±51.71, which increases to 159.43±48.84, with p value 0.156, serum creatinine before treatment was 4.66±1.96 which increases to 5.00±2.06, with statistically non-significant having p value 0.44, In our study serum sodium before treatment was 137.71±5.55 which increases to 138.24±5.46, with non-statistically significant having p value 0.66. Potassium is also non-significantly changed from 4.66±0.65 to 4.92±0.88 with p value 0.14. However, Beigel et al[6]. only reported adverse events of grade 2 or higher; Goldman et al [7]. did not specify the grade of adverse events included in the study.1,7,8

In our present study Four patients developed ALT more than the upper limit of normal and only two patients developed ALT more than 5 times, that may be contributory to other factor also. whereas Goldman et al[7]. reported grade 3 and 4 adverse events in 2–6% of the patients. None of the patients that started with transaminases above ULN, including patients meeting exclusion criteria, had grade 2 or higher transaminase elevation. It is important to emphasize that remdesivir is not the only independent factor that could cause nephrotoxicity or hepatotoxicity in these patients. Both Covid-related and non-Covid related risk factors are known, However, in our patients, age was not identified as an independent risk factor for nephro- or hepatotoxicity. Remdesivir is extensively metabolized; for the prodrug and its metabolites, respectively,

In our present study The mean Total bilirubin before treatment was 0.58±0.75, which increases to 1.26±0.56, with statistically significant difference having p value 0.0, The direct bilirubin before treatment was 0.43±0.65, which increases to 0.66±0.30, with p value 0.042, The mean SGOT level before treatment was 44.48±24.41, which increases to 65.85±23.88, with statistically significant difference having p value 0.0, The SGPT level before treatment was 33.09±22.20 which increases to 60.94±32.48 , with statistically significant difference

In study by Rosa Zampino et al[5] they report a comparison of median ALT and AST levels between RDV-treated patients and patient treated with other drug such as LPV, but without RDV. In this study bilirubin increase occurred in 4 of 5 index patients on LPV/r. In contrast, the switch to RDV translated into a fast reduction of bilirubin and a significant increase in AST/ALT by day 3 of therapy in 4 of 5 patients. The single patient who did not receive HCQ with RDV (patient 4) did not show increase of ALT/AST levels. In no cases, RDV was discontinued because of liver injury.

CONCLUSIONS

On the basis of our study, we can conclude that there may be no reason for considering remdesivir contraindicated in nephrotoxicity and hepatotoxicity, However, monitoring remains necessary. Our observations indicate that kidney and liver dysfunction should not be an absolute contraindication for the use of remdesivir in Covid-19 patients, and that by regularly monitoring kidney and liver function, treatment with remdesivir can be justified in these patients.

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