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Research Article

REMDESIVIR INDUCED HEPATOTOXICITY IN SARS - COVID 19 INFECTED PATIENTS – A RETROSPECTIVE STUDY

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A R T I C L E I N F O

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A B S T R A C T

Background: Severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2/COVID-19) is primarily a respiratory tract infection which can also affect gastrointestinal system and liver. Remdesivir is being used for the treatment of COVID infection, but its adverse effect on liver is not clear. This study was conducted to understand the prevalence and severity of remdesivir induced hepatotoxicity in remdesivir treated patients.

Material and Methods: It was a retrospective case control study which was conducted over 150 COVID-19 infected patients at a tertiary care center. Liver function tests were compared in remdesivir treated and non remdesivir treated patients.

Results: Out of 150 patients, 75 patients received remdesivir and 75 patients received supportive care. Median values for serum alanine transaminase (ALT) and aspartate transaminase (AST) values were significantly higher in the remdesivir treated group (P-value <0.001 for both ALT and AST). Grade-2 elevations of ALT and AST values were significantly higher among the remdesivir treated group.

Conclusion: Liver injury can occur in COVID-19 infection. Remdesivir is one of the most recognized cause of hepatotoxity in these patients. Monitoring of liver function test is mandatory for remdesivir treated COVID patients.

INTRODUCTION

Corona virus is a serious health threat to mankind, which was first noted in china as an outbreak in 2019. Since then, it has become pandemic involving whole world. RNA virus named severe acute respiratory syndrome coronavirus–2 (SARS-CoV-2/COVID-19) identified as a causative organism, which is responsible for this pandemic according to WHO nomenclature.[1] Droplet inhalation is the most common mode of transmission for this infection. Reported incubation period is 7 to 14 days.[2,3] Clinical presentation is variable which can range from asymptomatic infection to multi organ failure.[3]

Currently available literature suggests that it is a multisystem disease with primary lung involvement.[4,5]COVID-19 infection manifests mainly with fever, dry cough, and respiratory distress.[3] Generalized pain abdomen, decreased appetite, nausea, vomiting, diarrhea are the most commonly associated gastrointestinal symptoms which can be associated with respiratory symptoms or sometimes can present as an isolated symptom of COVID -19 infection. COVID-19 related liver injury is mentioned in literature.[4]Therefore, it is important to watch liver functions tests and to monitor safety of drugs which are known for hepatotoxicity and being prescribed for treatment of COVID-19 infection.

Remdesivir is a nucleotide analog with antiviral activity against a wide range of corona viruses including COVID-19. ICMR (Indian council of medical research) approved remdesivir for use in COVID-19 patients.[6] Transaminitis is one of the most commonly noticed side effect of remdesivir in COVID-19 patients.[7] In the initial randomized clinical trials assessing the efficacy of remdesivir in hospitalized COVID-19 patients, significant proportion of patients developed jaundice or deranged liver function test results requiring prematurely stopping of medication.[7] Although currently available data do not show higher incidence of severe liver injury in remdesivir treated COVID-19 patients, further analysis required to underst and the prevalence and pattern of liver injury in remdesivir treated COVID-19 patients.

MATERIALS AND METHODS

It is a retrospective observational study conducted at a tertiary care center, over the patients admitted between May 2021 to august 2021. Data was collected from hospital electronic database. One hundred fifty RT- PCR positive patients with severe infection and age more than 18 years of age were included in the study according to case definition. Severe infection was defined as - 1. Respiratory rate >30/min, 2. breathlessness or SpO2 < 90% on room air according to ICMR guidelines.[3]COVD-19 patients with severe infection were

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categorized in 2 groups–1.those received at least 6 days remdesivir(200mg loading dose on day1, followed by100 mg daily for 5 subsequent days), 2. those patients who received only supportive are. Liver function tests were compared between both groups. Transaminase levels were graded according to EASL guidelines as Grade1: aspartate transaminase (ALT)≤3ULN, as partatetransaminase (AST)≤3ULN, total bilirubin (TBL) ≤1.5ULN, alkaline phosphatase (ALP)≤2.5ULN. Grade2:ALT3–5ULN, AST3–5ULN, TBL1.5–3.0 ULN, ALP 2.5–5.0 ULN. Grade3 :ALT5–20ULN,AST5–20ULN,TBL3–10ULN,ALP5–20 ULN.[8] Patients with history of liver disease , positive for hepatitis Band C infection, history of alcohol intake or consumption of drugs known for hepatotoxicity in last3 months were excluded from study.

Statistical Analysis

The collected data was entered in MS Excel-2010 and Statistical Analysis was performed with help of Epi Info (TM) 7.2.2.2 which is a trademark of the Centre for Disease Control and Prevention (CDC).Continuous parameters were mentioned as mean and SD, while categorical parameters were described as frequency and percentage. Chi-square test, student t-test, and Mann Whitney test was conducted for categorical, normal, and skewed continuous variables respectively. P-value of <0.05 was considered statistically significant.

RESULTS

One hundred and fifty patients were included in study. Seventy patients received remdesivir along with other supportive treatment and 75 received only supportive care without remdesivir. Mean age in remdesivir and non remdesivir group is 49.4 + 14.45 and 46.8 + 12.89 years respectively. Male were predominant in both groups and Male female ratio in both groups were 48/27 and 52/23 respectively. Median values for serum bilirubin, INR and serum albumin values were comparable in both groups, and no significant difference was noted. ALT and AST levels were significantly higher in remdesivir treated patients in comparison to non remdesivir group(P value for both ALT and AST were < 0.001). Alkaline phosphatase (ALP) levels were not significantly different in both groups (P value 0.21). (Table 1)

Demographic and biochemical parameters. **Table 1**

Parameters	Remdesivir group	Non Remesivir group	P Value
Age (mean + SD)	49.4 +14.45	46.8 +12.89	0.83
Gender- male/female - N(percentage)	48/27(1.77)	52/23 (2.26)	0.92
Serum Bilirubin (mg/dl)	0.72 (0.42 – 2.41)	0.64 (0.62 – 2.37)	0.86
ALT (IU/ml)	116 (32 – 260)	34 (30 – 232)	<0.001
AST (IU/ml)	132 (29 – 276)	30 (32 – 154)	< 0.001
ALP (IU/ml)	64 (86 – 176)	78 (112 – 180)	0.21
INR	1.01 (0.90 – 1.32)	1.12 (0.88 – 1.39)	0.52
Albumin (gm/dl)	3.62 (3.26 – 4.55)	3.74 (3.64 – 5.21)	0.72

Values are presented as median (range), mean±SD and numbers (percentage) ALT – Alanine Transaminase, AST – Aspartate Transaminase , ALP – Alkaline Phosphatase

Alanine transaminase (ALT) levels in remdesivir and non remdesivir groups **Table 2**

ALT Elevation	Treatment Group	Number (%)	Odds ratio	95 % CI	P value
Grade 1	Remdesivir group	32 (42.66)	1.38	0.71 –2.16	0.078
	Non remdesivir group	21 (28)	0.72	0.42 –1.26	
Grade 2	Remdesivir group	28 (37.33)	1.96	1.28 – 2.89	0.004
	Non remdesivir group	4 (5.3)	0.32	0.06 – 1.12	
Grade 3	Remdesivir Group	3 (4)	1.32	0.32 – 3.12	0.91
	Non remdesivir group	1 (1.3)	1.10	0.21 – 2.86	

ALT, Alanine aminotransferase; CI, Confidence interval.

Aspartate transaminase (AST) levels in remdesivir and non remdesivir groups **Table 3**

AST elevations	Treatment Group	Number (%)	Odds ratio	95 % CI	P value
Grade 1	Remdesivir group	34 (45.33)	1.32	0.86 – 2.67	0.461
	Non remdesivir group	24 (32)	0.68	0.54 – 1.63	
Grade 2	Remdesivir group	32 (42.66)	1.92	1.01 –1.43	0.039
	Non remdesivir group	7 (9.33)	0.56	0.21 – 1.11	
Grade 3	Remdesivir group	4 (5.33)	1.12	1.42 – 2.91	0.06
	Non remdesivir group	0 (0)			

AST, Aspartate aminotransferase; CI, Confidence interval.

Statistically non significant grade 1 elevation of ALT and AST was noted in remdesivir group, in comparison to non remdesivir group (42.66 % vs 28 % and 45.33 % vs 32 % respectively).

Although significant grade 2 elevation was seen in ALT and AST in remdesivir group in comparison to non remdesivir group (37.33 % vs 5.33 % and 42.66 % vs 9.33 % respectively). Odds ratio for grade 2 elevation of ALT and AST in remdesivir group was 1.96 with 95 % confidence interval (CI) 1.28 – 2.89 and 1.92 with 95 % CI 1.01 – 1.43 respectively. Transaminase elevation levels were mentioned in table 2 and 3.

DISCUSSION

Liver injury is a commonly encountered problem in COVID-19 patients. It can be seen in 10 – 50 % of COVID infected patients.[9-11]Fortunately liver related complications including liver failure is quite rare in COVID patients.[11]Mechanism for liver injury in COVID19 is multi factorial. It can occur by virus itself due to its hepatotropic nature. Plenty of angiotensin converting enzyme 2 (ACE2) receptors are present on hepatocytes, which act as a source of entry for COVID-19 virus.[12]Intracellular replication and cytotoxicity have been demonstrated in invitro studies.[12]Reverse transcription polymerase chain reaction (RT-PCR) based studies have shown presence of corona virus inside of liver tissues. [12]

Beside virus induced liver injury, hypoxic liver injury by circulatory failure or by acute inflammatory response in COVID infection are the other possible mechanisms of liver injury in COVID patients.[13,14]Sometimes drugs also can cause liver injury in COVID-19 patients. Common drugs which can cause liver injury in COVID patients are acetaminophen, chloroquine, herbal medications, ritonavir, lopinavir, tocilizumab, and remdesivir.[15,16] Among the drugsused in COVID treatment, remdesiviris one

of the most characterized culprit of drug induced liver injury in current pandemic. Remdesivir is a nucleotide analogue RNA polymer as inhibitor, which was originally used for the treatment of Ebola virus infection, also showed effectiveness against COVID19. [7] Several studies conducted in last few years mentioned higher prevalence of transaminitis after receiving remdesivir.[07,17-20]Current study also found similar results. In the current study, authors observed that remdesivir caused mild to moderate transaminitis (grade1and 2), which did not cause drug discontinuation in most of the patients. It is difficult to conclude that these patients developed transaminitis due to remdesivir or due to other COVID related factors. Authors noted higher incidence of transaminitis in remdesivir treated patients incomparison to patients treated with other supportive care, particularly grade 2 elevation of transaminaselevels were found to be statistically significant in remdesivir treated patients. An tinori et al reported 42 % prevalence of transaminitisand 20% prevalence of higher bilirubin in remdesivir treated patients.[9] In contras tto current study, Wan g e tal analysed efficacy and safety profile of remdesivir in COVID patients, and found that drug related adverse events including liver toxicity in similar in remdesivir treated patients in comparison to non remdesivir groups.[7] Zampino et al reported that incidence of transaminitisis uncommon and usually mild in COVID patients and it is comparable in both remdesivir and non remdesivir treated patients, which does not required drug discontinuation.[18]Beige let al also reported similar incidence of drug related side effects in remdesivir and non remdesivir treated patients.[21]Gold manet al mentioned ALT elevation of6%and8%afterreceiving remdesivir therapy for 5and10 days respectively.[20]

Mild elevation in transaminase levels in COVID patients after starting remdesivir a rereported in multiple studies.[7]It is worth to mention that first three patients of COVID infection in US who received remdesivir, developed mild transaminitis. [22] Greinet al reported 23% prevalence of transaminitis in remdesivir treated COVID patients, few of which required early drug discontinuation.[10] None of the patient in the current study showed clinical jaundice or bilirubin level more than 2.5 mg/dl. Grein et al reported severe transaminitis of grade 3 and 4 in only 7% of remdesivir receiving COVID patients and rare elevation in bilirubin level in 1.3 %.[10]At this moment,it is not clear how remdesivir causes hepatotoxicity. Similar to other nucleotide analogues, there are few possible mechanisms which can help to explain the possible role of remdesivir in hepatotoxicity. Functional impairment in mitochondria because of mitochondrial DNA synthesis inhibition is the most widely accepted hypothesis.[18] Mitochondrial dysfunction can lead to liver injury, neuropathy, bone marrow injury, muscle damage and pancreatitis .Other possible mechanisms of remdesivir induced liver injury are idiosyncratic reactions and direct injury by toxic metabolites.[21]Data is limited regarding treatment of remdesivir induced hepatotoxicity. Abdulrab et al suggested addition of ursodeoxycolic acid to the standard treatment because of its anti-inflammatory and immunomodulating function, beside stopping the remdesivir. [23] APASL guidelines consensus recommends strictly not to use remdesivir in patients with decompensated chronic liver disease patients and patients with transaminase levels more than five times from normal range.[24]

CONCLUSION

Multiple COVID patients develop mild transaminitis after acquiring infection. If liver enzymes shows advancement after starting remdesivir, drug related adverse effect should be considered as a possibility. If transaminitis is severe, drug discontinuation should be done. Fortunately in most of the patients, remdesivir induced liver enzyme elevations are mild and usually recovers without any consequences. Still it is not clear that drug induced transaminitis can precede severe liver injury. Regular liver function testing is mandatory during remdesivir treatment. Preferably remdesivir should avoid in patients with pre-existing liver illness or patients receiving other drugs known for hepatotoxicity.

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