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HEPATIC INJURY IN COVID 19 PATIENTS TREATED WITH REMDESIVIR AND ITS INTERACTION WITH HCQ

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ABSTRACT

INTRODUCTION Novel severe acute respiratory syndrome corona virus 2 (SARS COV 2) can lead to direct liver injury. Therefore monitoring of liver function test is important. However, the hepatic safety of Remdesivir is not clear due to the limited experience. Relationship between drug-drug interaction of Remdesivir and HCQ is also not clear. **OBJECTIVES** To describe the incidence and characteristics of Remdesivir induced hepatic injury among COVID 19 patients and to assess its interaction with HCQ at Sree Mookambika Institute of medical sciences, Kulasekharam, Kanyakumari. **METHODOLOGY** Medical Record review of 51 patients who fulfilled eligibility criteria and treated with Remdesivir at Sree Mookambika Institute of Medical Sciences, Kanyakumari. **RESULTS** Among the patient treated with Remdesivir and HCQ, 25 patients had elevated liver enzymes above 5 times of upper normal limit. Among the Patient treated with Remdesivir alone, only 1 patient had elevated liver enzymes above 5 times of upper normal limit. The p value is 0.012 and it is significant. **CONCLUSION:** Elevated liver enzymes is more common in patients treated with both Remdesivir and HCQ than patients treated with Remdesivir alone. This clearly shows that the influence of p-gp inhibitors on hepatotoxicity of Remdesivir. Therefore, Physicians should be cautious while using p-gp inhibitors for patient who is on treatment with Remdesivir.

KEY WORDS : Remdesivir, COVID-19, Hepatotoxicity, Alanine Transaminase.

INTRODUCTION

The ongoing pandemic of severe acute respiratory distress syndrome (SARS COV2) has led to millions of death all over the world. As of now Remdesivir is the most active drug against SARS COV 2. Dexamethasone has been shown to decrease mortality, with more benefits seen among patients receiving invasive mechanical ventilation. Remdesvir (GS-5734) (RDV), a nucleoside analogue drug, has inhibitory effects on corona virus, including MERS corona virus, SARS COV 1 and SARS COV2. SARS COV 2 can cause direct liver damage, hence monitoring of liver function and evaluation of hepatic safety of drugs given to COVID 19 patients is important. P-glycoprotein inhibitors (HCQ, Cyclosporine, Amiodarone) is a efflux transporter, which pumps out xenobiotics into the bile duct. If concurrently P-gp inhibitors given along with Remdesivir, it decreases efflux rate of Remdesvir and lead to hepatocellular concentration of Remdesivir above the threshold. In this study we describe about the liver toxicity in patients treated with Remdesivir in ICU of Sree Mookambika Institute of Medical Sciences, Kulashekharam, Kanyakumari during July 2020 to September 2020.

METHODOLOGY

Sree Mookambika Institute Of Medical Sciences, Kulashekaram, Kanyakumari is a 1000 bedded tertiary care centre in south Tamilnadu. Department of General Medicine and Pulmonology provides care to the COVID 19 patients from the beginning of COVID 19 pandemic in India. We conducted the retrospective case record review of all the 51 critically ill COVID 19 patients who met eligibility criteria and got admitted between July 2020 and September 2020. Patients who cleared all the eligibility criteria were studied. (no multiorgan failure before initiation of Remdesivir, no vasopressor required before initiation of Remdesivir, AST/ALT levels < 5 upper normal limit, normal renal parameters, patient on invasive mechanical ventilation or spo2 < 94% at room air or tachypneic at rest with respiratory rate greater than 24/min, radiologically confirmed pneumonia, COVID RT PCR positive). The exclusion criteria were pregnancy, lactating mothers, cirrhosis, AST OR ALT > 5 upper normal limit, severe renal failure (GFR< 30ml/min), patient on hemodialysis or peritoneal dialysis. The comorbidities, age, sex, minimal blood investigations and blood investigation which were done 12th hourly for all critically ill patients were observed. Treatment with HCQ was permitted in the study.

Remdesivir was administered IV as a 200mg loading dose on day 1 and 100mg maintenance dose of day 2 to day 5. The timing of Remdesivir dose and subsequent reports of liver function test and the other investigations were also studied. Patient's medication history and rise or fall of laboratory value of blood investigations were studied. Any adverse event developed during the treatment period were noted. The data were analysed by SPSS version 10.

RESULTS

Table 1: Patient's characteristics (n = 51)

Variable	Frequency (n =100)	Percentage
1.Age (years)		
< 60 years	17	33%
>60 years	34	67%
2. Sex		
Male	34	67%
Female	17	33%
3. Comorbidities	14	27%
Hypertension	17	33%
Type 2 diabetes mellitus	12	24%
Coronary Art Disease		
4. Smokers	20	39%
5. Treated with Remdesivir and HCQ	40	78%
6. Treated with Remdesivir only	11	22%
7. Elevated Liver Enzymes more than 5 times upper normal limit in patients treated with:		
Remdesivir and HCQ	25	62.5%
Remdesivir alone	1	9%

Out of 51 patients who were studied 33% of patients were less than 60 yrs of age, 67% were more than 60 years. 67% were males and 33% were females. 20 Patients were smokers, that is 39% of the study population. 27% Patient had Hypertension, 33% had type 1 diabetes mellitus and 24% had Coronary artery disease. 40 Patients were treated with Remdesivir and HCQ and 11 patients were treated with Remedesivir alone. Among the patient treated with Remedesivir and HCQ, 25 patients had elevated liver enzymes

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above 5 times of upper normal limit. Among the Patient treated with Remdesivir alone, only 1 patient had elevated liver enzymes above 5 times of upper normal limit. The p value is 0.012 and it is significant.

DISCUSSION

In The Pamoja Tulinde Maisha (PALM)study, hepatotoxicity was not documented in patients treated with Remdesivir in 175 patients of ebola virus. The Adaptive Covid-19 Treatment Trial (ACTT-1) showed that hepatotoxicity was less seen in COVID 19 patients treated with Remdesivir compared with Placebo. Wang et al, showed that 1 out of 155 COVID 19 patients had hepatotoxicity on treatment with Remdesivir. Goldman et al, Remdesivir was discontinued because of ALT elevations in 3% of patients which according to the authors could also have been caused by COVID 19 itself.

But our study which was conducted among 51 critically ill COVID 19 patients (34 males and 17 females) who came to the emergency department of Sree Mookambika Institute Of Medical Sciences. Elevated liver enzymes is more common in patients treated with both Remdesivir and HCQ than patients treated with Remdesivir alone. This clearly shows that the influence of p-gp inhibitors on hepatotoxicity of Remdesivir. Therefore, Physicians should be cautious while using p-gp inhibitors for patient who is on treatment with Remdesivir.

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