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Case Report

Acute Hepatic Failure with Hyperbilirubinemia in a Cirrhotic Patient Receiving Glecaprevir and Pibrentasvir (Mavyret®) For Hepatitis C Infection

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ABSTRACT

The Hepatitis C Virus (HCV) causes both acute and chronic hepatitis C infection, requiring treatment with Direct Acting Antiviral (DAA) therapy for 8-24 weeks. Glecaprevir/pibrentasvir (Mavyret®) is a fixed-dose combination of an NS3/4A protease inhibitor and NS5A inhibitor, respectively, targeted to decrease replication of the Hepatitis C Virus (HCV). Since its initial approval in 2017, it has gained indications to include management of pan-genotypic HCV with or without compensated cirrhosis in treatment-naïve or treatment-experienced individuals from children 3 years of age and older. The most common reported adverse effects are headache and fatigue; however, the FDA recently published a warning about rare occurrence of serious liver injury with the use of glecaprevir/pibrentasvir in some patients with advanced liver disease.

We discuss a patient with compensated liver cirrhosis who presented with shortness of breath and fatigue four weeks after initiation of therapy with glecaprevir/pibrentasvir for hepatitis C infection (genotype 1a), and was found to have progressively elevated bilirubin level. However, after discontinuation of glecaprevir/pibrentasvir, the patient's bilirubin normalized with significant improvement in fatigue. Close monitoring of liver function is advised when prescribing glecaprevir/pibrentasvir to patients with advanced liver disease.

Keywords: Hepatitis C virus; Hepatic failure; Hyperbilirubinemia; Infection

INTRODUCTION

Hepatitis C Virus (HCV) causes both acute and chronic hepatitis C infection, which may result in the development of liver cirrhosis, hepatocellular carcinoma, and death if not treated. According to the WHO, the estimated annual incidence of chronic hepatitis C infection is 58 million cases worldwide, resulting in approximately 290,000 deaths each year [1].

The American Associated for the Study of Liver Diseases and Infectious Diseases Society of America (AASLD/IDSA) guidelines recommend treatment with pan-genotypic Direct Active Antiviral (DAA) for 8-24 weeks depending on presence of absence of liver cirrhosis [2]. Glecaprevir and pibrentasvir (Mayvert®) is a fixed-dose combination of an NS3/4A protease inhibitor and NS5A inhibitor, respectively, targeted to decrease replication of the HCV. It was initially approved in 2017 and has since then gained indications to include management of pan-genotypic HCV with or without compensated cirrhosis in treatment-naive or treatment-experienced individuals from children 3 years of age and older. The dosage in 12 years old and greater is glecaprevir 300 mg and pibrentasvir 120 mg once daily. Duration of therapy ranges between 8 to 16 weeks depending on genotype and previously used therapies for HCV, if applicable. Major drug-drug interactions include concomitant use of P-gp inhibitors and substrates, which may require dose modification of the interacting drugs. Other interactions include those that may reduce the fixed-dose concentrations such as anticonvulsants and anti-mycobacterial or those that may increase its concentrations such as Human Immunodeficiency Virus (HIV) antiviral agents [3].

We report a case of a woman treated with glecaprevir/pibrentasvir

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for hepatitis C infection, which developed acute decompensation of liver disease and mixed hyperbilirubinemia.

CASE PRESENTATION

Our patient is a 63-year-old female with past medical history of hypertension, Chronic Obstructive Pulmonary Disease (COPD), opioid dependence, and chronic hepatitis C infection (genotype 1a) with compensated cirrhosis. She was prescribed glecaprevir/pibrentasvir (Mavyret®) 100-40 mg tablets and instructed to take 3 tablets daily with food for the treatment of hepatitis C. Four weeks after the initiation, she presented with worsening shortness of breath, requiring increased home oxygen supplementation and nebulizer use, fatigue, bilateral lower extremity swelling, and scleral icterus. She denied coughing, increased sputum production, change in stool color, abdominal pain, nausea, and vomiting. On admission to the hospital, she was tachypneic with an oxygen saturation of 91% on 3 liters of nasal cannula. All other vital signs were within normal limits. A chest x-ray revealed mild pulmonary vascular congestion, but otherwise was unremarkable. Her blood work was notable for mixed hyperbilirubinemia, thrombocytopenia, elevated aspartate Aminotransferase (AST), and reactive hepatitis C antibody. She had a non-reactive result for hepatitis A IgM, Hepatitis B surface antigen, and Hepatitis B core IgM, with an undetectable hepatitis C RNA level. Liver malignancy was ruled out based on normal Alpha-Fetoprotein (AFP) tumor marker, and urine toxicology screen was negative. A Magnetic Resonance Cholangiopancreatography (MRCP) was performed, but was negative for biliary tract obstruction or disease. Her bilirubin level continued to rise from 2.3 mg/dL on admission to 7.5 mg/dL two days later (Table 1). At that point, glecaprevir/pibrentasvir was discontinued and the bilirubin level began to decrease to 3.4 mg/dL three days later. As per the Naranjo Algorithm score of 6, the acute worsening of liver function was probably and adverse reaction to glecaprevir/pibrentasvir as described below Table 2.

Table 1: Liver function test trend during hospital admission.

	Day 0	Day 2	Three days after cessation of glecaprevir/pibrentasvir
Total bilirubin (mg/dL)	2.3	7.5	3.4
Direct bilirubin (mg/dL)	1.4	5.3	2.5
Indirect bilirubin (mg/dL)	<1	<1	<1
ALT (unit/L)	23	26	22
AST (unit/L)	54	52	42
Alk phos (unit/L)	88	95	76

Table 2: Naranjo algorithm applied to reported case.

Question	Yes	No	Do not know	Score	Total score
Are there previous conclusive reports on this reaction?	(+1)	0	0	1	6
Did the adverse event appear after the suspected drug was administered?	(+2)	-1	0	2	
Did the adverse event improve when the drug was discontinued, or a specific antagonist was administered?	(+1)	0	0	1	
Did the adverse event reappear when the drug was re-administered?	2	-1	0	0	
Are there alternative causes that could on their own have caused the reaction?	-1	2	0	0	
Did the reaction reappear when a placebo was given?	-1	(+1)	0	1	
Was the drug detected in blood or other fluids in concentrations known to be toxic?	1	0	0	0	
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	1	0	0	0	
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	0	
Was the adverse event confirmed by any objective evidence?	(+1)	0	0	1	

RESULTS AND DISCUSSION

It is important to note the efficacy of the classes of the DAA agents to utilize them in achieving Sustained Virologic Response (SVR), also known as HCV cure, in patients that qualify for the treatment. There have been numerous studies conducted to evaluate the efficacy of this fixed-dose combination. In HCV genotypes without cirrhosis, well over 90% achieved SVR [4,5]. This was also seen in those who HCV genotypes with compensated cirrhosis [6,7]. Efficacy has also been shown in those with chronic kidney disease, HIV/HCV co-infection, and most recently in the pediatric population [8-10]. There are some warnings and risks that are outlined in the literature and included in the package insert of these DAA agents. One risk that is highlighted is reactivation of Hepatitis B (HBV) when an individual is coinfected with hepatitis B and C viruses. It has been shown that hepatitis B surface antigen levels decrease during treatment with DAA for HCV. Upon completion of HCV treatment, reactivation of HBV may occur which can lead to hepatic failure if not managed. The recommendation in HBV/HCV co-infected patients is to prophylactically treat the HBV along with the treatment with DAA for HCV [11]. This was not applicable to our patient case but worth noting to ensure appropriate management clinically. Incidence of acute decompensated liver failure in NS3/4A protease inhibitor-containing fixed dose regimens has been reported by the Food and Drug Administration (FDA) as a total of 63 cases as of January 2019. These three fixed-dose combinations are the following, including case stratification: glecaprevir/pibrentasvir (Mavyret®) (n=46), elbasvir/grazoprevir (Zepatier®) (n=14), and sofosbuvir/velpatasvir/voxilaprevir (Vosevi®) (n=3) [12]. A meta-analysis of the real-world safety events specifically on the glecaprevir/pibrentasvir drug combination was recently published. In this analysis, there is confirmation of its highly effective SVR in addition to the complications and adverse effects. The hepatic decompensation serious safety adverse events reported were in 4 out of 2,233, or 0.2% of the cases. Of those four reported cases, 1 experienced ascites, 1 experienced esophageal varices rupture, and 2 experienced jaundice [13].

In this case that we report, we utilized the Naranjo algorithm as the adverse drug reaction probability scale with a total score of 6 as in Table 1, which indicates a probable reaction related to the glecaprevir/pibrentasvir drug combination given that the interpretation for scores from 5-8 indicates a probable reaction by the following criteria: The reaction followed a reasonable temporal sequence after a drug, followed a recognized response to the suspected drug, was confirmed by withdrawal but not by exposure he drug, and could not be reasonably explained by the known characteristics of the patient's clinical state [14].

CONCLUSION

In conclusion, we advise caution and close monitoring of patients with advance liver disease who are prescribed glecaprevir/pibrentasvir for the treatment of hepatitis C. Viral hepatitis refers to inflammatory liver disease caused by viral infection. Worldwide, 600 million people are chronically or acutely infected with hepatotropic viruses. Here, we focus on the clinical features of these hepatitis viruses in terms of epidemiology, transmission, diagnosis, clinical course of infection, and treatment.

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