

## Severe Hyperbilirubinemia as a Side Effect of Three-Week Treatment with Glecaprevir/Pibrentasvir Resulting in Sustained Virologic Response

Bryce Yohannan M.D.<sup>1</sup>, Maham Hayat M.D.<sup>1</sup>, Taseen A. Syed M.D.<sup>2</sup>, Muhammad Hashim Hayat M.D.<sup>3</sup>, Diane Hughes<sup>4</sup> and Javid Fazili, M.D.<sup>5\*</sup>

<sup>1</sup>Resident Physician, Department of Internal Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, US.

<sup>2</sup>Gastroenterology Fellow, Virginia Commonwealth University, Richmond, VA, US.

<sup>3</sup>Medical Student, Services Institute of Medical Sciences, Lahore, Pakistan.

<sup>4</sup>VA Medical Center, Oklahoma City, OK, US.

<sup>5</sup>Associate Professor of Medicine, Section of Digestive Diseases & Nutrition, University of Oklahoma Health Sciences Center, Oklahoma City, OK, US.

### \*Correspondence:

Javid Fazili M.D. Associate Professor of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, US.

Received: 22 December 2019; Accepted: 20 January 2020

**Citation:** Bryce Yohannan, Maham Hayat, Taseen A. Syed, et al. Severe Hyperbilirubinemia as a Side Effect of Three-Week Treatment with Glecaprevir/Pibrentasvir Resulting in Sustained Virologic Response. *Gastroint Hepatol Dig Dis*. 2020; 3(1): 1-2.

### Keywords

Hepatitis C Virus, Infection, Alcohol abuse, Healthcare.

### Introduction

The advent of direct-acting antivirals (DAA) transformed the treatment of Hepatitis C Virus (HCV) from poorly tolerated interferon therapies to highly effective oral regimens. Glecaprevir/Pibrentasvir (GLE/PIB) is one such DAA approved for pan-genotypic HCV treatment in 2017. Its effectiveness in achieving sustained virologic response (SVR) across all HCV genotypes, and relatively short treatment duration of 8 to 12 weeks make it an ideal treatment for chronic HCV infection. Its side effect profile is considered to be largely benign, with headache and fatigue being the most common adverse effects. It has been associated with a 3.5% rate of incidental hyperbilirubinemia; these cases have not led to jaundice or the need for treatment cessation [1]. We report a case of severe cholestatic jaundice in a patient receiving GLE/PIB requiring hospitalization and treatment discontinuation.

### Case

A 63-year-old man with compensated cirrhosis secondary to alcohol abuse and chronic HCV infection [Child Pugh Class A; MELD score 10] was seen in Hepatology clinic three weeks after starting Glecaprevir/Pibrentasvir (GLE/PIB). His baseline lab values prior to starting treatment were as follows: total bilirubin

2.0 mg/dL; aspartate aminotransferase (AST) 92 IU/L; alanine transaminase (ALT) 39 IU/L; and alkaline phosphatase (AP) 112 IU/L; HCV viral load 16,200, Genotype 2b. Lab work obtained at the three week visit was notable for elevation in total bilirubin to 18.8 mg/dL with direct bilirubin of 9.9 mg/dL, AST 61 units/L, ALT 29 units/L, and AP 116 IU/L.

Notably, HCV viral load was undetectable. He was instructed to continue with treatment with repeat lab check in one week. Repeat labs at 4 weeks revealed a total bilirubin of 22.9 mg/dL with direct fractionation of 9.4 mg/dL. Patient was advised to stop GLE/PIB and was admitted to the hospital for further work up. On physical exam, patient was jaundiced and had scleral icterus; he did not have hepatomegaly, ascites, encephalopathy, or abdominal tenderness. Serology was negative for Hepatitis A and B. Liver ultrasound revealed cirrhosis with mild splenomegaly but no obstructive pathology. Urine drug screen was negative for illicit substances. Home medications were reviewed and were deemed not hepatotoxic. He was discharged the following day with close follow up scheduled. Repeat lab work the following week revealed total bilirubin 6.0 mg/dL; other liver chemistry tests were stable from previous values. HCV viral load remained undetectable. Follow up in 12 weeks revealed that Total bilirubin was down to 2.1 mg/dL, AST 41 units/L, ALT 21 units/L, and AP 42 IU/L. HCV viral load remained undetectable confirming SVR.

## Discussion

Hepatitis C Virus (HCV) infection is a global epidemic which affects more than 180 million people worldwide [2]. As acute HCV infection is often asymptomatic or relatively self-limited, most patients are not aware of chronic HCV infection until much later in the disease course, especially in populations with poor access to healthcare. Without treatment, HCV can progress to liver cirrhosis and its associated complications; it also increases the risk of development of hepatocellular carcinoma. In the United States, liver failure from chronic HCV infection is the most common indication for liver transplantation [3]. The rate of progression to cirrhosis is variable in HCV infection, ranging from 10-25%, and is dependent on various factors. For example, comorbid conditions such as nonalcoholic steatohepatitis (NASH), exposures such as concurrent alcohol use, and co-infection with Hepatitis B or HIV all increase the risk of developing cirrhosis [3].

There are six major genotypes of HCV with genotype 1 being the most common worldwide accounting for 49% of all HCV cases, followed by genotype 3 (18%), 4 (17%), 2 (11%), and 5 and 6 which make up the remaining ~5% [2,3]. Further research is needed to determine if different subtypes convey different prognoses. Currently, genotype sequencing is needed in order to predict response to therapy, as only certain regimens are effective across all genotypes.

The advent of oral direct-acting antiviral therapy (DAA) has revolutionized treatment due to its safer side effect profile, increased efficacy in attaining SVR, and improved patient adherence as compared to its interferon-based predecessors [4,5]. These medications target different steps in the viral replication process and are highly effective with cure rates greater than 95% [6]. Currently there are 7 oral DAA regimens approved in the United States by the Food and Drug Administration (FDA) for the treatment of chronic HCV infection.

Glecaprevir/Pibrentasvir is one such DAA regimen that was approved in the United States and European Union for treatment of all six genotypes in 2017 [7]. Its mechanism of action is as an NS3/4A protease inhibitor and NS5a inhibitor, respectively, which ultimately inhibits viral replication. It has been shown to have a >98% efficacy in attaining SVR across all genotypes [8]. The incidence of adverse effects is based on nine phase II and III trials that included a total of approximately 2300 patients [1]. Only patients without cirrhosis or compensated cirrhosis i.e. Child-Pugh A were included. All six genotypes were represented in this patient population as were different subsets of patients with chronic kidney disease stages 4 and 5 including those on dialysis, co-infection with HIV, adolescents, and liver and kidney transplant patients [1,8].

The most common adverse effects reported were headache (13%), fatigue (11%), and nausea (8%). Elevations in serum total bilirubin

greater than at least 2 times the upper limit of normal were reported in 3.5% of patients; there were no reported cases of jaundice [1]. It is thought that hyperbilirubinemia due to GLE/PIB may be due to inhibition of OATP1B1/3 and UGT1A1, which are key enzymes in the metabolism and transport of bilirubin in hepatocytes.

It is worth mentioning that our patient achieved SVR with an “ultra-short” treatment course of 4 weeks. There are clinical trials in progress examining the efficacy of these ultra-short treatment courses in attaining SVR. However, treatment courses of 4 and 6 weeks are not currently recommended based on several trials which showed that treatment courses of less than 8 weeks were associated with significantly lower rates of SVR as compared to the standard 8-week treatment course [6,9].

## Conclusion

In conclusion, this case highlights a rare side effect of GLE/PIB, namely severe hyperbilirubinemia leading to cholestatic jaundice. Further investigation is warranted to determine the incidence of severe hyperbilirubinemia resulting in jaundice as a side effect of GLE/PIB. Greater awareness of this side effect will allow for better assessment of risks vs. benefits of therapy and may prevent unnecessary diagnostic work up in similar cases.

## References

1. AbbVie Inc. MAVYRET™ (glecaprevir and pibrentasvir) tablets, for oral use. 2017.
2. Petruzzello A, Marigliano S, Loquercio G, et al. Global epidemiology of hepatitis C virus infection. An up-date of the distribution and circulation of hepatitis C virus genotypes. *World J Gastroenterol.* 2016; 22: 7824-7840.
3. Lingala S, Ghany MG. Natural History of Hepatitis C. *Gastroenterol Clin North Am.* 2015; 44: 717-734.
4. Younossi ZM, Stepanova M, Henry L, et al. Adherence to treatment of chronic hepatitis C: from interferon containing regimens to interferon and ribavirin free regimens. *Medicine (Baltimore).* 2016; 95: e4151.
5. Ahmed M. Era of direct acting anti-viral agents for the treatment of hepatitis C. *World J Hepatol.* 2018; 10: 670-684.
6. Baumert TF, Berg T, Lim JK, et al. Status of Direct-Acting Antiviral Therapy for Hepatitis C Virus Infection and Remaining Challenges. *Gastroenterology.* 2019; 156: 431-445.
7. Lamb YN. Glecaprevir/Pibrentasvir: First Global Approval. *Drugs.* 2017; 77: 1797-1804.
8. Puoti M, Foster GR, Wang S, et al. High SVR12 with 8-week and 12-week lecaprevir/pibrentasvir therapy: An integrated analysis of HCV genotype 1-6 patients without cirrhosis. *J Hepatol.* 2018; 69: 293-300.
9. Emmanuel B, Wilson EM, OBrien TR, et al. Shortening the duration of therapy for chronic hepatitis C infection. *The Lancet Gastroenterology Hepatology.* 2017; 2: 832-836.