CASE REPORT

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A Case of Acute Liver Failure during Ritonavir-Boosted Paritaprevir, Ombitasvir and Dasabuvir Therapy in a Patient with HCV Genotype 1b Cirrhosis

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ABSTRACT

Background: Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir plus Ribavirin is one of the current recommended therapies for HCV genotype 1b monoinfected patients in compensated (Child-Pugh A) cirrhosis. Whether it is known that the worsening of liver function is a rare but possible complication of Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir therapy, to our knowledge no description of treatment-related acute liver failure is available in the literature.

Case presentation: An 84-year-old Caucasian man with chronic compensated HCV genotype 1b cirrhosis received Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir plus Ribavirin therapy. After 13 days he developed grade 4 hyperbilirubinaemia and ascites. Even though treatment was promptly stopped, patient's clinical condition worsened, and he underwent hospitalization, several paracentheses, and developed sub-acute kidney injury. The bilirubinemia returned under three times the upper normal limit only after five months. Notably, he achieved sustained virological response despite the very short duration of therapy.

Conclusion: Hepatic decompensation and acute liver failure are rare but severe complications of Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir plus Ribavirin therapy in patients with compensated cirrhosis. Close monitoring for signs or symptoms of worsening of liver disease is mandatory, and further research for stratifying risk factors are required.

Key words: Ritonavir – Paritaprevir – Ombitasvir – Dasabuvir – liver failure – chronic hepatitis C – adverse drug event.

Abbreviations: 3D: Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir; AKI: Acute Kidney Injury; ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; GGT: gamma-glutamyl transpeptidase; GT1b: Genotype 1b; HCV: Hepatitis C Virus; INR: International Normalized Ratio; MELD: Model for End-Stage Liver Disease; RBV: Ribavirin; UNL: Upper Normal Limit.

INTRODUCTION

Paritaprevir (also known as ABT-450), Ombitasvir and Dasabuvir are inhibitors of non-structural HCV enzymes. Ritonavir is a CYP3A4 inhibitor that optimises Paritaprevir pharmacokinetics [1, 2]. These drugs are currently recommended by the European Association for the Study of the Liver (EASL) for treatment of HCV genotype 1b (GT1b) infected patients with compensated cirrhosis [1]. Grade 3 elevation in total bilirubin (less than 10 times the upper normal limit, UNL) was described in 37 out of 380 patients as a side effect in the Phase III trial TURQUOISE-II, but none of them discontinued treatment due to hyperbilirubinemia [2]. No acute kidney injury (AKI) was described.

A safety warning was issued from the Food and Drug Administration (FDA) in October 2015 about the risk of hepatic decompensation in cirrhotic patients treated with Viekira Pak [Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir (3D)] and Technivie [Ombitasvir-Paritaprevir-Ritonavir plus Ribavirin (RBV)] [3].

However, to the best of our knowledge, no description of a case of acute liver failure with grade 4 hyperbilirubinaemia, ascites and kidney injury has been published, and no articles were found performing a "Viekira Pak" [Supplementary Concept] AND"Liver Failure, Acute" [Mesh] search on the PubMed database.

CASE PRESENTATION

An 84-year-old Caucasian man with chronic compensated cirrhosis (Child-Pugh A 6, MELD 10, Shear Wave elastosonography stiffness 14.04 kPa, staging F3-F4, no ascites on abdominal ultrasound) received 3D plus RBV at the standard dosage for treatment-naïve HCV GT1b patients. He had portal hypertension with low bleeding risk esophageal varices, and in the past he had had partial portal vein thrombosis, completely resolved after Fondaparinux treatment. One year earlier he had been diagnosed with a hepatic cell carcinoma, treated by percutaneous etanol injection with no signs of recurrence. He had also diverticulosis coli and chronic gastritis, and in the past history pulmonary tuberculosis at the age of 20. When he started HCV treatment, he was taking also Carvedilol 6.25 mg twice daily and Pantoprazole 40 mg once daily.

After 13 days of therapy he came for the routine visit, presenting jaundice, without any associated symptoms. Laboratory tests revealed grade 4 mixed hyperbilirubinaemia (13.79 mg/dL, 11.5 fold the UNL), with normal aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values. Notably, the last control before the treatment demonstrated grade 1 hypertransaminasemia, with only discrete elevation of total bilirubinemia (1.7 fold the UNL). The abdominal ultrasound showed mild ascites, no signs of biliary tract abnormality. At the clinical examination he had mild to moderate pitting edema, jaundice, no signs of hepatic encephalopathy. No signs of acute infection, no history of alcohol abuse or other precipitant factors were identified, thus HCV-therapy was considered the culprit agent.

The 3D+RBV therapy was promptly stopped, and a low dose of canrenoate potassium was gradually introduced for ascites treatment. Nevertheless, serum bilirubin increased up to a maximum of 22.6 mg/dL (18.8 fold the UNL) at 20 days after treatment interruption (Fig. 1). Diagnostic paracentesis revealed no signs of spontaneous bacterial peritonitis. Vitamin K1 was administered for improving the INR (maximun 1.71 under Vitamin K1 therapy, reached 49 days after HCV treatment interruption). Albumin, canrenoate potassium and periodical paracenteses were performed for ascites treatment. Therapy with furosemide was contraindicated because of sub-acute kidney injury with glomerular filtration rate decreasing from 64.9 to 30.9 ml/min/1.73m^2 (sec. CKD-EPI). The recovery was complicated by a retrocardial hospital-acquired pneumonia (on day 54 after stopping treatment), which required cefixime therapy.

The serum HCV-RNA fell from 1,219,521 IU/ml before treatment to 938 IU/mL at day 7, 143 IU/mL at day 13 when treatment was stopped, and to 26 IU/mL at day 24. It remained undetectable from day 44 until today (6 month follow-up).

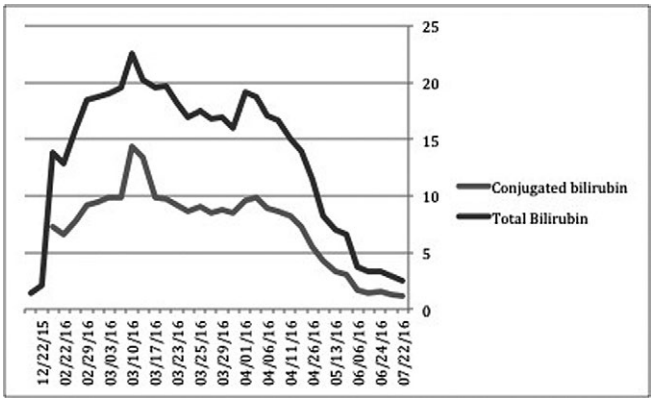

Fig. 1. Total and conjugated bilirubin serum levels (mg/dL).

DISCUSSION

Direct-acting antiviral drugs are replacing interferon in HCV treatment. High efficacy and low rate of adverse events are their strongest advantages against interferon therapy. Ritonavir-boosted Paritaprevir, Ombitasvir and Dasabuvir plus Ribavirin is one of the EASL-recommended treatments for HCV GT1b compensated cirrhosis [1]. Among the seven phase-III trials considered, only TURQUOISE-II enroled patients with cirrhosis (Child-Pugh class A score of less than 7, with no current or past evidence of Child-Pugh class B or C disease). No grade 4 elevation of total bilirubin was observed in treated patients [2].

In October 2015, the FDA issued a safety announcement with regard to 26 worldwide cases of hepatic decompensation and liver failure in cirrhotic patients treated with Viekira Pak (3D) and Technivie (Ombitasvir-Paritaprevir-Ritonavir plus RBV) [3]. Out of them, 10 experienced hepatic failure resulting in transplantation or death. The FDA stated that most of these cases occurred in patients with underlying advanced cirrhosis before starting treatment.

The case that we described shows the possibility of severe liver failure due to 3D therapy, characterized by grade 4 hyperbilirubinemia and coagulation disorders. On the other hand, only mild aminotransferase elevation and no gamma-glutamyltranspeptidase (GGT) or alkaline phosphatase (ALP) elevation from baseline were observed in our patient (Fig. 2), similarly to what was reported by the FDA [3]. This is consistent with an idiosyncratic pattern of drug-related acute liver failure, characterized by mainly subacute injury, signs of jaundice and coagulopathy, with only modest aminotransferase elevation, but elevated bilirubin and INR [4].

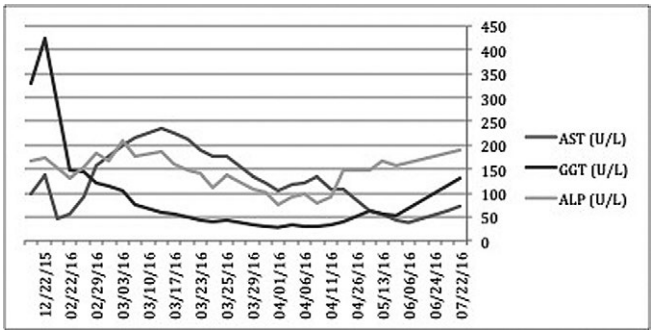

Fig. 2. Serum levels (U/L) of aspartate aminotransferase (AST), glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP).

Future genomic studies might help to identify those patients at the greatest risk of an unfavorable outcome, but it is not clear how these assays are expected to be specific for single drugs [4]. Moreover, it is possible that drug-drug interactions play a role as additional risk factors for developing acute

liver failure. Pantoprazole and Carvedilol are not considered contraindicated [1] in the case of 3D therapy, but both drugs are metabolized in the liver, even though none of them primarily by CYP3A4.

Notably, serum HCV-RNA values fell soon after treatment started, and a sustained virological response was achieved after a very short duration of treatment. It can be hypothesized that a cumulation of the antiviral drugs' effects may have occurred, determining a definitive arrest of viral replication.

CONCLUSION

Interferon-free treatments with direct acting antivirals, despite strong advantages in the safety profile against interferon-based therapy, should be closely monitored for potentially severe side effects, especially in elderly patients with cirrhosis and using multi-drug therapy. Most research focused on identifying risk factors for developing drug related acute liver failure is required, especially in high-risk patients such as those with liver cirrhosis and multiple drug use.

Conflicts of interest: No conflicts to declare.

Authors' contributions: All authors contributed significantly to this report. M.M., D.M., E. M. and M.Z. visited the patient during pre-hospital and hospital for assistance, A.S. and P.A. coordinated drug management, M.M., D.M. and P.A. wrote and revised this paper. All authors approved the final version of the manuscript.

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REFERENCES

1. European Association for Study of Liver. EASL Recommendations on Treatment of Hepatitis C 2015. J Hepatol 2015; 63: 199-236. doi: 10.1016/j.jhep.2015.03.025
2. Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med 2014; 370: 1973-1982. doi: 10.1056/NEJMoa1402869
3. FDA Drug Safety Communication: FDA warns of serious liver injury risk with hepatitis C treatments Viekira Pak and Technivie. 10/22/2015.
4. Lee WM. Drug-induced acute liver failure. Clin Liver Dis 2013; 17: 575-586. doi: 10.1016/j.cld.2013.07.001