Published in final edited form as:

Dig Dis Sci. 2015 April ; 60(4): 1031–1035. doi:10.1007/s10620-014-3422-x.

Hepatic Decompensation Likely Attributable to Simeprevir in Patients with Advanced Cirrhosis

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Abstract

Background—Hyperbilirubinemia is a common side effect of protease inhibitors used to treat chronic hepatitis C (HCV), and most patients do not experience without clinically overt hepatotoxicity. The safety of second-wave protease inhibitors, including simeprevir, has not been well studied in patients with advanced cirrhosis.

Materials & Methods—We report two cases of suspected drug-induced liver injury leading to hepatic decompensation in patients with advanced HCV cirrhosis treated with the combination of simeprevir and sofosbuvir on a compassionate basis. Both patients developed marked hyperbilirubinemia out of proportion to their aminotransferases, despite clearance of hepatitis C RNA. RUCAM scoring was probable and possible, respectively. While other factors may have

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Conflict of interest None.

contributed to the liver injury, including infection and concurrent administration of other medications, we believe that the potentially deleterious hepatic effects of simeprevir on transporters or other key functional components were the main reason for their decompensation.

Conclusions—Protease inhibitors should be used with caution, if at all, in patients with cirrhosis, especially in those with the most advanced disease. We await newer, safer, direct-acting antiviral therapies for such patients, especially those on our transplant list.

Keywords

Drug-induced liver injury; Cholestasis; Hepatitis C; Protease inhibitors; Liver transplantation

Introduction

The landscape of chronic hepatitis C (HCV) treatment continues its rapid change with the approval of two new oral direct-acting antiviral agents (DAAs), sofosbuvir (SOF) [1] and simeprevir (SMV) [2, 3]. Hyperbilirubinemia is reported as a rare side effect of SOF, which when used in combination with pegylated interferon (PEG-IFN) and/or ribavirin (RBV), occurred <3 % of the time [4]. It was also recognized as a common side effect with SMV [3, 5], having been discovered early in the clinical development of both first-generation protease inhibitors (PIs), boceprevir and telaprevir [6, 7]. For SMV, the mechanism of hyperbilirubinemia is due to decreased clearance from impaired hepatic transporters OATP1B1 and MRP2 [5]. Peak hyperbilirubinemia usually develops around week 2 of treatment and resolves by week 4, exhibiting a form of drug tolerance. Severe hyperbilirubinemia (grade 3 or 4) is listed as rare (<5 %) in prescribing information for SMV [8].

The US Food and Drug Administration has not reported an association between hyperbilirubinemia and clinically relevant hepatotoxicity. Safety data from the phase IIa COSMOS trial investigating the combination of SMV and SOF reported hyperbilirubinemia in 9.3 % of patients, but this was only seen with concurrent use of RBV [9]. The combination of SMV–SOF alone has become widely used as an all-oral alternative to either of these agents used in combination with PEG-IFN and/or RBV and is recommended for use in updated HCV treatment guidelines issued by both the AASLD [10] and EASL [11].

Our experience with this combination in patients with cirrhosis awaiting liver transplant (LT) suggests that SMV/SOF may be associated with cholestatic liver injury leading to hepatic decompensation despite clearance of HCV–RNA. As a consequence, we have decided to be highly selective with the use of SMV in our HCV patients on the transplant list and would prefer to use non-PI-containing regimens available in the near future.

Case 1

A 56-year-old male with cirrhosis from HCV genotype (GT) 1a and previous alcohol abuse presented for LT evaluation. His course was complicated by refractory ascites requiring transjugular intrahepatic portosystemic shunt (TIPS) placement 2 years prior and the presence of non-bleeding esophageal varices. The patient was a previous null responder to

PEG-IFN/RBV therapy on two separate occasions. He was classified as having Child–Pugh–Turcotte (CPT) Class B cirrhosis with a pre-treatment MELD score of 17 (baseline total bilirubin (TB) 5.3 mg/dL, AST 52 U/L, and ALT 29 U/L). SMV 150 mg daily and SOF 400 mg daily were prescribed under a compassionate use protocol with the approval of the drug manufacturers. By week 2, his TB increased to 6.6 mg/dL with a mildly increased AST of 89 U/L (Fig. 1). Therapy was continued with a rapid virologic response (RVR) achieved by week 4. However, the patient developed significant fatigue and anorexia shortly thereafter. The TB at that time had risen to 28.0 mg/dL, with AST 229 U/L and ALT 90 U/L, and therapy was discontinued before week 5. Roussel Uclaf Causality Assessment Method (RUCAM) scoring showed probable hepatotoxicity (score = 7 points, Table 1). The patient underwent successful LT 4 weeks later with a MELD score of 36 (TB 14.2 mg/dL of which 7.0 mg/dL was direct, INR 4.4). His AST and ALT had normalized at the time of LT. The explanted liver was described as showing gross cirrhosis and was shrunken, but did not specifically show any signs of drug-induced injury (DILI), such as eosinophilia on histologic examination, although it had been weeks since the SMV/SOF had been discontinued. The patient's HCV viral load continues to be undetectable several months post-transplant and his graft function continues to be excellent.

Case 2

A 43-year-old male with CPT Class B cirrhosis from chronic HCV GT1a (IL28b-CC) and two previous treatment failures with PEG-IFN/RBV presented for LT evaluation. His course was complicated by ascites requiring TIPS placement 4 months prior. His pre-treatment MELD score was 20 (TB 9.5 mg/dL) SMV 150 mg daily and SOF 400 mg daily was prescribed by the patient's local hepatologist under a compassionate use protocol with the approval of the drug manufacturers. His week 2 laboratory values demonstrated an increased TB to 25 mg/dL, with AST 53 U/L and ALT 31 U/L and normal serum creatinine. Despite this, he was continued on SMV/SOF by his local provider. During week 7, a course of trimethoprim/ sulfamethoxazole (TMP/SMX) was prescribed for a soft tissue infection. The patient was admitted to our institution during week 10 of SMV/SOF therapy because of hepatic decompensation with grade II–III portosystemic encephalopathy and a MELD score of 30 (bilirubin 41.8 mg/dL, creatinine 1.1 mg/dL). However, his AST and ALT were within normal limits. No fever, rash, or eosinophilia was present to suggest a hypersensitivity reaction to the course of TMP/SMX [12]. RUCAM scoring showed possible hepatotoxicity from SMV (score = 3 points), even in the setting of recent TMP/SMX use. SMV/SOF therapy was stopped shortly after admission, and the patient was eventually discharged in stable condition. Four months later, an interval improvement was noted in TB (18.1 mg/dL of which 10.8 mg/dL was direct) and his MELD score was 21. His HCV-RNA viral load remained undetectable and no additional DAAs were restarted. The patient was ultimately declined for listing for LT due to his poor functional status and inability to comply with substance abuse counseling.

Discussion

While recent advances in anti-HCV therapy have revolutionized the field, our experience raises concern that SMV, a second-wave first-generation PI, either singly or in combination

with SOF, may cause liver injury in patients with advanced disease, leading to hepatic decompensation despite their antiviral efficacy. The two cases we present developed hyperbilirubinemia out of proportion to other hepatic enzymes and despite clearance of HCV-RNA. While other factors may have contributed to the liver injury and decompensation in these cases, including infection, other medications (such as TMP/SMX) or the process of viral clearance itself (similar to what is observed with acute icteric infection with HCV), we believe that the potentially deleterious hepatic effects of these DAAs on transporters or other key functional components were most likely responsible.

Once suspected, prompt discontinuation of the offending drug and supportive care are the mainstays of managing DILI [13]. Strict stopping rules have been established to prevent serious liver toxicity, including fulminant hepatic failure in clinical trials, especially for cases meeting the definition of Hy's Law [14]. This was adhered to in case 1 but not in case 2, which may have led to the more clinically impressive hepatic decompensation. We cannot exclude the possibility that the course of patient 2 may have been affected by the concurrent administration of TMP/SMX, a known hepatotoxin [12]. However, the patient lacked the typical hallmark features of hypersensitivity suggestive of TMP/SMX toxicity, including fever, rash, and eosinophilia. The absence of these clinical features and the fact that his AST and ALT were normal at the time of the hepatic decompensation argue against TMP/SMX being causal and strengthen the argument that case 2 was in fact a form of DILI secondary to SMV/SOF. What is perhaps more convincing is the fact that the injury occurred after an undetectable HCV viral load was achieved, eliminating the possibility that viral reactivation might have been responsible.

Both of our patients were treated with the combination of SMV/SOF therapy prior to the widespread knowledge about testing GT 1a patients for the Q80K mutation, which confers decreased efficacy to SMV [15]. The FDA now recommends that all patients with a GT 1a infection be screened for Q80K before initiating SMV, and that alternative treatment options be considered for those with this polymorphism [15]; all three patients who had viral breakthrough and treatment failure with SMV–SOF in the COSMOS trial did have preexisting Q80K variants at baseline [9] despite the fact that there was no significant difference in SVR rates in this trial as well as in the PROMISE and QUEST 1 and 2 trials which investigated PEG-IFN based regimens [16–19]. The effect of Q80K on safety is unknown, as this viral mutation has a limited impact on the activity of SMV, with a less than tenfold change (7.7) in the half maximal effective concentration (EC₅₀), but its presence does lower the resistance barrier and facilitates additional mutations, resulting in higher treatment failure [20].

Newly published data from the phase IIb COSMOS trial [9] found that few hyperbilirubinemia events were reported as adverse events (AE) and that increases in bilirubin concentrations were predominantly indirect in nature and were transient, with peak values of 7–10 mg/dL at week 2 that resolved completely after the end of treatment. The majority of these patients were taking concurrent RBV, which is known to cause hyperbilirubinemia as a result of red blood cell hemolysis [21]. Only one grade 4 adverse event was reported related due to an increase in bilirubin. However, it is important to note that 25 % ($n = 41$) of the patients in the COSMOS trial had cirrhosis and 53 % had advanced

stage 3 or stage 4 fibrosis ($n = 87$), and 5 patients in the advanced fibrosis group had elevated bilirubin (9 %) when RBV was given concurrently. In contrast, none of the patients exhibited hyperbilirubinemia without RBV. Interestingly, the pharmacokinetics were similar for SMV for patients with stage 0–2 fibrosis when compared to those with advanced fibrosis (stage 3–4). What is unknown is how advanced the cirrhosis actually was, as CPT scores were not reported, even in the supplementary information (9). Therefore, pharmacokinetic data remain unknown in patients with advanced cirrhosis (CPT class B and C), who are typically excluded from clinical trials [22]. Furthermore, it is unclear whether hyperbilirubinemia correlates either positively or negatively with a sustained virologic response.

Adherence to appropriate prescribing remains one of the most important aspects in preventing DILI in patients with cirrhosis [22]. The drug package insert for SMV states that no dosing recommendation has been determined for patients with moderate or severe hepatic impairment (CPT Class B or C) due to higher SMV exposure and a lack of safety and efficacy data in patients with advanced cirrhosis [9]. SMV is not directly contraindicated when used without PEG-IFN/RBV as the package insert directs the prescriber to consider the risks and benefits when using this medication in patients with moderate or severe hepatic impairment [8]. Exposure to SMV in HCV-uninfected subjects with CPT Class B and C cirrhosis was 2.4-fold and 5.2-fold higher, respectively, than in subjects not infected with HCV with normal liver function [23].

Our LT team felt that the benefits of antiviral treatment and the potential for HCV eradication pre-transplant out-weighed the risks of prescribing this combination therapy. However, based on our experience with just these two patients, we have modified our practice and are highly selective when prescribing PIs to patients with cirrhosis due to the risk of hepatic decompensation, regardless of their status on or off the liver transplant list. In most cases, we are opting to wait until new all-oral DAA agents, such as NS5A replication complex inhibitors ledipasvir or daclatasvir become available [24]. SMV appears to be an effective agent in patients without cirrhosis (3). While the combination of SMV/SOF may be relegated to obsolescence as new combination of PI-free all-oral regimens, including SOF–ledipasvir become available, we would argue that SMV should be used with great caution, if at all, in CPT Class B or C patients. We have opted to be highly selective when using SMV and monitor these patients frequently due to the possibility of severe hepatic decompensation, which appears to be mediated by impaired metabolism from under-expression of hepatic transporters OATP1B1 and MRP2, which are known to be decreased in advanced liver disease and cirrhosis [25]. Higher blood levels of SMV are already known to be associated with an increased frequency of adverse reactions such as rash and photosensitivity, with both first- [7] and second-generation PIs [8]. It is also known that the enzyme inhibition caused by SMV is more pronounced when the dose is not adjusted for hepatic failure; more advanced cases of cirrhosis have lower CYP3A activity [22, 26] which would be expected to predispose to SMV toxicity. SMV, like telaprevir and to a lesser extent boceprevir, is metabolized by CYP3A4 [23]. The placement of a TIPS is also known to decrease CYP3A activity [22, 26] which may have contributed to the hepatic decompensation of the antiviral therapy in our two patients. Polypharmacy is also known to blunt RVR rates among patients receiving first-generation PIs [27].

Both our cases satisfy the definition of acute on chronic liver failure, which is defined as jaundice and coagulopathy, complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease [28]. A recent study of 511 HCV patients enrolled in the CUPID cohort with well-compensated genotype 1 HCV cirrhosis were treated with first-generation PIs [29]. The majority of these patients were classified as CPT Class A disease (94.5 %). Serious adverse events, including hepatic decompensation evidenced by ascites, hepatic encephalopathy, or variceal bleeding, were recorded in 49.9 % of the patients studied [29]. Death occurred in 2.2 % of patients and was predicted by more severe disease, defined as albumin less than 3.5 mg/dL and platelet counts less than 100,000/mm [29]. Reflecting on the lessons learned from Herzode and the CUPID cohort, especially the findings of increased death with PIs, and coupled with our experience with the two cases of hepatic decompensation seen at our institution, led us to make the decision to be highly selective in using PIs in both patients on the liver transplant list and with cirrhosis. We do so with the knowledge that promising newer, safer DAA regimens appear to be on the horizon.

Acknowledgments

This work was supported in part from a grant from the National Institutes of Health via the National Institute of Diabetes and Digestive and Kidney Diseases.

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Fig. 1.
SMV/SOF laboratory values

Table 1

Roussel Uclaf Causality Assessment Method (RUCAM) scoring [26]

RUCAM assessment	Time	Score
Time to onset of ALT > 2×ULN after drug start	5–90 days	+2
	15 days after stopping	+1
>50 % decrease in ALT after stopping drug	<8 days	+3
	<30 days	+2
Negative hepatitis screens and ultrasound		+2
Hepatotoxicity in product characteristics/label		+2
No concomitant medications		0
Concomitant medications		–1 to –3
Positive rechallenge		+3
Alcohol or pregnancy		+1
Age >55		+1

>8 highly probable, 6–8 probable, 3–5 possible, 1–2 unlikely, and 0 excluded