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CASE REPORT

Hepatitis B virus reactivation after effective sofosbuvir and ribavirin treatment in a patient with occult hepatitis B virus infection

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SUMMARY

Reactivation of the hepatitis B virus (HBV) has been reported in patients with occult infection (OBI), i.e. HBV surface antigen (HBsAg) negative, HBV core antibody (anti-HBc) positive ± antibodies against HBsAg (anti-HBs) and detectable HBV DNA in serum or liver, receiving immunosuppressive or cytotoxic therapies. Recently, concerns have been raised regarding the risk of HBV reactivation in OBI patients treated with direct acting antiviral agents (DAAs) for chronic hepatitis C (CHC). Here we describe a case of HBV reactivation in a 72-year-old woman with OBI as a possible consequence of effective treatment with sofosbuvir (SOF) and ribavirin (Rbv) for genotype 2a/2c CHC.

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INTRODUCTION

Treatment of chronic hepatitis C virus (HCV) infection has been revolutionized in the last few years by the introduction of highly effective and well-tolerated DAAs able to achieve high rates of sustained virological response (SVR) in many groups of patients (EASL Guidelines, 2015). In areas with a high prevalence of HBV infection, HCV and HBV co-infection is common as an overt infection (HBsAg positive) and even more likely as an OBI (hepatitis B surface antigen (HBsAg) negative, hepatitis B core antibody (anti-HBc) positive ± antibodies against HBsAg). In patients with HCV/HBV co-infection, the HBV DNA level is often low or undetectable, although it may fluctuate widely, and HCV is usually the main driver of liver disease. In past years, HBV reactivation occurring in HBV/HCV-co-infected patients treated with IFN-based therapy has been reported, probably as a consequence of an unbalanced HBV replication caused by treatment-related suppression of HCV, although a direct immunomodulatory effect of IFN might also be advocated for either on- or off-treatment HBV reactivation (Chen *et al*., 2017; Viganò *et al.*, 2009, Chuang *et al.*, 2005; Villa *et al.*, 1993). Mitigating these concerns about the use of IFN in HBV/HCV co-infected patients was the ability of IFN to suppress HBV replication, resulting in long-term response. In contrast, DAAs are not effective for HBV replication, and such therapies may release HBV from HCV suppressive effects, resulting in HBV reactivation in CHC patients with a concomitant overt or occult HBV infection, leading to acute hepatitis with the risk of liver failure both on- or off-treatment (De Monte *et al*., 2016; Ende *et al.*, 2015; Collins *et al.*, 2015; Hayashi *et al.*, 2016; Takayama *et al*., 2016; Wang *et al.*, 2016). Despite this, up to 2015 EASL and AASLD guidelines on HCV treatment did not provide specific indications for the management of OBI during or after HCV clearance by DAAs (EASL Guidelines 2015; AASLD/IDSA Guidelines 2015). Herein, we describe a case of HBsAg seroreversion with acute hepatitis after a successful treatment with SOF and Rbv in a woman with OBI and genotype 2a/2c CHC.

CASE REPORT

A 72-year-old Italian woman followed since 2000 at Department of Infectious and Tropical Diseases, Spedali Civili of Brescia for genotype 2a/2c HCV infection and cryoglobulinemic syndrome with mild renal impairment and motor and sensory neuropathy presented in November 2015 for HCV re-treatment. She was previously a non virological responder to IFN-alpha. Cryoglobulinemic syndrome was treated with several cycles of rituximab (RTX) until August 2011 and patient had been taking low doses (5 mg/die) of prednisone since 1997. Although liver stiffness was low (transient elastrography by Fibroscan =5.4 kPa) and the abdominal ultrasound (US) and liver tests excluded severe liver disease, HCV treatment was considered because of the HCV-related extra-hepatic manifestations. SOF plus Rbv was started on 5th November 2015 and intended to continue for 12 weeks. Pre-treat-

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ment HBV serologic study revealed positive anti-HBc with negative HBsAg and anti-HBs, suggesting an OBI. HCV viral load was 3.9 Log_{10} UI/mL and transaminases were within normal limits. After two weeks of antiviral treatment, HCV VL was undetectable and biochemical and virological response was maintained until the end of treatment (EOT) in February 2016. One month after the EOT, she turned to the Emergency Department of Spedali Civili of Brescia for weakness. Blood tests revealed elevated liver enzymes [aspartate aminotransferase (AST) =956 IU/L, alanine aminotransferase (ALT)=1311 IU/L, gamma glutamyl transpeptidase (□-GT) =325 IU/L, alkaline phosphate (ALP)=841IU/L] and slightly increased serum bilirubin levels (1.8 mg/dL) with preserved hepatic function, and was therefore admitted to our Clinic for suspected HCV breakthrough. Other causes of hypertransaminasemia were excluded after careful questioning. The patient was not receiving any medications apart from prednisone. The patient was afebrile, physical examination revealed normal vital signs and the abdomen was soft and not distended without tenderness. Serum HCV RNA was undetectable while HBsAg was positive with HBV VL of 76.290 UI/mL. Abdominal US revealed absence of ascites, portal hypertension or focal liver lesions. Antiviral HBV treatment with Entecavir (ETV) 0.5 mg/day was initiated with rapid decrease of liver enzymes and HBV DNA levels. Five months later, all liver chemistries had returned to normal values, HCV RNA and HBV DNA are undetectable, and the patient in good clinical condition though she remains HBsAg positive. The analysis of the stored serum collected at start of DAAs revealed a low amount of serum HBV DNA (38 IU/mL), genotype D3 viral strain without amino acid substitutions in the polymerase region conferring resistance to lamivudine, telbivudine, adefovir, ETV and tenofovir disoproxil fumarate (TDF), but amino acid substitutions in the S region (134H) as possible immune escape mutant.

DISCUSSION

Several studies have shown that in HBV/HCV-co-infected patients the viruses interact with each other and HCV infection can usually suppress HBV replication (Wiegand *et al*., 2015; Chuang *et al.*, 2005). Hence, the potential for reactivation of HBV following HCV treatment has long been a concern (Viganò *et al.*, 2009) and seems to occur earlier and be clinically more significant in those CHC patients coinfected with overt and occult HBV, treated with pan-oral DAAs compared to IFN-based therapy (Chen *et al.*, 2017). In patients with OBI, this risk was almost exclusively reported in patients with hematological malignancies undergoing cytotoxic chemotherapies or allogeneic hematopoietic stem cell transplantation, being negligible in the other settings of immunosuppression (Viganò *et al.*, 2016). Although the treatment of CHC patients has been revolutionized in the last few years by the introduction of highly effective and well tolerated DAAs (EASL Guidelines 2015; AASLD/IDSA Guidelines 2015) concerns have been raised regarding the risk of HBV reactivation in those with HBV/HCV co-infection undergoing DAAs (De Monte *et al.*, 2016; Ende *et al.*, 2015; Collins *et al.*, 2015; Hayashi *et al.*, 2016; Takayama *et al.*, 2016). These events that occurred not only in HBsAg positive patients but also in patients with OBI have recently prompted the European Medicines Agency (EMA) to assess the extent of HBV reactivation in patients treated with DAAs and to evaluate whether any measures are needed to optimise the anti-HCV treatment (EMA, 2016). However, all the cases reported so far in OBI patients should be interpreted with caution before establishing a clear correlation between effective DAAs treatment and HBV reactivation, due to the presence of at least one possible confounding factor. Hayashi *et al.* report should be considered an acute HBV infection rather than an HBV reactivation (Hayashi *et al.*, 2016) as the previous patient's serological profile was lacking and the last available negative result of HBsAg refers to a decade before the start of DAAs. Moreover, the fact that the patient had rapidly become negative for HBsAg makes the diagnosis of de novo hepatitis the most likely, maybe acquired as outpatient. Also the report by Ende *et al.* that refers to a woman with a previous Burkitt's lymphoma in remission for 2 years before starting DAAs, has as a confounder the onco-hematological disease and the relative therapies, as well as the negative HBsAg result dating back two years before anti-HCV treatment (Ende *et al.*, 2015). De Monte *et al*. reported HBV reactivation in an HIV/HCV co-infected male who discontinued TDF 14 months before starting DAAs due to bone toxicity (De Monte et al., 2016). In this case the role of HIV infection and/or the immune reconstitution after effective HAART cannot be excluded as causes of the HBV reactivation, not to mention discontinuation of TDF that is effective on HBV. Finally, the case reported by Collins *et al.* had detectable serum HBV DNA at the start of DAAs and a very rapid increase in viremia in parallel with a HCV virological response (Collins *et al.*, 2015). Our case is also not entirely free from possible confounding factors that are the previous RTX treatment, although it ended four years before DAAs, and the concomitant long-term treatment with low dose steroids. In our patient the retrospective evaluation of the stored serum, collected at the start of

List of Abbreviation:

HBV: Hepatits B virus
OBI: Occult B infection
HBsAg: HBV surface antigen
HbcAb: HBV core antibody
anti-HBs: Antibodies against HBsAg
DAA: Direct acting antiviral agents
CHC: Chronic hepatitis C
SOF: Sofosbuvir
RBV: Ribavirin
HCV: Chronic hepatitis C Virus
SVR: Sustained virological response
IFN: Interferon
EASL: European Association for the Study of the Liver
AASLD: American Association for the Study of Liver Diseases.
RTX: Rituximab
AU: Abdominal ultrasound
VL: Viral load
EOT: End of treatment
AST: aspartate aminotransferase
ALT: alanine aminotransferase
GGT: gamma glutamyl transpeptidase
ALP: alkaline phosphate
ETV: Entecavir
TDF: Tenofovir
EMA: European Medicines Agency

DAAs, showed a low amount of serum HBV DNA. Moreover, spontaneous reactivation of HBV in elderly patients has also been described and we cannot entirely rule out this possibility (Kamitsukasa *et al.*, 2015). However, to establish unequivocally the risk of HBV reactivation in this group of patients there is a recent Asian study in 124 OBI patients treated with DAAs showing no cases of HBV reactivation (Wang *et al.*, 2016).

Although the reciprocal HCV/HBV interaction is well known, as is the risk of HBV reactivation in HBsAg positive patients successfully treated with DAAs, we believe the risk should be considered very low, if not negligible in OBI patients. Other studies confirm our position. Yeh *et al.* observed a minimal impact of anti-HBc seropositivity on HCV efficacy and safety, while the risk of reactivation was present for CHC patients with current infection (Yeh *et al.*, 2017). Similarly, Belperio *et al.* and Sulkowski et al. affirmed the rarity of HBV reactivation after DAA, even in the setting of isolated anti-HBc (Belperio *et al.*, 2017; Sulkowski *et al.*, 2016).

However, due to the lack of consistent evidence, in our opinion it is important to screen all CHC patients for HBV markers (HBsAg, anti-HBc and anti-HBs) before starting DAAs and all HBsAg positive patients need to be evaluated for nucleos(t)ides analogues, if appropriate. On the other hand, in OBI patients serum HBV DNA should be assessed with a very sensitive test at baseline and monitored during and after DAAs in those patients with positive baseline VL, whereas no periodic monitoring of serum HBV DNA or HBsAg during and after DAAs treatment is recommended in patients with undetectable baseline serum HBV DNA. In the latter patients periodic monitoring of ALT may be enough to detect hepatic flare reflecting HBV reactivation to be treated with anti-HBV therapy. Current EASL guidelines even suggest starting concurrent HBV nucleoside/nucleotide analogue therapy if HbsAg is present or HBV-DNA is detectable in OBI (EASL Guidelines, 2016). However, further prospective studies in large cohorts of OBI patients better characterized from the virological point of view at baseline and during and after EOT are needed to quantify and stratify the risk of HBV reactivation in parallel with HCV eradication, and to standardize the management of such patients in order to avoid the risk of fatal complications.

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Author contribution
SO contributed to data collection, interpretation and first drafted the paper. PL, AS contributed to data collection and reviewed the paper. MV contributed in drafting and critically reviewing of the paper. All authors read and approved the final manuscript.

Conflict of interest
MV declares that he received grants for speaking and teaching from Roche, Gilead Sciences and BMS. All the other authors declare no conflicts of interest.

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