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

Silvia Odolini1, Paola Lanza1, Angiola Spinetti1, Serena Zaltron1, Lucia Urbinati1, Andrea Vavassori1, Paola Nasta1, Elena Festa1, Franco Gargiulo2, Anna Rodella2, Arnaldo Caruso3, Salvatore Casari1, Francesco Castelli1, Mauro Viganò3

1Clinic of Infectious and Tropical Diseases, University of Brescia and Spedali Civili General Hospital, Brescia, Italy; 2Laboratory of Microbiology, Brescia Spedali Civili General Hospital, Brescia, Italy; 3Hepatology Unit, Ospedale San Giuseppe, University of Milan, Italy

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) 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.

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 elastography 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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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., 2009). 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 DAAIs 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 DAAIs (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 DAAIs (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 DAAIs 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 DAAIs 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 DAAIs. 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 DAAIs, 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 DAAIs 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 DAAIs 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 DAAIs, 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

**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 DAAIs 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 DAAIs (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 DAAIs (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 DAAIs 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 DAAIs 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 DAAIs. 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 DAAIs, 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 DAAIs 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 DAAIs 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 DAAIs, 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: Hepatitis B virus
- OBI: Occult B infection
- HBsAg: HBV surface antigen
- HbsAb: 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
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 DAA 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 DAA 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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