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Hepatitis B virus in patients with chronic hepatitis C treated with direct antiviral agents

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ABSTRACT

Introduction: cases of hepatitis B virus (HBV) reactivation have been reported in patients with hepatitis C virus (HCV) treated with direct antiviral agents (DAA).

Objectives and methods: the main objectives of the present study are: a) to determine the prevalence of HBV/HCV coinfection in HCV patients treated with DAAs in the Autonomous Community of Madrid (CM) and also to determine the incidence and clinical relevance of HBV reactivation; and b) to determine the HBV screening rates in HCV patients in our region. For that purpose, 1,337 HCV patients were consecutively treated with DAAs in two hospitals located in South CM between January 2015 and June 2017.

Results: nine of the 1,337 (0.67%) participants were HBsAg positive and 356 (26.6%) had previous HBV infection markers. Two of the four (50%) HBsAg positive patients with untreated HBV developed a virological reactivation, but not a biochemical reaction. Of the 356 patients with previous HBV infection markers, all had normal

transaminases at the end of treatment and during follow-up. The HBV screening rate amounted to 92.9% of the cohort.

Conclusions: the prevalence of HBV (HBsAg positive) infection in patients with chronic hepatitis C in the southern area of the CM is low. HBV reactivation in HBsAg positive patients treated with DAAs is common, although without clinical relevance. In our region, there is a high rate of HBV screening in patients with HCV that are likely treated with DAAs.

Key words: HBV/HCV coinfection. Direct acting antiviral. HBV reactivation.

INTRODUCTION

HBV/HCV coinfection is common as both share the same transmission pathways. These patients have a higher risk of progression to cirrhosis and hepatocellular carcinoma development (1). The prevalence of HBV/HCV coinfection depends on the chosen geographical area, method of patient selection and study design. HBV/HCV coinfection is estimated to occur in 2-10% of HCV patients (2) and between 12-44% of patients with HCV infection and a previous HBV infection (HBsAg negative, anti-HBc positive) (3).

An increased risk of reactivation of HBV has been described in HBV/HCV patients treated with interferon (IFN) who achieved a sustained virological response (SVR) to HCV, compared to those who did not achieve a virological response (31% *vs* 11%) (4). Following the publication of cases of reactivation of HBV in patients with HCV treated with DAAs (5-8), the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and the Spanish Agency for Medicines and Sanitary Products (AEMPS) issued recommendations to perform serology against HBV before initiating therapy in patients with HCV (9,10). However, the adequate management of these patients (HBsAg positive and anti-HBc positive) before and during treatment with DAAs is unknown.

There is little information in Spain about the prevalence of coinfection and the incidence of HBV reactivation in patients treated with DAAs (11). The objectives of our study were: a) to determine the HBV screening rates in our area; b) to determine the

prevalence of HBV/HCV coinfection in HCV candidates for DAAs; and c) to determine the incidence of HBV reactivation in treated patients and the clinical relevance.

MATERIAL AND METHODS

A multicenter observational study was designed to evaluate HCV patients consecutively treated with DAAs in two hospitals in the southern area of the CM from January 2015 to June 2017. These patients also had a HBV infection (HBsAg positive) or pattern of a previous HBV infection (HBsAg negative, anti-HBc positive). The study was conducted in two hospitals in the CM and was approved by the Ethics Committee of the Hospital Universitario Fundación Alcorcón. The committee was asked if informed consent was exempt, as it was a retrospective study of the clinical practice, without follow up of patients with a virological response and no advanced fibrosis.

This study included 1,337 patients who had been treated with different available treatments, depending on the genotype, viral load, fibrosis stage and if they had been treated previously. Treatments received included 3D (paritaprevir/ombitasvir/dasabuvir)/2D ± RBV (ribavirin), SOF/LDP (sofosbuvir/ledipasvir) ± RBV; EBR/GZR (elbasvir/grazoprevir), SOF + DCV; SOF/VEL (sofosbuvir/velpatasvir) and SOF + RBV. Whether the reference hepatologist requested determinations of HBsAg, anti-HBc, anti-HBs, HBeAg and anti-HBe was investigated in all patients.

Variables commonly used in clinical practice were collected from patients with active HBV or a previous HBV infection as follows: age, gender, HBV serology, HBV viral load (baseline, intra-treatment and 12-week post-treatment), HCV typing, HCV viral load (baseline, intra-treatment and 12-weeks post-treatment), fibrosis stage, type and duration of treatment with DAAs. Furthermore, HBV reactivations were reported, which conferred an increase in viral load of > 1 log from the baseline. In patients without HBV viral load data, biochemical reactivation was defined as a persistence of elevated transaminases after a virological response, after ruling out other causes. HIV and transplanted patients were excluded.

Prevalence and incidence studies were performed. Categorical variables were summarized by frequency and quantitative measures using the mean or median. The

data were analyzed using the SPSS statistical program.

RESULTS

In 1,337 HCV patients, 95 (7.1%) had no HBV serology markers before starting treatment, 293 (21.9%) had a negative HBV serology (HBsAg, anti-HBc, anti-HBs), 584 (43.6%) presented a vaccination pattern, nine (0.7%) had HBV (HBsAg positive) and 356 (28.6%) had a pattern of a previous HBV infection (HBsAg negative/anti-HBc positive). Furthermore, there were 129 isolated anti-HBc positive and 227 anti-HBc/anti-HBs positive cases. Figure 1 shows the flowchart of the patients included in the study.

Of the 365 HCV patients with HBsAg positive or HBsAg negative/anti-HBc positive, 225 (61%) were male with an average age of 59 years (range 20-85), 357 (98%) were Caucasian, 118 (51.5%) were genotype 1b and 164 (44.9%) had stage F4 fibrosis. They had previously been treated with regimens containing IFN 252 (69%) and the DAA regimen received was SOF/LDP ± RBV (n = 155, 42.4%), 3D/2D ± RBV (n = 111, 30.4%) and other combinations (n = 99, 27.2%). Sustained virological response (SVR) was obtained in 298 (99%) of the patients who could be evaluated. Demographics, stage of liver disease, virology and treatment modality administered are shown in table 1.

Of the nine patients who were HBsAg positive, five received treatment for HBV before starting HCV treatment as four were F4 and one was F2 with a viral load > 20,000 IU/ml. Of the four untreated patients who were HBsAg positive, two (50%) received a virological HBV reactivation but neither had a biochemical reactivation (Table 2). One patient in week 4 of treatment with DAA was treated with tenofovir with a virological response; this treatment was suspended six months after treatment with DAA (Fig. 2). The other patient in week 4 of follow-up did not receive treatment. The two patients who had a reactivation also had a detectable baseline viral load.

Of the 356 patients with a pattern of a previous HBV infection (HBsAg negative, anti-HBc positive), three were undergoing prophylactic treatment for HBV. One had Crohn's disease that was treated with adalimumab, another had completed chemotherapy for breast cancer one month prior to starting DAA treatment and the third one had rheumatoid arthritis that was treated with azathioprine. All three were F4, which undoubtedly conditioned the prophylactic treatment. There was no viral load data in

the remaining 353 patients as it was a retrospective study. Moreover, the transaminase follow-up was normal in these patients, indicating the absence of biochemical reactivations.

DISCUSSION

HBV reactivation in co-infected patients after clearance of an HCV infection can range from biochemical reactivations without virological reactivation (most common) to fulminant hepatic failure (6). There has only been a small number of observational studies, until now, which have assessed the risk of reactivation of HBV in HCV patients treated with DAA (11-13). A recent meta-analysis (14) showed that the incidence of HBV reactivation in HBsAg positive patients treated with DAA was similar to that in patients treated with IFN (12% *vs* 14%). However, reactivation in patients treated with DAA occurs at an earlier stage and is associated with an increased incidence of hepatitis than in cases treated with IFN (12% *vs* 0%). There have also been cases of reactivation in anti-HBc positive patients, with less frequent counts but occurring as isolated cases.

The prevalence of HBV/HCV coinfection within the Madrid community treated with DAAs, the incidence and risk factors associated with HBV reactivation and the clinical impact on the CM in patients treated with DAA is unknown. This study shows that the prevalence of HBV/HCV coinfection in the southern area of Madrid is low, there is a high rate of screening for HBV in HCV candidates for DAA and the HBV reactivation in HBsAg positive patients receiving DAA is common, although there is no clinical relevance.

The risk of HBV reactivation in patients receiving chemotherapy or immunosuppression is well known by specialists who prescribe these drugs. Currently, the majority not only undergo a routine screening for HBV before starting these treatments but also preventive treatment to prevent reactivation in risky situations. We investigated how often hepatologists screen for HBV before starting antiviral treatment with DAA based on the publication of cases with HBV reactivation in HCV patients treated with DAAs. In our study, we show that the rate of adherence to HBV screening was high in the context of the real clinical practice, as more than 90% of HCV

patients had undergone HBV screening prior to starting antiviral therapy.

There are few national studies of prevalence. One study performed in Catalonia described a prevalence of 2.8% of HBV/HCV coinfection and 18% of previous infection (11). In Spain, the prevalence of coinfection seems somewhat lower than in other areas. Risk factors for HBV/HCV coinfection include IV drug use, hemodialysis, transplants and a HIV positive status. As HIV and transplanted patients were not included in our series, this may explain the lower prevalence of coinfection in our study.

The baseline characteristics of our population co-infected with HBV/HCV are very similar to those of the mono-infected population in terms of sex, age and genotype. However, there are differences in the fibrosis stage, as nearly 50% of patients co-infected cases present F4. This supports the observation of an increased risk for the progression to cirrhosis in this population. In another series, HBV/HCV coinfection does not imply a lower response to treatment with DAA as demonstrated in our study, as the SVR was obtained in 99% of our series.

With regard to the incidence of reactivation, a study was carried out in Catalonia that included 352 HCV patients treated with DAA. In this study, five (50%) HBsAg positive and one (1.6%) anti-HBc positive patient presented a virological reactivation, in the absence of any clinical reactivation. This study concluded that virological reactivation was common but with little clinical impact. The findings of our study are similar, since half of the HBsAg positive untreated patients had a virological HBV reactivation, but none had a biochemical or clinical reactivation.

In the study by Londoño et al., cases of virological reactivation (defined as elevations > 1 log) and elevations of viral load were discrete (< 20,000 IU/ml) and transient. However, they were higher in our two cases (> 20,000 IU/ml), which led to treatment with tenofovir in one case (the one that took place after four weeks of treatment) in order to achieve a virological response after one month. In the other case, we decided to wait and subsequently confirm a progressive decrease in the viral load to its baseline values as the elevation occurred during follow-up.

With regard to the timing of the virological reactivation, previous studies have shown that this usually occurs early in relation to antiviral treatment, i.e., in the first weeks of

treatment, coinciding with negativization of HCV viremia. This may support the theory of the inverse relationship/interference of both viruses. However, in our two cases of virological reactivation, one occurred early after four weeks of treatment, but the other took place four weeks after treatment discontinuation. This suggests that close monitoring of recovery should not only be performed at the time of treatment but must be maintained during follow-up, at least during the first few months after treatment discontinuation.

With regard to patients with a pattern of a previous HBV infection (HBsAg negative, anti-HBc positive), although we did not have a viral load as it was a retrospective study, all patients had normal transaminase levels at the end of treatment and follow-up. Thus indicating the absence of biochemical reactivations and clinical manifestations.

Risk factors associated with reactivation in HBsAg positive cases are unknown. It seems that the baseline of HBV viral load is not associated with a higher risk of reactivation. However, two HBsAg patients who showed reactivation in our study had a detectable viral load at baseline. The cause of HBV reactivation with HCV clearance has not been clarified. However, there is recent evidence that shows that CD56 NK Dim cells are responsible for monitoring antiviral activity. These cells are more activated in HCV patients than in healthy controls and this activation reverses with HCV clearance (15). Recently, there has been a unified hypothesis change associated with HCV clearance. The current new unified hypothesis states that the result of elimination of HCV with DAA causes an increased production of gamma interferon and decreased activity of CD8, which may partly explain the risk of reactivation of HBV in these patients (16).

One of the strengths of our study is that it investigated HBV screening rates in HCV patients who are candidates for treatment with DAA, and also a significant number of patients have been included. In addition, it is the second national series that reports the coinfection prevalence and incidence of reactivation. With regard to the limitations, the fact that it was a retrospective study meant that viral loads were not available in patients with a previous infection pattern (anti-HBc).

There is a high awareness of HBV/HCV coinfection in our field among hepatologists, as only 7% of cases did not have baseline HBV serology. The prevalence of HBV infection (HBsAg positive) in the southern area of the CM is 0.7% and previous HBV infection

(HBsAg negative, positive anti-H) rates are 28.6%. The baseline characteristics of the population co-infected with HBV/HCV are very similar to those of the mono-infected population, except with regard to fibrosis stage, as nearly 50% of patients have fibrosis stage F4. The incidence of virological reactivation in HBsAg patients is 50%, with no biochemical reactivation in HBsAg positive or HBsAg negative/anti-HBc positive cases.

The results of our study support current recommendations for the management of HBV reactivation as follows: a) DNA-HBV should be monitored closely in HBsAg positive patients and close monitoring should be maintained during the first months of DAA treatment discontinuation; and b) HBV DNA analysis should be performed in anti-HBc positive patients when there is an elevation of transaminase levels. Larger scale studies are needed in order to determine the true incidence of reactivation, as well as its clinical relevance and proper management.

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REFERENCES

1. Konstantinou D, Deutsch M. The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viral interactions and management. Gastroenterology 2015;28:221-8.

2. Bini EJ, Perumalsswami PV. Hepatitis B virus infection among American patients with chronic hepatitis C virus infection: prevalence, racial/ethnic differences, and viral interactions. Hepatology 2010;51:759-66.

3. Fukuda R, Ishimura N, Niigaki M, et al. Serologically silent hepatitis B virus coinfection in patients with hepatitis C virus-associated chronic liver disease: clinical and virological significance. J Med Virol 1999;58:201-7. DOI: 10.1002/(SICI)1096-9071(199907)58:3<201::AID-JMV3>3.0.CO;2-2

4. Liu JY, Sheng YJ, HU HD, et al. The influence of hepatitis B virus on antiviral treatment with interferon and ribavirin in Asian patients with hepatitis C virus/hepatitis B virus coinfection: a meta-analysis. Virol J 2012;9:186. DOI:

10.1186/1743-422X-9-186

5. Takayama H, Sato T, Ikeda F, et al. Reactivation of hepatitis B virus during interferon-free therapy with daclatasvir and asunaprevir in patient with hepatitis B virus/hepatitis C virus co-infection. Hepatol Res 2016;46:489-91. DOI: 10.1111/hepr.12578

6. Ende AR, Kim NH, Yeh MM, et al. Fulminant hepatitis B reactivation leading to liver transplantation in a patient with chronic hepatitis C treated with simeprevir and sofosbuvir: a case report. J Med Case Rep 2015;9:164. DOI: 10.1186/s13256-015-0630-8

7. Collins JM, Raphael KL, Terry C, et al. Hepatitis B virus reactivation during successful treatment of hepatitis C virus with sofosbuvir and simeprevir. Clin Infect Dis 2015;61:1302-6. DOI: 10.1093/cid/civ474

8. De Monte A, Courjon J, Anty R, et al. Direct-acting antiviral treatment in adults infected with hepatitis C virus: reactivation of hepatitis B virus coinfection as a further challenge. J ClinVirol 2016;78:27-30. DOI: 10.1016/j.jcv.2016.02.026

9. EMA's Pharmacovigilance Risk Assessment Committee. PRAC warns of risk of hepatitis B re-activation with direct-acting antivirals for hepatitis C. 2016. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Directacting_antivirals_for_hepatitis_C_20/Recommendation_provided_by_Pharmacovigilance_Risk_Assessment_Committee/WC500217495.pdf

10. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA warns about the risk of hepatitis B reactivating in some patients treated with direct acting antivirals for hepatitis C. 2016. Available from: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM523499.pdf

11. Londoño MC, Sens S, Mariño Z, et al. Hepatitis B reactivation in patients with chronic hepatitis C undergoing anti-viral therapy with an interferon-free regimen. Aliment Pharmacol Ther 2017;45:1156-61. DOI: 10.1111/apt.13985

12. Wang C, Ji D, Chen J, et al. Hepatitis due to reactivation of hepatitis B virus in endemic areas among patients with hepatitis C treated with direct/acting antiviral agents. Clin Gastroenterol Hepatol 2017;15:132-6. DOI: 10.1016/j.cgh.2016.06.023

13. Belperio P, Shahoumian T, Mole L, et al. Evaluation of hepatitis B reactivation among 62920 veterans treated with oral hepatitis C antivirals. Hepatology 2017;66:27-36. DOI: 10.1002/hep.29135

14. Chen G, Wang C, Chen J, et al. Hepatitis B reactivation in hepatitis B and C coinfected patients treated with antiviral agents: a systematic review and meta-analysis. Hepatology 2017;66:13-26. DOI: 10.1002/hep.29109

15. Serti E, Chepa-Lotrea X, Kim YJ, et al. Successful interferon-free therapy of chronic hepatitis C virus infection normalizes natural killer cell function. Gastroenterology 2015;149(1):190-200.

16. Mondelli MU. Direct-acting antivirals cure innate immunity in chronic hepatitis C. Gastroenterology 2015;149(1):25-8.

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Table 1. Characteristics of HBV/HCV cases treated with DAAs

Characteristics	*n = 365 (%)*
Sex (M)	225 (61)
Age, median (rank)	59 (20-85)
Caucasian race	357 (98)
HBsAg	9 (2,4)
Ac HBc	356 (97.6)
Genotype	
1a	88 (24.1)
1b	118 (51.5)
2	6 (1.6)
3	54 (14.8)
4	26 (7.1)
5	2 (0.5)
6	1 (0.3)
Elastography T.	
F1	81 (22.2)
F2	70 (19.2)
F3	50 (13.7)
F4	164 (44.9)
Naive	113 (31)
DAAs	
SOF/LDV	155 (42.4)
3D/2D	111 (30.4)
SOF/DAC	54 (14.8)
EBR/GZR	27 (7.4)

Others	18 (4.9)
SVR	298 (99)

SOF/LDV: sofosbuvir/ledipasvir; 3D: paritaprevir/ombitasvir/dasabuvir; 2D: paritaprevir/ombitasvir; SOF/DAC: daclatasvir; EBR/GZR: elbasvir/grazoprevir; SVR: sustained virological response

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Table 2. DNA-HBV kinetics (UI/ml) in HBsAg+ treated with DAA

n	*Genotype*	*Fibrosis*	*DAA*	*Basal*	*4 s**	*12 s**	*+4 s†*	*+12 s†*	*Virological reactivation*	*Biochemical reactivation*
1	1b	F4	SOF/LDV	0	75	0	0	0	No	No
2	1b	F1	SOF/LDV	0	0	0	0	0	No	No
3	1b	F3	EBR/GZR	604	33.479	0	0	0	Yes	No
4	5	F1	SOF/DAC	833	350	380	21,900	4,120	Yes	No

*4 s/12 s: 4 and 12 weeks intra-treatment. †+4 s/+12 s: 4 and 12 weeks post-treatment.

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Fig. 1. HBV screening flowchart in patients with HCV.

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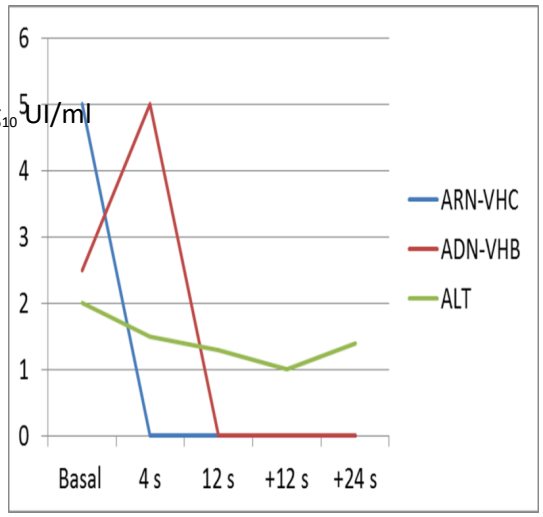

Fig. 2. Patient 1: virological reactivation at week 4 of treatment. *4 s/12 s: 4 and 12 weeks intra-treatment. †+4 s/+12 s: 4 and 12 weeks post-treatment.

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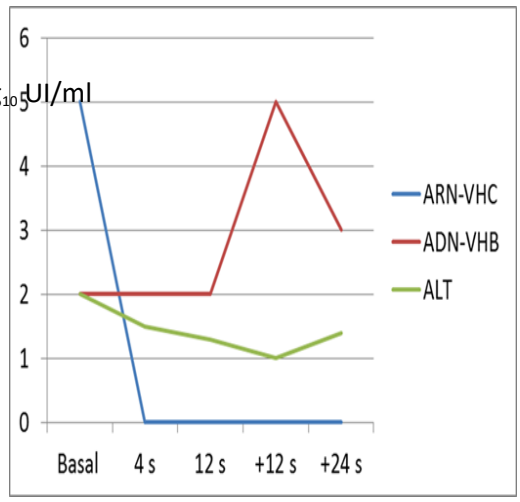

Fig. 3. Patient 2: virological reactivation at week 4 of follow up. *4 s/12 s: 4 and 12 weeks intra-treatment. †+4 s/+12 s: 4 and 12 weeks post-treatment.