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CASE REPORT

HBsAg loss with HBsAg/anti-HBs seroconversion and non-detectable HCV-RNA in a patient with chronic HBV e-minus/HCV hepatitis treated with two cycles of antiviral therapy

Perdita di HBsAg con sieroconversione HBsAg/anti-HBs e negativizzazione di HCV-RNA in paziente con epatite cronica a doppia eziologia virale (HBV e-minus/HCV) trattata con due cicli di terapia antivirale

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Peginterferon-alfa;
Ribavirin.

Summary

Introduction: Loss of HBsAg is observed in only 3–4% of patients who receive interferon for chronic HBV+HCV hepatitis, and there are few reports of HBsAg loss induced by treatments other than interferon. We report a case of chronic HBV+HCV hepatitis, in which a positive outcome was achieved with a new therapeutic strategy.

Case report: The patient was a 49-year-old Caucasian woman found to be HBsAg+ in 1978 and HCVAb+ in 1997. During 2000–2003, the patient had markedly increased AST/ALT, histology grade 5, stage 1 (Ishak) disease with HBsAg positivity, HBV-DNA 1,450 cp/mL, HCV-RNA 7.57x10⁵ IU/mL (genotype 1b). In May 2003 she began a 48-week course of PEG-IFN α 2b (80 μ g/week) without ribavirin. The latter drug was not used because it had recently been observed that in some

Abbreviations: ALT, (serum) Alanine Transaminase; Anti-HBs (HBsAb), Antibody to Hepatitis B surface (antigen); AST, (serum) Aspartate Transaminase; CH, Chronic Hepatitis; ETR, End Term (Therapy) Response; EVR, Early Virological Response; HBeAg, Hepatitis B "e" Antigen; HBsAg, Hepatitis B surface Antigen; HBV, Hepatitis B Virus; HBV-DNA, Hepatitis B Virus-Deoxyribonucleic Acid; HCV, Hepatitis C Virus; HCV-RNA, Hepatitis C Virus-Ribonucleic Acid; IFN α , Alpha-interferon; NR, Not Responder; PCR, Polymerase Chain Reaction; PEG-IFN, Pegylate-Interferon; RVR, Rapid Virological Response; SVR, Sustained Virological Response; ULNV, Upper Limit of Normal Value.

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HBV/HCV-coinfecting patients treated with the two drugs, the hepatic flares preceding the seroconversion to HBsAb caused fulminant liver failure. Neither the HBV and HCV infections responded to this treatment, but during follow-up the HBV-DNA dropped to 40 cp/mL and the patient presented persistently normal transaminase values (6th month) followed by loss of HBsAg (24th month) and the appearance of anti-HBs (36th month). By December 2008, the HBV negativity and HBsAg/anti-HBs seroconversion were well-established, but HCV replication persisted. The decision was therefore made to administer PEG-IFN α 2a (180 μ g/week) and ribavirin (1,000 mg/day). There was no evidence of an RVR or EVR, so therapy was continued for 48 weeks. At the scheduled 12-month treatment, the patient was found to be HCV-RNA negative by TaqMan PCR.

Conclusions: In our opinion this case is of great interest because: 1) it is the first report of a virological response in a HBV/HCV-coinfecting CH patient treated with PEG-IFN; 2) control of the two viral infections was achieved with a new therapeutic strategy that included two phases: a) HBV-DNA loss at 6 months and HBsAg/anti-HBs seroconversion between months 24 and 36, after PEG-IFN α 2b mono-therapy, which was administered when the HCV replication seemed to prevail over that of HBV; b) ETR for HCV after 72 weeks of PEG-IFN α 2a+ribavirin, which was continued in spite of the lack of an EVR, as this does not preclude the possibility of a SVR.

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Introduction

HBV and HCV infections are the main cause of CH, cirrhosis and hepatocellular carcinoma in the Western hemisphere [1–5]. The majority of CH patients are mono-infected; however, in a minority of cases, the patients are coinfecting with both the hepatic viruses. Of note, in the CH coinfecting patients the disease progresses more rapidly and seriously to cirrhosis and hepatocellular carcinoma [2,6,7]. Usually, in the HBV/HCV-coinfecting patients, the replication of one of the two viruses suppresses the other one. The mutual inhibiting effect of the hepatic viruses has been described in several clinical studies; nevertheless, the dynamics and the interactions between the two viruses after an antiviral therapy remain still quite unknown [4,7–10]. In HBV-mono-infected patients therapy with IFN α induces HBsAg loss in only 3–4% of the cases [4], SVR being attained in 30% of the cases [4,5,11,12]. The IFN α therapy is instead much more effective in HCV-mono-infected CH patients when combined with ribavirin (SVR 50% in genotype 1–4; SVR 80–90% in genotypes 2–3) [13–16]. The CH treatment in HBV and HCV-coinfecting patient is not well-standardized yet [17–20]. There are cases in literature reporting the B virus reactivation in HBV/HCV-coinfecting CH patients treated with IFN α +ribavirin for HCV [8,21,22]. Few cases of HBsAg loss and HBsAg/anti-HBs seroconversion have been described in CH coinfecting patients, treated with IFN α alone, when the C virus replication prevailed [4,7–10,23,24]. In 2009 Liu et al. [23] reported the HBsAg serum loss in the 11.2% of coinfecting patients treated with PEG-IFN+ribavirin. Here we describe an interesting clinical case of a CH patient coinfecting with HBV e-minus and HCV. The patient was firstly treated with PEG-IFN α 2b without ribavirin, obtaining, after 6 months from the suspension of the antiviral treatment, the HBsAg loss and, remarkably, during the 24th/36th months of follow-up, the HBsAg/anti-HBs seroconversion. In a second phase, due to the persistence of the HCV replication, the patient was treated again with PEG-IFN α 2a+ribavirin for a period of 72 weeks, finally obtaining the ETR for the HCV infection.

Clinical case

49-years-old woman. Caucasian. First detection of HBsAg+ in 1978 and of HCVAb+ in 1997: the patient did not report any AST/ALT fluctuation. From 2000 increase in AST/ALT 1.5–2 ULNV. In 2001 she was admitted in the Department of Hepatology; however, she did not attend the further scheduled controls. She was again examined in the Hepatology Day Hospital in 2003, when she was also subjected to a percutaneous echo-guided hepatic biopsy. Histology: grading 5 and staging 1 (Ishak). Laboratory: HBsAg+ (HBsAg levels were not quantified because at that time the technique was not available in our laboratory); HBV-DNA 1,450 cp/mL; HCV-RNA (TaqMan PCR) 7.57x10⁵ IU/mL; viral genotype 1b (Simmonds); ALT 1.5 ULNV.

In May 2003 she began a mono-therapy with PEG-IFN α 2b 80 μ g/week, scheduled for 48 weeks. We first decide to not combine PEG-IFN with ribavirin because, at that time, in literature severe hepatitis flares, some culminating in fulminant hepatic failure, had been reported in HBV/HCV patients treated with the association of the two drugs.

In May 2004, at the end of the therapy, the patient was classified as both HBV and HCV non-responder. However, during the follow-up, we detected at 6th month the loss of HBV-DNA (40 cp/mL) and, at 24th month, the loss of HBsAg; moreover, we detected, at 24th/36th month, the appearance of anti-HBs.

In December 2008, by now well established the HBV negativity and the HBsAg/anti-HBs seroconversion, we decided, due to the persisting HCV replication (HCV-RNA 10.76x10⁵ by TaqMan PCR), to treat the patient with both PEG-IFN α 2a (180 μ g/week) and ribavirin (1,000 mg/day). Although neither a RVR at the 4th week nor an EVR at the 12th week of therapy were obtained, we continued the treatment for the already scheduled 48 weeks, at the end of which the patient was found to be HCV-RNA negative by TaqMan PCR (ETR). The patient was NR to the previous treatment with PEG-IFN α and affected by genotype 1b. Thus, we decided to continue the therapy for the treatment of the

HCV-caused CH for 72 weeks, at the end of which the patient was still HCV-RNA negative by TaqMan PCR with the persistence of negative HBsAg and high HBsAb (96 IU/mL).

Discussion and conclusions

We consider this clinical case of great interest because of the limited number, in literature, of any exhaustive report about the virological responses in HBV/HCV-coinfected CH patients treated with IFN/PEG-IFNs. Moreover, it shows that the control of the two viral infections has been achieved in two subsequent steps.

- 1) The HBsAg loss at the 6th month and the HBsAg/HBsAb seroconversion between the 24th and the 36th month during the follow-up of the PEG-IFN α 2b mono-therapy administered when the HCV replication seemed to prevail on the HBV one. Of note, Yu et al. [25] have recently showed that the HBsAg levels measured in the serum before the treatment with PEG-IFN+ribavirin correlate with the post-therapy HBsAg loss and HBsAg/HBsAb seroconversion. Unfortunately, we could not quantify the pretreatment HBsAg serum levels in our patient.
- 2) The ETR for HCV after 72 weeks of therapy with PEG-IFN α 2a+ribavirin, although in absence of any early virological response.

In rare cases reported in literature, in coinfecting patients treated with IFN α /PEG-IFN α +ribavirin, the HBV reactivation, preceding the hepatic flares, seems to be linked to the HCV replicative inhibition by the antiviral therapy. In our case, the first therapeutic treatment with PEG-IFN α 2b in mono-therapy, aimed at treating HCV which was then prevailing, was not sufficient to obtain a SVR for HCV but it was, instead, able to induce an exhaustive response for HBV, probably by stimulating the immune system when the HBV viremia was at very low levels. For these reasons, we would like to emphasize how the clinical case here reported might suggest, for the first time, to the best of our knowledge, the possibility of an innovative two-step therapeutic strategy, for HBV e-minus/HCV-coinfected CH patients: in a first phase, PEG-IFN α in mono-therapy for reactivating the immune system towards the B virus when the levels of HBV viremia are very low and, in a second phase, PEG-IFN α +ribavirin to obtain a SVR for HCV. Of course, the ideal control of the HBV infection here reported in a single patient does not mean, at the moment, that our new two-step therapeutic strategy will be successful in modifying the natural disease progression in all the HBV/HCV-coinfected patients. Evidences by more reports or, more significantly, the results of ad hoc clinical trials will be required for definitively proving this novel approach as a valid, generalizable therapeutic strategy.

Conflict of interest statement

The authors have no conflict of interest.

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