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BRIEF REPORT

Poor Response to Treatment with Peg-IFN Containing Regimens in Patients Coinfected with Hepatitis B and Hepatitis C Virus

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Background and Aims: **To investigate the clinical charcteristics and treatment response of patients with chronic coinfection of hepatitis B virus (HBV) and hepatitis C virus (HCV).**

Methods: **The study included nine consecutive patients with chronic HBV/HCV coinfection. Diagnosis was performed by liver biopsy and/or clinical and laboratory evaluation. Six patients received 48 weeks of pegylated interferon (Peg-IFN) monotherapy or combination therapy with Peg-IFN plus ribavirin according to the dominant virus.**

Results: **The dominant infection was hepatitis C in six cases. Of the four patients who completed the treatment and follow-up period, only one had a sustained viral response (SVR) to HCV, but unfortunately, this was accompanied by a reactivation of HBV-DNA without flaring of hepatitis. No patient had an HBV-DNA response. Another two patients are still in the follow-up period. One of these patients had an undetectable level of HCV-RNA, and the other had an undetectable level of HBV-DNA at baseline. At the end of treatment, both HBV-DNA and HCV-RNA were negative in these patients. The HBV-DNA-negative patient showed a transient HBV-DNA positivity after clearance of HCV-RNA.**

Conclusions: **In the majority of HBV/HCV coinfected cases in our sample, HCV was the dominant virus. Currently, the standard treatment regimens are not effective for clearance of HBV and/or HCV. HCV clearance may induce HBV reactivation without flaring of hepatitis.**

Keywords: **Coinfection, Hepatitis B, Hepatitis C, Treatment**

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) share modes of transmission, and their combined infection is not uncommon in high-endemic areas [1-3]. In general, anti-HCV prevalence is around 10-20% in patients with chronic HBV infection, and 2-10% of anti-HCV-positive patients have markers of HBV infection [4]. Although several studies have suggested that HBV/HCV coinfection may be associated with more severe forms of chronic liver disease, there are inconsistent reports about the interaction between the two viruses in influencing the severity and nature of liver disease [5, 6].

Despite its considerable clinical importance, scant

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information is currently available on the treatment of the HBV/HCV-coinfected population. Moreover, most of the studies evaluating treatment for coinfection are related to monotherapy or a combination of therapy of conventional interferon (IFN) and ribavirin.

We performed a retrospective analysis to evaluate the frequency, clinical characteristics, and efficacy of pegylated IFN (Peg-IFN) plus ribavirin therapy in patients with HBV/HCV coinfection.

Materials and Methods

This study included nine consecutive patients with chronic HCV/HBV coinfection, recruited between 2003 and 2008 at the Department of Infectious Diseases and Clinical Microbiology at the Ataturk University Medical School. They were all seropositive for HCV antibody (anti-HCV) and hepatitis B surface antigen (HBsAg) for more than 6 months. HCV-RNA was positive in all but one patient, and HBV-DNA was positive in five patients at baseline. No patient had human immunodeficiency virus (HIV) infection; active alcohol abuse or drug addiction; or evidence of metabolic, autoimmune, or genetic causes of liver disease. The diagnosis was performed by liver biopsy in five cases and by clinical/laboratory evaluation in four cases.

Both HBV-DNA and HCV-RNA quantification were performed using a real-time polymerase chain reaction (RT-PCR) method (BioRad, iCycler, Hercules, CA, USA) with a sensitivity of 200 copies/ml for HBV-DNA and 10 copies/ml for HCV-RNA.

Levels of serum HBV-DNA and HCV-RNA are commonly used as surrogate markers of viral activity. As described previously [7], we used the conventional--and arbitrary--level of 10^4 copies/mL of serum HBV-DNA as the cutoff for distinguishing between active and inactive HBV infection. Similarly, active HCV infection was arbitrarily defined on the basis of virus RNA values above 10 copies /ml, which is the detection limit of the kits used for quantifying HCV viremia.

Six patients received 48 weeks of monotherapy with Peg-IFN or combination therapy with Peg-IFN plus ribavirin according to the dominant virus. Patients were followed for an additional 24 weeks after the end of therapy. The patients had biweekly outpatient visits during the first 4 weeks of treatment and monthly thereafter for 68 weeks. HBV serological markers, HCV-RNA, and HBV-DNA were tested for at 12, 24, and 48 weeks of treatment, as well as at 12 and 24 weeks after the end of treatment.

For HCV and HBV infections, sustained viral response (SVR) was defined as having no detectable HCV-RNA or HBV-DNA at the end of treatment and after 24 weeks of follow-up. The patients who failed to achieve SVR were classified as non-responders. An increase of HBV-DNA was defined as greater than two logs elevation of serum HBV-DNA from the baseline level on at least one occasion. Sustained biochemical response was defined as the persistence of normal serum alanine aminotransferase (ALT) values up to 24 weeks after the end of treatment.

Results

Of the 83 patients with chronic HCV infection, 9 (10.8%) were coinfected with HBV (7 were male, 2 were female; mean age 43.9 ± 11.5 years), and 4 had known risk factors for parenterally transmitted viruses (3 had history of blood transfusion, and 1 had history of dental-care procedures). Two patients were hepatitis B e antigen (HBeAg) positive and 7 were hepatitis B e antibody (anti-HBe) positive. The baseline characteristics and treatment responses for patients who were coinfected with HBV and HCV are shown in Table 1.

Of the nine coinfected patients, four were both HBV-DNA and HCV-RNA positive, four were only HCV-RNA positive, and one was only HBV-DNA positive. The dominant infection was hepatitis C in six (66.6%) cases.

A liver biopsy was performed in five patients, and specimens were evaluated by Knodell's scoring system. The results are shown in the Table 1. No patient had previously received antiviral therapy.

One patient did not receive antiviral treatment because a liver biopsy revealed a mild liver disease, and another two patients refused treatment. Finally, six patients received antiviral treatment as shown in Table 1.

Of the six treated patients, four (Patients 1, 3, 6, and 8) completed the treatment and a 24-week follow-up period. Two of these patients (Patients 3 and 6) had detectable serum HBV-DNA levels at baseline. One patient did not achieve a virological response for HBV or HCV. The other patient had an SVR to HCV but no response to HBV infection. Furthermore, that patient had an increase of HBV-DNA level after the clearance of HCV, without an outbreak of hepatitis. Two other patients who completed the treatment and follow-up (Patients 1 and 8) already had undetectable HBV-DNA levels at

baseline. These two patients became HCV-RNA negative at the 12th week of treatment and reached end of treatment response. However, the reappearance of HCV-RNA was detected in both patients in the follow-up period. Finally, only one of the four patients who completed the treatment and follow-up had an SVR to HCV, and unfortunately, this was accompanied by a reactivation of HBV-DNA.

Another two patients (Patients 2 and 7) completed the treatment, but they are still in the follow-up period as of this writing. One of these patients (Patient 2) was the only patient who had an undetecable HCV-RNA at baseline and whose HBV-DNA and HCV-RNA levels were negative at the end of treatment. The second patient (Patient 7) had an undetectable HBV-DNA level at baseline, but after the clearance of the HCV-RNA, the HBV-DNA level became detectable for three months (during the 6th, 7th, and 8th months of treatment). However, this patient tested negative for both HBV-DNA and HCV-RNA at the end of the treatment. Hepatitis flare was not observed in that patient.

No patient achieved loss of HBsAg or HBeAg by the end of treatment or follow-up period. Three patients had sustained biochemical response.

Discussion

Our present study, which revealed a prevalence rate of 10.8% among patients with chronic HCV infection, agrees with the findings of previous studies [4]. A multicenter prospective study from Italy showed that being more than 42 years old, having a history of intravenous drug use and/or blood transfusion, and residing in the south of the country were independent factors associated with HBV/HCV coinfection [8]. In our study, five patients had no known risk factors. Male circumcision, which is an almost universal surgical procedure among Muslim men, may contribute to coinfection with HBV and HCV.

Several studies have suggested an interplay between the two viruses in cases of dual infection with a prevalent negative influence of HCV on HBV activity [5, 6, 9]. All clinical studies, however, do not uniformly report a dominant role of HCV. Some findings suggest a reciprocal interference, or even a dominant effect of HBV [10-12]. Although most patients appear to have active HCV and inactive HBV infection, some patients have high HBV viremia levels and undetectable HCV-RNA [13]. In our series, HCV was dominant in six patients, and

Table 1. Baseline characteristics and treatment response of HBV/HCV-coinfected patients.

Patient No	Age (years) / Gender	Liver biopsy	ALT/AST	HBV-DNA/ HCV-RNA (copy/ml)	HBeAg / AntiHBe	Treatment regimen	Response to treatment
1	48/M	HAI 11, FS3	67/38	-/ 7 000 000	-/+	Peg-IFN 120µgr/week + ribavirin 1000 mg/day	* HBV-DNA(-) HCV NR
2	40/M	HAI 11, FS3	66/32	4 000 000/ -	-/+	Peg-IFN 180µgr/week	&HBV-DNA(-) HCV-RNA (-)
3	64/M	NA	54/39	7800/ 200 000	-/+	Peg-IFN 180µgr/week +ribavirin 1000 mg/day	*HCV NR HBV NR
4	20/M	NA	36/24	10 000 000/1000 000	+/-	no	-
5	39/F	NA	248/206	-/100 000 000	-/+	no	-
6	45/F	NA	75/58	100 000/2 000 000	+/-	Peg-IFN 180µgr/week +ribavirin 800mg/day	*HCV SVR HBV-DNA reactivation
7	47/M	HAI 11, FS1	250/194	-/600 000 000	-/+	Peg-IFN120µgr/week + ribavirin1000mg/day	&HBV-DNA(-) HCV-RNA(-)
8	46/M	HAI 7, FS1	65/48	-/ 700 000	-/+	Peg-IFN 180µgr/week + ribavirin 1200 mg/day	*HCV NR HBV DNA (-)
9	46/M	HAI 3, FS1	74/41	3000/1 000 000	-/+	no	-

M: male, F: female, HAI: histological activity index, FS: fibrosis score, ALT: alanine aminotransferase, AST: aspartate aminotransferase, SVR: sustained virological response, NR: non responder, NA: not available.

*End of follow-up response

&End of treatment response

44.4% of the patients were HBV-DNA negative. In contrast, in a recent study from Turkey, 70.6% of coinfected patients were HBV-DNA negative [9].

There is no scientific evidence indicating the most appropriate follow-up procedure for coinfected patients, and no guidelines have been established for their treatment. A key step to identifying this category of patients is the behavior of the viruses involved in the coinfection. Sustained response to conventional IFN monotherapy is low in coinfected patients [14]. More recent studies have shown that IFN-α/ribavirin combination therapy is effective for eradicating HCV infection in coinfected patients [15, 16]. HBV eradication rates in these studies, however, were lower. In a recent study, conventional IFN-α2a plus ribavirin were evaluated in 21 coinfected patients over a 24-week period [15], and the results were compared with those of 30 HCV monoinfected patients. The groups were similar with respect to age, gender, serum ALT levels, and genotype distribution. Serum HCV-RNA clearance rates were comparable in both groups (43% vs. 60%, P > 0.05). Sustained HBV-DNA clearance was obtained in 17.6% of the HBV viremic patients but was not accompanied by loss of HBsAg. Chung *et al.* [16] Evaluated 42 chronicly coinfected patients and 84 HCV monoinfected controls receiving conventional IFN-α plus ribavirin combination therapy. The SVRs of the monoinfected and coinfected patients were 67.2% and 69%, respectively. Of 16 baseline HBV viraemic patients, 31.3% achieved HBV SVR. Only one patient had simultaneous seroclearance of HCV and HBV. Anti-HBe developed in 11.9% of the patients during the long-term follow-up. The authors concluded that IFN-α /ribavirin combination therapy was effective in eradicating HCV infection and might promote HBV seroclearance for HCV/HBV-coinfected patients. In contrast, Senturk *et al.* [17] reported much lower HCV clearance rates for coinfected patients with either conventional or Peg-IFN-based regimens (5.3% and 5.9%, respectively). All of their 36 patients had negative serum HBV-DNA levels at baseline. The authors suggested that the reason for the low clearance rate may have been due to the high proportion of male patients and a unique genotype 1 virus infection among cases.

In fact, there are limited data regarding Peg-IFN containing regimens. Two recent case reports have suggested that Peg-IFN plus ribavirin treatment was effective for HBV/HCV coinfection [18, 19]. Rotou *et al.* (18) reported HCV eradication and HBeAg to anti-HBe seroconversion after Peg-IFN-α2b plus ribavirin treatment in a coinfected patient. The second case tested negative for HBV-DNA and HBeAg at baseline [19]. HBsAg levels showed a linear decline during a 48-week treatment period. At this point, the patient received active HBV immunization and another 4 weeks of Peg-IFN plus ribavirin treatment. Forty-three weeks after the treatment, the patient showed a robust HBsAg seroconversion. Recently, in a large-scale prospective study, coinfected patients were treated for 48 weeks for HCV genotype 1 or 24 weeks for genotypes 2 and 3 [20]. The results revealed high rates of SVR for HCV in both genotype 1 (73%) and 2/3 (86%) patients. Of the 68 patients who had detectable HBV-DNA levels at baseline, 69% achieved HBV-DNA negativity by the end of treatment. HBV-DNA remained undetectable in 56% of the cases during 24 weeks of follow-up. In addition, HBsAg clearance occurred in 10% of the patients. However, 36% of the patients who were HBV-DNA negative at baseline demonstrated HBV-DNA rebound during the treatment period or follow-up. In our series, despite our limited data, HBV viraemic and non-viraemic coinfected patients had poor results for HCV-RNA and HBV-DNA clearance with Peg-IFN and ribavirin combination treatment. No patients achieved loss of HBsAg or HBeAg. Interestingly, three patients had a sustained biochemical response at the end of the follow-up period. Our findings were similar to the results of Senturk *et al.* [17], who reported very low response rates in patients coinfected with genotype 1 virus. As in their study, the majority of our cases were male, and HCV clearance was seen only in one female patient. Unfortunately, HCV genotypes were not specified in our study. According to previous studies, the most prevalent genotype of HCV in Turkey is genotype 1, at 91% to 100% [21-23]. It is probable that genotype 1 was also the most prevalent genotype in the present study and caused a poor treatment response.

Successful treatment of HCV infection may induce HBV reactivation and flaring of hepatitis in patients who had an undetectable level of HBV-DNA prior to treatment [20, 24]. We did observe HBV-DNA reactivation, but no clinical hepatitis flare, in two cases. Unlike previous reports, one of these cases had a detectable level of HBV-DNA at baseline. That patient was also the only case who reached an HCV SVR in this study.

It is generally agreed that it is important to determine "the dominant virus" before initiation of therapy to specify the most appropriate antiviral regimen for HBV/HCV-coinfected patients [14, 25]. According to Chu *et al.* [14], although the phenomenon of reciprocal viral interference can develop during or after therapy and this may cause exacerbation of liver disease, in coinfected patients

with negative HBeAg and a low level of viremia (<10^4 IU/mL, which is approximately equivalent to 0.5′ 10^5 copies/mL), Peg-IFN plus ribavirin is the recommended regimen. For patients with dually-active HBV/HCV coinfection (*i.e.* HCV-RNA positive, HBeAg positive, or HBV-DNA >10^4 IU/mL), very little relevant information is available. The limited data indicate that IFN/ Peg-IFN plus ribavirin might be inadequate. Adding one or more nucleotide analogs to suppress HBV replication might be feasible, but more studies are needed to elucidate the problem [14].

In conclusion, this study found that HCV was the dominant virus in the majority of HBV/HCV-coinfected cases in the sample. Current standard treatment regimens are not effective for clearance of HBV and/or HCV. Sustained clearance of HCV seems difficult in both viraemic and non-viraemic HBV patients. Reactivation of HBV replication without clinical hepatitis flaring may be observed in HBV-DNA-positive or HBV-DNA-negative patients who achieve SVR for their HCV infection. Improved strategies for dealing with HBV/HCV coinfection are required.

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