Treatment of the hepatitis B virus and hepatitis C virus co-infection: Still a challenge for the hepatologist

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See Article, pages 688–694

Chronic co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is generally associated with severe forms of liver disease that may have a serious prognosis and high risk of death mostly due to their propensity to progress toward cirrhosis and to develop hepatocellular carcinoma [1–11]. In spite of the considerable clinical impact, many aspects concerning this dual infection have been insufficiently explored so far. In particular, very little is known from the therapeutic point of view, and guidelines for its treatment have not been drawn up to date. This paucity is mainly due to the fact that most studies on the natural and post-therapeutic course of chronic hepatitis C foresee, among the main exclusion criteria, the coexisting presence of the HBV “s” antigen (HBsAg). Vice versa, antibody to HCV (anti-HCV) positive subjects are excluded from the studies on HBV-related liver disease.

Nevertheless, the few available studies in this field acknowledge that this particular form of chronic viral hepatitis is particularly difficult to cure [12–16]. Several reports suggested an interplay between HBV and HCV in the case of co-infection (reviewed in [4] and [17]), with a prevalent role of HCV suppressing the HBV activity through the core protein that is able to inhibit HBV replication, as “in vitro” studies showed [18–21]. In this context, some anecdotal reports concerning co-infected patients treated with interferon (IFN) therapy for the productive HCV infection showed the reactivation of the previously suppressed HBV when a favourable response to therapy was achieved in terms of serum HCV RNA disappearance [15,22]. In other words, the cure of the HCV infection in these cases would produce the loss of the inhibitory effect exerted by HCV on HBV, thus allowing its reactivation. In this issue of the Journal, Potthoff and co-workers report the results of their pilot study on the effect of pegylated interferon (PEG-IFN) plus ribavirin therapy in a group of HBV/HCV co-infected patients with chronic liver disease [23]. They found an excellent response concerning the HCV infection, with a sustained virological response (documented by the absence of viral RNA 6 months after the end of treatment) in 14 out of the 15 patients who completed the study. Thus, PEG-IFN plus ribavirin treatment maintains its therapeutic efficacy on HCV in cases with HBV co-infection. Concerning the behaviour of HBV, two patients with detectable HBV DNA at baseline became HBV DNA negative at the end of post-treatment follow-up, whereas in four individuals the viral DNA, which was negative at baseline, became detectable 6 months after stopping therapy when they tested negative for HCV RNA. These results led the authors to consider the former two cases as good responders to the PEG-IFN therapy for both the viruses, whereas in the latter four cases the cure of the HCV infection would have produced the loss of the suppressive effect of HCV with consequent HBV reactivation.

A major question arises from this study: is it sufficient to test HBV DNA just once before starting antiviral therapy to distinguish between productive and suppressed HBV infection in this category of patients?
In this context, one should consider that the classic antibody to HBV “e” antigen (anti-HBe) positive hepatitis B is often characterized by phases of low levels of HBV replication interspersed with episodes of viral reactivation [24–27], and actually all but one of the 19 cases initially included in the study by Potthoff et al. were anti-HBe positive.

In a recent Italian multicenter study that examined the largest series of HBsAg and anti-HCV positive patients longitudinally analysed so far, it was shown that a wide and complex spectrum of virological profiles may occur in cases of co-infection [28]. This study enrolled 133 untreated HBsAg/anti-HCV positive patients who were followed up for one year with bimonthly evaluation of HBV/HCV viremia levels and liver biochemistry. One third of these patients presented alternate phases of inhibition and recurrence of the activity of one or both the viruses, as revealed by broad changes over time of the amount of circulating HBV DNA or, less frequently, HCV RNA. Moreover, the longitudinal profile of each virus in all the cases with fluctuating virological patterns appeared to be totally independent of the viremia levels of the other virus. Finally, a similarly dynamic virological profile was observed in a subgroup of individuals with triple viral hepatitis infection (HBV, HCV and Delta hepatitis virus).

A subsequent study investigated the behaviour of apparently inactive HBV infection in patients under treatment for a concurrent HCV infection [29]; the inactive HBV status was maintained independently of the HCV response to therapy in all but two non-responder cases with persistently high HCV viremia levels. These two patients showed HBV DNA flares during the antiviral treatment, indicating a status of productive HBV infection and risk of hepatocellular carcinoma in patients with compensated viral cirrhosis. Cancer 1999;85:2132–2137.

Therefore, a single point evaluation of viral DNA levels cannot allow any reliable conclusion about the status of activity of the HBV in cases with single infection as well as in patients with HCV co-infection. Thus, the definition of the behaviour of each virus implied in the dual infection should be longitudinally evaluated before starting any antiviral treatment in order to define whether one or both the virus(es) is (are) responsible for the liver injury in each individual case and, consequently, to choose the best therapeutic option that also has to take into account the possible use of anti-HBV nucleos(t)ide analogues. Moreover, once therapy is started, the virological follow-up should be continued in order to recognize possible reactivation of a previously quiescent infection and to adapt the therapy to the new virological scenario.

In conclusion, the study by Potthoff and co-workers clearly confirms that international guidelines for the treatment of HBV/HCV co-infection are needed. For this purpose, larger therapeutic trials should urgently be designed and performed, and these trials must take into account the complex and frequently unpredictable virological profile of this clinically important – but until now understudied – category of patients.

References


