Influence of occult hepatitis B virus infection in chronic hepatitis C outcomes

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ABSTRACT

Persistence of hepatitis B virus-DNA in the sera, peripheral blood mononuclear cells or in the liver of hepatitis B surface antigen (HBsAg)-negative patients with or without serological markers of previous exposure (antibodies to HBsAg and/or to HB-core antigen) defines the entity called occult hepatitis B infection (OBI). Co-infection with hepatitis B and hepatitis C viruses is frequent in high endemic areas. While this co-infection increases the risk of developing hepatocellular carcinoma (HCC), the effect of occult hepatitis B infection (OBI) on the natural history of chronic hepatitis C infection remains elusive.

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potential effect on liver histology, on clinical outcomes such as the risk of developing HCC or disease decompensation in these patients.

LITERATURE SEARCH

Electronic searches of the National Library of Medicine’s (PubMed and OVID Technologies), EMBASE (OVID Technologies), Current Contents (Institute for Scientific Information) and manual of selected specialty journals were made to select all relevant literature. The key words “Occult hepatitis B virus AND hepatitis C virus”, “Impact of occult hepatitis B virus on chronic hepatitis C”, were used. All articles were identified by a search from June 1999 to May 2010. Eligibility and exclusion criteria were previously specified. Case reports and human immunodeficiency virus co-infection articles were excluded while case-series, cross sectional, retrospective and prospective studies of occult hepatitis B and chronic hepatitis C were included.

DO HEPATITIS B AND HEPATITIS C VIRUSES INTERACT IN THE HOST?

Some in vitro studies have shown that the HCV “core” protein suppresses HBV replication[13-15]. However, these results have not been confirmed by more recent studies which have demonstrated little or null interaction between HCV and HBV in a Huh7 cells culture[16,17]. Nonetheless, in vitro experiments cannot be extrapolated to the host viral infection scenario as a host active immunological and cytokine response to the human infection is lacking in ex vivo experiments. This immunological response may determine both the liver damage and the clinical outcome. In the clinical setting, Jardi et al[18] found that HCV displayed strong inhibitory action in the reciprocal viral inhibition seen in HBV/HCV coinfected individuals. An inhibition of HCV replication by HBV-DNA was also observed in hepatitis B surface antigen (HBsAg)-negative Austrian patients[19]. However, Alberti et al[20] studied 30 patients with symptomatic acute hepatitis and markers of active HBV and HCV coinfection; all patients underwent long-term follow-up and their chronic infection rates were similar to those patients with single HBV and HCV infection. Nevertheless, the risk of fulminant/subfulminant hepatitis is increased in cases of acute HCV superinfection in chronic hepatitis B[21-23] and causes a higher cumulative risk of cirrhosis and HCC than HDV superinfection does[24].

OBI AND CHRONIC HEPATITIS C: EFFECT ON HISTOLOGY AND CLINICAL OUTCOMES

Cacciola et al[25] found that patients with chronic hepatitis C and OBI more frequently had cirrhosis than patients with chronic hepatitis C alone. Likewise, Mrani et al[26] found that 47 of a cohort of 203 HCV positive French patients (23%) had occult HBV infection with a low HBV load (10^2-10^4 copies/mL). The serum HCV-RNA titer, the liver inflammatory activity and the stage of fibrosis were significantly higher in HBV-DNA positive than in HBV-DNA negative patients. However, these findings have not been confirmed by other studies. Sagnelli et al[27] found occult HBV infection by using PCR as defined by two different positive results of HBV-DNA in plasma, peripheral blood mononuclear cells (PBMCs) and liver compartments in 37 of 89 patients with biopsy proven chronic hepatitis C (41.6%) and found no association between occult HBV infection and the degree of liver necro-inflammation and fibrosis. Fabris et al[28] studied a cohort of 51 HBsAg-negative patients with chronic hepatitis C, and studied liver fibrosis progression by using paired liver biopsies. HBV-DNA was found by nested PCR in 1.9% of sera and 29.4% of liver tissue samples. The authors found no significant differences in mean serum aminotransferase values, baseline HCV viral load, HCV genotypes, or grading and staging in patients with or without HBV-DNA. Hui et al[29] retrospectively compared fibrosis progression and progression to severe fibrosis (fibrosis stage 3 or 4) in 74 HCV patients with at least two consecutive biopsies, and found occult HBV infection in 31 (41.9%). Patients with occult HBV co-infection did not progress more than patients without occult HBV infection. Kannangai et al[30] reported liver flares that were associated with serum HBV-DNA detection in a small group of patients with OBI and hepatitis C; the authors proposed that flares might be the pathogenetic mechanism underlying liver disease progression in patients with OBI and chronic hepatitis C[31]. By contrast, no effect on liver biochemistry was observed in other studies[32,33]. In summary, results of the combined effect of OBI and chronic hepatitis C on liver disease progression have yielded controversial results and no firm conclusion can be reached on this issue.

EFFECT OF OBI ON THE RISK FOR DEVELOPMENT OF HCC IN CHRONIC HEPATITIS C

Pollicino et al[34] found a significant association between OBI and HCC, and provided persuasive evidence that OBI maintains several of the oncogenic mechanisms of HBV such as the capacity to be integrated in the host’s genome and production of transforming proteins. Therefore, it is conceivable that OBI might increase the risk for developing HCC in patients with chronic hepatitis C in the same way as HBV infection does. Adachi et al[35] found that positive HBeAb, which indicates a previous HBV infection, but not positive HBV-DNA patients, was associated with an increased risk for developing HCC. Independent risk factors for development of HCC were male gender, α-fetoprotein ≥ 20 ng/mL, serum ALT ≥ 80 IU/L and the presence of anti-HBc. Likewise, Ikeda et al[36] prospec-
tively studied a large multicenter cohort of patients with chronic HCV infection and occult HBV infection (negative results for HBsAg and HBV-DNA but positive for anti-HBc on serologic testing). Patients with HCV-related cirrhosis and positive anti-HBc were at higher risk for HCC. Anti-HBc positivity was associated with increased risk for HCC, even in patients with a prior virological response to interferon therapy. Shetty et al.[31] prospectively examined the rate of HCC in 44 explanted livers from patients with HCV-associated cirrhosis and found that those patients with occult HBV infection had a significantly higher rate of explant-proven HCC (59%) compared to patients without OBI (36%); OR: 3.1 (2.1-5.4). In another large prospective study, Matsuoka et al.[30] investigated the influence of occult HBV infection on the histopathological features and clinical outcomes of 468 HBsAg-negative patients with chronic hepatitis C. These authors determined the HBV-DNA in serum and the hepatitis B core (HBc) particles in hepatocytes by immunohistochemistry and electron microscopy. The authors found a significant increase in the degree of inflammatory cell infiltration, higher irregular regeneration of hepatocytes and a higher probability of developing HCC in patients with OBI. Tamori et al.[34] found that patients with chronic hepatitis C who achieved sustained viremia and developed HCC had a higher rate of OBI than a control group of 50 patients with chronic hepatitis C without OBI. Miura et al.[33] found that occult HBV infection, high ALT levels (≥ 80 IU/L) and the staging of liver fibrosis after interferon (IFN) therapy were important independent factors affecting the appearance of HCC. By contrast, Toyoda et al.[37] found that circulating low-level HBV does not appear to play an important role in hepatocarcinogenesis in HBsAg-negative HCC. Overall, these results suggest that OBI may increase the likelihood of developing HCC in patients with chronic hepatitis C.

Table 1  Studies assessing the effect of occult hepatitis B infection on liver histology, clinical outcomes and effect on the sustained virological response rate in patients with chronic hepatitis C

| Author and references | Type of study | Population of HCV infected | OBI | Method of HBV-DNA detection | Geographic area | Effect on histology and/or clinical outcomes | Effect on CHC SVR |
|-----------------------|--------------|-----------------------------|-----|------------------------------|----------------|-------------------------------------------|------------------|
| Cacciola et al.[2]    | Cross-sectional | n = 200                    | 33.0% | Nested PCR                  | Italy           | Increased cirrhosis                       | Less sustained virological response rate |
| Sagnelli et al.[7]    | Cross-sectional | n = 89                     | 41.6% | PCR                          | Italy           | No effect on histology                    | Not reported     |
| Chen et al.[8]        | Cross-sectional | n = 126                    | 4.8%  | bDNA assay                   | Taiwan          | No effect on histology                    | Not reported     |
| Mrani et al.[9]       | Cross-sectional | n = 203                    | 23.0% | Real-time PCR                | France          | Increased proportion of patients with inflammatory activity and liver fibrosis | Less sustained virological response rate |
| Adachi et al.[10]     | Longitudinal  | n = 123                    | 11.4% | Real-time PCR                | Japan           | Increased risk of HCC in patients with HBcAb (+) but not in patients with DNA-+HBV | Not reported     |
| Fabris et al.[11]     | Cross-sectional | n = 51                     | 1.9% of HBV-DNA in sera and 29.4% in liver | Nested PCR | Italy | No effect on aminotransferases, HCV-RNA titre or liver histology | No effect on sustained virological response |
| Hui et al.[12]        | Retrospective | n = 74                     | 41.9% | Real-time PCR                | USA             | No effect on fibrosis progression         | Not reported     |
| Kannangai et al.[13]  | Cross-sectional | n = 15                     | 12% IgM HBc | Real-time PCR | USA | Increased proportion of flares in patients with OBI | Not reported     |
| Shetty et al.[14]     | Prospective | n = 50                     | 50% in explant livers and 29.4% in serum | Real-time PCR | USA | Increased prevalence of HCC | Not reported     |
| Ikeda et al.[15]      | Multicenter prospective-observational | n = 872 F-U 846 | 46.3% HBcAb (+) | DNA probe assay | Japan | Increased risk of HCC in HBcAb (+) | Less sustained virological response rate |
| Matsuoka et al.[16]   | Prospective | n = 468                    | 43.6% in serum | Nested-PCR | Japan | Increased inflammation and increased risk of HCC | Not reported     |
| Tamori et al.[17]     | Retrospective | n = 16 and a control group; n = 50 | 50% in liver | Nested-PCR in liver | Japan | Increased rate of OBI in chronic hepatitis C patients with SVR who subsequently developed HCC | Not reported     |
| Hasegawa et al.[18]   | Retrospective | n = 140                    | 7.9%  | Real-time PCR                | Japan           | No effect on HCC risk                     | No effect on sustained virological response |
| Levast et al.[19]     | Retrospective | n = 140                    | 0% in sera and 4.4% in liver tissue | Real-time PCR | France | No effect on histology                  | No effect on sustained virological response |

OBI: Occult hepatitis B infection; HBV: Hepatitis B virus; HCV: Hepatitis C virus; PCR: Polymerase chain reaction; SVR: Sustained virological response; CHC: Chronic hepatitis C; HCC: Hepatocellular carcinoma; F-U: Follow up.
DOES OCCULT HBV INFECTION IMPAIR SUSTAINED ANTIVIRAL RESPONSE RATE IN CHRONIC HEPATITIS C INFECTED PATIENTS?

Cacciola et al. found that the sustained virological response (SVR) rate to alfa IFN monotherapy was lower in patients with chronic hepatitis C and OBI. By contrast, Fabris et al. studied twenty-five patients who were treated with alfa IFN and ribavirin and followed for at least 18 mo; there was no significant difference in the SVR among patients with and without OBI. Mrani et al. reported that sustained response to IFN and Ribavirin was achieved in 11 (28%) of 40 HBV-DNA positive cases with chronic hepatitis C, compared with 65 (45%) of the 144 HBV-DNA negative cases (P < 0.05). Hasegawa et al. analyzed 140 HCV patients without HBSAg and found that 7.9% of the cohort patients were positive for serum HBV-DNA; 4 of these 11 patients achieved SVR with IFN compared with 39 of 129 without HBV-DNA (NS). However this small group of patients precluded drawing firm conclusions regarding the SVR. Levast et al. retrospectively studied a cohort of 140 HCV patients in France and found no effect on the SVR. Overall, these results do not support the concept that OBI impairs SVR in patients with chronic hepatitis C. Table 1 summarizes the main results analyzing the effect of OBI on liver damage, on clinical outcomes, risk of developing HCC and on response to antiviral treatment in patients with chronic hepatitis C.

CONCLUSION

Prospective studies using standardized laboratory techniques and well-designed large prospective studies with homogeneous cohorts and uniform selection criteria of patients are needed to elucidate the effect of OBI on individuals with chronic hepatitis C. Currently available data do not support a conclusive role of OBI in accelerating liver disease progression in patients with chronic hepatitis C or a potential negative effect of OBI on the SVR in patients with chronic hepatitis C. However, populations studied were small and heterogeneous and most of them included patients prior to the current standard of treatment, i.e. peginterferon-alpha plus ribavirin. By contrast, most studies including those with a longitudinal design that incorporated large cohorts strongly suggest that the risk of HCC is increased in OBI/HCV co-infection.

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