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TOPIC HIGHLIGHT

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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 highly endemic areas. While this co-infection increases the risk of liver disease progression, development of cirrhosis and hepatocellular carcinoma and also increases the rate of therapeutic failure to interferon-based treatments than either virus alone, a potentially negative effect of OBI on clinical outcomes and of therapeutic response to current antiviral regimes of patients with chronic hepatitis C remains inconclusive.

Key words: Occult hepatitis B infection; Chronic hepatitis C; Outcomes

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INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) share common routes of transmission, which explains the high prevalence of occult HBV infection reported in patients with chronic hepatitis C[1-5]. While there is persuasive evidence suggesting that HBV-HCV co-infection accelerates the liver disease progression and increases the risk of developing hepatocellular carcinoma (HCC)[6] the effect of occult hepatitis B infection (OBI) on the natural history of chronic hepatitis C infection remains elusive. Despite its potential clinical importance, knowledge on the effect of OBI on chronically HCV infected subjects is limited as HBV-DNA detection may require liver tissue and liver biopsies are not routinely performed in the majority of patients. In addition, most studies addressing this issue are cross-sectional or have included small size cohorts or heterogeneous populations. Furthermore, the use of different methods with variable sensitivity for HBV-DNA determination in serum, PBMCs and liver may explain the discrepant results on the effect of OBI on chronic hepatitis C[1-3,7-12]. The purpose of this review is to critically examine the current evidence for a potential effect of OBI on HCV chronic infection. Specifically, we will review possible mechanisms of viral interaction, the

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*[2] found that patients with chronic hepatitis C and OBI more frequently had cirrhosis than patients with chronic hepatitis C alone. Likewise, Mrani *et al*[10] 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*[7] 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*[12] 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*[25] 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*[26] 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[19]. By contrast, no effect on liver biochemistry was observed in other studies[27,28]. 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*[29] 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*[11] found that positive HBcAb, 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*[30] prospec-

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*[9]	Cross-sectional	*n* = 126	4.8%	bDNA assay	Taiwan	No effect on histology	No effect on sustained virological response
Mrani *et al*[10]	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*[11]	Longitudinal F-U	*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*[12]	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*[25]	Retrospective	*n* = 74	41.9%	Real-time PCR	USA	No effect on fibrosis progression	Not reported
Kannangai *et al*[26]	Cross-sectional	*n* = 15	12% IgM HBc	Real-time PCR	USA	Increased proportion of flares in patients with OBI	Not reported
Shetty *et al*[31]	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*[30]	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*[28]	Prospective	*n* = 468	43.6% in serum	Nested-PCR	Japan	Increased inflammation and increased risk of HCC	Not reported
Tamori *et al*[32]	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*[35]	Retrospective	*n* = 140	7.9%	Real-time PCR	Japan	No effect on HCC risk	No effect on sustained virological response
Levast *et al*[36]	Retrospective	*n* = 140	0% in sera 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.

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*[28] 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*[32] found that patients with chronic hepatitis C who achieved sustained virological response 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*[34] 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.

DOES OCCULT HBV INFECTION IMPAIR SUSTAINED ANTIVIRAL RESPONSE RATE IN CHRONIC HEPATITIS C INFECTED PATIENTS?

Cacciola *et al*[2] 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*[12] 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*[10] 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*[35] 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*[36] 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-alfa 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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