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The spectrum of HBV/HCV coinfection: epidemiology, clinical characteristics, viralinteractions and management

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Abstract

Monoinfection with either hepatitis B (HBV) or C virus (HCV) represents one of the major causes of chronic liver disease globally. However, in endemic areas a substantial number of patients are infected with both viruses mainly as a result of the common routes of transmission. Numerous studies have demonstrated that dually infected patients carry a greater risk of advanced liver disease, cirrhosis and hepatocellular carcinoma compared with monoinfected patients. The choice of treatment is based on the virological profile of each patient taking into account the dominant virus pattern. In predominant HCV, standard combination treatment with pegylated interferon and ribavirin has proven equally effective in HBV/HCV-coinfected patients as well as in HCV-monoinfected patients. Strikingly, approximately 60% of patients with inactive HBV infection before HCV treatment may present HBV reactivation while others experience hepatitis B surface antigen seroconversion after clearing HCV, demonstrating the complexity of the interaction between the two viruses during the follow up. The therapeutic strategies for the predominant HBV dually infected patients are more vague, although high genetic barrier nucleos(t)ide analogues play an indisputable role. Finally, the recently approved combination treatments for chronic hepatitis C containing direct-acting antivirals may definitely change the treatment protocols in the future although there is no experience with these drugs in dually infected patients until today.

Keywords Hepatitis B virus, hepatitis C virus, occult hepatitis B virus, pegylated interferon, ribavirin

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Introduction

Chronic hepatitis B (HBV) and C virus (HCV) infections represent significant public health issues globally. An estimated 400 million persons are carriers of HBV in worldwide, 75% of whom reside in Asia and the Western Pacific. Likewise, HCV infection is estimated at approximately 170 million people globally [1-3], and a marked geographic variation exists, with infection rates ranging from 1.3-1.6% in the USA to 15% in Egypt [4]. Because of the shared modes of transmission, HBV/HCV coinfection is not uncommon in highly endemic areas and among subjects with a high risk of parenteral transmission. Patients with dual HBV/HCV infection have a higher risk of progression to cirrhosis and decompensated liver disease [5,6], and have an increased risk of hepatocellular cancer (HCC) [7,8]. Coinfected patients represent a diverse group with various patterns of viral replication and great variations of immune profiles. The aim of this review article is to summarize the risk factors and epidemiology of HBV/HCV coinfection, to describe its clinical features and impact on liver disease pointing out the therapeutic options for this special category of patients.

Epidemiology

Due to lack of large-scale population-based studies the exact number of HBV/HCV coinfected patients is unknown. Moreover, the true number of patients with HBV/HCV coinfection is further underestimated due to the unknown prevalence of occult HBV infection (negative hepatitis B surface antigen [HBsAg] but detectable serum HBV DNA) in patients with chronic HCV infection. The reported prevalence of HBV/HCV infection in different studies reveals wide differences depending on the geographical region, the study population, the method of the patients' selection criteria and the study design.

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Conflict of Interest: None

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In this context, for example, two studies, one from India [9] and one from Egypt [10], report contradictory results with a prevalence of dual infection of 16% and 0.7% respectively. Another study from Turkey recruited 51 cases with dual infection of 1950 tested patients (2.6%) [11]. Other data from Spain [12], Italy [13,14], Japan [15,16], Taiwan [17], and Iran [18] have demonstrated that approximately 10-15% of patients with chronic HBV infection are also infected with HCV. On the other hand, about 2-10% of anti-HCV-positive patients are HBsAg positive. HBV/HCV coinfection is more frequently found in several high-risk populations, i.e., persons who inject drugs, patients on hemodialysis, patients undergoing organ transplantation, HIV-positive and β-thalassemia patients [19-23].

In a large multicenter Italian study [24], the prevalence and risk factors for dual HBV/HCV coinfection have been assessed. Anti-HCV was present in 7% of chronic HBV carriers and about 40% of these patients also had detectable HCV RNA. In this study, independent predictors of dual infection were: age >42 years, history of IV drug use, blood transfusion, and residence in the South of the country. In another prospective American study the prevalence of HBV coinfection in a total of 1257 patients with chronic HCV infection was 5.8% [2]. Age <40 years, Asian race, injection drug use, and a greater number of lifetime sexual partners were independent risk factors for dual infection. Likewise, Tyson *et al* [25] estimated the prevalence and the predictors of HBV coinfection in a US cohort of HCV-infected patients. The prevalence of HBV coinfection was 1.4%. Independent associations with HBV coinfection compared with HCV monoinfection were age ≤50 years, male sex, positive HIV status, history of hemophilia, sickle cell anemia or thalassemia, history of blood transfusion, cocaine and other drug use while there was decreased risk in patients of Hispanic ethnicity.

Viral interactions

The virological and molecular aspects of HBV/HCV coinfection are poorly comprehended. Although liver disease activity and progression are generally more severe in the presence of double infection, an inverse relationship in the replicative levels of the two viruses exists, suggesting direct or indirect (i.e., mediated by host immune responses) viral interference [26,27]. Patients with chronic HBV who developed acute HCV infection presented a suppression of the HBV replication [28]. Likewise, inhibition of HCV replication has been noted in patients with chronic HCV superinfected with HBV infection [29]. Finally, HBV reactivation was observed in some coinfected patients after successful clearance of HCV with pegylated interferon-α (peg-IFN-α) and ribavirin (RBV) [30]. An interesting example is described in the study of Hamzaoui *et al* [31]. A dually infected patient received initially treatment with (peg-IFN-α) and RBV for the dominant HCV component resulting in HCV early virological response but an increase in HBV DNA, requiring the use of a nucleoside analogue. This was followed by a good response regarding HBV but a relapse of HCV, posing a therapeutic dilemma for the continuation of the treatment. Two recent publications by Eyre *et al* [32] and Bellecave *et al* [33] analyzed this subject. The Huh-7 human HCC cell line can support HBV replication and HBV virion formation together with the HCV life cycle. By applying this cell culture system, these authors independently concluded that HBV and HCV could replicate *in vitro* in the same hepatocyte without evidence of interference. Therefore, the viral interference observed in coinfected patients is probably due to indirect mechanisms mediated by innate and/or adaptive host immune responses. Moreover, the HCV core inhibited HBV replication and HBsAg expression in the mouse models of acute and chronic HBV infections [34]. In the clinical setting, studies have also revealed that HCV can suppress HBV replication and this effect is mediated by the HCV core protein. One study found that the inhibitory effect of HCV was genotype-dependent being more evident in the case of genotype 1 [35]. Finally, an Italian study [36], demonstrated that HBV/HCV coinfection is not a stable condition, but may present dynamic and possibly evolving profiles. The study enrolled 133 untreated HBV/HCV-positive patients, longitudinally followed up for 1 year with evaluation HBV/HCV viremia levels and liver biochemistry. Approximately one third of the patients presented alternating phases of inhibition and recurrence of the activity of one or both the viruses. Furthermore, patients with chronic HBV infection superinfected with HCV can undergo seroconversion of HBeAg and HBsAg [37-39]. Sheen *et al* [40] estimated an annual rate of HBsAg seroconversion of 2.08% in HBV/HCV coinfection patients compared to 0.43% in patients with HBV monoinfection. The reverse is also true: there is an inhibitory effect of HCV on HBV [41,42]. Zarski *et al* [42] showed that HCV RNA levels were significantly decreased in HBV/HCV co-infected patients with positive serum HBV DNA as compared to HBV DNA-negative cases. One study showed that co-infected patients had a higher rate of HCV RNA clearance compared to those with HCV monoinfection (71% vs. 14%) [43].

In summary, patients with combined HBV and HCV infection show a large spectrum of virological profiles. Although, most HBV/HCV coinfected patients appear to have active HCV and inactive HBV replication, some patients experience high HBV DNA levels and undetectable HCV RNA, while others present alternating phases of dominance of one virus over the other [44].

Clinical features of HBV/HCV coinfection

Acute coinfection of HBV/HCV is rare but more prevalent in IV drug abusers [45-47]. In acute infection with HBV and HCV, patients showed delayed HBsAg appearance and a shorter HBs antigenemia compared to those with acute HBV alone [48]. A study from Italy [26] included 30 patients presenting with acute hepatitis and markers of active HBV/HCV coinfection. The chronicity rates were comparable to patients with monoinfection with either of the viruses, although a biphasic alanine aminotransferase elevation was

observed in some patients. The latter phenomenon was also evident in a patient with acute coinfection and a subsequent spontaneous clearance of both viruses [49]. In the context of acute coinfection, spontaneous clearance of either or both viruses has been documented in the literature [26,49-51].

HCV superinfection is frequent in endemic areas of HBV infection, such as Asia, South America and sub-Saharian Africa [52]. Several reports have documented that *de novo* HCV superinfection in the setting of chronic HBV infection can result in HBeAg seroconversion and, in some cases, clearance of HBsAg. Fulminant hepatic failure was significantly higher among patients with underlying HBV infection than those without (23% vs. 3%) [53]. In a more recent study [29] during a follow-up period of 1-21 years, patients with HCV superinfection had a significantly higher cumulative incidence of cirrhosis and HCC than acute hepatitis Delta superinfection or active chronic HBV infection.

HBV superinfection was less frequently reported than HCV superinfection. In one report a patient became seronegative for HCV RNA after HBV superinfection [54]. Sagnelli *et al* [30] have shown that HBV superinfection may be associated with acute deterioration of liver function among patients with chronic HCV infection, and the risk of fulminant hepatitis may be increased.

Finally, a more recent study by the same authors [6] examined the impact of HBV superinfection in chronic HCV infection during a long-term follow up of 29 chronic anti-HCV-positive patients with acute hepatitis B and 29 anti-HCV-negative patients with acute hepatitis B. Acute hepatitis B had a more severe course in the first group of patients in comparison with the second (34.5% vs. 6.9%, $P<0.05$), nevertheless, some patients experienced HCV RNA clearance.

Occult hepatitis B (OHB) is defined as the presence of HBV DNA, in serum and/or the liver tissue without detectable HBsAg with or without anti-HBc or anti-HBs outside the pre-seroconversion window period [55]. Occult HBV infection has been identified in up to 50% of patients with chronic HCV infection [56]. Morever, Georgiadou *et al* [57] investigated 540 subjects for the presence of occult HBV in Greek HCV patients, in patients with nonviral liver diseases, and in healthy donors. The authors showed that HBV DNA was detected in 26.2% of HCV-infected patients in the absence of HBsAg, while in the non-HCV group the ratio was significantly lower. Considerable data suggest that occult HBV coinfection with HCV may contribute to chronic liver damage and the development of HCC. Cacciola *et al* [58] studied the prevalence and clinical significance of occult HBV infection in patients with chronic HCV infection. The result showed that 21 of the 66 patients with HCV infection and OHB (33%) had cirrhosis compared to 26 of the 134 patients with HCV infection and no OHB (19.8%, $P=0.04$). This finding suggests that OHB in patients with chronic HCV infection present a greater danger of evolution to cirrhosis and progressive liver disease. In contrast, a more recent study found that occult HBV infection occurred in almost half of the patients with HCV examined, but was not of clinical significance [59]. Finally, while several studies have implicated occult HBV infection in a kind of "resistance" to treatment with IFN in patients with chronic HCV infection [60,61], others have reported contradictory results concluding that virological responses to combined peg-IFN and RBV therapy are similar in chronic HCV patients with and without occult HBV infection [62].

HBV/HCV coinfection and cirrhosis

Compared with HBV monoinfected patients, higher rates of cirrhosis (44% vs. 21%) and decompensated liver disease (24% vs. 6%) are reported in coinfected patients [63]. Likewise, compared to HCV-monoinfected patients, a higher rate of cirrhosis (95% vs. 49%) and more decompensated liver disease (Child-Pugh class C 37% vs. 0%) were also demonstrated in HBV/HCV-coinfected patients [64]. There are, however, studies that do not support these conclusions [65,66]. Recently, in a cohort of Egyptians dually infected, patients had no difference regarding the histologic score in comparison to monoinfected patients [10]. These discrepancies can be explained by biases in the design of the studies (small sample size, retrospective design) and technical reasons (sensitivity of anti-HCV assays). On the other hand, the fact that the dual infection of HBV and HCV ends up in the dominance of either virus and the suppression of the other could partially explain the similarity in histologic findings between dually infected and monoinfected patients [67].

Impact of HBV/HCV coinfection on development of HCC

Epidemiologic studies in patients with dual HBV/HCV infection have documented an increased risk of HCC confirmed by three meta-analyses [7,8,67]. Given the role of the chronic necroinflammation and especially cirrhosis in the pathogenesis of HCC together with the higher incidence of cirrhosis and a greater degree of hepatic damage in dual infection, a synergistic carcinogenic interaction between the two viruses is most probable. The different mechanisms that have been hypothesized as being associated with the development of HBV- or HCV-related HCC suggest that both viruses could play an active role at different steps of the carcinogenic process when they are present together in hepatocytes. Most evidence suggests that HBV is capable of initiating the neoplastic process, while HCV could act as a promoter, and that they may be synergistic in causing HCC [7].

A prospective analysis evaluated the role of HBV/HCV dual infection in 290 cirrhotic patients regarding the risk of HCC [68]. The authors concluded by both univariate and multivariate analyses that, apart from male sex and previous alcohol abuse, dual infection with HBV and HCV is the greatest predictor for developing HCC in cirrhotics. In a longitudinal study [69], the incidence of HCC was 6.4 per 100 person years in HCV/HBV-coinfected patients compared to 2.0 in HBV and 3.7 in HCV monoinfection. In the same study, the cumulative risk of developing HCC after 10 years was 45% in HBV/HCV-coinfected patients compared to 16% in HBV- and 28% in HCV-monoinfected patients. Finally, Liu *et al* conducted a

retrospective cohort study which principally examined the impact of treatment in dually infected HBV/HCV patients in respect of diminishing the risk of HCC. They reached the conclusion that combination therapy with peg-INF+RBV significantly reduced the risk of HCC and improved overall survival [70].

Treatment issues

In patients with dual chronic HCV and HBV infections, the disease outcomes, including the development of liver cirrhosis and HCC, are generally more severe than those in patients with monoinfection [71-73]. In addition, it has been confirmed that the incidence of HCC in co-infected patients is higher than in monoinfected patients [74]. As previously mentioned [70], Liu *et al* proceeded in a comparison of HCC risk, liver-related mortality and all-cause mortality between treated and untreated HBV/HCV-coinfected patients; the authors assessed the same outcomes in treated HBV/HCV-coinfected patients and treated HCV-monoinfected patients. They demonstrated that peg-IFN/RBV therapy is not only safe and effective, but translates into important clinical benefits such as reduction in liver-related complications and improved patient survival. Therefore, patients dually infected with HCV and HBV require effective treatments.

HBV/HCV-coinfected patients are very heterogeneous both in terms of infection modality with most patients from Asia acquiring HBV infection at birth and later having HCV superinfection, whereas patients from Europe and the USA either acquire both infections concomitantly or present a superinfection of HBV on chronic HCV infection [75]. In terms of viral dominance, it is not often to have a co-dominance of both viruses. There is either HBV dominance, which means high HBV DNA levels and low HCV RNA levels or HCV dominance defined by the high HCV RNA levels and absent HBV DNA. The first pattern is more common in Asian patients and shows a disease progression similar to that of HBV monoinfection, while the second pattern is typical of North American and European patients and is met in HCV-monoinfected patients.

The first step in the treatment of HBV/HCV-coinfected patients is to determine which is the dominant virus that should be eradicated. Careful longitudinal follow up of serum HBV DNA and HCV RNA levels is essential before the diagnosis of the viral dominance [36]. These viral interactions will very likely influence the therapeutic strategies in dually infected patients.

Treatment of HCV in dual HCV/HBV patients with active HCV infection

Villa *et al* [76] reported that 9 million IU of standard IFN 3 times weekly for 3 months could clear HCV in 31% of patients with HCV/HBV coinfection. Liu *et al* [77] used standard IFN and RBV and discovered that sustained HCV eradication (sustained virological response, SVR) was achieved at rates comparable to those in patients with HCV alone while, interestingly, up to 21% of their patients lost HBsAg.

In 2008 Potthoff *et al* [30] published a small prospective multi-center pilot study that evaluated the efficacy of weight-adjusted peg-IFN-α-2β and RBV for 48 weeks in 19 patients with chronic HBV/HCV coinfection (all were HBsAg/HCV RNA-positive and 6 were HBV DNA-positive and 13 negative). A fraction of 15 patients fulfilled treatment schedule with an SVR rate of 93% (86% in genotype 1 and 100% in genotypes 2 or 3).

Liu *et al* [78] subsequently conducted a multicenter study using peg-IFN and RBV in HCV/HBV-coinfected patients. This regimen proved equally effective in patients with HCV monoinfection and in those with chronic HCV/HBV infection. This study represents the largest prospective, randomized, controlled trial using peg-IFN and RBV therapy in HBV/HCV coinfection, and reports a high SVR rate (72% and 83% in genotypes 1 and 2/3 respectively). The same authors investigated the durability of HCV clearance in HCV-monoinfected and HCV/HBV dually infected patients by conducting a 5-year prospective follow-up study [79]. The findings revealed that after a median follow up of 4.6±1.0 years, HCV reappearance developed only in 6 (2.6%) of the 232 patients who achieved SVR. This suggests that the durability of the SVR obtained by using peg-IFN and RBV therapy was satisfactory and not influenced by HBV coinfections.

As peg-IFN is one of the first-line choices for the treatment of chronic HBV infection [80], it is reasonable to conclude that peg-IFN-based therapy in dually infected patients will also act on the HBV. Indeed, the 2 previous studies remarkably found that HBsAg disappeared 6 months after the end of therapy in 18 (11.2%) of the 161 dually infected patients with a rate of HBsAg seroclearance of 5.4% per year. Baseline low pretreatment serum HBsAg level correlated significantly with HBsAg seroclearance. In another study [81], the rs9277535 polymorphism for HLA-DPB1 region was recognized as a host genetic factor associated with spontaneous HBsAg seroclearance.

The reactivation of HBV activity is another clinical entity in dually infected patients receiving anti-HCV therapy. In a treatment cohort of 76 patients with pretreatment serum HBV DNA <200 IU/mL, reappearance of HBV DNA was found in 47 (61.8%) patients [79]. These patients should be put under surveillance and treatment should be initiated if clinically indicated.

At present, no data have been published regarding the efficacy of direct-acting antivirals (DAAs) in combination with peg-IFN plus RBV or with IFN-free regimens in treating patients with chronic HBV/HCV coinfection. Whether the new DAA-based therapies will be effective in HBV/HCV coinfection represents an issue for further studies.

Treatment of HBV in dual HCV/HBV patients with active HBV infection

The data published on the use of anti-HBV drugs for patients with chronic HBV/HCV coinfection are scanty,

Table 1 Pegylated interferon and ribavirin for HBV/HCV coinfection

Patients (n)	HCV SVR (%)	HBV DNA negative (%)	HBsAg loss (%)	HBV reactivation (HBV DNA negative pretreatment) (%)	Reference
19	70*,78**	33	0	31	Potthoff 2008 [30]
161		56	11	35	Liu 2009 [78]
17	6	N/A	N/A	N/A	Senturk 2008 [84]
50	40*,75**	100	0	24	Yu 2009 [85]
18	60*,88**	12	N/A	N/A	Kim 2011 [86]

**HCV genotype 1, **HCV genotype 2/3, N/A, not applicable; SVR, sustained virological response; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus*

Table 2 Standard interferon with ribavirin for HBV/HCV coinfection

Patients (n)	Serology	HCV RNA/HBV DNA	HCV SVR	HBV reponse	References
21	Anti-HCV+, HBsAg +	+/+ *N=17(81%)	N=9 (43%)	HBsAg loss (0%) HBeAg loss (N=3, 100%) HBV DNA (N=6, 35%)	Liu *et al* (2003) [77]
36	Anti-HCV+, HBsAg +	+/+ *N=18 (50%)	N=25 (69%)	HBsAg loss (0%) HBeAg loss (0%) HBV DNA (N=2, 11%)	Hung *et al* (2005) [87]
42	Anti-HCV+, HBsAg +	+/+ *N=16 (38%)	69%	HBsAg loss (N=5, 12%) HBeAg loss (50%) HBV DNA (N=5, 31%)	Chuang *et al* (2005) [88]
51	Anti-HCV+, HBsAg +	+/N/A	N=23 (17%)	N/A	Myers *et al* (2003) [89]
51	Anti-HCV+, HBsAg +	+/+ *N=15 (29%) liver tissue	N=20 (40%)	N/A	Fabris *et al* (2004) [90]
47	Anti-HCV+, HBsAg +	+/+	N=11 (28%)	N/A	Mrani *et al* (2007) [91]

*number of HBV DNA-positive patients. *HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; N/A, not applicable; SVR, sustained virologic response*

Table 3 Serologic and virological profiles in HBV/HCV-coinfected patients with chronic hepatitis

	HBV and HCV active	Occult HBV in chronic active HCV	HCV active in HBsAg carrier
HBsAg	+	-	+
HBV DNA	+	+	-
Anti-HCV	+	+	+
HCV RNA	+	+	+

HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen

most probably because HBV predominates less frequently than HCV. In a small study [82], 8 patients with dually active HBV and HCV were treated with 5 MU IFN and 100 mg/day lamivudine (LAM) for 12 months, followed by LAM alone for 6 more months. The SVR for HCV was 50%. HBeAg clearance was observed in three patients, two of them seroconverted to anti-HBe. HBV DNA became undetectable in 3 patients at the end of treatment, but appeared again later in two patients.

In a recent study, tolerability and efficacy of anti-HBV nucleos(t)ide analogues [LAM plus adefovir (n=10), entecavir (n=7), telbivudine (n=4), tenofovir disoproxil fumarate (n=3)] was investigated in a cohort of 24 HBV/HCV-coinfected cirrhotic patients [83]. Clearance of HBV DNA was found in 96% of patients after 18 months, while HCV reactivation was low (12.5%). However, while the virological response was favorable in all patients and treatment was well tolerated, progression of liver cirrhosis was seen in as many as 33%. HCV RNA-positive patients at baseline deteriorated more frequently. Thus, a favorable clinical impact in HBV/HCV cirrhotic patients was seen only in HCV RNA-negative patients at baseline.

Concluding remarks

HBV/HCV dual infection is not uncommon in endemic areas and among subjects at risk of parenterally transmissible infections. The first step in initiating treatment is to define which the dominant virus is, by performing serological and virological examinations. For dually infected patients with active HCV infection, the same genotype-dependent treatment recommendations as for HCV monoinfection apply. In these

patients treatment with peg-IFN and RBV has been well studied and proven effective. The introduction of new DAAs has opened new pathways in treating HCV, which need to be evaluated in HBV/HCV-coinfected patients, but currently no data exist for DAA-based therapies. HBV DNA and HCV RNA positivity in chronic hepatitis patients occurs infrequently since a dominant pattern is the usual result of viral interaction. The information on the treatment of this subset is scanty but it seems reasonable that a first-line therapy could be peg-IFN plus RBV with the addition of or a shift to a high potency and high genetic barrier nucleos(t)ide analogue for patients with HBV DNA persistence.

It should be pointed out that a high level of clinical suspicion is required during treatment in order to early diagnose any reactivation of HBV or HCV replication and start an appropriate treatment.

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