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Current Concepts of HBV/HCV Coinfection: Coexistence, but Not Necessarily in Harmony

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Abstract

Hepatitis B and hepatitis C are important causes of chronic liver disease globally. Although HBV/HCV coinfection is not uncommon, its epidemiology is poorly defined. Numerous studies provided evidence that coinfection accelerates liver disease progression and increases the risk of hepatocellular carcinoma. By applying new cell culture models to examine the interaction of both viruses, investigators concluded that HBV and HCV replicate in the same hepatocyte without interference. The roles of innate and adaptive immunity in determining the viral replication and disease outcomes still need rigorous investigation. To date, no standard-of-care recommendation exists for HBV/HCV coinfection. Pegylated interferon and ribavirin combination therapy demonstrated similar efficacy in suppressing HCV RNA in coinfection and HCV monoinfection. However, HBV reactivation during therapy can be a challenge. Future clinical trials evaluating the addition of a nucleoside/nucleotide analog for selective patients with HBV/HCV coinfection are essential for successful management of HBV/HCV coinfection.

Keywords

Hepatitis B virus; Hepatitis C virus; Epidemiology; Natural history; Pathogenesis; Pegylated interferon

Introduction

Hepatitis B and hepatitis C are both significant public health issues globally. It is estimated that about 350 and 170 million people worldwide are infected with hepatitis B virus (HBV) and hepatitis C virus (HCV), respectively [1]. HBV and HCV are distinct viruses with completely different life cycles. HBV belongs to a family of hepatotropic DNA viruses (Hepadnaviridae), whereas HCV is classified in the *Hepacivirus* genus within the Flaviviridae family [2]. Coinfection with HBV and HCV is common because of their common route of transmission, especially in regions of the world where both viruses are endemic. The interactions between HCV and HBV in the cellular levels and their resulting pathogenesis are not well understood, but important progress has been made with the availability of the novel cell culture model. Our knowledge of the epidemiology, disease progression, and clinical outcomes from HBV/HCV coinfection is still limited, because most of the reported literature is based on cross-sectional studies with heterogeneous populations

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and small sample sizes. Furthermore, the definition and terminology of HBV and HCV coinfection are not standardized. Hence, study results cannot be universally compared or compiled.

This review summarizes our current understanding and limitation of knowledge in the epidemiology, natural history, pathogenesis, and therapy of HBV/HCV coinfection and future research needs and directions. To prepare for this review, we performed a detailed Medline search on the subject of HBV and HCV dual infection published between the years 1990 and 2010, and included the 58 most relevant articles in the References.

Pathogenesis of HBV/HCV Coinfection

Both HBV and HCV are hepatotropic viruses whose primary site of replication is in the liver. Clinical observations on disease outcomes and progression among patients with both HBV and HCV are variable and contradictory. Reports suggest reciprocal replicative suppression of the two viruses, or viral interference [3,4]. The virological and molecular aspects of HBV and HCV coinfection were not well understood in the past because of the lack of appropriate model systems [2]. Until recently, studies addressing the mechanisms of HBV and HCV coinfection were based on heterologous overexpression of viral proteins, and yielded conflicting results. For example, some studies demonstrated that HCV core and NS5A inhibit HBV replication, but other studies could not confirm that [5–7]. It is critically important to resolve the question whether direct interference occurs between HBV and HCV in order to understand the disease process and outcomes. Two recent publications by Eyre et al. [8••] and Bellecave et al. [9••] shed new insights into this subject. The Huh-7 human hepatocellular (HCC) can support HBV replication and HBV virion formation. At the same time, the Huh-7 cell line can be applied to study the entire HCV life cycle; namely, the viral entry, RNA replication, and release of infectious particles. By applying this cell culture system to conduct experiments of different designs, these authors independently concluded that HBV and HCV could replicate in the same hepatocyte without evidence of interference. Furthermore, the inhibition of one virus did not affect the replication or gene expression of the other. Most importantly, their findings argued against the long-held concept of superinfection exclusion. The cells supporting HBV could be infected with cell culture-derived HCV and the efficient production of infectious HCV. These in vitro observations, however, cannot explain the possible roles of the host factors such as the innate and adaptive responses in determining the viral replication and ultimate disease outcomes in HCV and HBV coinfection.

Epidemiology of HBV/HCV Coinfection

HBV and HCV are among the most common causes of liver disease globally, although their prevalence of infection varies in different parts of the world. HBV and HCV share common modes of transmission and as a result, combined HBV and HCV infection is frequent, especially in HBV-endemic areas and among injection drug users. The exact prevalence of dual HBV and HCV infection is not known because most of the published statistics focused on highly selective and limited populations. Multiple studies evaluated the rates of HCV coinfection among hepatitis B surface antigen (HBsAg) carriers; the statistics range from 3% and 18%, depending on the geographic centers and selective patients [10–12]. According to the third National Health and Nutrition Survey (NHNS III), about 25% patients with hepatitis C in the United States had positive HBV serological markers. This rate is nearly six times higher than populations without hepatitis C [13]. The prevalence of occult HBV infection, defined by the presence of HBV DNA in the absence of HBsAg, ranged from 11.9% to 44.4% in HCV-infected patients. The prevalence of occult HBV infection in HCV-positive patients increased to 40% to 50% when the liver tissue was

examined for the presence of HBV DNA [14]. Antibody to hepatitis B core antigen (anti-HBc) is the long-lasting serological marker of past HBV infection. Although the seroprevalence of isolated anti-HBc in blood donors is 2% to 5%, the rates are significantly higher, ranging from 18.6% to 71%, among patients with chronic hepatitis C [14–16]. Two separate studies done in Saudi Arabia detected HBV DNA in 15.8% and 22.5% of HCV patients with isolated anti-HBc [14,15].

Natural History of HBV/HCV Coinfection

The presentation of HBV and HCV coinfection can be variable, so unravelling the natural history and progression of this disease is challenging. Similar to patients with chronic hepatitis from a single infectious agent, coinfected patients can have acute hepatitis, chronic hepatitis with potential progression to cirrhosis and hepatocellular carcinoma (HCC).

Among the published literature, different patient characteristics have been reported under the broad topic of HBV and HCV coinfection. Hence, the different study conclusions could be a result of the heterogeneous study populations. For clarification, we systematically summarize the natural history of HBV and HCV dual infection based on the following five categories of clinical features and immune profiles: 1) acute coinfection: acute hepatitis with concurrent HBV and HCV infection; 2) HCV superinfection: acute HCV in chronic hepatitis B; 3) HBV superinfection: acute HBV in chronic hepatitis C; 4) chronic HCV with occult HBV: HBsAg negative, anti-HBs negative, HBV DNA positive, HCV RNA positive; and 5) chronic coinfection: chronic hepatitis with HBV DNA positive and HCV RNA positive.

Acute coinfection

Simultaneous acquisition of both HBV and HCV is uncommon. Most of the reports on acute coinfection occur in the settings of intravenous drug use, accidental needle stick, and blood transfusion [17–19]. Acute coinfection can result in clearance of one or both viruses as described below, or can result in fulminant hepatitis or chronic coinfection. Patients who presented with fulminant and subfulminant hepatitis were often found to have acute HBV and HCV coinfection, but superinfection was described also. Feray et al. [19] reported 40 patients with fulminant and subfulminant hepatitis. Five of 40 patients (12.5%) were identified to have acute coinfection with HBV and HCV, and 3 of 40 (7.5%) had HCV superinfection [19]. Another study by Wu et al. [20] evaluated 25 patients with subfulminant and fulminant hepatitis. Again, the rate of coinfection (9.4%) was higher than HCV superinfection of chronic hepatitis B (3.1%) [20].

In the setting of acute coinfection, spontaneous clearance of either or both viruses has been documented in the literature [17,21–23]. Mimms et al. [21] observed that patients with coinfection had lower alanine transaminase (ALT) levels, delayed HBsAg appearance, and decreased HBs antigenemia, suggesting HCV suppression of HBV. Coppola et al. [22] monitored three patients with acute coinfection. The HBV infection presented first and quickly resolved, resulting in anti-HBs seroconversion. HCV infection became evident only 30 days after the onset of symptoms, as determined by the detection of plasma HCV RNA, whereas anti-HCV seroconversion became evident only on day 45 [22]. Reciprocal inhibition of HBV and HCV genome leading to clearance of one virus and persistence of the other was postulated; however, the exact immunological mechanisms have not been studied. The different patterns of viral clearance or persistence can also be related to the variable incubation periods, concentration of viral inoculums, or genotypes.

Superinfection with HCV

HCV superinfection is commonly seen in Asian countries where HBV is prevalent. Several reports have documented that de novo HCV superinfection in the setting of chronic hepatitis B can result in HBeAg seroconversion and in some cases, the clearance of HBsAg [3,24]. Those patients had persistence of chronic hepatitis C after successful clearance of HBV. Fulminant hepatitis was reported to be associated with HCV superinfection at rates from 3.1% to as high as 23% [23,25,26]. Chu et al. [23] conducted a prospective study in Taiwan that included 11 patients with acute hepatitis C. They observed that patients with HCV superinfection were 10 times more likely to have had a fulminant hepatitis compared to those without preexisting chronic hepatitis B [23]. Mortality associated with HCV superinfection has been reported as high as 10% [25]. The difference in rates of fulminant hepatitis is likely secondary to various viral factors, host immune response, and relatively small study sample size.

Superinfection with HBV

HBV superinfection was less frequently reported than HCV superinfection. According to the available literature, serious complications, including fulminant hepatitis, were more common in acute HBV superinfection compared to acute HBV infection alone. Several case reports suggest the dominant role of HBV leading to HCV clearance after HBV superinfection [27,28•]. Sagnelli et al. [28•] conducted a long-term follow-up study in Italy on 29 anti-HCV carriers with acute HBV superinfection and an equal number of anti-HCV negative patients with acute HBV infection for a median of 5 years. More than 90% of this cohort had HBV genotype D. Severe hepatitis with hepatic dysfunction and presence of ascites or encephalopathy occurred in 34.5% of patients with HBV superinfection and in only 6.9% of those with acute HBV alone. During follow-up, more than 90% of patients cleared HBsAg. All patients had undetectable HCV RNA during acute hepatitis B. At the end of follow-up of 24 patients, 6 had persistent undetectable HCV RNA and 18 had chronic hepatitis C with detectable HCV RNA. Those with HCV clearance had more severe hepatitis during the acute presentation. Because the levels of serum HCV RNA and HCV genotypes were not well documented prior to HBV infection, future studies would need to take these factors into consideration to understand the outcome of HCV after HBV superinfection.

Occult HBV infection

Numerous studies evaluated the clinical manifestations of occult or serologically silent HBV infection in the setting of chronic HCV, and the results were conflicting. Most studies reported the association of occult HBV with more severe hepatic inflammation and outcomes such as cirrhosis and HCC [29–31]. In a detailed, controlled study from Italy, Cacciola et al. [32] found that 33% of patients with chronic HCV and occult HBV had evidence of cirrhosis compared to only 19% of those with chronic HCV without occult HBV; the difference is statistically significant. In contrast, several studies observed no significant difference regarding inflammatory disease activity or hepatic fibrosis in HBV/HCV-coinfected patients [16,33,34]. Kao et al. [34] suggested in their study that occult HBV infection does not have clinical significance in chronic HCV patients residing in HBV-endemic areas. The discrepancies noted in these observations may be secondary to the absence of appreciate controls, small sample size, and different methods of HBV DNA measurements, in addition to host and viral factors from different geographical regions.

Chronic HBV/HCV coinfection resulting in cirrhosis and HCC

Chronic coinfection with HBV and HCV can result after acute coinfection or superinfection with HBV or HCV as described above. Similar to monoinfection with either virus, the

clinical spectrum of chronic coinfection include variable degrees of hepatic inflammation, progressive hepatic fibrosis to cirrhosis, decompensated liver disease, and HCC.

Most studies, to date, suggest that HBV/HCV coinfection has worse disease progression and outcome when compared to HBV or HCV alone [4,35,36]. In a study by Tanaka et al. [37] in Japan, 3% of patients with HCC were positive for HCV alone, 2% were positive for HBsAg, and a significantly higher 12% were positive for both. A South African study observed that HBV and HCV had synergistic risk of HCC [38]. Benvegnu et al. [39] conducted a prospective study on 290 cirrhotic patients and confirmed that coinfection was an independent predictor for development of HCC by both univariate and multivariate analyses. In a meta-analysis study by Donato et al. [40], the relative risk of developing HCC was found to be significantly higher in coinfected patients (OR 165) than in HBV (OR 22.5) or HCV alone (OR 17.3). Chiaramonte et al. [41] further calculated that the cumulative HCC risk at 10 years was 45% for coinfected patients, 28% for HCV, and 18% for HBV patients. Although the association of coinfection with progressive liver disease and HCC is known, the mechanisms behind the observations are not clear. Furthermore, most of the studies did not examine the contribution of viral genotypes, mutations, and host factors such as metabolic syndrome or genetic predispositions in the pathogenesis.

Therapy of HBV/HCV Coinfection

National and international treatment guidelines are well-established for HBV and HCV monoinfected patients. However, no standard-of-care recommendation exists for patients with HBV and HCV coinfection. Furthermore, the early treatment trials on HBV and HCV dual infection included small numbers of patients and the serological markers, genotypes, viral replicative status, and duration of therapy were not standardized; hence, direct comparisons between studies were not possible. In our literature search, we found only 11 published clinical trials on populations with both HBV and HCV serological markers and five on patients with chronic hepatitis C and occult HBV. Interferon-based therapy accounted for all the therapeutic studies because of its effectiveness against both viruses. Among these articles, six were published between 1995 and 2005 and reported on standard interferon monotherapy [42–47]; 10 were published between 2003 and 2009 and focused on the findings of combination therapy with either standard interferon ($N = 6$) [48–53] or pegylated interferon ($N = 4$) [54••,55•,56,57•] with ribavirin; and one on interferon plus lamivudine [58]. The key findings and limitations of the published treatment trials of HBV and HCV coinfection are summarized in Tables 1, 2, and 3.

Standard Interferon Monotherapy

Limited conclusions can be drawn from studies evaluating standard interferon for HBV and HCV coinfection because of the heterogeneous patient populations and methods of viral load measurements. Guptan et al. [42] and Villa et al. [45] included patients with chronic coinfection with replicative HBV and HCV in their trials. Their observations suggested that interferon is safe and can lead to both HBV and HCV viral clearance in a proportion of patients. Liaw et al. [44] reported that the coinfected patients had lower HBV response to therapy. However, that was a retrospective analysis on a small number of subjects. Factors such as HCV RNA levels and liver histology were not evaluated or controlled for. Several studies cautioned that hepatitis flare may be more frequent and can be severe during interferon therapy for patients with dual infection. However, hepatitis flare can result in HBsAg clearance in some. Two studies examined the effects of occult hepatitis B in HCV response to interferon [43,47]. Zignego et al. [47] concluded that hepatitis C patients with occult hepatitis B had significantly lower biochemical and virological response to interferon compared to those who were HBV DNA negative. In contrast, Hasegawa et al. [43]

observed that neither the presence of anti-HBc nor HBV DNA influenced the virological response of hepatitis C. The limitations of both studies are the relatively small number of patients with occult hepatitis B. Furthermore, the levels of HBV DNA or HCV genotypes were not taken into account in the analyses or conclusions.

Combination Therapy With Standard Interferon and Ribavirin

With the proven synergistic beneficial effects between interferon and ribavirin for the treatment of chronic hepatitis C, several clinical trials evaluated the efficacy of this combination regimen for patients with HBV/HCV coinfection. Three randomized, controlled studies published between 2003 and 2005 compared the results of a 6-month course of standard interferon (3–6 million IU three times weekly) and ribavirin for HBV/HCV dual infection and HCV monoinfection [48,50,51]. All three trials reported similar sustained virological response (SVR) rates for hepatitis C in both dual and monoinfection. The actual SVR varied between 43% and 69%. This significant difference between studies could be related to the different HCV genotype distributions in the study populations, because all subjects received 6 months of combination therapy regardless of viral genotypes. The response for hepatitis B is more difficult to compare between studies. Although all patients must be HBsAg positive to be enrolled in all studies, the proportions with HBeAg and undetectable serum HBV DNA were variable. Despite these limitations, the general trend is that a proportion of patients can achieve HBV DNA suppression and clearance of HBsAg and HBeAg on this combination regimen. Most importantly, all three studies reported that a proportion of patients with undetectable HBV DNA at baseline experienced HBV DNA resurgence after therapy. The exact rate is unclear because of the relative small patient sample size. Three articles examined the effects of standard interferon and ribavirin combination therapy on patients with chronic hepatitis C and evidence of past hepatitis B exposure or occult hepatitis B [49,52,53]. Myers et al. [53] concluded that the presence of anti-HBc did not affect the virological response of chronic hepatitis C. However, they did not evaluate serum HBV DNA prior to or during the course of therapy. Fabris et al. [49] identified HBV DNA in liver tissues in 15 of 51 HCV patients without HBsAg. Only one patient had detectable HBV DNA in serum. They concluded that the presence of HBV DNA in liver did not influence the liver histology or treatment response of hepatitis C. In contrast, Mrani et al. [52] reported that HCV patients with HBsAg-negative, serum HBV DNA-positive status experienced more severe hepatic inflammation and fibrosis, and decreased treatment response compared to HCV monoinfected patients. On closer examination, only 38 of 47 patients with occult HBV infection had quantifiable HBV DNA in serum by reverse transcriptase–polymerase chain reaction (RT-PCR). Because of the generally low level of HBV DNA among patients with occult HBV and the variable detection limits of virological assays, the impact of occult HBV on HCV treatment response remains debatable.

Combination Therapy With Pegylated Interferon and Ribavirin

More recently, in 2008 and 2009, four publications evaluated the efficacy of pegylated interferon and weight-based ribavirin on HBV/HCV coinfection. Senturk et al. [56] compared the efficacy of standard interferon/ribavirin ($N = 19$) and pegylated interferon/ribavirin ($N = 17$) combination therapy in HBV/HCV coinfection. The study was inconclusive because of the small number of patients in each group and the high dropout rate. None of the HBsAg carriers had detectable HBV DNA in serum prior to therapy and serum HBV DNA and HBsAg were not monitored during therapy. Potthoff et al. [55•] prospectively treated 19 Caucasian patients with chronic hepatitis C and HBsAg-positive status. They found that the HCV genotype 1 patients had SVR of 70% and non-genotype 1 patients had SVR of 78%. They observed that four patients with undetectable serum HBV DNA at baseline had reactivation of HBV after HCV RNA clearance. A prospective,

controlled study conducted by Yu et al. [57•] in Taiwan concurred that the HBV reactivation rate was significantly higher among those who achieved HCV SVR (9/27 or 33%) compared to those without SVR (2/23 or 8.7%). Serum ALT became elevated in 5 of 11 patients with HBV reactivation. All five patients were treated with lamivudine and had normalization of serum aminotransferases and undetectable HBV DNA within 1 month.

To date, the largest prospective, randomized, controlled trial using pegylated interferon and ribavirin therapy on HBV and HCV coinfection was conducted in Taiwan. Liu et al. [54••] compared the treatment outcome of 161 patients with chronic hepatitis C and HBsAg positive, HBeAg negative serology, and 160 matched, HCV-monoinfected patients. They reported similar HCV SVR rates between HBV/HCV dually infected and HCV monoinfected patients. In agreement with the two studies mentioned previously, the authors also observed a relatively high rate (36%) of HBV reactivation among the 77 patients with undetectable HBV DNA at baseline. However, they did not observe a preferentially higher incidence of HBV reactivation among those with HCV SVR. Encouragingly, they reported 11% of patients achieved HBsAg loss and 10 patients with occult HBV (HBsAg negative, detectable HBV DNA at baseline) had undetectable HBV DNA after therapy.

Combination Therapy With Standard Interferon and Lamivudine

What is the role of oral nucleoside/nucleotide analogs in the setting of HBV/HCV dual infection? Marrone et al. [58] reported their observation using a combination of lamivudine and standard interferon for 12 months followed by lamivudine for an additional 6 months on eight patients with HBV/HCV coinfection. All patients were HBeAg-positive and had replicative HBV DNA and HCV RNA in serum. Three patients achieved HBeAg loss and four had HCV SVR. This pilot study suggests that an oral nucleoside/nucleotide in combination with interferon may be an attractive strategy in treating patients with chronic hepatitis C and active HBV replication.

General Treatment Recommendations

Although no standard-of-care guideline exists for the treatment of HBV/HCV coinfection, the principles of patient evaluation and management remain the same as for patients with HBV or HCV monoinfection. The general treatment recommendations based on the authors' experience are summarized below. It is important to establish a complete virological, serological, biochemical, and whenever possible, histological baseline. Because patients with HBV genotype A respond better to interferon therapy, knowledge of the genotyping information is important for the selection of antiviral agents. It is the strategy of the authors to initiate pegylated interferon and weight-based ribavirin combination therapy for those with active chronic hepatitis C regardless of their HBV status. HCV RNA and HBV DNA should be monitored every 4 weeks during therapy. The decision to continue or discontinue HCV therapy is based on established national guidelines. For those patients with replicative HBV DNA and less than 1 log reduction of HBV DNA by 12 weeks, it is reasonable to add a nucleoside/nucleotide analog and continue to monitor viral load monthly for the duration of the triple therapy. Similarly, nucleoside/nucleotide analog should be considered for those with resurgence of HBV DNA while on interferon-based therapy. Depending on the individual treatment response, nucleoside/nucleotide may be necessary for prolonged suppression of HBV DNA after completion of the HCV therapy, especially if patients have significant hepatic fibrosis. All patients with cirrhosis or persistent HBsAg should undergo regular HCC surveillance with abdominal ultrasound every 6 months. Patients with signs of hepatic decompensation should be referred for liver transplantation evaluation.

Conclusions

HBV/HCV coinfection is a challenging and important medical condition because of its variable clinical manifestations, increased risk of cirrhosis and HCC, and unpredictable treatment response. Recent advances have occurred in the understanding of HBV and HCV interactions in vitro; however, the immune response and other host factors contributing to viral replication, disease progression, and development of HCC remain poorly understood. The terminology of HBV/HCV coinfection based on serological and virological profiles needs to be uniformly defined to allow comparison of future studies on epidemiology, natural history, and therapeutic trials. The presence or absence of HBV DNA and HCV RNA should be determined by standardized RT-PCR methods. The roles of HCV and HBV genotypes, level of viremia, and HBV mutants such as pre-core and core promoter mutations, as well as host factors such as metabolic syndrome, should be considered in evaluating natural history and treatment response. Therapeutic trials evaluating combinations of pegylated interferon, ribavirin, and nucleoside/nucleotide analog are necessary prior to establishing standard-of-care treatment recommendations for this important disease.

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Table 1

Standard interferon for HBV/HCV coinfection

Study (year)	*N*	Serology	HCV RNA/HBV DNA	HCV SVR	HBV response	Comments/limitations
Weltman et al. [46] (1995)	8	Anti-HCV+ HBsAg+	NA/NA	N/A	HBsAg loss (*N* = 1)	Coinfected patients had more severe liver histology.
Liaw et al. [44] (1997)	15	Anti-HCV+ HBsAg+	?/+	N/A	HBeAg loss (*N* = 1) HBV DNA- (*N* = 1)	Retrospective evaluation of anti-HCV in 2 HBV clinical trials. Lower HBV response in coinfection. Severe flare from HCV with HBV DNA clearance in 1 case.
Guptan et al. [42] (1999)	7	Anti-HCV+ HBsAg+	+/+	*N* = 2	HBsAg loss (*N* = 2) HBV DNA- (*N* = 6)	IFN therapy is safe and effective, but can be associated with hepatitis flare.
Villa et al. [45] (2001)	30	Anti-HCV+ HBsAg+	+ (100%)/+ (*N* = 6, 20%)	*N* = 10 (31%) 9 IU IFN	HBsAg loss (*N* = 1) HBV DNA- (*N* = 6)	Higher dose of IFN is more effective. All patients were tested HBV DNA- by hybridization, 6 positive by PCR at baseline.
Zignego et al. [47] (1997)	14	Anti-HCV+ HBsAg-	+/+	0%	HBV DNA- (0%)	Lower HCV response in patients with occult HBV.
Hasegawa et al. [43] (2005)	140	Anti-HCV+ HBsAg-	+ (100%)/+ (*N* = 11, 7.9%)	*N* = 43 (30.7%)	HBV DNA- 6 mo post but + during follow-up	Anti-HBc or HBV DNA+ did not affect HCV virologic response, no HCV genotype information.

HBV—hepatitis B virus; HBc—hepatitis B core; HBeAg—hepatitis B e antigen; HBsAg—hepatitis B surface antigen; HCV— hepatitis C virus; IFN—interferon; NA—not available; PCR—polymerase chain reaction; SVR—sustained virologic response.

Table 2

Combination therapy for HBV/HCV coinfection: standard interferon with ribavirin

Study (year)	*N*	Serology	HCV RNA/HBV DNA	HCV SVR	HBV response	Comments/limitations
Liu et al. [51] (2003)	21	Anti-HCV+ HBsAg+	+/+ *N* = 17 (81%)	*N* = 9 (43%)	HBsAg loss (0%) HBeAg loss (*N* = 3,100%) HBV DNA- (*N* = 6, 35%)	Similar SVR rates between coinfected and HCV alone for both HCV genotype 1 and non-1. Serum HBV DNA became positive in all 4 with undetectable HBV at baseline.
Hung et al. [50] (2005)	36	Anti-HCV+ HBsAg+	+/+ *N* = 18 (50%)	25 (69%)	HBsAg loss (0%) HBeAg loss (0%) HBV DNA- (*N* = 2, 11%)	Similar HCV SVR rates between coinfected and HCV alone patients. HCV genotype was not determined, and all treated for 6 mo. HBV DNA became positive in 8 of 18 patients.
Chuang et al. [48] (2005)	42	Anti-HCV+ HBsAg+	+/+ *N* = 16 (38%)	69%	HBsAg loss (*N* = 5, 12%) HBeAg loss (50%) HBV DNA- (*N* = 5, 31%)	Similar HCV SVR rates between coinfected and HCV alone patients. HCV responders had significantly higher rates of HBV DNA resurgence than nonresponders during and after treatment.
Myers et al. [53] (2003)	51	Anti-HCV+ HBsAg-	+/NA	*N* = 23(17%)	NA	Anti-HBc+ status did not affect the rate of SVR in HCV. HBV DNA levels was not assessed before or after therapy.
Fabris et al. [49] (2004)	51	Anti-HCV+ HBsAg-	+/+ *N* = 15 (29%) liver tissue	*N* = 20 (40%)	NA	HBV DNA frequently identified in liver of HCV patients. Its presence did not affect liver histology, treatment response.
Mrani et al. [52] (2007)	47	Anti-HCV+ HBsAg-	+/+	*N* = 11 (28%)	NA	HBV DNA in serum was associated with more severe liver disease and decreased HCV treatment response.

HBV—hepatitis B virus; HBc—hepatitis B core; HBeAg—hepatitis B e antigen; HBsAg—hepatitis B surface antigen; HCV— hepatitis C virus; NA—not available; SVR—sustained virologic response.

Table 3

Combination therapy for HBV/HCV coinfection: pegylated interferon with ribavirin

Study (year)	*N*	Serology	HCV RNA/HBV DNA	HCV SVR	HBV response	Comments/limitations
Senturk et al. [56] (2008)	17	Anti-HCV+ HBsAg+	+/-	1 (6%)	N/A	All HCV genotype 1 patients treated for up to 48 wk but 5 (29%) discontinued therapy because of side effects. None had replicative HBV DNA at baseline.
Potthoff et al. [55•] (2008)	19	Anti-HCV+ HBsAg+	+ (100%)/+ (*N* = 6, 32%)	G1 7/10 (70%) G2/3 7/9 (78%)	HBsAg loss (0%) HBeAg loss (0%) HBV DNA- (*N* = 2, 33%)	Prospective. Excellent HCV response. Suboptimal HBV response. HBV reactivation after HCV RNA clearance in 4 (31%) patients with initial undetectable HBV DNA.
Yu et al. [57•] (2009)	50	Anti-HCV+ HBsAg+	+ (100%)/+ (*N* = 4, 8%)	G1 12/30 (40%) G2/3 15/20 (75%)	HBsAg loss (0%) HBeAg loss (*N* = 2, 33%)	Prospective, controlled. HCV response similar to HCV alone. HBV reactivation rate was significantly higher with HCV SVR (9/27, 33%) than those without SVR (2/23, 8.7%).
Liu et al. [54••] (2009)	161	Anti-HCV+ HBsAg+(excluded HBeAg+)	+ (100%)/+ (*N* = 68, 42%)	G1 70/97 (72%) G2/3 53/64 (83%)	HBsAg loss (*N* = 18, 11%) HBV DNA- (*N* = 38, 56%)	Prospective, controlled. HCV response similar to HCV alone. Good HBV response. HBV reactivation rate was high (*N* = 28/77, 36%) but no difference between those with or without HCV SVR. 10 patients with occult HBV had undetectable HBV DNA after therapy.

HBV—hepatitis B virus; HBeAg—hepatitis B e antigen; HBsAg—hepatitis B surface antigen; HCV—hepatitis C virus; NA—not available; SVR—sustained virologic response.