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TOPIC HIGHLIGHT

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Hepatitis B virus and hepatitis C virus dual infection

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Abstract

Hepatitis B virus (HBV) and hepatitis C virus (HCV) share common mode of transmission and both are able to induce a chronic infection. Dual HBV/HCV chronic coinfection is a fairly frequent occurrence, especially in high endemic areas and among individuals at high risk of parenterally transmitted infections. The intracellular interplay between HBV and HCV has not yet been sufficiently clarified, also due to the lack of a proper *in vitro* cellular model. Longitudinal evaluation of serum HBV DNA and HCV RNA amounts has revealed that complex virological profiles may be present in coinfected patients. Dual HBV/HCV infection has been associated to a severe course of the liver disease and to a high risk of developing hepatocellular carcinoma. Despite the clinical importance, solid evidence and clear guidelines for treatment of this special population are still lacking. This review summarizes the available data on the virological and clinical features as well as the therapeutic options of the dual HBV/HCV infection, and highlights the aspects that need to be better clarified.

Key words: Hepatitis B virus/hepatitis C virus coinfection; Chronic hepatitis; Viral interaction; Cirrhosis; Hepatocellular carcinoma; Antiviral therapy

Core tip: This review analyses the available virological and clinical data about the dual hepatitis B virus/hepatitis C virus infection. In particular, it highlights the aspects concerning the possible viral interactions, the impact on liver disease progression and hepatocellular carcinoma development as well as the therapeutic options in this special population.

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INTRODUCTION

Hepatitis B virus (HBV) and hepatitis C virus (HCV) share several important similarities, including considerable diffusion worldwide, the modes of transmission, the hepato-tropism and the capacity to induce a chronic infection that may lead to cirrhosis and hepatocellular carcinoma (HCC) development[1-3]. Consequently, it is not surprising that their combined infection is a fairly frequent occurrence particularly in highly endemic areas and among subjects with a high risk of parenteral infections[4]. In this context it is of importance to stress that a large body of evidence shows that the prevalence of occult HBV infection [*i.e.*, the long-lasting persistence of HBV genomes in individuals negative for HBV surface antigen (HBsAg)[5] is particularly elevated in HCV patients[6-8]. Nevertheless, the condition of occult HBV and HCV coinfection is not the subject of the present paper that is, instead, strictly focused on reviewing the available data concerning virological interaction, clinical course and treatment options of the chronic HCV and overt HBV (*i.e.*, HBsAg positive) dual infection. The review begins

with very concise but necessary notes of epidemiology and virology concerning the two viruses.

NOTES OF EPIDEMIOLOGY

The World Health Organization estimates that more than 500 Million people all around the world are chronically infected with HBV or HCV and approximately 1 million people die each year (about 2.7% of all deaths) from causes related to viral hepatitis and liver disease, including liver cancer[1-3].

Despite some differences in the geographical distribution of the two viruses (HBV is more prevalent in Far East, Sub-Saharian Africa, and Southern America with 2%-15% of populations infected, whereas HCV is more prevalent in Asia, North-Africa and Europe with 2.5%-10% of population infected), they quite frequently co-exist especially in countries at high endemicity for one or both viruses and among patients with a high risk of parenterally transmitted infections. The estimated prevalence of HBV/HCV dual infection is approximately 5%-20% in HBsAg positive patients and 2%-10% in HCV positive patients, with a quite different geographical distribution, as showed in Table 1[4,9-29]. A large cohort study recently conducted in the United States. By Tyson *et al*[4] in HCV positive patients, showed a 1.4% prevalence of overt HBV coinfection, whereas about one third of the study population showed positivity for antibody directed to HBV antigens. Moreover, there was a significantly increased risk of HBV coinfection associated with male sex, age lower than 50 years, positive human immunodeficiency virus (HIV) status, a history of genetic haematological disease, of blood transfusion or of cocaine and other recreational drug use[4]. Of note, hepatitis Delta virus (HDV) and HIV also share common modes of transmission with HBV and HCV. For this reason - and mostly in highly endemic areas, in economically depressed regions and among intravenous drug addicts - they can be responsible, with HBV and HCV, for triple (HBV/HCV/HDV, HBV/HDV/HIV or HBV/HCV/HIV) or quadruple (HBV/HCV/HDV/HIV) infection[30-34]. The virological and clinical patterns of these very complex kinds of multiple infection will not be discussed in this review.

NOTES OF VIROLOGY

Despite the considerable similarities in terms of diffusion, transmission and tropism, HBV and HCV are biologically very different from each other.

HBV is a DNA virus belonging to the Hepadnavirus family. The viral DNA is a closed, circular, partially double stranded molecule of 3.2 kilobases [relaxed circular DNA (rcDNA)], and contains four partially overlapping open reading frames: the S gene, coding for the envelope proteins; the Core gene, coding for the core and "e" proteins; the P gene, coding for a protein with multiple functions, including reverse transcriptase and DNA polymerase activities; the X gene, coding for the "X" protein of yet not well defined functions, but with transcriptional transactivating properties and a likely important role in the viral replication[35]. Once it has penetrated into the hepatocyte, the viral core is transported to the nucleus and the rcDNA is converted into a circular, covalently closed, fully double stranded supercoiled DNA (cccDNA) that is the template for the production of the virus messenger RNAs including a RNA pregenome that - similarly to the retroviruses - is reverse transcribed in the cytoplasm of the infected cells for the synthesis of the viral DNA[35,36]. HBV cccDNA molecules bind histons and other proteins and are organized as a stable, long-term persisting chromatinized episomes that - together with the long half-life of hepatocytes - imply that HBV infection, once it has occurred, may continue indefinitely over time[37-39]. HBV-DNA can be directly integrated into the host DNA but, unlike what happens for retroviruses, integration has no role in the viral replicative cycle since it involves only fragments of the viral genome. Integration is possibly a cofactor related to the development of HCC[40,41]. Moreover, HBV may exert its direct pro-oncogenic role also through the production of proteins - such as X and truncated preS-S proteins - with potential transforming properties[39-42].

HCV is an enveloped, single-stranded, positive-sense RNA virus, with a genome of approximately 9600 nucleotides[43,44]. Due to its considerable sequence heterogeneity HCV is classified as a separate genus in the Flaviviridae family and distinguished into six major genotypes showing a fairly different geographic distribution[45]. Its genome consists of 5' and 3' non coding regions and a single open reading frame that encodes a single viral polyprotein of 3010-3033 amino acids[44,46]. The viral polyprotein undergoes post-translational cleavages to form functional viral proteins, both structural (core and envelope proteins) and non-structural (NS2-NS5 proteins), which produce the enzymes required for viral growth and replication[44,46]. Because of its rapid replication and the high rate of error insertion of the RNA-dependent RNA polymerase, HCV spontaneously mutates within a given infected individual, resulting in related but distinct "quasispecies[47]. The generation of these mutants appears to be one of the key mechanisms by which HCV escape the host's immunoresponse, maintaining persistent infection[48]. Very importantly, the replication cycle of the HCV occurs totally in the cytoplasm and - once the replication is stopped - the virus can be cleared from the cells and thus the infection definitively cured[49].

VIROLOGICAL INTERACTION

From both the biological and clinical points of view, a crucial question is whether HBV and HCV may interfere in the life cycle of each other in cases of co-infection. *In vitro* studies performed since the early 90s had clearly demonstrated that the HCV "core" protein strongly inhibits HBV replication[50-53]. Two subsequent reports

Table 1 Selection of papers concerning the prevalence of hepatitis B virus/hepatitis C virus dual infection in different countries and populations

Ref., country	Study population	Cases (*n*)	Co-infected individuals
Tyson *et al*[4], United States	Anti-HCV$^+$	102971	1.3%
Bini *et al*[9], United States	Anti-HCV$^+$	1257	5.8%
Siddiqui *et al*[10], United States	Anti-HCV$^+$	743	3%
Fong *et al*[11], United States	HBsAg$^+$	148	11%
Chen *et al*[12], China	HBsAg$^+$	712	14.47%
Li *et al*[13], China	HBsAg$^+$	193	11.39%
Tsatsralt-Od *et al*[14], Mongolia	Children	655	1.2%
Tsatsralt-Od *et al*[15], Mongolia	Chronic liver disease	207	7.7%
Liaw *et al*[16], Taiwan	HBsAg$^+$	1498	12%
Dai *et al*[17], Taiwan	HBsAg$^+$	100	18%
Chan *et al*[18], Taiwan	HBsAg$^+$	323	3.4%
Sato *et al*[19], Japan	HBsAg$^+$	82	23%
Ohkawa *et al*[20], Japan	HBsAg$^+$	156	12.8%
Saravanan *et al*[21], India	Chronic liver disease	251	5.9%
Chakravarti *et al*[22], India	Chronic liver disease	150	16%
Semnani *et al*[23], Iran	HBsAg$^+$	139	12.3%
Murad *et al*[24], Yemen	Pregnant women	400	0%
Gaeta *et al*[25], Italy	HBsAg$^+$	837	7%
Di Marco *et al*[26], Italy	HBsAg$^+$	302	14.2%
Fattovich *et al*[27], Italy	HBsAg$^+$	184	15%
Crespo *et al*[28], Spain	HBsAg$^+$	132	13%
Voiculescu *et al*[29], Romania	Subjects asking for a medical examination	2540	0.24%

HCV: Hepatitis C virus; HBsAg: Hepatitis B virus surface antigen.

indicated that also the HCV NS5A protein may influence HBV activity, although they produced contrasting data in terms of inhibition or enhancement of the HBV replication[54,55]. However, more recent studies have brought into question the interplay between HCV and HBV, and when the *in vitro* co-transfection experiments were conducted with full-length HBV genomes and HCV replicons (thus, not limiting the study to a single HCV protein) it was shown that the two viruses could replicate in the same hepatocyte without evidence of interference[56], and that hepatocytes with replicating HBV could be infected by HCV without superinfection exclusion[57] (as a note, the possible co-existence of HBV and HCV in the same hepatocytes form liver biopsy specimens has been reported)[58]. Because of several limitations, however, the transformed-hepatocyte cell culture systems used so far are not ideal for exploring the co-existence of the two viruses and, consequently, the experimental data available at present do not definitively clarify the possible interaction between them. Similarly, an *in vivo* model to study the dynamic process of a possible reciprocal interference in the replicative cycle and the production of respective viral proteins is not yet available[59].

The HBV and HCV virological patterns have also been investigated in quite a large number of clinical studies. Most of these studies were cross-sectional evaluation of the viral load of the two viruses at a single time point, showing an apparent dominant role of the HCV (high HCV RNA and low HBV DNA levels) in the majority of the cases. Other reports, however, suggest a reciprocal interference or even a dominant effect of HBV[20,28,60-62], and ethnic factors have also been proposed to influence the dominant role of one virus on the other[63]. In the middle of the last decade, an Italian multicenter study longitudinally examined a large series of HBsAg and anti-HCV antibody positive patients and showed that a wide and complex spectrum of virological profiles may occur in cases of coinfection[64]. In fact, about one third of the cases presented broad changes over time of the amount of circulating HBV DNA or - less frequently - HCV RNA, thus revealing alternate phases of activity of one or both viruses. In this context, one should consider that the typical anti-HBe positive chronic hepatitis B is often characterized by phases of low levels of HBV replication interspersed with episodes of viral reactivation[65-68], and many HBsAg/anti-HCV cases are anti-HBe positive. Similarly, also HCV - although infrequently - may show alternating phases of active and suppressed replication also in cases of single infection[69-71]. In the context of the hypothesized interaction between the two viruses and particularly of the inhibitory effect operated by HCV on HBV, some anecdotal reports concerning co-infected patients treated with interferon (IFN) therapy for the productive HCV infection had showed the reactivation of the previously, apparently suppressed HBV once a favorable response to therapy had been achieved as shown by the permanent disappearance of serum HCV RNA[72,73]. Therefore, curing the HCV infection would produce the loss of the suppression on HBV that may reactivate[74]. However, a more recent study longitudinally evaluating the behavior of apparently inactive HBV infection in patients under treatment for the simultaneous HCV infection showed that 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 who showed HBV DNA flares during the antiviral treatment, thus indicating a status of productive HBV infection with fluctuating virological profiles and

suggesting that the HBV activity can be independent of the HCV during anti-HCV therapy[75].

Summarizing, the available information indicates that in a considerable portion of cases with coinfection the behaviour of each virus appears to be independent of the contemporary presence of the other and a serial evaluation overtime of the viral loads of both viruses is mandatory for a correct identification of a true active (as well as inactive) infection of one or both of them, also in the course of antiviral treatments.

The immunology of the HBV-HCV dual infection has been evaluated in a few studies focused on T-lymphocyte response and analyzing small numbers of cases[76,77]. Larger studies are needed to better clarify the complex immunological aspects of this condition.

CLINICAL ASPECTS

Dual infection with HBV and HCV is usually first identified in clinical practice by serum positivity for HBsAg and anti-HCV, although the subsequent detection of viral genomes (particularly of HCV RNA) is essential for proofing the current status of productive infection. In the majority of the cases this finding is occasional and it is impossible to date back to the time of the coinfection. Less frequently, there is a clinical history of acute hepatitis that could be related to three different events: (1) simultaneous HBV and HCV infections in a subject previously unexposed to both viruses[78-81]; (2) HCV superinfection occurring in a chronic HBsAg carrier[82-84]; and (3) HBV superinfection occurring in a chronically HCV RNA positive patient[85-87]. Although all typical outcomes of the acute hepatitis may be observed in each of these three events (the acute hepatitis may result in fulminant or subfulminant hepatitis or in chronic coinfection or in complete recovery from one or both infections), indeed in the majority of cases these three conditions present substantial differences from clinical/virological points of view. In fact, acute hepatitis in cases with simultaneous infection often has a self-limiting, benign course with complete recovery from one or both infections[78-81], whereas the acute hepatitis due to superinfection frequently has a severe and sometimes fatal course[82-87]. Moreover, in cases of HCV superinfection, the pre-existing HBV - after an initial phase of strong suppression of its activity - usually goes back to being a productive chronic infection[87-89], whereas in cases with HBV superinfection the HCV can be suppressed and then cleared[85-88]. The clinical pattern of the chronic HBV/HCV coinfection is indistinguishable from that of a chronic monoinfection. The liver histology from these patients does not show any peculiar characteristic but the coexistence of the typical features of HBV or HCV mono-infection such as lymphoid follicles or ground-glass hepatocytes[90]. Moreover, studies comparing the histological degree of liver damage between co-infected and mono-infected patients produced conflicting results since some of them did not observe any difference[90,91] whereas others reported a higher necroinflammatory activity and fibrosis progression in cases with coinfection[61,92-94].

Much evidence indicates that HBV/HCV coinfection has a more severe evolution in the long term compared to HBV or HCV monoinfection. Indeed, several cross-sectional studies found that coinfection is associated with a higher prevalence of liver cirrhosis and hepatic decompensation as compared with HBV or HCV monoinfection[11,27-28,61,95,96]. Moreover, co-infection has been associated with increased risk of progression of the liver fibrosis and the establishment of cirrhosis[96-98] and is an independent predictor of HCC development[96,99-103]. In this context, however, it has to be mentioned that various meta analysis performed over time have produced contrasting results concerning the risk of HCC occurrence in the HBV/HCV coinfected population[96,97]. In this context, it has to be stressed that dually infected patients are an extremely heterogeneous population and most of the clinical studies performed so far did not examine the differences among patients, either those concerning the viruses (*i.e.,* viral genotypes, main HBV genomic mutations, activity status of one or both viruses, *etc.*) or those regarding the host factors (*i.e.*, presence of metabolic syndrome, diabetes, alcohol intake, *etc.*)[99].

THERAPY

Despite the evident clinical importance of the chronic HBV/HCV coinfection, the therapeutic studies focused on these patients are still limited in number and often also in methodological quality. Consequently, solid evidence and clear guidelines for treatment of this special population are still lacking. Nevertheless, some aspects of primary importance for making proper therapeutic decisions have been identified. In fact, it is well established that the virological profiles must be defined in each individual patient before starting any treatment to verify whether one or both infections are active and thus to identify the agent(s) likely responsible for the liver damage and against which antiviral treatment should be addressed[98]. This careful evaluation may allow the identification of several different clinical/virological conditions that may require particular therapeutic approaches[98,101]. Obviously, HBsAg/anti-HCV patients found to be persistently HCV RNA negative (indeed, a minority of the cases) must be considered as HBV mono-infected individuals, thus treated or not treated with anti-HBV therapy on the basis of the active or inactive status of the HBV infection. Similarly, HCV RNA positive patients with inactive HBV infection must be treated like HCV mono-infected individuals. The therapeutic approach to patients with double active infection is much more difficult, and indeed this important event has been understudied so far[102]. For many years these individuals were considered a difficult to cure category of patients since the first studies based on traditional IFN therapy demonstrated very low chances of HCV eradication whereas the HBV infection status has been taken into

Table 2 Differences in relevant studies concerning the pegylated inteferon + ribavirin treatment of patients with hepatitis B virus/hepatitis C virus dual infection

Ref., country	Type of study	*n*	Severe CH or cirrhosis	HCV genotype 1b	HCV RNA SVR	Anti-HBe positive	HBV DNA detectable at baseline (*n*)	HBV DNA disappearance after therapy (*n*)	HBV DNA reappearance after therapy (*n*)
Senturk *et al*[109], Turkey	Retrospective, single center	36	13.9%	100%	5%-6%	100%	0	Not reported	Not reported
Pothoff *et al*[110], Germany	Prospective, multicenter, pilot study	19	10.5%	52%	93%	94.7%	6	2	4
Liu *et al*[111], Taiwan	Prospective, multicenter	161	40.4%	60%	72.2%-82.8%	100%	81	47[1]	28
Viganò *et al*[112], Italy	Prospective, single center	22[3]	50%	50%	41%	100%	3	2[2]	4
Yu *et al*[113], China	Retrospective, single center	50	10%	60%	54%	88%	4	4	11

[1]18 hepatitis B virus surface antigen (HBsAg) seroclearance; [2]2 HBsAg seroclearance; [3]6 cases with undetectable hepatitis B virus (HBV) DNA at baseline serocleared HBsAg after treatment. CH: Chronic hepatitis; SVR: Sustained virological response; HCV: Hepatitis C virus.

account very little[103-105]. However, more recent studies [despite their heterogeneity in terms of study populations and parameters evaluated (Table 2)] clearly showed that the combination of pegylated inteferon (PEG-IFN) and ribavirine (RBV) has the same possibilities to be effective in coinfected than in HCV monoinfected individuals[106-110]. In fact, the PEG-IFN plus RBV therapeutic schedules for the HCV treatment are at present identical in cases with coinfection and monoinfection (of note, there are no data concerning the use of anti-HCV direct antiviral agents in this special population). In this context, one should consider that PEG-IFN may also have an effect on the HBV. In fact there is evidence of an increased possibility of HBsAg loss and HBeAg seroconversion during or off-treatment with PEG-IFN and RBV in coinfected patients[111-113]. The beneficial effects of treatment appears to be stable up to five years, and patients who responded to the treatment for the HCV infection appear to have a high rate of HBsAg seroclearance and a low recurrence rate of HCV infection in the long term[114]. Nevertheless, in the large majority of cases the HBV status is not modified by the anti-HCV therapy, and this might explain the data from a recent metanalysis showing that coinfected patients successfully treated for HCV infection had a lower rate of end of follow-up serum ALT normalization than monoinfected patients[115]. In this context and also considering what is reported in the above section "Virological Interactions", the possible fluctuating profile of the HBV DNA levels also during the anti-HCV therapy should be taken into account. In fact, these cases (as well as, of course, those with persistently high levels of HBV viremia) must be considered for treatment with a nucleot(s)ide analogue (NA) to suppress the HBV replication and block the HBV-induced liver injury, independently of a positive or negative response to the anti-HCV treatment[98,101]. However, no data are available and - very importantly - no trial has been performed using a triple therapy (PEG-IFN + RBV + NA) for the treatment of the coinfection.

CONCLUSION

In conclusion, HBV/HCV dual infection is a complex clinical/virological entity. This co-infection appears to be associated with the most severe forms of chronic liver disease and it is an important risk factor for hepatocellular carcinoma development. Different, often dynamic virological profiles may be observed that are strictly related with the activity of one or both the viruses overtime. Thus, a careful longitudinal evaluation of the HBV and HCV viremia levels is mandatory for a correct diagnosis and proper therapeutic approach.

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