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TOPIC HIGHLIGHT

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Updates on the treatment and outcomes of dual chronic hepatitis C and B virus infection

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Abstract

Dual hepatitis C virus (HCV)/hepatitis B virus (HBV) infection is found in HBV or HCV endemic areas, and in specific populations exhibiting a high risk of parenteral viral transmission. Clinical observations have revealed that HCV/HBV dually infected patients demonstrate a higher risk of liver disease progression compared with HBV or HCV monoinfected patients. The viral activity responsible for liver disease progression can be determined by examining the viral loads of HCV and HBV and by conducting liver biopsy examinations. Recent trials have confirmed that the combination therapy of peginterferon alpha-2a or 2b and ribavirin for dual hepatitis patients with HCV dominance appears to be as effective and safe as it is in patients with HCV monoinfections. Strikingly, approximately 60% of dually infected patients with inactive hepatitis B before treatment develop HBV reactivation after the clearance of the HCV. The clinical significance of this HBV reactivation and the strategy to prevent and treat this event should be determined. Furthermore, approximately 30% of dually infected patients lost hepatitis B surface antigen (HBsAg) within 5 years after the start of peginterferon-based therapy, and 40% of them harbored occult HBV infection. The underlying mechanisms of their accelerating HBsAg seroclearance and the development of occult HBV await further investigations. Moreover, the optimal treatment strategies for dually infected patients who are seropositive for the hepatitis B e antigen must be explored. Finally, the advent of new direct-acting antiviral-based anti-HCV therapy may change the optimal therapies for patients with dual hepatitis in the near future, which warrants further clinical trials.

Key words: Dual infection; Hepatitis B virus; Hepatitis C virus; Interferon; Pegylated interferon; Ribavirin; Sustained virological response; Hepatitis B surface antigen clearance

Core tip: Patients with dual hepatitis C virus (HCV)/hepatitis B virus (HBV) infections have a higher risk of liver disease progression compared with patients with HBV or HCV monoinfections. The combination peginterferon alpha/ribavirin treatment for dual hepatitis patients with HCV dominance appears to be just as effective in the clearance of HCV RNA and safe as it is in patients with HCV monoinfections. The durability of HCV response was 97%. Furthermore, approximately 30% of dually infected patients lost hepatitis B surface antigen within 5 years after the start of peginterferon-based therapy. A population-based study revealed the benefits of combination therapy in the improvement of long-term outcomes in dually infected patients.

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INTRODUCTION

Most patients with chronic hepatitis C have a hepatitis C virus (HCV) monoinfection. However, in areas where the hepatitis B virus (HBV) is endemic, a substantial proportion of the patients are coinfected with hepatitis C and B[1-3]. If the prevalence of anti-HCV positivity worldwide is approximately 1%-4% in the general population, the number of individuals with HCV/HBV dual infection among the 320 million HBV carriers would be approximately 3.2-12.8 million. Moreover, HCV/HBV dual infections can also be found in people at risk of parenteral hepatotropic viral transmissions such as people who use intravenous drugs, patients with thalassemia and patients with hemophilia.

In patients with dual chronic hepatitis B and C, the disease outcomes, including the development of liver cirrhosis (LC) and hepatocellular carcinoma (HCC), are generally more severe than those in patients with either hepatitis B or hepatitis C[1-8]. In additional to these cross-sectional data, a long-term community-based study was conduced and the results confirmed the effect of dual HCV/HBV infections on the cumulative incidences of HCC[9]. Therefore, patients dually infected with hepatitis C and B need attention and require effective antiviral treatments.

The treatment priorities in patients with dual viral infections can be determined by analyzing the relative viral activity of both viruses[10]. Data from recent clinical trials suggested that pegylated interferon (Peg-IFN) alpha plus ribavirin (RBV) is effective in the clearance of HCV in dually infected patients with active hepatitis C[11-14]; the HCV sustained virologic response (SVR) was durable in approximately 97% of the patients during a 5-year post-treatment follow-up[15]. By contrast, the optimal treatment strategy for dually infected patients with active hepatitis B is still unknown.

The current data concerning the treatment and outcomes of patients with dual chronic hepatitis C and B will be summarized in this review article.

TREATMENT STRATEGIES FOR DUAL HBV AND HCV INFECTIONS

The primary goal of the treatment of HCV and HBV dual infections is to eliminate or permanently suppress both viruses. In the meantime, the long-term goal is to reduce or terminate hepatic necroinflammation, prevent progression to LC and the development of HCC, and ultimately prolong the survival of patients[16,17].

We hope to achieve these goals by eradicating both viruses after providing an effective antiviral therapy for dually infected patients. In the next scenario, we may provide treatment to control the virus that is likely responsible for liver injury in most patients; or we may prioritize the treatment of the virus most responsive to antiviral therapy.

VIROLOGIC PROFILES AND THE SELECTION OF VIRAL TARGET(S) FOR TREATMENT

A previous study revealed that active hepatitis C can be found in more than 50% of dually infected patients[10]. Besides, HCV can be successfully eradicated in approximately 70% of the patients with chronic HCV monoinfection using Peg-IFN plus RBV combination therapy[16,17]. Accordingly, HCV infection seems to be the priority treatment target in dually infected patients with active hepatitis C. Although this may be true among Asian populations, SVR rates are lower in people from Caucasian populations with the genotype 1 disease, partially because of the differences in *IL-28* genotype distribution.

TREATMENT OF PATIENTS WITH DUAL CHRONIC HEPATITIS C/B AND ACTIVE HEPATITIS C USING PEG-IFN PLUS RIBAVIRIN

In the treatment of chronic hepatitis C monoinfections, interferon (IFN) plus RBV or Peg-IFN plus RBV was effective in clearing the HCV[18,19], and the latter remains the standard of care in many Asian-Pacific countries. Recently, the efficacy of IFN plus RBV or Peg-IFN plus RBV in the treatment of dually infected patients with active hepatitis C was confirmed[11,15,20-22].

The treatment outcomes at the end of treatments and during posttreatment follow ups are shown in Figure 1A. Six months after the end of treatment, the HCV SVR rates were generally similar between dually infected patients and HCV monoinfected patients who had genotype 1 or genotype 2/3 infection. A satisfactory HCV SVR rate obtained by treating dual HBV/HCV infections by using Peg-IFN alpha-2b plus RBV was also documented in a series of 19 German patients[14] and in other small cohorts[12,13].

DURABILITY OF THE HCV RESPONSE

The clearance of HCV RNA at 6 mo after the end of treatment may indicate that an HCV infection is cured. Previous studies demonstrated that 0.9%-10% of single chronic hepatitis C patients from whom virologic responses (VRs) were obtained after the end of the treatment developed a hepatitis C relapse[23]. To address this issue, the durability of hepatitis C clearance in HCV-monoinfected and HCV/HBV dually infected patients was investigated

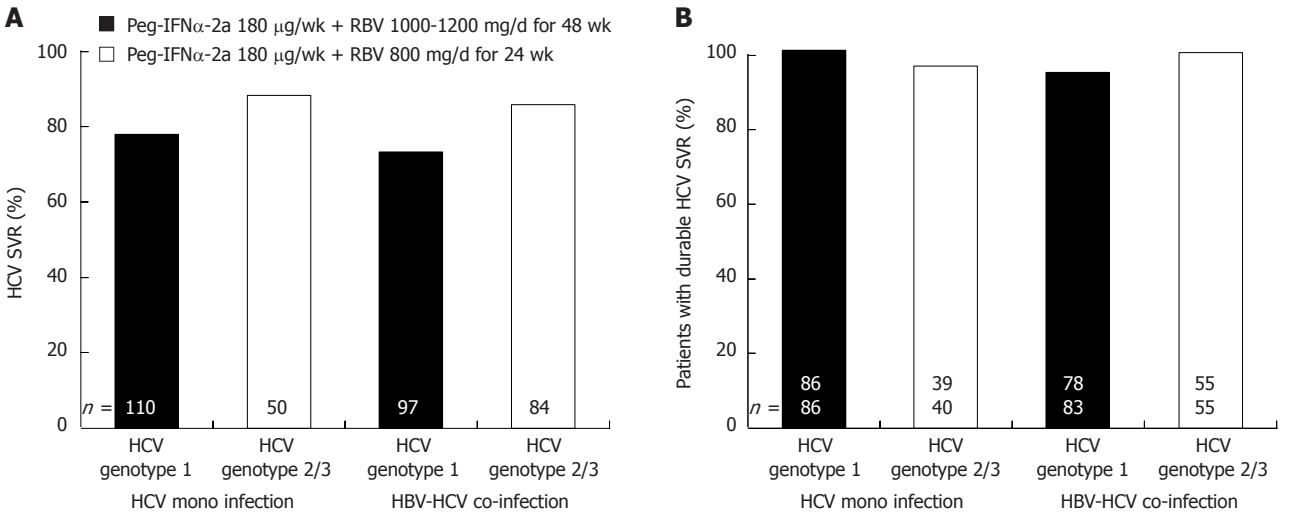

Figure 1 The treatment of patients with dual chronic hepatitis C/B and the durability of the hepatitis C virus response. A: Hepatitis C virus (HCV) sustained virologic response (SVR) rate at 6 mo after end of peg-interferon plus ribavirin combination treatment; B: Durability of HCV SVR in patients who initially obtained HCV SVR at 6 mo after end of therapy. Median 4.6-years (range: 1-5 years) post-treatment follow-up. SVR: Sustained virologic response; Peg-IFN: Peg-interferon; RBV: Ribavirin.

by conducting a 5-year prospective follow-up study[15]. The findings revealed that after a median follow-up of 4.6 ± 1.0 years, HCV RNA reappearance developed in only 6 (2.6%) of the 232 patients who achieved SVR (Figure 1B). This suggests that the durability of the HCV SVR obtained by using Peg-IFN alpha and RBV therapy was satisfactory and not influenced by HBV coinfections.

HBV RESPONSE AND REACTIVATION

Peg-IFN is one of the first-line choices for the treatment of chronic hepatitis B[24,25]. Thus, in addition to the cure of HCV infections, Peg-IFN-based therapy may also be used to help control chronic HBV infections in patients with dual HCV/HBV infections. Remarkably, we found that hepatitis B surface antigen (HBsAg) disappeared 6 months after the end of therapy in 18 (11.2%) of the 161 dually infected patients[11]. During a 5-year posttreatment follow-up, the rate of HBsAg seroclearance was 5.4% per year[15]. Among the analyzed baseline variables, only low pretreatment serum HBsAg levels substantially correlated with sustained HBsAg seroclearance during follow-up ($P < 0.05$)[15,26].

In addition to HBsAg loss, VR was also analyzed in this study. Before treatment, the serum HBV DNA level was > 200 IU/mL in 62 patients (45.7%) of a long-term follow-up subcohort[15]. Five years after the end of treatment, HBV VR was obtained in 33 (53.2%) of the 62 patients; the serum HBV DNA level was < 80 IU/mL in 32 of the 33 patients. Serum HBsAg seroclearance regularly occurred in patients who developed HBV VR (51.5%, 17/33).

The reactivation of HBV activity is another clinical concern in dually infected patients receiving anti-HCV therapy[27]. Of 76 patients with pretreatment serum HBV DNA levels < 200 IU/mL, the reactivation of HBV DNA was found in 47 (61.8%) patients; either during the course of treatment (n = 18, 38.3%) or during the post-treatment follow-up (n = 29, 61.7%)[15]. Reactivation was merely transient in 21 (44.7%) of the 47 patients. Serum HBsAg seroclearance was found in 18 (62.1%) of the 29 patients without hepatitis B reactivation. The elevation of serum ALT levels was noted in some patients with HBV reactivation; effective anti-HBV therapy should be provided for these patients if clinically indicated.

TREATMENT OF HEPATITIS B IN PATIENTS WITH DUAL CHRONIC C/B AND ACTIVE HEPATITIS B

Our study data confirmed that Peg-IFN alpha-2a plus RBV successfully treats patients with active hepatitis C who are also coinfected with HBV. However, whether this approach is suitable for dually infected patients with active HBV infections is unknown. In an earlier report, 8 patients with dual chronic hepatitis C and hepatitis B e antigen (HBeAg)-positive chronic hepatitis B were treated using a combination of IFN and lamivudine[28]. After treatment, 3 patients (37.5%) lost HBeAg, 3 (37.5%) achieved undetectable HBV DNA, and 4 patients (50%) had a sustained clearance of HCV RNA at 12 months. This small series suggested that combining lamivudine with IFN might be helpful in dually infected patients with chronic hepatitis C and active HBV replication. Theoretically, we may also use a combination of Peg-IFN alpha, RBV, and nucleos(t)ide analogues to treat both viruses at the same time; this strategy awaits further investigation.

TREATMENT OF DUALLY INFECTED PATIENTS WITH ESTABLISHED LIVER CIRRHOSIS

Patients with dual chronic HCV/HBV and established

LC may not tolerate Peg-IFN plus RBV combination therapy. For this group of patients with evidence of HBV replication, the tolerability and effects of anti-HBV nucleos(t)ide analogues have been evaluated in a small cohort[29]. Coppola *et al*[29] used nucleos(t)ide analogues to treat 24 HBV DNA-positive patients with LC and HBV/HCV dual infections, defined by positivity for HBsAg, serum HBV DNA, and anti-HCV. At the 18th month of treatment, 23 (96%) patients had undetectable serum HBV DNA. However, a deterioration of liver reserve was observed in 8 (47%) of the 17 patients who were HCV RNA-positive at the baseline. These data suggested a favorable HBV virological effect in all HBV/HCV dually infected patients; but favorable clinical results were only observed in patients who were HCV-RNA negative before treatment. Therefore, the efficacy of these strategies remains unknown without being applied in large clinical trials.

IMPROVEMENT OF LONG-TERM CLINICAL OUTCOMES

The reduction of HCC development, overall mortality, and liver-related mortality

In patients with HCV monoinfections, successful anti-HCV therapy has been demonstrated to effectively decrease the incidence of newly developed HCC and liver-related mortality[30]. Whether an anti-HCV therapy using Peg-IFN plus RBV could obtain similar effects in HCV/HBV dually infected patients was investigated in a hospital-based cohort[31]. A total of 135 dually infected patients with active hepatitis C receiving IFN or Peg-IFN plus RBV therapy were enrolled. The cumulative incidence of HCC was compared with that of 1470 HCV-monoinfected patients. Dual infection was an independent factor for HCC development. In dually infected patients, age (HR = 1.175, 95%CI: 1.070-1.291, $P = 0.001$) and non-HCV SVR (HR = 7.874, 95%CI: 2.375-26.32, $P = 0.001$) were independent factors for HCC development. Four (4.2%) of the 96 dually infected patients with HCV SVR developed HCC after a mean follow-up of 4.6 years (annual rate of HCC development: 0.91%); 11 (28.2%) of the 39 patients with HCV SVR developed HCC after a mean follow-up of 3.5 years (annual rate: 8.1%). Moreover, the rate of HCC development was lower in patients with serum HBV DNA levels < 2000 IU/mL at the end of treatment or follow-up compared with those with HBV DNA levels ⩾ 2000 IU/mL ($P < 0.05$). These findings supported that HCV SVR achieved by treating with IFN or Peg-IFN plus RBV therapy may significantly reduce HCC in HBV/HCV dually infected patients, whereas the persistence or reactivation of the HBV dampens the benefits of HCV SVR.

The benefits of anti-HCV therapy in dually infected patients was confirmed in another large population-based survey in Taiwan[32]. We found that, compared with the patients in an untreated dually infected cohort, the risk of developing HCC, all-cause mortality, and liver-related mortality decreased by 35%, 62%, and 59%, respectively, in patients who received active anti-HCV therapy.

Despite the control or eradication of hepatitis virus after treatment, patients may be still at risk of developing advanced liver diseases, including HCC. In our long-term follow-up of the treatment cohort, 9 patients developed HCC[15]. At baseline, 8 (88.9%) of the 9 patients had dual HCV/HBV infections, and only 1 (11.1%) had HCV monoinfection. After treatment, 7 obtained HCV SVR during long term follow-up, and 3 developed seroclearance of HBsAg. Five (55.6%) of the 9 patients had established LC before treatment. This data suggested that some subjects with dual infections still developed HCC after obtaining HCV SVR and even HBsAg seroclearance posttreatment. Therefore, in addition to active antiviral therapy, regular examinations for the occurrence of HCC should be performed in these dually infected patients.

HOST AND VIRAL FACTORS AFFECTING TREATMENT OUTCOMES

The outcomes of chronic viral hepatitis B and C are possibly determined by both host and viral genomic factors. The effects of certain viral factors (including HCV genotype, HBV genotype, HCV interferon sensitivity determining region polymorphisms, and HBV precore/basal core promoter subgenomic polymorphisms) and host factors (including miR-122 expression and *IL28B* genotype) on the clinical outcomes of dually infected patients are only partially ascertained.

Factors associated with the seroclearance of HBsAg

Among the baseline and end-of-treatment variables analyzed in our treatment cohort, only low serum HBsAg levels substantially correlated with sustained HBsAg seroclearance during follow-up ($P < 0.05$)[11,15]. Baseline hepatitis B viral load did not correlate with HBsAg seroclearance. A subgroup analysis revealed that serum HBsAg seroclearance occurred in 17 (51.5%) of the 33 patients with HBV VR, but in none of the remaining 29 patients without HBV VR.

In another study, the host genetic factors associated with spontaneous HBsAg seroclearance were identified[33]. In this case-control study, we collected 100 CHB patients who lost HBsAg spontaneously and 100 matched patients without HBsAg loss. Baseline viral factors including viral load, HBV genotype, and HBsAg level, as well as host genetic factors, including 2 single nucleotide polymorphisms (rs3077 for the HLA-DPA1 region and rs9277535 for the HLA-DPB1 region) were investigated. We found that a low baseline ALT, serum HBsAg level, HBV DNA level, and rs9277535 non-GG genotype frequency are associated with a higher likelihood of spontaneous HBsAg seroclearance in chronic hepatitis B patients.

Factors associated with the development of occult HBV infection in patients with seroclearance of HBsAg

Occult HBV infection (OBI) may exist in patients expe-

Table 1 Proposed strategies for the treatment of patients positive for both anti-hepatitis C virus and hepatitis B surface antigen

HCV RNA	HBV activity	Treatment goals	Potential strategies	Level of evidence	Potential benefit of DAA-added therapy
Detectable	< 2000 IU/mL	Cure of HCV infection	P + R	Large multicenter trial	Increase rate of hepatitis C virus (HCV) sustained virologic response (SVR) in naïve or experienced patients
Detectable	≥ 2000 IU/mL	Cure of HCV infection and potentially control of HBV infection	P + R	Large multicenter trial	Increase rate of HCV SVR in naïve or experienced patients
Detectable	≥ 2000 IU/mL	Cure of HCV infection and control of HBV infection	P + R + NUC	Case report	Increase rate of HCV SVR in naïve or experienced patients
Detectable or undetectable	≥ 2000 IU/mL	Control of HBV infection	NUC	Small case-control study	Uncertain, wait for interferon-free regimen
Undetectable	≥ 2000 IU/mL	Control of HBV infection	P or NUC	Case report	None
Undetectable	< 2000 IU/mL	Not necessary	Clinical observation	No	None

P: Peginterferon; R: Ribavirin; NUC: Nucleos(t)ide analogue; DAA: Direct-acting antiviral.

riencing HBsAg seroclearance. We examined the clinical and virologic features of OBI in 15 dually infected patients who lost HBsAg posttreatment[34]. We found that the prevalence of OBI was 40% (6/15). One mutation, C3050T (preS1T68I), in the surface promoter/polymerase region was identified to be associated with the seroclearance of HBsAg in all 6 cases. This mutation does not change the amino acid sequence of the polymerase protein. The S-promoter activity was significantly lower in the construct containing the C3050T mutation compared with the wild-type ($P = 0.0008$). However, this mutation did not affect HBV replication, transcription, or translation in the context of the full-length HBV genome. Our data suggested that other factors may have more active roles in the clearance of HBsAg in these patients with OBI.

Virologic factors associated with treatment outcomes

The prevalence and distribution of precore/basal core promoter (BCP) mutations and HBV genotypes in HBV/HCV dually infected patients and their effects on the long-term HBV response of IFN-based therapy were investigated[35]. The HBV genotypes and sequences of the precore/BCP regions were determined in 180 HBV/HCV dually infected patients and were compared with 90 age, sex, and HBeAg-matched chronic hepatitis B patients as the control group. Dually infected patients had a higher prevalence of genotype C HBV ($P = 0.022$) and a lower frequency of the *G1896A* mutation ($P = 0.004$) compared with those in the control group. Based on the Cox proportional hazards model, young age (HR = 0.952, $P = 0.001$), HCV SVR (HR = 4.638, $P = 0.044$), C1766T mutation (HR = 5.216, $P = 0.003$) and A1846T mutation (HR = 2.332, $P = 0.031$) correlated with HBV DNA reactivation after therapy. Age (HR = 1.068, $P = 0.020$), G1896A mutation (HR = 0.140, $P = 0.01$), and A1846T mutation (HR = 0.086, $P = 0.018$) were independently associated with HBsAg seroclearance. These data demonstrated that specific mutations in the precore/BCP regions could be useful in predicting the long-term HBV response in HBV/HCV dually infected patients receiving IFN-based therapy.

INTERNATIONAL GUIDELINES OR RECOMMENDATIONS REGARDING THE TREATMENT OF PATIENTS WITH DUAL CHRONIC HEPATITIS C AND B

In summary, the combination therapy of Peg-IFN alpha and RBV appears to be just as effective for the treatment of HBsAg-positive patients chronically infected with active hepatitis C as it is in patients with HCV monoinfections. The treatment recommendations regarding therapy duration according to genotype in HCV monoinfections appear to be applicable for this patient group as well[18,19].

CONCLUSION

HBV/HCV dual infection is not uncommon in endemic areas and among subjects at risk of parenterally transmissible infections. How 2 viruses interact with each other in the same liver awaits further in situ and *in vitro* studies. Apart from academic interests, these data can be used to develop more effective antiviral therapies. Before the administration of antiviral therapy, thorough serological and virological examinations are required to determine the viral dominance and determine the optimal antiviral regimen. For dually infected patients with active hepatitis C, the same genotype-dependent treatment recommendations for single chronic hepatitis C remain valid. Another intriguing matter concerns the role of *IL28B* genotypes in the natural course and treatment responses of dual hepatitis patients. The *IL28B* was effectively influenced in the Peg-IFN therapy for single hepatitis C, but it might also be involved in hepatitis B surface antigen clearance in single hepatitis B. Whether *IL28B* genotypes participate in the host interactions with HBV and HCV and the outcomes deserves further investigation in a larger group of patients with dual hepatitis.

The prevention and management of HBV reactivation in dually infected patients receiving Peg-IFN-based therapy should be investigated. Moreover, the treatment outcomes using a similar Peg-IFN/RBV combination regimen in other ethnic groups and populations exhibit-

ing different chronologic sequences of HCV and HBV infections should be evaluated[36,37]. For patients with active hepatitis B, more studies are necessary to determine the optimal regimen to treat both viruses (Table 1). The host and viral factors affecting the natural and treatment outcomes of patients with dual chronic HCV/HBV should be identified. Finally, the value of direct-acting antiviral-based therapy in treating HCV/HBV dually infected patients seems promising; however, the extent of its efficacy requires further clarification.

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