Gastrointestinal & Digestive System

Shizuma T, J Gastroint Dig Syst 2014, 4:2
http://dx.doi.org/10.4172/2161-069X.1000181

Mini Review Open access

Efficacy of Treatments for Patients with Chronic Liver Disease due to Coinfection with Hepatitis B and C Viruses

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Received Date: Mar 21, 2014 **Accepted Date:** Apr 25, 2014 **Published Date:** Apr 30, 2014

Abstract

The hepatitis B virus (HBV) and the hepatitis C virus (HCV) are the leading causes of chronic liver disease. Patients with chronic liver disease who are co infected with both HBV and HCV develop cirrhosis and hepatocellular carcinoma (HCC) more rapidly than patients with monoinfection with HBV alone or HCV alone. However, standard-of-care recommendations have not been well established for patients with HBV/HCV co infection. In this study, a literature review was conducted on the efficacy of therapies for patients with HBV/HCV coinfection. Many papers reported that following combination therapy with interferon (IFN) plus ribavirin (RBV), there were no significant differences in the rate of achievement of a sustained virological response (SVR) to HCV between patients with HBV/HCV coinfection and patients with HCV monoinfection. However, the efficacy of these therapies for HBV infection in coinfected patients is complex. In patients with HBV/HCV coinfection characterized by a predominance of HCV, it is highly probable for serum hepatitis B surface antigen (HBsAg) titers to decrease or disappear during or after IFN/RBV combination therapy. On the other hand, reactivation of HBV due to the suspected inhibition of HCV replication is sometimes detected in coinfected patients during or after IFN/RBV combination therapy.

Keywords Hepatitis B virus; Hepatitis C virus; Coinfection; Interferon; Ribavirin

Introduction

The hepatitis B virus (HBV) and the hepatitis C virus (HCV) are both hepatotrophic viruses. Globally, more than 350 million and 170 million individuals are estimated to be infected with HBV and HCV, respectively [1-3], although the prevalence of infection varies in different geographic areas of the world [2]. The worldwide prevalence of coinfection with both HBV and HCV is unknown [1,2]; however, in the Asia-Pacific region, 2-10% of patients with chronic HCV infection are reportedly hepatitis B surface antigen (HBsAg)-positive and 5-20% of patients with chronic HBV infection are reportedly HCV antibody-positive [1,3-5]. Moreover, according to the U.S. National Health and Nutrition Examination Survey (NHANES), about one-quarter of U.S. patients with chronic hepatitis C have positive HBV serological markers; this frequency is nearly six times higher than that in populations without HCV infection [2].

Patients with dual HBV/HCV coinfection can be classified into several categories: those with 1) acute hepatitis with HBV/ HCV coinfection, 2) HCV superinfection in chronic HBV infection, 3) HBV superinfection in chronic HCV infection, and 4) chronic HBV/HCV coinfection [2]. In the presence of HBV/HCV coinfection, acute hepatitis progressesrapidly towards the development of severe disease [2,6]. Moreover, according to the available literature, both patients with acute HCV superinfection in chronic HBV infection and those with acute HBV superinfection in chronic HCV infection tend to develop fulminant hepatitis than patients with either acute HCV infection alone or acute HBV infection alone[2,7].Maev et al. [8] reported that serum levels of several cytokines such as tumor necrosis factor-α, interleukin (IL)-6, and IL-8 are higher in patients with HBV/HCV coinfection than in those with monoinfection. This may explain one of the mechanisms of development of severe hepatitis or liver failure in coinfected patients[9].

Infection with HBV and HCV are the leading causes of chronic liver disease and hepatocellular carcinoma (HCC). Chronic liver disease in the presence of HBV/HCV coinfection rapidly develops into cirrhosis and HCC [1,2,10-14], and it is reportedly correlated with an increased risk of both liver-related death and overall death [3], although the precise mechanisms of this association are unclear [2].

Interferon (IFN) is an antiviral agent approved for the treatment of chronic liver disease due to HBV or HCV infection [2,15,16]. In general, patient responses to IFN monotherapy for chronic liver diseases with HBV/HCV coinfection have not been favorable. However, many reports have indicated that combination therapy using IFN plus ribavirin (RBV) is more effective for coinfection, although additional data are needed. Moreover, HBV/HCV-coinfected patients' risk of developing HCC, as well as their risk of liver-related mortality, has recently been reported to decrease significantly after treatment with a combination therapy of pegylated IFN (PEG-IFN) and RBV [12,17].

The present report reviews the literature regarding the interactions between HBV and HCV and the efficacy of treatments using either standard IFN/RBV or PEG-IFN/RBV combination therapy for patients with HBV/HCV coinfection.

Impact of HBV and HCV Infections on Other Viruses

Interference effects can occur during simultaneous viral infections, and the virological interference effects between HBV and HCV have not been well understood[18]. Early in vitro studies indicated a suppression of HBV-DNA transcription by the HCV core protein in

Huh7 cell lines [3,9,19]. However, other authors using the same in vitro examination techniques later reported that HBV and HCV could replicate in the same hepatocyte without any evidence of interference effects [2,20,21]. Moreover, early clinical studies suggested that in HBV/HCV coinfection, HBV proliferation was inhibited by HCV [1,22-25], and conversely, HCV proliferation was inhibited by HBV [1,26]. However, in most coinfection cases, HCV is predominant and HBV is inactive [1,17,22,23], although there are regional differences worldwide [12]. Furthermore, in patients with HBV/HCV coinfection, a shift in the predominant virus may occur during the infection period [27]. Therefore, when selecting a therapeutic agent, it is important to take into account the predominant virus [1,23,28]. The combination of PEG-IFN and RBV therapy is believed to be an effective treatment for coinfection cases in which the predominant pathogen is HCV [1,28,29].

HBV Markers in Coinfected and MonoinfectedPatients

In patients with type B chronic liver disease, the frequency of HBsAg clearance due to the natural course of the disease or in response to treatment is believed to be relatively low, with an annual rate of 0-3%[18,28]. However, it is interesting to note that the frequency of HBsAg clearance due to the natural course of the disease is significantly higher in patients with HBV/HCV coinfection than in those infected with HBV alone[23,24]. The underlying mechanism of this finding is thought to be a result of the effects of HCV interference on HBV.

Therapies for HBV/HCV Coinfection

Because the available data have been limited, standard-of-care recommendations have not been well formulated for patients with HBV/HCV coinfection, although national and international treatment guidelines for patients with HBV or HCV monoinfection are well established [2,3]. However, to select the most appropriate therapy, it is clearly important to determine which the predominant virus is using detailed serological and virological testing [3]. Further, therapeutic trials evaluating combinations of IFN, RBV, and nucleoside/nucleotide analogs may be necessary prior to establishing firm standard-of-care treatment guidelines for patients with HBV/HCV coinfection [3].

Changes in HCV Markers due to IFN-Based Therapies

Because of the mechanism of action of HBV and its interference with HCV, patients with HBV/HCV coinfection reportedly have lower HCV-RNA levels before treatment than those infected with HCV alone [26]. Nonetheless, in patients with HBV/HCV coinfection who received IFN monotherapy, the sustained viral response (SVR) rate of HCV was generally low [15,16,30]. In contrast, differences in the HBV seroclearance rate between patients with HBV/HCV coinfection and patients with HBV monoinfection have not been evident.

In patients with HBV/HCV coinfection who were treated with IFN/RBV combination therapy, the SVR rate of HCV was reportedly the same as that of patients with HCV monoinfection [1,21,22,27,31-33], regardless of the HCV genotypic differences (genotype 1 or 2/3) [34]. Moreover, Yu et al. [34] reported that in patients with HBV/HCV coinfection who achieved an SVR of HCV after treatment with PEG-IFN/RBV combination therapy, the rate of HCV-RNA recurrence after treatment was 2.3% (0.4% every year). However, there is no evidence to indicate that in patients who achieved SVR of HCV after PEG-IFN/RBV combination therapy, the rate of HCV-RNA recurrence is significantly higher in patients with coinfection than in those with monoinfection.

Changes in HBV Markers due to IFN-Based Therapies

In case of patients with HBV/HCV coinfection who received IFN monotherapy, Liaw et al. [35] reported that the rate of seroclearance of HBV-DNA in coinfected patients tended to be low compared with that in patients with HBV infection alone. On the other hand, Guptan et al. [36] reported that 2/7 patients with HBV/HCV coinfection became negative for serum HBsAg, and 6/7 patients became negative for HBV-DNA, at the conclusion of IFN monotherapy (usually a 6-month course).

Among HBV/HCV coinfected patients treated with IFN/RBV combination therapy, some of these patients reportedly achieved HBsAg clearance, whereas others experienced an increase in serum HBV-DNA levels. Flares and HBV reactivation were observed in approximately one-third of patients [1,12,22,28,37]. However, it has also been reported that patients with HBV reactivation usually do not develop clinically apparent hepatitis [34], although Yalcin et al. [38] reported a case of severe hepatitis induced by a flare of HBV in an HBV/HCV coinfected patient receiving IFN/RBV. While there are relatively few reports regarding changes in HBsAg titers resulting from IFN/RBV combination therapy in patients with HBV/HCV coinfection, comparative studies conducted with lamivudine demonstrate that a higher frequency of HBsAg clearance was achieved with PEG-IFN therapy [39].

With regard to the use of standard IFN-alpha/RBV in HBV/HCV-coinfected patients, Chuang et al. [33] reported that 5/16 (31.3%) of patients who were HBV-DNA positive became HBV-DNA negative after therapy, and 5/42 (11.9%) of patients became HBsAg-negative during longterm follow-up (48 weeks). Moreover, they reported that HCV responders had significantly higher rates of HBV-DNA resurgence than HCV non-responders during and after IFN-alpha/RBV therapy [33]. Further, Hung et al.[16] reported that 5/18 (27.8%) of HBV/HCV-coinfected patients became HBV-DNA negative at the end of IFN-alpha/RBV treatment. Furthermore, Liu et al. [15] reported that 6/17 (35.3%) coinfected patients became HBV-DNA negative 24 weeks after the conclusion of a 6-month course of IFN-alpha/RBV combination therapy, although none of these patients became negative for serum HBsAg. However, they also found that a high proportion of these patients (21%) tested negative for serum HBsAg at a follow-up visitmore than or equal to 2 years later [40].

Among the studies examining the use of PEG-IFN/RBV combination therapy for patients with HBV/HCV coinfection, Liu et al. [28] reported that the rate of HBsAg clearance in these patients at 24 weeks after completion of treatment was 11.2% (18/161), and the rate of positivity for anti-HBs antibody was 5.0% (8/161). In addition, Yu et al. [34] reported that after a follow-up period of 4.6 ± 1.0 years following treatment, the rate of HBsAg clearance was 29.0% (40/138), and the cumulative frequency of HBsAg clearance was as high as 5% every year [34].

Finally, the incidence of HBV reactivation in cases in which HCV-SVR was achieved after PEG-IFN/RBV treatment was significantly higher than that in cases in which HCV-SVR was not achieved[41]. In other words, cancellation of the interference effects of HCV may be involved in the process of HBV reactivation.

Factors Related to HBsAgClearance

HBsAg clearance is influenced by gender, age, serum HBV-DNA levels, and hepatitis B envelope antigen (HBeAg) positivity[37]. In addition, serum HBsAg titers are useful as a predictor of the efficacy of IFN therapy[34,37,42]. Because of the interference effect of HCV on HBV, most patients with coinfection have low HBsAg titers, and serum HBV-DNA levels often decrease, which may be one of the reasons why HBsAg clearance can be easily achieved after treatment [25,22,37]. Gordon et al. [9] reported that only low pretreatment serum HBsAg titers are correlated with post-treatment HBsAg clearance or sustained antigen seroconversion on multivariate analysis.

The specific HBV genotype is also believed to affect HBsAg clearance rates. The distribution of HBV genotypes varies widely in different geographic areas of the world; however, few investigators have identified the HBV genotypes in studies of patients with HBV/HCV coinfection [32]. A decrease in HBsAg titers is reportedly less likely with genotype D [32], whereas no significant difference in HBsAg clearance has been reported for genotypes C and B [34,43]. In addition, Yu et al. [34] reported that in coinfected patients, mutations in the HBV precore/basal core promoter regions were not related to HBsAg clearance.

Combination Therapy of IFN PlusLamivudine for HBV/HCV Coinfection

There have been few studies of combination therapy with IFN plus lamivudine for patients with HBV/HCV coinfection. Marrone et al. [44] reported the results of standard IFN therapy for 12 months, followed by lamivudine treatment for 6 months, in 8 patients with HBV/HCV coinfection who were positive for both HBeAg and serum HBV-DNA. They reported that 3/8 patients achieved HBeAg clearance, and 4/8 patients achieved HCV-SVR.

Conclusions

When using IFN/RBV combination therapy, many researchers have found no significant differences in the rate of achieving HCV-SVR between patients with HBV/HCV coinfection and patients with HCV monoinfection. Therefore, IFN/RBV may be considered the treatment of choice in HBV/HCV-coinfected patients with predominant HCV replication. However, the efficacy of these therapies for HBV infection in coinfected patients is complex. In patients with HBV/HCV coinfection and a predominance of HCV with inhibition of HBV proliferation, it is highly probable that serum HBsAg titers will decrease or disappear during or after IFN/RBV combination therapy. On the other hand, reactivation of HBV due to the suspected inhibition of HCV replication occurs in approximately one-third of coinfected patients during or after IFN/RBV therapy. Therefore, it is important to evaluate the predominance of the viruses before treatment and to continue monitoring HBV/HCV markers levels after treatment.

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