

# Treatment of HBV–HCV coinfection

Rocío Torres Ibarra<sup>1</sup>

Hepatitis B and C viruses are the most frequent causes of chronic disease worldwide. Chronic liver disease can progress to cirrhosis and develop into hepatocarcinoma (HCC). Coinfection with both viruses may occur because they share the same transmission routes. Coinfection with hepatitis C virus (HCV) and hepatitis B virus (HBV) is a more serious disease with a higher risk of progression to HCC than HCV infection alone.<sup>1</sup>

According to estimates of the World Health Organization (WHO), approximately 350 million people are infected with HBV and 170 million are infected with HCV. The number of HBV–HCV-coinfected patients is unknown, but it is estimated that it is in between 9%–30%, depending on the geographical region. In Western Europe, the frequency of HBV–HCV coinfection is 0.68% in a selected healthy population.

In an Italian study, it was found that the possibility of coinfection is increased with age, being most frequent in patients older than 50 years. At present, there are large trials, therefore the prevalence may be over- or underestimated.<sup>1,2</sup>

In all patients presenting with a first episode of acute hepatitis, serological studies must be carried out for various hepatotropic viruses, including HBV and HCV. HBV superinfection may exist in patients with HCV and HCV superinfection may exist in patients with HBV. The possibility of coinfection should be considered for patients with chronic HBV or HCV infection who have been exposed to risk factors such as intravenous drug use.<sup>3,4</sup>

## Interaction of hepatitis viruses

Several studies have proved that HBV and HCV interact and affect host immune response. HCV infection may suppress HBV replication, as proved by studies which found low levels of HBV DNA polymerase and reductions in the expression of hepatitis B surface antigen (HB<sub>s</sub>Ag) and hepatitis B core antigen (HB<sub>c</sub>Ag) in the livers of coinfecting patients. On the other hand, patients with chronic HBV infection superinfected by HCV may eliminate HB<sub>c</sub>Ag and HB<sub>s</sub>Ag by seroconversion of anti-HB<sub>c</sub> and anti-HB<sub>s</sub> antibodies.<sup>3,4</sup> Sheen et al. carried out a longitu-

nal study of a large population of HBV-infected patients and found that the annual incidence of seroconversion of HB<sub>s</sub>Ag was higher (2.08%) in HCV coinfecting patients than in HBV mono-infected patients (0.43%).

Several mechanisms have been proposed for the inhibition of HBV replication by HCV. Shih et al. suggested that the core protein of HCV suppresses HBV. Another study found that the core protein of HCV suppresses the activity of HBV, affecting transcription. This inhibitory effect seems to be most evident in genotype 1 HCV *in vitro* and *in vivo*.<sup>2</sup> Other authors have reported that HBV may inhibit replication of HCV. The replication of HBV DNA is negatively correlated to HCV RNA levels in coinfecting patients. An Italian study showed that HCV RNA was eliminated from 71% of coinfecting patients and from 14% of HCV mono-infected patients. HBV replication is associated with high levels of ALT, but HCV replication is not.<sup>6–8</sup>

The foregoing proves either virus may play a dominant role, as both have the ability to induce seroconversion and eliminate the other. The chronology of infection plays a role in the determination of the dominant virus.<sup>9</sup>

## Clinical characteristics

Various immunological profiles for HCV and HBV infections have been described: acute dual viral hepatitis, chronic hepatitis C with hidden coinfection with HBV, and superinfection by either virus. One of these manifestations will prevail, depending on the location.

### 1. Acute dual HBV–HCV hepatitis

In acute infections, HBV and HCV interact in a manner similar to that observed in chronic infections. In 1982, Liaw et al described coinfection caused by accidental puncture of health-care personnel for the first time. These patients presented with acute HCV infection, but diagnosis of HBV infection was delayed by 6 weeks because of the masking effect of HCV. Acute dual HBV–HCV hepatitis can also occur because of blood transfusion. Mimms et al. studied patients with acute infections with both viruses and compared them to patients who were mono-infected by HBV. They observed decreased levels of alanine aminotransferases (ALT), delayed appearance of HBsAg, and a shorter period of HBsAg antigenemia in coinfecting patients than in mono-infected patients, suggesting that HCV suppresses HBV activity.<sup>2,4</sup>

<sup>1</sup> Servicio de Infectología, IMSS Centro Médico la Raza, México, D.F. México.

Address for correspondence:  
E-mail: drarociortorres@prodigy.net.mx

## 2. Hidden hepatitis B

Hidden hepatitis B entity refers to a condition in which patients have low levels of HBV DNA and in whom serological markers of HBV are absent. Liver cirrhosis occurs in 33% of HBV–HCV coinfecting patients and in only 19% of HCV carriers with undetectable HBV DNA.<sup>3,8</sup>

## 3. HCV superinfection

HCV superinfection has been described in Asiatic areas in which there is a high prevalence of HBV. This superinfection results in suppression of HBV replication and elimination of HBsAg carriers. After this stage, HCV infection prevails and patients develop chronic hepatitis, a much more severe disease with a much greater risk of fulminant hepatitis and for which the mortality rate is as high as 10%.<sup>2,3</sup>

## 4. HBV superinfection

HBV superinfection is less common in patients with chronic hepatitis caused by HCV. Only two cases have been reported in which there was suppression of HCV and replication of HBV. HBV superinfection is associated with an increased risk of fulminant hepatitis.<sup>2,3</sup>

## 5. Fulminant hepatitis

Chu et al. carried out a study of patients in Taiwan who were hospitalized with acute hepatitis caused by HCV infection. Eleven patients had fulminant hepatitis, 23% of whom had chronic infection by subacute HBV compared with 2.9% patients without fulminating hepatitis. These findings were confirmed by studies carried out in France and Taiwan.<sup>2,8</sup>

## 6. Chronic hepatitis

Treatment should be considered for patients in whom both HBV DNA and HCV RNA are present, because of the possibility of progression to cirrhosis and decompensated liver disease. It is also possible that inactive HBsAg carriers can exhibit symptoms of active HCV monoinfection. Conversely, an active HBV infection may be present together with inactive HCV infection (HBV DNA-positive, HBeAg-positive, HCV RNA-negative, anti-HCV-positive). Active HBV infection and inactive HCV infection is less common than active HCV infection and inactive HBV infection, which indicates that HCV is suppressed by HBV. Treatment regimens differ according to individual profiles.<sup>2</sup>

## 7. Cirrhosis

HBV–HCV coinfecting patients have a higher frequency of cirrhosis than subjects with chronic HBV monoinfection (44% vs 21%, respectively) and a higher

incidence of decompensated liver disease (24% vs 6%, respectively) than subjects with chronic HBV monoinfection.<sup>9</sup>

## 8. Hepatocellular carcinoma

HBV/HCV coinfection increases the risk of hepatocarcinoma. The frequency of hepatocarcinoma is 63% in coinfecting patients and 15% in HCV monoinfecting patients. Benvegnu et al. reported that the coinfection was an independent predictor of HCC.<sup>(1)</sup> Of the 290 cirrhosis patients studied, 45% of coinfecting patients developed HCC after 10 years, and 16% and 28% of HBV and HCV patients, respectively, developed HCC after 10 years. Another South African study reported that the risk of HCC in coinfecting patients was 83 times higher than that in patients monoinfecting with either HBV or HCV.<sup>1,10</sup>

## Treatment

Coinfecting patients have several profiles of viral replication and immunity, and the disease has various clinical courses. Because of this, identification of prospects for treatment and selection of optimum antiviral therapy is difficult. Guidelines have been established for treatment of chronic HBV and HCV hepatitis.<sup>2,3</sup>

For viral hepatitis B infection, the Asian Pacific Association for the Study of the Liver (APASL), the European Association for the Study of the Liver (EASL) and the American Association for the Study of Liver Diseases (AASLD) recommend that treatment of patients with:

1. mild to serious chronic hepatitis,
2. levels of aminotransferases twice normal levels or biopsy evidence of significant liver damage,
3. HBV DNA levels > 105 copies/mL, and
4. HBeAg positivity or HBeAg negativity.

Interferon alfa-2b, lamivudine, adenovirus, entecavir, and peginterferon alfa-2a. Treatment indications have also been established for patients with chronic HCV infection.

## Contraindications

The presence of decompensated liver disease or liver failure in chronic HBV or HCV infections constitutes an indication for liver transplantation. Until now, there was no standard management protocol for subjects coinfecting with HBV and HCV. In general, the criteria for treatment of monoinfections may be applied for HBV–HCV coinfections with chronic hepatitis or compensated cirrhosis. The antiviral regime should be chosen based on serological indexes and levels of viremia.

### 1. Interferon

Interferon has immunomodulatory, antiviral, and antiproliferative activities. In chronic HCV infection, combined antiviral therapy with peginterferon and ribavirin results in a sustained viral response (SVR) of up to 56%. In chronic HBV infection, regular interferon is indicated for patients with elevated levels of ALT and HBV DNA, as it results in a SVR of 35% without inducing viral drug resistance. Peginterferon alfa-2a was recently accepted in the USA for treatment of chronic HBV infection.

Interferon is the most studied drug for coinfecting patients. The first report on the use of interferon for coinfecting patients was published by Burt et al. in 1993 and showed that interferon resulted in a decrease in of HB<sub>e</sub>Ag and a sustained HCV response. In 1995, Ghent et al. compared the effects of treatment with interferon alfa (3 million units three times per week for 6 months) between 16 chronic coinfecting hepatitis patients (anti-HCV positive, HCV RNA positive, AgsHB positive, and HBV DNA negative) and patients with HCV alone. Nineteen percent of patients who received interferon alfa had normal ALT levels and sustained virological responses (control group = 21%), and two patients seroconverted to AgsHB negative. This study showed that the use of interferon is indicated when there is no evidence of HBV replication. Weltman et al. treated eight coinfecting patients with 3 million units of interferon alfa three times per week for 6 months and obtained similar results. In an Indian study, seven coinfecting patients (AgsHB positive, HBV DNA positive, anti-HCV positive, HCV RNA positive) were treated with high doses of interferon alfa-2b (6 million units three times per day for 6 months). After 6 months of treatment, none of the patients was positive for HBV DNA, all were positive for AgeHB, and HCV RNA was absent in 29% (sustained virological response = 29%).

Villa et al. studied 30 patients with coinfection (AgsHB positive, anti-HCV positive, HCV RNA positive) who received 6 or 9 million units of interferon alfa three times per week for 6 months. The high dose of interferon was most effective for clearance of HCV RNA (31.2%) and HBV DNA (100%). The level of histological damage was less in patients given the high dose of interferon.

Most patients with inactive hepatitis B and HCV who are HBV DNA positive relapse after interferon treatment and do not exhibit a SVR. There are no studies on the use of peginterferon for treatment of coinfection.

### 2. Interferon plus ribavirin

Liu et al. treated 24 patients (AgsHB positive/anti-HCV positive) with interferon alfa-2a (6 million units three times per week for 12 weeks followed by 3 million units three times per week for 12 weeks) and ribavirin (1200 mg daily for 24 weeks). Seventeen patients were positive for HBV DNA and HCV RNA, with an SVR of

43) for HCV RNA clearance vs 60) in control patients with HCV monoinfected, 6 of the 17 patients with detectable baseline HBV DNA disappearing at the end of the treatment remaining negative 24 weeks after the treatment (35%) and sustained biochemical response of 43%

Hung et al. treated 36 patients with coinfection (AgsHB positive, anti-HCV positive, HCV RNA positive) with 3 or 5 million units of interferon alfa-2b three times per week and 800–1200 mg ribavirin daily for 24 weeks. The SVR was 69% and the sustained biochemical response was 56%. Two (11%) of the 18 patients with detectable HBV DNA at the beginning of treatment were free of HBV DNA after treatment and 53% patients who were HBV DNA negative at the initiation of treatment experienced reactivation of HBV DNA in week 48 of the follow-up phase.

Chiang et al. administered combined therapy with high doses of interferon-2b (6 million units three times per week for 24 weeks) and ribavirin (1000–1200 mg/day for 24 weeks) to 42 coinfecting patients and a group with HCV monoinfection. The SVR was 69% and 67.2% in HCV coinfecting and HCV monoinfected patients, respectively. HBV DNA was absent after treatment in five of 16 patients (31%) who were HBV DNA positive at the initiation of treatment. These results prove that combination treatment is effective for coinfecting patients, mainly those who have replication of active HCV. However, possible reactivation of HBV infection should be taken into account.

### 3. Interferon and lamivudine

Marine et al. treated eight patients (AgeHB positive, HBV DNA positive, HCV RNA positive) with five million units of interferon plus 100 mg of lamivudine daily for 12 months followed by 100 mg per day of lamivudine only for 6 months. AgeHB and HBV DNA were eliminated in three patients (37.5%). ALT concentrations were normalized in four patients (50%) who also had persistent HCV RNA clearance 12 months after treatment (SVR = 50%). The results of this study suggest that lamivudine may be effective for treatment of patients with chronic hepatitis C and active replication of HBV.

### 4. Adefovir and entecavir

There are no published studies on the use of these drugs for patients with coinfection, but they may be useful for treatment of coinfecting patients in whom the dominant virus is HBV.

### 5. Liver transplantation

The unit of participant organs systems (UNOS) reported that 14 patients in the USA received transplants because of coinfection with HBV and HCV in 2004 and that 434

transplants were performed on such patients since 1988. However, posttransplantation data were limited.

Serological and virological tests of HBV–HCV coinfecting patients are necessary before considering treatment. Identification of the dominant virus is useful for determining the treatment strategy, because treatment can exacerbate liver disease by inducing loss of viral suppression of the dominant virus. All coinfecting patients are prospects for therapy provided that they meet the inclusion criteria for treatment of patients with HBV or HCV mono-infection. When HCV infection is the dominant disease, the treatment of choice is interferon plus ribavirin. When HBV infection is the dominant disease, the treatment of choice is interferon with or without lamivudine. Further studies on treatment with adefovir, entecavir, and triple therapy with lamivudine, ribavirin and interferon for coinfecting patients are required before recommendations can be made. Further studies are necessary on peginterferon in coinfecting patients, even though it is already a standard treatment for HCV or HBV mono-infection.

### Recommendations of the consensus panel

In patients with HCV–HBV coinfection, which of the two viruses must be treated?

Although consensus was not reached, most panelists (55%) recommended individualizing each case according to the level or replication of the HBV, while the remaining 44% preferred to treat the HCV infection first.

### Evidence quality: 2

What treatment is recommended?

Most members of the panel of consensus recommended combined treatment with pegylated interferon and ribavirin. A minority (22%) preferred triple therapy with pegylated interferon, ribavirin, and a nucleotide analog.

### Evidence quality: 2

What follow-up visits are required for patients with HCV–HBV coinfection?

The frequency and number of follow-up consultations are similar to those required by a HCV mono-infecting pa-

tient, but departures from this schedule may be required because of individual circumstances.

### Evidence quality: 3

What criteria should be applied to determine the SVR of these patients?

The panel of consensus considers that the criteria for viral responses in HCV and HBV mono-infecting patients should apply.

### Evidence quality: 2

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