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Treatment and Prognosis of Hepatitis B Virus Concomitant with Alcoholism

Chih-Wen Lin, Chih-Che Lin and Sien-Sing Yang

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Abstract

Hepatitis B virus (HBV) infection is a global disease worldwide. The Asia-Pacific region has a high prevalence of viral hepatitis, and Taiwan is a region of high prevalence of chronic hepatitis B (CHB) with increasing alcoholic liver disease. We have investigated the prognosis and treatment of patients with concomitant hepatitis B virus (HBV) infection and alcoholism. The 10-year cumulative incidence of hepatocellular carcinoma (HCC) is much higher in patients with concomitant alcoholism and HBV infection than in those with alcoholism or HBV infection alone. Treatment with antiviral therapy and abstinence may be started in patients with decompensated cirrhosis and compensated cirrhosis with high HBV DNA. In pre-cirrhotic cases, treatment with antiviral therapy and abstinence may be started in patients with persistently elevated ALT levels and high HBV DNA, and significant fibrosis with minimal elevated or normal ALT levels and mild high HBV DNA. Treatment with antiviral therapy and abstinence reduces the incidence of HCC in patients with concomitant HBV infection and alcoholism. In conclusion, patients with concomitant HBV infection and alcoholism have high incidence of cirrhosis, HCC, and mortality. Treatment with antiviral therapy and abstinence may be started to reduce the incidence of cirrhosis, HCC, and mortality in these patients.

Keywords: chronic hepatitis B, hepatitis B virus DNA, nucleos(t)ides analogues, alcoholism, hepatocellular carcinoma, treatment, prognosis

1. Introduction

Hepatitis B virus (HBV) infection is a global disease, affecting approximately 350 million people worldwide [1]. The Asia-Pacific region has a high prevalence of viral hepatitis, and Taiwan is a region with high prevalence of chronic hepatitis B (CHB) [2]. It is particularly

endemic in Taiwan, where the infection is usually acquired perinatally or in early childhood [2]. The morbidity and mortality associated with CHB are substantial in that 15% to approximately 40% of infected patients will develop serious sequelae including persistent hepatitis, hepatic failure, liver cirrhosis and hepatocellular carcinoma (HCC) during their lifetime [2].

Alcohol-related morbidity and mortality represent a major public health issue worldwide [3, 4]. The United States National Institute on Alcohol Abuse and Alcoholism defines “heavy drinking” as consuming more than fourteen drinks per week for males and seven drinks per week for females. The risk threshold for developing alcohol-related liver disease is consuming 20–30 g of alcohol per day, and the development of cirrhosis occurs in 10–20% of those consuming more than 80 g of alcohol daily [3]. The Asia-Pacific region has a high prevalence of viral hepatitis, and Taiwan is a region of high prevalence of chronic hepatitis B (CHB) with increasing alcoholic liver disease [5–7]. The affordability of alcohol and changes in life style and drinking behavior have the causes for the increase in cases of hospitalization for alcoholic liver disease [6].

In the animal model system, mice fed with ethanol have an increased serum hepatitis B surface antigen (HBsAg) by up to seven folds accompanied by an increased in viral DNA load [8]. In addition, these ethanol-fed mice have elevated expression of HBV surface, core, and X antigens in the liver, accompanied by an increase in HBV RNA levels. Chronic ethanol consumption is found to stimulate hepatitis B virus replication and gene expression in HBV transgenic mice [8]. Our recent study also reveals that patients with concomitant alcoholism and HBV infection have high percentages of hepatitis B viral load in clinics [9]. Moreover, the lipid composition of cellular membranes in lipid rafts is altered by alcohol exposure, and alcohol exposure may thereby influence HBV infectivity [10]. Furthermore, alcohol can influence anti-HBV immunity, an effect involving the cellular membrane as well as the lipid rafts. HBV is known to interfere with the T-cell receptor (TCR) responsible for interacting and recognizing foreign antigens, thereby preventing the initiation of an immune response. This results in a defective adaptive immune response during chronic HBV infection [8, 11]. Thus, alcohol can act synergistically with HBV to limit antiviral immunity. Since the adaptive immunity plays a key role in viral clearance, the consequences of alcohol's effects on the TCR of HBV infection are of high interest in the field of hepatology [12].

2. Epidemiology

HBV infection is a serious global health problem, with 2 billion people infected worldwide and 350 million suffering from chronic HBV infection. HBV infections result in 0.5–1.2 million deaths per year caused by chronic hepatitis, cirrhosis, and HCC. HBV-related end-stage liver disease or HCC is responsible for over 0.5–1 million deaths per year and currently represents 5–10% of cases of liver transplantation. Morbidity and mortality in CHB are linked to persistence of viral replication and evolution to cirrhosis and/or HCC [1, 2].

In Taiwan, the introduction of universal vaccination of neonates in 1983–1985 has drastically decreased the prevalence of HBsAg in children below the age of 15 from 9.8 % in 1984 to 0.5 % in 2004 [13]. This is accompanied by a significant decrease in the incidence of infant fulminant hepatitis associated with chronic liver disease, mortality, and HCC [14, 15].

Alcohol is abused by more than 18 million adults in the United States. A daily consumption of alcohol exceeding 80 g for more than 10 years increases the risk for HCC by fivefold, while daily consumption of alcohol below 80 g is not significantly associated with an increased risk for HCC [3, 4]. The risk for HCC in decompensated alcoholic cirrhosis is close to 1% per year [3, 4]. Alcohol consumption is one of the top five causes of disease and disability in almost all European countries [16]. In the United States, about 50% of liver-related death is attributed by alcohol consumption, accounting for \$3 billion annually loss, and is the third leading cause of preventable deaths in the U.S. [17]. It is estimated that alcohol is responsible for 5.9% of global mortality worldwide [18] and 2.5 million deaths per annual [19, 20].

3. Prognosis

Based on a large nationwide Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study performed in Taiwan for CHB without alcoholism, detectable serum HBV DNA at study entry is demonstrated to be a significant risk predictor of HCC in HBV patients [21–23]. Those with detectable HBsAg are at 5- to 98-fold higher risk of developing HCC [24]. The seropositivity for HBeAg is also found associated with an increase in risk for HCC [25]. Compared to those who are seronegative for HBsAg and HBeAg, the hazard ratio (HR) of developing HCC is about 10 and 60, respectively, for individuals with seropositivity for HBsAg and both HBsAg and HBeAg [25, 26]. The serum level of HBV DNA is therefore a strong risk predictor of HCC [21], and it is also an important and independent risk factor for disease progression prognosis (including cirrhosis, risk of death, metastasis, and recurrence following surgery) in chronic hepatitis B [22]. Alcohol has a synergistic effect in increasing the risk of HCC incidence in HBsAg-positive men [27].

In one of our study, 966 cirrhotic patients in Taiwan, consisting of 632 patients with HBV infection, 132 patients with HBV infection and alcoholism, and 202 patients with alcoholism, are evaluated for HCC development [6]. We show that 15.8, 28.8 and 10.4% of the patients with HBV infection alone, concomitant HBV infection and alcoholism, and alcoholism alone, respectively, are found to have newly developed HCC after a period of 10 years of follow-up. The 1-, 3-, 5-, and 10-year cumulative incidence of HCC is 1.2, 9.4, 18.4, and 39.8%, respectively, for patients with HBV infection alone; 3.1, 28.7, 36.8, and 52.8%, respectively, for patients with concomitant HBV infection and alcoholism; and 1.1, 6.1, 10.7, and 25.6%, respectively, for patients with alcoholism alone (**Figure 1**). The 10-year cumulative incidence of HCC is much higher in patients with concomitant alcoholism and HBV infection than in those with alcoholism alone or HBV infection alone (52.8% vs. 25.6% vs. 39.8%, $p < 0.001$). The mean

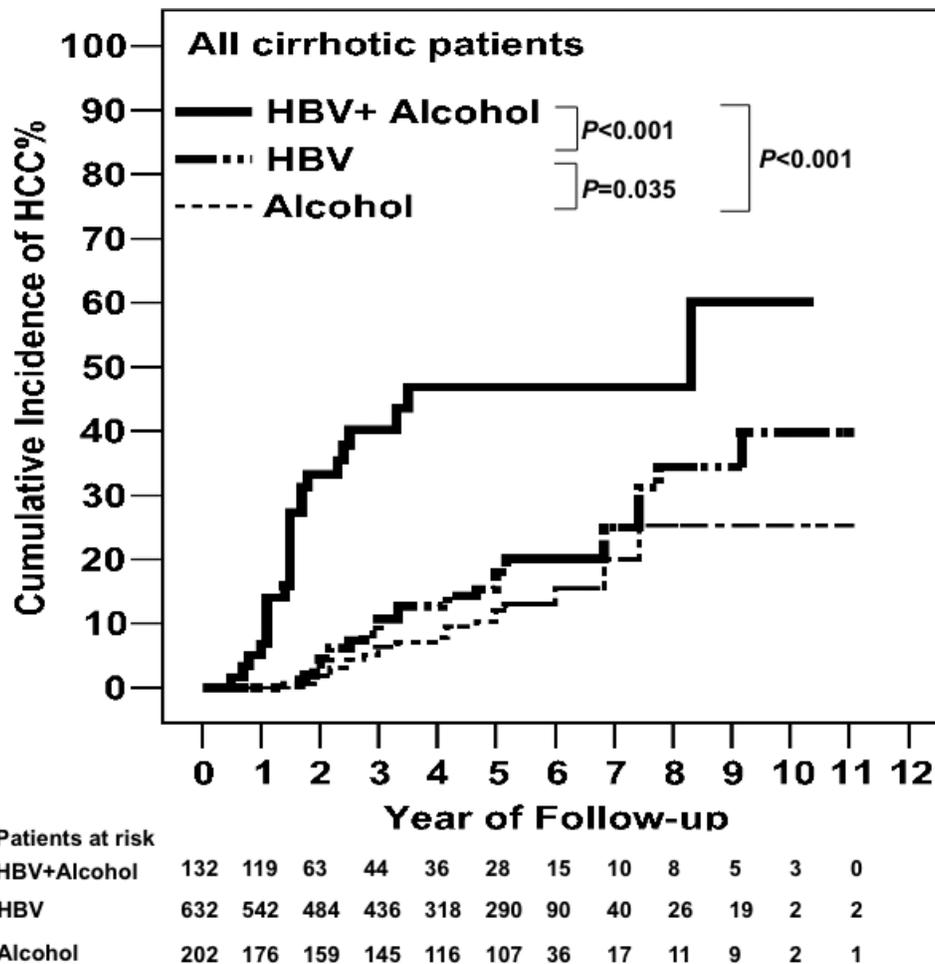


Figure 1. Cirrhotic patients with concomitant HBV infection and alcoholism have higher cumulative incidence of HCC than those with alcoholism alone or HVB infection alone.

follow-up period is 2.9, 5.2, and 3.9 years for patients with concomitant HBV infection and alcoholism, alcoholism alone, and HBV infection alone, respectively. The annual incidence of HCC is 9.9, 2.1, and 4.1%, respectively, for patients with concomitant HBV infection and alcoholism, alcoholism alone, and HBV infection alone. Our findings reveal that heavy alcohol consumption significantly increases the risk of developing HCC in HBV-related cirrhotic patients [6].

The baseline serum HBV DNA level, antiviral nucleos(t)ide analogues [NA(s)] therapy, serum α -fetoprotein, daily amount of alcohol intake, and years of alcohol intake are also found to be significantly associated with the incidence of HCC by univariate analyses. In multivariate logistic regression analyses, antiviral NUCs therapy (OR = 0.01) and baseline high serum HBV DNA levels (OR = 16.8) are significantly linked to a reduction in the incidence of HCC. In addition, the cumulative incidence of HCC during the follow-up period is significantly higher in patients with higher baseline serum HBV DNA levels than those with lower baseline serum HBV DNA levels. Alcoholic cirrhotic patients with higher serum HBV DNA levels have higher incidence of HCC than those with lower serum HBV DNA levels, and increasing HBV DNA levels precipitates the progression of liver cirrhosis to HCC [6].

In another case-control and hospital-based study conducted in Italy, the relative risks of HCC for HBsAg and heavy alcohol intake are 11.4 and 4.6, respectively [28]. Positive synergisms between HBsAg positivity and heavy alcohol intake are reported, suggesting a stronger additive effect of viral infections and alcohol drinking on the risk of HCC. On the basis of population attributable risks (AR), heavy alcohol intake seems to be the single most relevant cause of HCC in this area (AR: 45%) followed by HBV (AR: 22%) infection [28]. Similarly, another study by Sagnelli and colleagues has demonstrated that alcohol abuse can increase the risk of hepatitis B infection progressing to liver cirrhosis by threefold [29].

Furthermore, in another hospital-based, case-control study carried out in USA, the ORs for HCC based on multivariate analysis are 12.6, 4.5, and 4.3, respectively, for patients with HBsAg, heavy alcohol consumption (daily consumption of more than 80 mL of alcohol), and diabetes mellitus. Based on the additive model, synergistic interactions are observed between heavy alcohol consumption and diabetes mellitus (OR, 9.9) and chronic hepatitis virus infection (OR, 53.9). The significant synergy observed between heavy alcohol consumption, hepatitis virus infection, and diabetes mellitus may suggest the presence of a common pathway for hepatocarcinogenesis [30].

In another Taiwanese men prospective and community-based study carried out in the REVEAL-HBV study cohort over a period of 14 years, 20% of the patients are reported to be alcohol users [27]. Based on analyses adjusted for multivariable, alcohol abuse and extreme obesity (BMI ≥ 30 kg/m²) have synergistic effects on the risk of incident HCC (HR, 3.40). Obesity and alcohol are also reported to have synergistic effects in increasing risk of incident HCC in HBsAg-positive men [27]. It is therefore concluded that lifestyle interventions might significantly reduce the incidence of HCC [27].

4. Treatment in patients with concomitant HBV infection and alcoholism

Antiviral therapies including lamivudine, adefovir dipivoxil, entecavir, telbivudine, tenofovir, and Peg-interferon have been widely prescribed for the treatment of HBV-related liver diseases worldwide [14, 31, 32]. Several large population-based and international studies have revealed that antiviral therapy could reduce the incidence of hepatic failure, cirrhosis, HCC, and mortality in CHB patients without alcoholism [33–40].

In patients with concomitant HBV infection and alcoholism, the prescription of both antiviral therapy and abstinence is important for the treatment of disease progression. Oral NA(s) can reduce the disease progression for HBV infection-induced liver diseases. Abstinence is one of the most important therapies for patients with alcohol-induced liver diseases [41]. In addition, abstinence has been shown to improve the histological features of hepatic injury and reduce the outcome of disease progression to cirrhosis, HCC, and mortality in patients with alcoholic liver diseases [5, 6, 41–45].

The indications of treatment for patients with concomitant HBV infection and alcoholism are based on three criteria: severity of liver disease, serum HBV DNA levels, and serum ALT

Alcoholic patients with HBsAg positive	HBV DNA (IU/mL)	ALT	Treatment
Decompensated cirrhosis	Detectable	Any	Treat with NA(s) and abstinence
Compensated cirrhosis	>2000	Any	Treat NA(s) and abstinence
Severe reactivation of chronic HBV	Detectable	Elevated	Treat with NA(s) or Peg-interferon and abstinence immediately
Non-cirrhotic HBeAg-positive chronic hepatitis B	>20,000	>2× ULN	Observation for 3 months. Treat with NA(s) or Peg-interferon and abstinence
		1–2× ULN	Monitor every 3 months Treat with NA(s) or Peg-interferon and abstinence if noninvasive tests suggest significant fibrosis
		Persistently normal	Monitor every 3 months Treat with NA(s) or Peg-interferon and abstinence if noninvasive tests suggest significant fibrosis
	2000–20,000	Any ALT	Monitor every 3 months. Assess fibrosis noninvasively.
			Monitor every 3 months Treat with NA(s) and abstinence if noninvasive tests suggest evidence of significant fibrosis.
	<2000	<ULN	Monitor every 3 months Treat with NA(s) or Peg-interferon and abstinence if noninvasive tests suggest significant fibrosis
>ULN			Monitor every 3 months Treat with NA(s) or Peg-interferon and abstinence if noninvasive tests suggest significant fibrosis
Non-cirrhotic HBeAg-negative chronic hepatitis B	Undetectable	Any ALT	Treat with abstinence
	>2000	>2× ULN	Observation for 3 months. Treat with NA(s) or Peg-interferon and abstinence
		1–2× ULN	Monitor every 3 months Treat with NA(s) or Peg-interferon and abstinence if noninvasive tests suggest significant fibrosis

Alcoholic patients with HBsAg positive	HBV DNA (IU/mL)	ALT	Treatment
		Persistently normal	Monitor every 3 months Treat with NA(s) or Peg-interferon and abstinence if noninvasive tests suggest significant fibrosis
	<2000	>ULN	Monitor every 3 months Treat with NA(s) or Peg-interferon and abstinence if noninvasive tests suggest significant fibrosis
	Undetectable	Any	Treat with abstinence

Table 1. Treatment indications for patients with concomitant HBV infection and alcoholism.

levels [14]. The treatment in patients with concomitant HBV infection and alcoholism is summarized in **Table 1**.

4.1. In cirrhotic patients or patient with severe HBV reactivation with concomitant HBV infection and alcoholism

1. Alcoholic cirrhotic patients with decompensated cirrhosis and detectable HBV DNA require urgent antiviral treatment with NA(s) and abstinence [46, 47].
2. Alcoholic cirrhotic patients with compensated cirrhosis and HBV DNA >2000 IU/mL should be treated with NA(s) and abstinence.
3. Alcoholic patients with severe reactivation of HBV infection (the presence of high ALT, high bilirubin, INR more than 1.5 with impending or overt hepatic decompensation, and detectable HBV DNA) should be treated immediately with NA(s) and abstinence to prevent the development or deterioration of hepatic decompensation.

4.2. In pre-cirrhotic patients with concomitant HBV infection and alcoholism

1. Patient have persistently elevated ALT levels >2 times the upper limit of normal (ULN) (at least 3 months between observations) and HBV DNA >20,000 IU/mL if HBeAg positive and >2000 IU/mL if HBeAg negative. Treatment with antiviral therapy [NA(s) or Peg-interferon] and abstinence may be started. A noninvasive method for the estimation of the extent fibrosis is useful in such patients. Antiviral therapy and abstinence prevent further progression of fibrosis and other complications of liver disease.
2. Patients have minimally elevated or normal ALT levels (at least 3 months between observations) and HBV DNA >20,000 IU/mL if HBeAg positive and >2000 IU/mL if HBeAg negative, and a noninvasive method shows the presence of a significant fibrosis.

Treatment with antiviral therapy [NA(s) or Peg-interferon] and abstinence may be started. Antiviral therapy and abstinence prevent further progression of fibrosis and other complications of liver disease.

3. Patients have persistently elevated, minimally elevated, or normal ALT levels or HBV DNA <20,000 IU/mL if HBeAg positive and <2000 IU/mL if HBeAg negative, and a noninvasive method shows the presence of a significant fibrosis. Treatment with antiviral therapy [NA(s) or Peg-interferon] and abstinence may be started. NA(s) and abstinence prevent further progression of fibrosis and other complications of liver disease.
4. Patients have normal or elevated ALT levels and undetectable HBV DNA. Treatment with abstinence may be started. Abstinence prevents further progression of fibrosis and other complications of liver disease.

Our previous study shows that oral antiviral therapy significantly reduces the incidence of HCC in alcoholic cirrhotic patients with concomitant HBV infection (**Figure 2**) [6]. Therefore, aggressive NA(s) therapy should be considered in patients with alcoholic cirrhosis and detectable serum HBV DNA, in order to reduce the incidence of HCC [6].

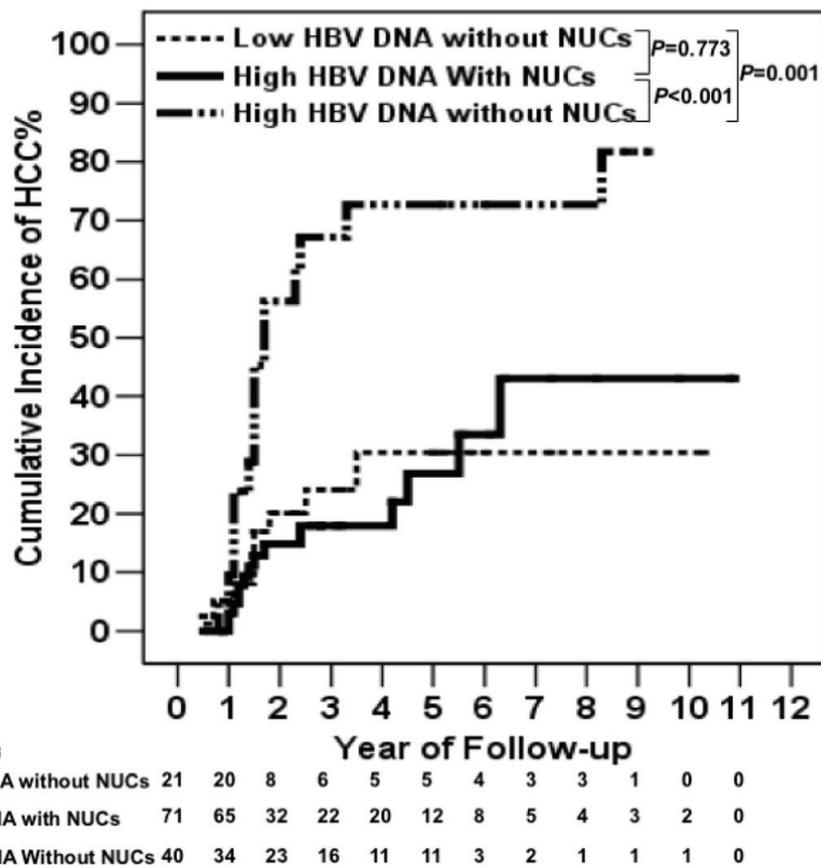


Figure 2. The cumulative incidence of HCC in cirrhotic patients with concomitant alcoholism and HBV infection is significantly reduced in patients receiving oral antiviral therapy.

5. Conclusion

Patients with concomitant HBV infection and alcoholism have high incidence of cirrhosis, HCC, and mortality. Treatment with antiviral therapy and abstinence may be started with the aim to reduce the incidence of cirrhosis, HCC, and mortality in patients with concomitant HBV infection and alcoholism.

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