

Antiviral Therapy of Liver Cirrhosis Related to Hepatitis B Virus Infection

Lun-Gen Lu*

Department of Gastroenterology, Shanghai First People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China

Abstract

Hepatitis B virus (HBV) infection is a leading cause of liver disease worldwide, with 75% of those affected distributed in the Asia-Pacific region. Approximately one million HBV-infected patients die of liver cirrhosis and hepatocellular carcinoma (HCC) each year. If left untreated, 6–20% of chronic hepatitis B (CHB) patients will develop cirrhosis over five years. The cumulative incidence of HBV-related cirrhosis, disease progression, and prognosis are closely associated with serum HBV DNA levels. Antiviral therapy in HBV-related cirrhosis has been documented by several long-term cohort studies to decrease disease progression to hepatic decompensation and HCC. The approval and availability of oral antiviral agents with better safety profiles has greatly improved the prognosis for HBV-related cirrhosis. Here, we discuss the significance of antiviral therapy for HBV-related cirrhosis and the management of HBV-related diseases in the future.

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Introduction

Hepatitis B virus (HBV) infection, the major cause of liver cirrhosis and hepatocellular carcinoma (HCC), is a serious global health concern. The World Health Organization (WHO) reported that approximately 45% of the population lives in an area with a high prevalence of chronic hepatitis B (CHB).¹ CHB is particularly prevalent in the Asia-Pacific region. Of approximately 350–400 million chronically infected carriers, approximately 75% are found in Asia.^{2,3} HBV is the tenth leading cause of death worldwide, and each year more than one million chronic HBV carriers worldwide die of liver cirrhosis and HCC, the most severe adverse sequelae of CHB.⁴ Approximately 6–20% of CHB subjects will develop cirrhosis within five years if left untreated. The incidence of

HBV-related cirrhosis, disease progression, and outcomes are closely associated with serum HBV DNA levels. Despite the availability since 1982 of a highly effective immunization program against HBV that decreased the incidence of HBV,^{5,6} the mortality from HBV-related cirrhosis and HCC has actually increased because of the high rate of HBV infection.⁷ Given the natural course of HBV infection and disease progression, timely management of CHB is of great importance for effective HBV therapy. The goal of antiviral treatment for HBV cirrhotic patients is to prevent disease progression to decompensated cirrhosis, end-stage liver disease, and HCC and to improve survival.^{8,9} Here, we review the significance of antiviral therapy for HBV-related cirrhosis and discuss concerns regarding the future management of HBV-related liver diseases.

Progression of CHB from fibrosis to cirrhosis

HBV primarily interferes with liver function by replicating in hepatocytes, and it is not directly cytopathic. However, infection with HBV does cause irritation and swelling (inflammation) of the liver. Acute hepatitis B infection does not usually require treatment, and most adults clear the infection spontaneously.^{10,11} If the virus remains in the blood for more than six months, this is chronic HBV infection. CHB is a dynamic state of interactions among HBV, hepatocytes, and the host immune system. CHB elicits varying degrees of predominantly lymphocytic infiltrates in the portal tracts associated with portal inflammation, interface hepatitis, and spotty lobular inflammation.¹² Inflammation can lead to liver damage, including fibrosis (light to medium scarring of the liver), cirrhosis (extensive scarring of the liver), and liver cancer. Liver fibrosis refers to the hyperplasia of extracellular matrix, including collagen, in liver tissues. It is a scarring process that represents the liver's response to injury. Advanced liver fibrosis results in cirrhosis, liver failure, and HCC.

The replication of HBV in hepatocytes plays a key role in driving the progression of liver disease. Following development of fibrosis or compensated cirrhosis in patients with CHB, liver disease may continue to progress and decompensation or HCC may occur, especially in those with active viral replication. If left untreated, approximately 20% will decompensate over five years and develop complications of end-stage liver disease.⁹ Once decompensation occurs, the cost for CHB therapy increases and the prognosis is poor. Therefore, the primary aim of therapy is to eliminate or permanently suppress HBV to reduce disease activity and thereby reduce the risk or slow the progression of liver disease. The ultimate long-term goal is to achieve a sustained

Keywords: Hepatitis B virus; Chronic HBV infection; Liver cirrhosis; Antiviral therapy.

Abbreviations: AASLD, American Association for the Study of Liver Disease; ADV, adefovir dipivoxil; ALT, alanine transaminase; CHB, chronic hepatitis B; CI, confidence interval; ETV, entecavir; HBeAg, hepatitis B envelope antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IFN α , interferon alpha; LAM, lamivudine; Ldt, telbivudine; TDF, tenofovir; WHO, World Health Organization.

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*Correspondence to: Lun-Gen Lu, No 100, Haining Road, Department of Gastroenterology, Shanghai First People's Hospital, Shanghai Jiaotong University School of Medicine, Shanghai 200080, China. Tel: +86-21-63240090, Fax: +86-21-63241357, Email: lungenlu1965@163.com

response to prevent or reduce the development of hepatic decompensation, cirrhosis, or HCC and to prolong survival.¹³

Although none of the available drugs can clear the infection, they can stop the virus from replicating, thus minimizing liver damage and decreasing the progression to cirrhosis, hepatic decompensation, and HCC. According to the guideline on prevention and treatment of chronic hepatitis B in China (2010),¹⁴ the goal of antiviral therapy for CHB is to maximize the suppression or elimination of HBV, decrease liver inflammation and fibrosis, decrease the liver disease progression to cirrhosis, hepatic decompensation, HCC, and complication of end-stage liver disease, and prolong survival. The American Association for the Study of Liver Disease (AASLD) Practice Guidelines on Chronic Hepatitis B (2009) stated that to gain the goal of preventing cirrhosis, liver failure, and HCC, antiviral therapies are needed to restore liver function and improve survival in patients with CHB.¹⁵ A recent meta-analysis by Mommeja-Marin *et al.* showed that antiviral therapy in hepatitis B envelope antigen (HBeAg) positive patients was associated with continuing improvement in liver histology.¹⁶ The 2012 update of the Asian-Pacific consensus statement on the management of CHB also stated that active HBV replication is the key driver of liver injury and disease progression, and thus, sustained viral suppression is of paramount importance.¹⁷ Oral antiviral therapy for CHB should be instituted regardless of HBV DNA level as early as possible to prevent the occurrence of hepatic decompensation and HCC. Therefore, the key to treating HBV-related cirrhosis is to decrease infectivity and pathogenicity of the virus by using antiviral agents.

Serum HBV DNA level and risk of cirrhosis and HCC

Cirrhosis develops during CHB disease progression as a result of hepatic inflammation and subsequent fibrosis. Risk factors associated with cirrhosis progression include viral replication, age, alcohol intake, co-infection with other viruses, and possibly HBV genotype.¹⁸ Several cohort studies have revealed the link between HBV replication and the development of cirrhosis and HCC. Multivariate analysis of a prospective study with 93 CHB patients who developed cirrhosis during regular follow-up (mean 102 months) showed that persistent HBeAg seropositivity was significantly ($p=0.035$) associated with the development of decompensation. The risk of hepatic decompensation was six-fold higher in persistently HBeAg positive patients than in patients who were seronegative for HBeAg at entry.¹⁹ Another population-based prospective cohort study of 3,582 untreated hepatitis B-infected patients in Taiwan found that having a baseline HBV DNA level $>10^4$ copies/ml was the strongest independent predictor of cirrhosis.¹³ During a mean follow-up time of 11 years, it was found that when the baseline HBV DNA level increased from <300 copies/ml to 1×10^6 copies/ml, the cumulative incidence of cirrhosis significantly increased. For those with HBV DNA levels <300 copies/ml, $300-9.9 \times 10^3$ copies/ml, $1 \times 10^4-9.9 \times 10^4$ copies/ml, $1 \times 10^5-9.9 \times 10^5$ copies/ml, and $\geq 1 \times 10^6$ copies/ml, the incidence of cirrhosis was 4.5%, 5.9%, 9.8%, 23.5%, and 36.2%, respectively ($p < 0.001$), and the relative risk of cirrhosis was 1.0, 1.4, 2.5, 5.9, and 9.8, respectively ($p < 0.001$). After adjusting for age, sex, smoking, alcohol, HBeAg status, and serum alanine transaminase (ALT) level, the multivariate-adjusted relative risk (95% confidence interval, CI) of cirrhosis in all patients was 1.0, 1.4, 2.5,

5.6, and 6.5, respectively ($p < 0.001$). In the 2,923 HBeAg-negative patients with a normal ALT level, the adjusted relative risk (95% CI) of cirrhosis was 1.0, 1.4, 2.5, 5.6, and 6.6, respectively ($p < 0.001$). These data suggested that active HBV replication following the onset of cirrhosis is an important prognostic factor for disease progression and that the progression to HBV-related cirrhosis is strongly correlated with the level of circulating virus. The risk for cirrhosis increases significantly with increasing HBV DNA levels and is independent of HBeAg status and serum ALT level.

Intervention of HBV-related cirrhosis disease progression by antiviral therapy

The immediate goal of antiviral therapy of CHB is to improve hepatic dysfunction and rescue patients from mortality.^{9,14} Antiviral agents in use clinically are interferon alpha ($IFN\alpha$) and nucleos(t)ide analogues, such as lamivudine (LAM), adefovir dipivoxil (ADV), telbivudine (LdT), entecavir (ETV) and tenofovir (TDF). Both $IFN\alpha$ and nucleos(t)ide analogues can be effective, but the duration of treatment, side effects, treatment costs, and drug resistance must be taken into consideration when determining an optimal choice based on individual patient characteristics.²⁰

An effective antiviral agent should be able to achieve potent and durable viral suppression to low or undetectable levels and possess a high genetic barrier to prevent the occurrence of resistance.²¹

IFN

Long-term follow-up studies of IFN therapy show inconsistent results.²²⁻²⁹ An early pilot study by Ikeda *et al.* demonstrated that $IFN\alpha$ decreased hepatocellular carcinogenesis in patients with cirrhosis caused by HBV infection.²³ Of the 313 patients evaluated, the cumulative occurrence of HCC was significantly lowered by the intermittent administration of $IFN\alpha$ ($n=94$) compared with those receiving no therapy ($n=219$) at three (4.5% vs. 13.3%), five (7.0% vs. 19.6%), and 10 years (17.0% vs. 30.8%), respectively. The rate of HCC development in the treated group was significantly lower than that of the untreated group ($P=0.0124$). In another study of 233 HBeAg-positive IFN-treated patients (8.1% with cirrhosis) and 233 matched controls (10.7% with cirrhosis),²⁴ the incidence of HCC appeared to be reduced by therapy (2.7% vs. 12% in controls, $p < 0.01$) but was limited to patients with pre-existing cirrhosis. However, other studies have shown no benefit of $IFN\alpha$ in the prevention of HCC in HBV infected patients because HBeAg seroconversion was used as the endpoint of treatment and detectable serum HBV DNA, a relevant risk factor for HCC, remained in most of the patients.¹³ It was also reported that pegylated (PEG)- $IFN\alpha$ did not influence the development of HCC in patients with mild or moderate fibrosis.^{25-27,30} Thus, the efficacy of $IFN\alpha$ in preventing HBV-related HCC is controversial, and there are several limitations to most studies with positive results. A recent meta-analysis¹³ evaluated the efficacy and safety of adjuvant IFN therapy in patients with HCC who have undergone hepatic resection, transplantation, or locoregional ablation therapy. It showed that adjuvant IFN therapy can improve both recurrence-free survival and overall survival. However, the benefits of using this agent should be weighed against its side effects.

IFN α is not recommended for patients with decompensated cirrhosis. No significant benefit was found in two studies evaluating the use of IFN treatment in HBV patients with Child-Pugh B or C cirrhosis.^{31,32} Virologic and biochemical responses were observed in only 33% and 0% of Child-Pugh B and C patients, respectively.³² In addition, even at low doses of IFN α , severe side effects due to bacterial infections and worsening liver failure occurred.³² At present, IFN therapy is now contraindicated for the treatment of decompensated cirrhotic patients, even with the availability of safer alternative agents and modalities.

Nucleos(t)ide analogues

Currently, the use of nucleos(t)ide analogues has been widely reported for antiviral therapy in active and decompensated HBV-related cirrhosis. Relative to placebo therapy, treatment with nucleos(t)ide analogues offered improved liver histology and survival benefits.

A recent study investigated long-term outcomes and prognostic factors in patients with HBV-related cirrhosis in the era of oral nucleos(t)ide analog antiviral agents.³³ It was found that in 78% of patients who received antiviral treatment, sustained viral suppression (serum HBV DNA < 10⁵ copies/mL) was achieved during a mean follow-up period of 46 months. The five year cumulative incidences of death, hepatic decompensation, and HCC were 19.4% vs 43.9% (log-rank $P < 0.001$), 15.4% vs 45.4% ($p = 0.001$), and 13.8% vs 23.4% ($p = 0.074$), respectively. Therefore, oral antiviral agents have improved the prognosis of patients with HBV-related cirrhosis.

In a study with 651 CHB patients who had confirmed cirrhosis or advanced fibrosis, LAM therapy was shown to delay clinical progression by significantly reducing the incidence of hepatic decompensation and the risk of HCC.³⁴ The patients were randomly assigned in a 2:1 ratio to receive LAM (100 mg per day, $n=436$) or placebo ($n=215$) for a maximum of five years. An increase of two points or more in the Child-Pugh score was pre-set as the primary endpoint for disease progression. Due to a significant difference between treatment groups in the number of end points reached, the study was terminated after a median treatment duration of 32.4 months (range, 0 to 42). At the time of data analysis, the Child-Pugh score increased in 3.4% of patients receiving LAM and 8.8% of those receiving placebo (hazard ratio, 0.45; $P=0.02$). LAM treatment significantly reduced the rate of disease progression relative to placebo controls (7.4% vs. 18.0%, $p=0.001$) and HCC development (3.9% vs. 7.4% placebo controls, hazard ratio, 0.49; $p=0.047$). Overall, the magnitude of protection conferred by LAM is substantial, with an approximately 50% reduction in disease progression. This study suggested that long-term LAM treatment can prevent complications of CHB and reduce the incidence of hepatic decompensation and HCC.

However, LAM-resistant HBV mutations with amino acid substitutions in the tyrosine-methionine-aspartate-aspartate (YMDD) motif of the RNA-dependent DNA polymerase (rtM204 I/V) developed in 49% of the patients treated with LAM, and the Child-Pugh score was more likely to increase in patients with these mutations than in patients without the mutations (7% vs. <1%). The emergence of rtM204 I/V is followed by viral breakthrough and ALT elevation (> 5 times the upper limit of normal) in over 90% of the patients.³⁵ A study by Liaw *et al.*³⁶ compared the efficacy and safety profile

of ADV monotherapy in 18 cirrhotic patients and ADV add-on LAM therapy in 10 comparable cirrhotic patients with LAM-resistant rtM204 I/V. After switching to ADV monotherapy or ADV add-on, Child-Pugh's score, serum ALT, bilirubin, albumin, and HBV DNA response (defined as HBV DNA decreased to below 10⁵ copies/mL or $\geq 2 \log_{10}$ reduction from baseline) improved significantly ($p < 0.01$). A transient ALT flare without concurrent changes in serum bilirubin or prothrombin time was observed in only two patients (11%).

Another three large, randomized, multicenter, phase III studies³⁷ evaluated the efficacy and safety of entecavir in CHB patients and advanced liver fibrosis/cirrhosis. Histologic improvement was observed in 57%, 59%, and 43% of nucleos(t)ide-naïve HBeAg(+) patients, nucleos(t)ide-naïve HBeAg(-) patients, and LAM-refractory HBeAg(+) patients with ETV treatment. The overall performance in histologic, virologic, biochemical, and serologic outcomes in ETV-treated groups were better than those observed in LAM-treated patients with advanced liver fibrosis/cirrhosis, which were comparable with the overall study populations in each trial.

A recent randomized, open-label comparative study³⁸ with a mean duration of 280 weeks comparing ETV and ADV therapy was performed in CHB subjects with hepatic decompensation (Child-Pugh score ≥ 7). It was found that 96% of patients achieved liver histological improvement by reducing necroinflammation (a decrease of Ishak score ≥ 1). The ETV group exhibited a greater change from baseline in HBV DNA levels for the primary and key secondary virologic endpoints and had a higher proportion of subjects achieve HBV DNA < 300 copies/mL at weeks 24 (ETV 49%; ADV 16%; $P < 0.0001$) and 48 (ETV 57%; ADV 20%; $P < 0.0001$). Eight-six percent of patients achieved ALT < 1-fold of the upper limit of normal. Approximately two-thirds of subjects in both groups showed improvement/stabilization in Child-Pugh status. Therefore, both ETV and ADV treatments provided clinical improvements with suppression of serum HBV DNA level. Given the favorable safety profile, potency, and high barrier to resistance, ETV appears to be a favorable choice for naïve patients who have decompensated liver disease.

Marcellin *et al.*³⁹ recently reported the results of a five year open-label follow-up study of a double-blind phase III trial of the nucleotide analogues tenofovir disoproxil fumarate and adefovir dipivoxil for chronic hepatitis B. Of the 348 patients who had paired biopsies both at baseline and at year five, 304 (87%) had histological improvement, defined as a ≥ 2 -point decrease in Knodell necroinflammatory score (0–18) and no worsening in Knodell fibrosis score (0–4). Moreover, 176 (51%) had regression of fibrosis, defined as a ≥ 1 -point decrease in Ishak fibrosis score (0–6) at year five. Of note, 71 of 96 (74%) patients who had cirrhosis at baseline no longer had cirrhosis at year five. In the on-treatment analyses, 98% of the patients had HBV DNA < 169 copies/ml (~35 IU/ml). These results are remarkable and demonstrate that long-term therapy with a potent antiviral agent that has a high genetic barrier to resistance can maintain viral suppression in nearly 100% of patients.

Treatment selection for HBV-related cirrhosis

In the management of HBV related cirrhosis, viral suppression with safe and effective antiviral agents is essential as patients with HBV-related cirrhosis have compromised liver function and may manifest with endocrine dyscrasia,

jaundice, portal hypertension, bleeding from varices, hepatic encephalopathy, and bacterial peritonitis. In addition, side effects from antiviral treatments should also be weighed. Once drug-resistance occurs, the treatment regimen should be adjusted or a second agent should be added as an alternative. Recent studies showed that the one to five year occurrences of drug resistance were 23%, 46%, 55%, 71%, and 65% in LAM-naïve HBeAg-positive patients,⁴⁰ 0%, 3%, 11%, 18%, and 29% in ADV-naïve HBeAg-negative patients,⁴¹ and 0.2%, 0.5%, 1.2%, 1.2%, 1.2% in ETV-naïve HBeAg-positive and ETV- naïve HBeAg-negative patients.⁴² The one to two year occurrences of drug resistance were 5% and 22% in LdT-naïve HBeAg-positive patients, whereas they were 2% and 9%, respectively, in LdT-naïve HBeAg-negative patients.⁴³

Conclusions

Taking both efficacy and drug resistance profiles into account, an ideal antiviral treatment for HBV-related cirrhosis should be safe and affordable in order for long-term use to achieve a high rate of sustained HBV suppression with a low risk of drug resistance. With the ultimate goal to confer beneficial effects on liver functions and survival, the optimal choice for HBV-related cirrhosis in each case depends on specific patient characteristics.

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Conflict of interest

None

Author contributions

Writing the paper (LGL).

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