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TOPIC HIGHLIGHT

WJG 20th Anniversary Special Issues (11): Cirrhosis

Does antiviral therapy reduce complications of cirrhosis?

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Abstract

Chronic hepatitis B infection is associated with the development of cirrhosis, hepatocellular carcinoma, and finally liver-related mortality. Each year, approximately, 2%-5% of patients with hepatitis B virus (HBV)-related compensated cirrhosis develop decompensation, with additional clinical manifestations, such as ascites, jaundice, hepatic encephalopathy, and gastrointestinal bleeding. The outcome of decompensated HBV-related cirrhosis is poor, with a 5-year survival of 14%-35% compared to 84% in patients with compensated cirrhosis. Because the risk of disease progression is closely linked to a patient's serum HBV DNA level, antiviral therapy may suppress viral replication, stabilize liver function and improve survival. This article briefly reviews the role that antiviral therapy plays in cirrhosis complications, particularly, in decompensation and acute-on-chronic liver failure.

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Key words: Antiviral therapy; Cirrhosis; Complication; Hepatitis B; Decompensation

Core tip: The goals of antiviral therapy in hepatitis B virus-related cirrhosis would be to improve the hepatic disease severity, improve the clinical symptoms and quality of life, and prolong patient's survival. Despite the limitations, antiviral therapy with nucleos(t)ide in patients with HBV-related cirrhosis can prevent the development of complications from cirrhosis, particularly, decompensation and acute-on-chronic liver failure (ACLF). Early antiviral treatment is important for patients with severe decompensated cirrhosis and ACLF. Thus, physicians could treat these patients using lamivudine with careful monitoring for the development of resistance or using the most potent antiviral agent, such as entecavir or tenofovir.

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INTRODUCTION

Chronic hepatitis B (CHB) infection is associated with the development of cirrhosis, hepatocellular carcinoma (HCC), and finally, liver-related mortality[1,2]. According to studies of the natural course of cirrhosis, every year, 2%-5% patients with hepatitis B virus (HBV)-related compensated cirrhosis develop decompensation (*i.e.*, ascites, jaundice, hepatic encephalopathy, and gastrointestinal bleeding)[3,4]. The prognosis of patients with decompensated HBV-related cirrhosis is poor, with a 5-year survival rate of 14%-35% compared to 84% in patients with compensated cirrhosis[4,5].

Abundant evidence indicates that the risk of disease progression is closely linked to a patient's serum HBV DNA level[6-9]. A population-based prospective cohort study in Taiwan showed that the progression to cirrhosis in HBV-infected patients was strongly associated with the

serum level of the circulating virus. The risk of cirrhosis significantly increased with an elevated hepatitis B viral load and was independent of the hepatitis B e antigen (HBeAg) status and the serum alanine aminotransferase (ALT) level[2].

Currently, six drugs are approved by the US Food and Drug Administration to manage CHB: interferon (IFN) or its pegylated version, lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (TBV), and tenofovir disoproxil fumarate (TDF). This article briefly reviews the effects of antiviral therapy on the complications of cirrhosis, particularly, in decompensation and acute-on-chronic liver failure (ACLF).

ANTIVIRAL THERAPY IN PATIENTS WITH COMPENSATED CIRRHOSIS

A cohort study of the natural history of compensated cirrhosis has shown that the risk of the development of a decompensation episode (*i.e.*, ascites, jaundice, hepatic encephalopathy or variceal bleeding) is higher in HBV-DNA positive patients compared to HBV-DNA negative patients (RR = 4.05, 95%CI: 1.09-15.1)[4]. A randomized study using LAM in patients with HBV-related compensated cirrhosis found that the Child-Turcotte-Pugh (CTP) scores increased in 3.9% of the patients in the LAM group compared to 7.4% in a placebo group ($P = 0.047$), and LAM significantly reduced the rate of disease progression, which was defined as an increase of at least 2 points in the CTP score, 7.8% in the LAM group *vs* 18% in the placebo group ($P = 0.001$)[10]. A study evaluated the effect of LAM on portal pressure using hepatic venous pressure gradient (HVPG), which precisely reflects portal pressure[11]. Among the 19 patients with HVPG > 10 mmHg, HVPG significantly decreased at 12 mo of LAM therapy (14.4 mmHg *vs* 12.4 mmHg, $P = 0.007$). These data suggest that long-term LAM treatment can prevent complications from chronic HBV infection.

Another study evaluated the long-term results in 69 patients treated with ETV using liver biopsy after a median of 6 years[12]. Overall, 88% had a reduction in Ishak fibrosis score by ≥ 1 points including all 10 patients with advanced fibrosis or cirrhosis at baseline (Ishak score ≥ 4). A randomized double blind comparison of TDF with ADF has reported the long-term effect of TDF in patients with CHB, including patients with advanced fibrosis. Among the 641 patients enrolled the trial, 96 (28%) had cirrhosis at baseline with Ishak fibrosis scores ≥ 5, 71 (74%) of the patients with cirrhosis initially had reduced fibrosis (≥ 1 unit score decrease) at year 5 and were no longer cirrhotic[13]. These findings suggest the role of antiviral therapy in cirrhosis regression.

ANTIVIRAL THERAPY IN PATIENTS WITH DECOMPENSATED CIRRHOSIS

Until now, liver transplantation has been the ultimate therapeutic option for decompensated cirrhosis. However, because of the shortage of donor organs, transplantation has not been an option for many patients. Thus, the management goal for decompensated cirrhosis is to reduce disease-related complications and the liver-related mortality rate.

Patients with decompensated HBV-related cirrhosis tend to have low or undetectable HBV DNA levels. However, some patients have high rates of HBV replication with high serum HBV DNA levels. The natural history of decompensated HBV-related cirrhosis is influenced by the levels of HBV replication, and sustained viral suppression may result in reduced hepatic necroinflammation and fibrosis progression, thereby preventing decompensation in patients with cirrhosis[14].

Among the antiviral therapy options, IFN has been associated with serious complications, including life-threatening hepatitis flares and infectious complications in decompensated HBV-related cirrhosis[15,16]. In contrast, oral nucleos(t)ide analogues (NAs) are well-tolerated in patients with decompensated HBV-related cirrhosis. Most clinical guidelines strongly recommend using oral NAs for patients with decompensated HBV-related cirrhosis independent of the HBV DNA levels[17,18].

LAM is a nucleoside analogue that inhibits HBV DNA synthesis. Yao *et al*[19]. showed a dramatic decline in the CTP scores (≥ 3 points) of 69% of the severely decompensated cirrhosis patients with LAM treatment. In 38% of patients, the CTP scores decreased to < 7, and their statuses on the United Network of Organ Sharing waiting list changed to inactive. A randomized controlled trial in Asia demonstrated less liver-related morbidity in the LAM-treated patients with HBV-associated advanced compensated cirrhosis compared to the untreated controls because of the reduced incidence of hepatic decompensation and lower risk of HCC. Increased CTP scores were noted in 3.4% of the patients in the LAM group compared to 8.8% of the patients in the placebo group ($P = 0.02$). Variceal bleeding occurred in 2 patients in the LAM group *vs* 3 patients in the placebo group. Spontaneous bacterial peritonitis and liver-related death did not occur in either group[10]. LAM generally improved the liver functions and prognosis of the patients with HBV-related cirrhosis. However, some of the patients died or underwent liver transplantation. Another study evaluated patients with decompensated HBV-related cirrhosis treated with LAM and found that most deaths occurred within the first 6 mo because of hepatic failure complications. Elevated pretreatment serum bilirubin, creatinine and HBV DNA levels were significantly associated with 6-mo mortality rates[20]. This finding suggests that early treatment with antiviral agents might be important.

During long-term LAM therapy, a substantial proportion of cirrhotic patients exhibited viral resistance to LAM and virologic response loss[21,22]. LAM resistance develops in up to 70% of patients after 5 years of continuous therapy, with an annual incidence of up to 20%

in antiviral-naïve patients[18]. On the contrary, the resistance rate to ETV at 4 years of treatment is ≤ 0.5% in antiviral-naïve patients[23]. Thus, LAM treatment is no longer considered to be the first-line therapy in CHB or cirrhosis patients because of its lower genetic barrier and higher resistance rate compared to ETV or TDV[24].

ADV is an acyclic nucleotide analogue of adenosine monophosphate. A total of 128 patients with LAM-resistant HBV-related decompensated cirrhosis were treated with 10 mg/d of ADV and achieved undetectable serum HBV DNA levels (< 400 copies/mL) in 81% of cases; the CTP scores improved in ≥ 90% of the patients at 48 wk of treatment[25]. In a long-term follow-up study of up to 240 wk, 73% of the patients showed improved fibrosis compared to the baseline. However, the cumulative probability of subsequent genotypic resistance to ADV was 20%, and renal toxicity was confirmed in 3% of patients[26]. Although ADV has a better genetic resistance profile than LAM, a lower antiviral potency and the potential risk of nephrotoxicity remain a concern for routine use as a first-line treatment in patients with HBV-related decompensated cirrhosis.

ETV is a cyclopentyl guanosine analogue that shows potent inhibition of the priming, DNA-dependent synthesis and reverse transcription of the HBV polymerase. ETV has a more potent activity against wild type HBV compared with LAM or ADV[27,28]. Several studies have used ETV in cirrhotic patients. A retrospective study from Korea evaluated the effect of ETV in 70 CHB patients with decompensated cirrhosis (CTP scores ≥ 7)[29]. Compared to the baseline, the 55 patients treated with ETV for 12 mo showed improved CTP (8.1 *vs* 6.6, respectively, $P < 0.05$) and Model for End-Stage Liver Disease (MELD) scores (11.1 *vs* 8.8, respectively, $P < 0.05$). The 2-year cumulative incidence of HCC was 6.9%, and the cumulative death rate was 17%. Theses findings suggest that ETV monotherapy improves hepatic function and provides overall benefits that are comparable to antiviral therapy in patients with HBV-related decompensated cirrhosis.

A randomized, open-label study compared the efficacy of ETV 1.0 mg ($n = 100$) or ADV 10 mg ($n = 94$) daily for up to 96 wk in subjects with decompensated cirrhosis (CTP scores ≥ 7)[30]. ETV showed more profound reductions in the HBV DNA levels than ADV (treatment difference, -1.74 log copies/mL, $P < 0.0001$). The ETV group showed a greater reduction of the HBV DNA levels at all time points through week 48 and a greater proportion of subjects who achieved HBV DNA < 300 copies/mL at weeks 24 (ETV 49% *vs* ADV 16%, $P < 0.0001$) and 48 (ETV 57% *vs* ADV 20%, $P < 0.0001$). In both groups, two-thirds of the subjects showed improvement or stabilization in CTP and MELD score. The cumulative HCC and death rates were 12% and 23% for ETV, respectively, and 20% and 33% for ADV, respectively. However, mean time to HCC and HCC-free survival did not differ significantly between the groups. These findings suggest that although clinical benefits were demonstrated in both groups, ETV is superior to ADV in its virologic efficacy through week 48.

A recent study investigated the efficacy of ETV on the clinical outcomes of two cohorts: the ETV cohort (subjects administered ETV 0.5 mg/d) and the historical control cohort (subjects who underwent routine clinical care). In the patients with cirrhosis (482 ETV-treated patients, 69 treatment-naïve patients), the ETV-treated patients had reduced risks for all clinical outcomes compared to the treatment-naïve patients after adjusting for the MELD score: hepatic events (HR = 0.51, 95%CI: 0.34-0.78, $P = 0.002$); HCC (HR = 0.55, 95%CI: 0.31-0.99, $P = 0.049$); liver-related mortality (HR = 0.26, 95%CI: 0.13-0.55, $P < 0.001$); and all-cause mortality (HR = 0.34, 95%CI: 0.18-0.62, $P < 0.001$). However, the risk for hepatic events in the ETV-treated cirrhotic patients who failed to achieve undetectable HBV DNA levels was comparable to that in the untreated patients.

TBV is a synthetic thymidine nucleoside analogue with potent antiviral activity against HBV. A double-blind randomized trial using TBV ($n = 114$) and LAM ($n = 114$) for 104 wk has shown that TBV was an independent predictive factor for HBV DNA < 300 copies/mL and ALT normalization ($P = 0.037$) in patients with HBV-related decompensated cirrhosis (CTP score ≥ 7)[31]. The changes in the CTP and MELD scores were comparable between both the groups. Cumulatively, 27% of the TBV patients and 36% of the LAM patients developed genotypic resistance during the 2-year period. These results suggest that because of the significant rate of virologic breakthrough, TBV has limitations as a first-line therapy in patients HBV-related decompensated cirrhosis.

TDF is an ancyclic nucleotide analogue and a potent inhibitor of HBV polymerase/reverse transcriptase. A multicenter study in Turkey determined the long-term effects of LAM, ETV and TDF. The mean CTP score change was comparable in 3 groups. A minimum 1-point decrease in the CTP score occurred in 29.6% of patients in the TDF group, 37.7% of patients in the ETV group and 21.9% of patients in the LAM group ($P = 0.35$). The MELD score (per year) decreased more in the TDF group than in the ETV group ($P = 0.04$). Regarding the complications from cirrhosis, variceal bleeding-free time and encephalopathy free-time were longer in the ETV group than in the TDF group, but theses differences were not statistically significant ($P = 0.38$ and $P = 0.87$, respectively)[32]. Until now, TDF has been the most potent suppressor of HBV replication, and no-resistance has been reported. Considering both the potency and resistance profiles, TDF and ETV are superior to LAM, ADV and TBV and can be considered to be a first-line therapy in HBV-related decompensated cirrhosis.

ANTIVIRAL THERAPY IN PATIENTS WITH ACUTE SEVERE EXACERBATION OR ACUTE ON CHRONIC LIVER FAILURE

The definition of reactivation of hepatitis B is the reap-

pearance of necroinflammatory activity of the liver in a person known to be in an inactive HBsAg carrier state or with resolved hepatitis B[33]. The definition of flare or exacerbation is the intermittent elevation of aminotransferase activity to > 10 times the upper limit of normal and more than twice the baseline value[34]. Severe acute exacerbations characterized by high ALT level, jaundice and hepatic decompensation may progress to ACLF with sepsis-like immunological changes[35]. ACLF is defined as an acute hepatic insult with manifestations of jaundice and coagulopathy (INR > 1.5) that are complicated within 4 wk by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed compensated chronic liver disease[36]. ACLF is accompanied by the development of multi-organ failure, thereby leading to a high mortality rate. The prognosis of ACLF in CHB is poor, with 3-mo mortality rates > 50% without liver transplantation. Liver transplantation remains the only definite therapeutic option for these patients. In recent years, data have emerged regarding the efficacy of NA.

IFN-based therapy may aggravate the hepatic decompensation in the severe exacerbation of CHB. Previous studies using LAM for patients with severe acute exacerbation have not shown any survival benefit from antiviral therapy[37,38]. However, there is a study that suggests the beneficial effects of antiviral treatment on short-term survival. Among the patients with severe acute exacerbation of CHB, more patients in the LAM treatment group with baseline bilirubin levels < 20 mg/dL survived compared to patients in the control group (P = 0.013). However, the mortality rates in the two groups did not differ among the patients with baseline bilirubin level ⩾ 20 mg/dL[39]. Another prospective study from Hong Kong used ETV (n = 36) and LAM (n = 117) to evaluate the overall mortality rate at week 48 in patients with severe acute CHB exacerbation. By week 48, the patients in the ETV group had a higher liver-related mortality rate (P = 0.044) and more liver-related complications than the LAM group despite their better virological responses (P = 0.007). However, the cause of the increased mortality in the ETV group is not completely understood[40]. Lactic acidosis might be one possible cause[41], but this finding must be confirmed by other centers. This study has a limitation of small number of patients in the ETV group.

A matched retrospective cohort study from China using patients with ACLF showed that the 3-mo mortality rate in the LAM group (n = 130) was lower than that of the control group (n = 130), with a MELD score of 20-30 (50.7% *vs* 75.7%, P = 0.0021)[42]. A retrospective study compared ETV 0.5 mg (n = 33), LAM 100 mg (n = 34) and no-NA (n = 37) in patients with HBV-associated ACLF. The HBV DNA levels and the ACLF recurrence rate were lower in both treatment groups. However, no significant difference in the 3-mo mortality rate was found (51.5% for ETV, 50% for LAM and 59.5% for no-NA)[43]. A recent study from China compared the short-term and long-term efficacies of ETV, LAM or no-NA in patients with HBV-related ACLF. The ETV and LAM groups showed similar cumulative mortality rates in the first 3 mo of treatment (P = 0.374). The no-NA group had a significantly higher mortality rate compared with the ETV group (P = 0.007) and the LAM group (P = 0.006). The recurrence of ACLF was found in 33.3% of patients in the no-NA group, 11.1% from the LAM group and 0% from the ETV group (P = 0.003)[44].

A prospective randomized study from India using TDF (n = 14) and placebo (n = 13) in patients with ACLF from the spontaneous reactivation of CHB showed that TDF significantly reduced the HBV DNA levels and improved the CTP and MELD scores and the 3-mo survival rate compared to a placebo [8/14 (57%) *vs* 2/13 (15%), P = 0.03]. A > 2 log reduction in the HBV DNA levels at 2 wk was found to be an independent predictor of survival[45]. However, the limitations of this study include its small sample size and the unavailability of liver transplantation.

Although most patients with acute exacerbation of CHB resolve spontaneously, a certain proportion of patients may progress to liver failure and death. Antiviral therapy has no obvious benefit for short-term survival. However, antiviral treatment may prevent future exacerbation and ongoing hepatic injury. Thus, an antiviral agent should be administered as early as possible and liver transplantation should be considered for patients with severe disease.

CONCLUSION

The goals of antiviral therapy in HBV-related cirrhosis would be to stabilize or improve the hepatic disease severity, improve the clinical symptoms and quality of life, and extend patient survival. Despite the limitations of the existing data, it is likely that antiviral therapy with nucleos(t)ide in patients with HBV-related cirrhosis can prevent the development of complications from cirrhosis, particularly decompensation and ACLF. In addition, early antiviral treatment is important for patients with severe decompensated cirrhosis and ACLF. Thus, hepatologists could treat these patients using LAM with careful monitoring for the development of resistance or using the most potent antiviral agent such as ETV or TDF.

However, there are several unmet needs with regard to antiviral agents. First, the designs of published studies have been heterogeneous and the sample sizes have been small and until now, the antiviral agent could not reverse advanced cirrhosis. Second, because the NAs are less effective against cccDNA formation in the hepatocyte, antiviral therapy should be maintained for life. Third, the long-term safety of NAs has not been confirmed in cirrhosis patients. The carcinogenicity of ETV has been reported in rodents after exposure to doses > 35-fold the dose administered in humans. Thus, the cumulative risk of human will require post-marketing surveillance. Regarding TDF, patients with pre-existing renal impairment may be at risk of nephrotoxicity from TDF and decreases in bone mineral density have been rarely reported in

HIV-positive patients treated with TDF. Fourth, patients with drug-resistance are limited in their choices of new antiviral agents.

Several innovative antiviral approaches have been evaluated *in vitro* and in animal models, such as selectively targeting antiviral agents to the liver or using antisense approaches, RNA interference, and HBV-specific immunomodulatory therapy (*i.e.*, S and pre-S antigen vaccines, DNA vaccination, T-cell vaccines and adoptive immunity transfer), alpha-glucosidase inhibitor derivatives, and monoclonal antibodies). Further studies are needed to examine patient outcomes after using newer antiviral therapy to prevent the complications of cirrhosis.

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