MINIREVIEWS

Benefits of nucleos(t)ide analog treatments for hepatitis B virus-related cirrhosis

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Abstract

Chronic hepatitis B infection induces progressive liver disease. Before nucleos(t)ide analogs (NUCs) became established as a safe and effective treatment for hepatitis B, it was difficult to suppress the activity of the hepatitis B virus (HBV). Currently, many patients with hepatitis or cirrhosis associated with HBV are treated with NUCs for an extended period of time, and the effects, benefits, and limitations of these treatments have been apparent. This article reviews HBV-related cirrhosis, its natural course and survival, histological improvement after NUC treatments, treatment effects for decompensated cirrhosis, the incidence of hepatocellular carcinoma (HCC) after NUC treatments, and the efficacy of NUC treatments before and after the treatment of patients for HBV-related HCC. Of particular interest are the histological improvements, including regression of fibrosis, that have been achieved with NUC treatments. Liver function of patients with decompensated cirrhosis has significantly improved regardless of the type of NUC applied, and treatment with NUCs has reduced the incidence of HCC in cirrhotic patients. However, cirrhosis remains the strongest risk factor for HCC occurrence following NUC treatments, and the long-term cumulative incidence of HCC after NUC treatments remains high. When recurrence does occur, it is important to reconsider the treatment modality according to the degree of improved liver function that was achieved.

Key words: Hepatitis B; Nucleos(t)ide analogue; Liver cirrhosis; Lamivudine; Entecavir

Core tip: We presented the benefits of nucleos(t)ide analogs (NUCs) treatments for HBV-related cirrhosis in this article. NUC treatments have been found to improve inflammation and fibrosis in the liver of cirrhotic patients. Moreover, even in patients with decompensated cirrhosis, liver function has improved in many cases. Furthermore, although NUC treatments can reduce the incidence of hepatocellular carcinoma (HCC), rates of HCC remain high in patients with cirrhosis. NUC treatments have been found to improve liver function and the survival of patients with HCC. Improved liver function was also achieved by providing NUC treatments for hepatitis B virus-related HCC when recurrent tumors

developed. Therefore, it is important to select the most appropriate treatment method considering the alterations in liver function that may occur following NUC treatments.

INTRODUCTION

An estimated 400 million people worldwide are chronically infected with hepatitis B virus (HBV)[1]. Chronic hepatitis B infection induces a progressive liver disease that can lead to cirrhosis and hepatocellular carcinoma (HCC)[2]. Prior to establishing the antiviral drug, lamivudine, as an effective treatment for hepatitis B[3], it was difficult to prevent disease progression. Lamivudine was the first nucleos(t)ide analog (NUC) to be extensively characterized and it inhibits DNA synthesis. Subsequently, it has been found to rapidly reduce serum levels of HBV and to reduce inflammation in the liver[3]. Moreover, several NUCs, including adefovir dipivoxil, telbivudine, entecavir, and tenofovir disoproxil fumarate, have been developed. Initially, the indication of these drugs was limited to patients with chronic hepatitis or compensated cirrhosis, although they have gradually been applied to the treatment of decompensated cirrhosis. In this review article, we describe the effects, benefits, and limitations of using NUCs to treat cirrhotic patients.

NATURAL COURSE OF HBV INFECTION AND CIRRHOSIS IN PATIENTS

Several studies have documented the natural history of chronic hepatitis B prior to the availability of NUCs (Table 1). For example, Weissberg *et al*[4] studied 379 histologically confirmed chronic hepatitis B patients and reported the following estimated 5-year survival rates: 97% for chronic persistent patients, 86% for chronic active hepatitis patients, and 55% for chronic active hepatitis patients with cirrhosis. Liaw *et al*[5] also reported the natural history of chronic HBV infection following the recent development of histologically confirmed cirrhosis in a cohort of 76 patients. The annual incidences of hepatic decompensation and HCC development were calculated to be 2.3% and 2.8%, respectively. Furthermore, Liaw *et al*[5] estimated the 5-year survival rate to be 80%. de Jongh *et al*[6] conducted a follow-up study of 98 hepatitis B surface antigen - positive cirrhosis patients with histopathologically confirmed cirrhosis. The reported survival probability was 71% after 5 years. For the 21 patients with decompensated cirrhosis, the

survival probability was only 14%. Consistent with these previous studies, Realdi *et al*[7] found that the 5-year survival rate for 366 patients with histologically confirmed cirrhosis was 84%. With the exception of the study by Liaw *et al*[5], these studies analyzed the factors affect their prognosis using multivariate analysis: Patient age, total bilirubin levels, albumin levels, platelet counts, hepatitis B e antigen (HBeAg) positivity, ascites, spider nevi, and splenomegaly were reported as significant prognostic factors. Patient age and total bilirubin were the factors that were included in each of the studies. Overall, the 5-year survival rates for HBV-related cirrhosis reported in these studies ranged from 55% to 84%, which may be due to differences in lead time bias, study design, country, ethnicity, HBV genotype, and/or HBeAg positivity.

HISTOLOGICAL IMPROVEMENT IN PATIENTS WITH CIRRHOSIS

Histologically, fibrosis has improved with long-term treatment with NUCs[8-17]. In early studies, lamivudine was administered for a short period of time (*e.g.*, 6-12 mo)[3,8,9]. In 52%-95% of patients that received lamivudine treatment for at least one year, an improvement in necroinflammatory activity was observed [which was defined as at least a 2-point decrease in the histologic activity index (HAI) score][3,9-11]. In contrast, the rate of hepatic fibrosis improvement (defined as at least a 1-point decrease in the HAI fibrosis score) associated with short-term lamivudine treatments were not as high[3,9] and ranged from < 10% to 35%. Since then, long-term use of NUCs has led to improvements in liver fibrosis, even in cases of advanced fibrosis or cirrhosis[11,13,14]. For example, Chang *et al*[13] followed 57 hepatitis B patients that were treated with entecavir for 3-7 years (median, 6 years) and underwent repeated histological examinations. Improved Ishak fibrosis scores (≥ a 1-point decrease) were reported for 88% of these patients. In addition, four patients with cirrhosis also demonstrated an improvement in their Ishak fibrosis scores (median decrease: 3 points, range: 1-4). Table 2 summarizes the primary studies that have described histological changes after an initial NUC treatment. Dienstag *et al*[11] reported that fibrosis improved (defined as a decrease in the HAI fibrosis score of at least 1-point) in 45.5% of patients treated with lamivudine (*n* = 11) after 1 year, and this rate increased to 72.7% after an additional 2 years of treatment. Marcellin *et al*[14] reported that 51% of patients with hepatitis B that were treated with tenofovir (*n* = 348) showed improvement in fibrosis (defined as a decreased in the Ishak fibrosis score of at least 1-point). In addition, fibrosis improved in 74% of patients with cirrhosis (*n* = 97) at 5 years. Taken together, these results demonstrate that long-term treatment with NUCs can potentially lead to histological improvements in patients with cirrhosis.

Table 1 Studies characterizing the natural history of hepatitis B-related cirrhosis

Ref.	Publication year	Country	Number of patients with cirrhosis	5-yr survival for patients with compensated cirrhosis (%)	Cause of death
Weissberg *et al*[4]	1984	United States	130	55	Liver failure (70.3%)
					Unrelated disease (18.9%)
					Unknown causes (10.8%)
Liaw *et al*[5]	1989	Taiwan	76	80	Hepatic failure or variceal bleeding (100%)
de Jongh *et al*[6]	1992	The Netherlands	98	71	Hepatocellular carcinoma (38.5%)
					Liver failure or fatal upper gastrointestinal bleeding (38.5%)
					Unrelated disease (23.1%)
Realdi *et al*[7]	1994	Italy	366	84	Liver failure (53.6%)
					Hepatocellular carcinoma (27.4%)
					Unrelated disease (19.0%)

Table 2 Rates of fibrosis improvement in patients with chronic hepatitis or cirrhosis treated with lamivudine, entecavir, or tenofovir

Ref.	Publication year	Nucleos(t)ide	No. of patients	Treatment duration	Cirrhosis percentage	Improvement ratio of fibrosis
Honkoop *et al*[8]	1997	LAM (25 mg, 100 mg, 300 mg)	13	6 mo	Not described	No difference in fibrosis was observed
Lai *et al*[3]	1998	LAM (25 mg, 100 mg, placebo)	358	52 wk	5%	25 mg (n = 72) 5%[1,4]
						100 mg (n = 142) 2.5%[1,4]
						Placebo (n = 143) 0%[1,4]
Suzuki *et al*[9]	1999	LAM (100 mg)	20	52 wk	0%	All patients (n = 20) 35%[1]
Dienstag *et al*[10]	2003	LAM (100 mg, placebo)	63	1 yr + additional 2 yr	17%	Bridging fibrosis (HAI fibrosis score of 3; n = 19)
						63% (1 yr + additional 2 yr)[2]
						Cirrhosis (HAI fibrosis score of 4; n = 11) 45.5% (1 yr)[2]; 72.7% (1 yr + additional 2 yr)[2]
Schiff *et al*[12]	2008	LAM (100 mg) Entecavir (0.5 mg)	245	48 wk	Not described[5]	ETV (n = 120) HBeAg+ 57%[3]
						HBeAg- 59%[3]
						LAM (n = 125)
						HBeAg+ 49%[3]
						HBeAg- 53%[3]
Chang *et al*[13]	2010	ETV (0.5 mg)	57	48 wk, long-term (range: 3-7 yr, median: 6 yr)	7%	All patients (n = 57) 32% (48 wk)[3]
						88% (long-term)[3]
						Cirrhosis (n = 4)
						100% (long-term)[3]
Marcellin *et al*[14]	2012	TDF	348	5 yr	28%	All patients (n = 348)
						51% (5 yr)[3]
						Cirrhosis (n = 97) 74% (5 yr)[3]

[1]Fibrosis improvement was defined as an HAI fibrosis score decrease of at least 1-point; [2]Bridging fibrosis improvement was defined as achieving an HAI fibrosis score of 0 or 1. Cirrhosis improvement was defined as achieving an HAI fibrosis score of 0, 1, or 3; [3]Fibrosis improvement was defined as a decrease in the Ishak fibrosis score of at least 1-point; [4]Approximate value estimated from the published graph; [5]All patients had advanced fibrosis or cirrhosis (Ishak fibrosis scores of 4-6). LAM: Lamibudine; ETV: Entecavir; TDF: Tenofovir; HBeAg: Hepatitis B e antigen; HAI: Histologic activity index.

NUC TREATMENT FOR DECOMPENSATED CIRRHOSIS

Once lamivudine treatment was established as an effective and safe drug for the treatment of chronic hepatitis B or compensated cirrhosis[3,10], it was gradually applied to the treatment of decompensated cirrhosis[18-30]. The 1-year, 3-year, and 5-year survival probabilities for patients with decompensated cirrhosis without NUC treatment were: 70%-71%[6,31], 35%-40%[6,31] and 14%-35%[6,31,32], respectively. These survival rates increased dramatically following the use of NUC treatments to: 70%-94%, 63%-87%, and 55%-86%, respectively[18,23,26,29] (Table 3). The liver function of the latter patients also significantly improved regardless of

the type of NUC administered[18-30]. In addition, NUC treatment led to a reduction in the Child-Pugh class or a decrease in the Child-Pugh score ($\geq$ 2-points or $\geq$ 3-points decrease), in a substantial number of cases[18-28,30]. However, there were a small number of patients that were treated with NUCs who progressed to death or required a liver transplant[18-30]. Studies that analyzed the determinants of early mortality in patients with decompensated cirrhosis B treated with NUCs found that poor baseline liver function was associated with poor prognosis[23,26,30]. Furthermore, most of the deaths occurred within 1 year after NUC treatment, and the most common causes of death were liver failure or complications from liver failure[23,26,30]. In work by Hyun *et al*[26], Child-Turcotte-Pugh scores at baseline and the

Table 3 Effects of treatment with nucleos(t)ide analogs in patients with decompensated cirrhosis

Ref.	Nucleos(t)ide	Patient number	Treatment duration	Improvement ratio of Child-Pugh score	Cumulative survival rate[3]
Villeneuve *et al*[18]	LAM (100 mg or 150 mg)	35 (CPB: 10, CPC: 25)	Mean: 19 mo	62.9% (22/35)[1]	1 yr: 78%[4] 2 yr: 63%[4]
Kapoor *et al*[19]	LAM (150 mg)	18 (CPB: 14, CPC: 4)	Mean: 17.9 mo (range: 9-31 mo)	CPB to CPA: 50% (4/14) CBC to CPB: 50% (2/4)	No deaths attributed to liver disease
Yao *et al*[20]	LAM (150 mg)	13 (CPB: 0, CPC: 13)	Mean: 17.5 mo (range: 3-39 mo)	69% (9/13)[2]	Not described
Hann *et al*[22]	LAM (100 mg)	75 (CPA: 4, CPB: 28, CPB: 43)	Mean: 12.7 mo (range: 0.5-33 mo)	31% (23/75)[1]	Not described
Tseng *et al*[23]	LAM (100 mg)	30 (CPB: 16, CPC: 14)	Mean: 39.7 mo (range: 3-128 mo)	CPB to CPA: 62.5% (10/16) CBC to CPB: 35.7% (5/14)	1 yr 70%[4] 2 yr 66%[4] 3 yr 55%[4] 5 yr 55%[4]
Bae *et al*[24]	LAM (100 mg)	17 (CPB: 12, CPC: 5)	Mean: 28 mo (range: 14-42 mo)	CPB to CPA: 83% (10/12) CBC to CPA (1/5) or CPA (3/5): 80% (4/5)	Not described
Shim *et al*[25]	ETV (0.5 mg)	55 (mean CP score 8.1 ± 1.7)	12 mo	49% (27/55)[1]	12 mo: 87.1% 24 mo: 83.0%
Hyun *et al*[26]	LAM (100 mg) ETV (0.5 mg)	86 (CPB: 45, CPC: 41)	Mean: 2 yr	Mean Child-Pugh score Baseline LAM: 9.5, ETV: 9.6 12 mo LAM: 6.7, ETV: 6.6	1 yr LAM: 92.4% ETV: 90.7% 3 yr LAM: 86%[4] ETV: 76%[4]
Liaw *et al*[27]	TDF (300 mg)/FTC (200 mg) + TDV (300 mg)/ETV (0.5 mg or 1 mg)	112 (median CP score: 7, range: 6-9)	48 wk	TDF: 25.9% (7/27)[1] FTC/TDF: 48.0% (12/25)[1] ETV: 41.7% (5/12)[1]	Not described
Chan *et al*[29]	LAM (100 mg), TdT (600 mg)	228 (CPS < 7: 18, CPS 7-9: 155, CPS 9 <: 55)	52-104 wk	52 wk LAM: 38.6% (44/114), TdT: 31.6% (36/114)[1] 104 wk LAM: 40.4% (46/114), TdT: 38.6% (44/114)[1]	52 wk LAM: 88%, TdT: 94% 104 wk LAM: 79%, TdT: 87%

[1]Improvement of Child-Pugh score was defined as a decrease in the CPS greater than or equal to 2-points; [2]Improvement of Child-Pugh score was defined as a decrease in the CPS greater than or equal to 3-points; [3]Cumulative survival rates calculated by Kaplan-Meier method; [4]Approximate value from the published graph. LAM: Lamibudine; ETV: Entecavir; TDF: Tenofovir; FTC: Emtricitabine; TdT: Telbivudine; CPB: Child-Pugh class B; CBC: Child-Pugh class C; CPS: Child Pugh score; CPA: Child-Pugh class A.

Model for End-stage Liver Disease score at 3 mo after beginning a NUC treatment were found to be significant predictors of early mortality.

INCIDENCE OF HCC IN PATIENTS WITH CIRRHOSIS THAT RECEIVED NUC TREATMENT

Worldwide, HBV infection has been identified as an important risk factor for the development of HCC[31]. Longitudinal studies of patients with chronic hepatitis B infection have described the cumulative incidence of HCC[5,31-35]. Incidence of HCC has been found to vary by region and is influenced by the underlying stage or condition of the liver disease present. For patients with compensated cirrhosis that were not treated with NUCs, the annual incidence of HCC has been reported to range from 2.2%-2.8%[5,31,36,37]. In a comparison of cumulative HCC incidence for patients with and without lamivudine treatment, the former had a significantly lower incidence than the latter in a randomized study[38]. Non-randomized studies have also demonstrated that NUCs

reduce the incidence of HCC[39-41]. Furthermore, in three meta-analyses[42-44] and a systematic review[45], NUC treatments were found to consistently reduce the risk of HCC compared with an absence of NUC treatment. In addition, two Asian studies reported that entecavir-treated patients had a reduced risk of HCC compared with treatment-naïve patients with cirrhosis[40,46], and Wong *et al*[46] reported that the 5-year cumulative probability of HCC development among cirrhotic patients was 13.8% in an entecavir cohort *vs* 26.4% in a control treatment-naïve cohort (*P* = 0.036). Hosaka *et al*[40] conducted a propensity score-matched control study and found that the cumulative 5-year incidence of HCC among cirrhotic patients treated with entecavir (7.0%) was lower than that of a control non-treated group (38.9%) (*P* < 0.001). Furthermore, the entecavir-treated group had a significantly lower incidence of HCC than a lamivudine-treated group of cirrhotic patients (*P* = 0.043)[40]. Liver cirrhosis has been found to be the strongest risk factor for the occurrence of HCC after NUC treatment[40,47,48], and the long-term cumulative incidence of HCC after NUC treatment remains high in cirrhotic patients[40,45,46].

EFFICACY OF NUC TREATMENTS FOR PATIENTS WITH HBV-RELATED HCC

Several studies have documented that antiviral therapy with NUCs is beneficial after the treatment of HBV-related HCC[49-52]. For example, improved liver function has been observed following curative liver resection and following radiofrequency ablation for the treatment of HCC[48-50]. Moreover, in a longitudinal randomized clinical trial conducted by Yin *et al*[49] to evaluate the effects of NUC treatments following radical hepatectomy, patients who received NUCs exhibited significantly improved liver function and decreased HCC recurrence. NUC treatment following curative therapy for HCC has also improved overall survival[49-52]. In a study by Kuzuya *et al*[50], NUC treatment improved liver function in patients with recurrent HCC, and allowed all of the treated patients to be eligible for curative treatment for recurrent HCC. In contrast, two-thirds of the untreated group were not eligible for curative therapy for recurrent HCC due to deterioration of remnant liver function[50]. Furthermore, an increasing number of treatment options have become available for recurrent tumors[53,54]. We previously reported that a patient with decompensated cirrhosis was able to undergo a right hepatectomy four years after starting a lamivudine treatment regimen[54].

CONCLUSION

Here, the benefits of NUC treatments for patients with HBV-related cirrhosis have been presented. NUC treatments have been found to improve inflammation and fibrosis in the liver of cirrhotic patients. Moreover, even in patients with decompensated cirrhosis, liver function has improved in many cases. Given that hepatitis B can occasionally lead to death, or the need for a liver transplant, in patients with highly deteriorated liver function even after NUC treatment, it is recommended that a NUC treatment be started as early as possible. Furthermore, although NUC treatments can reduce the incidence of HCC, rates of HCC remain high in patients with cirrhosis. However, NUC treatments have been found to improve liver function and the survival of patients with HCC. Improved liver function was also achieved by providing NUC treatments for HBV-related HCC when recurrent tumors developed. Therefore, it is important to select the most appropriate treatment method considering the alterations in liver function that may occur following NUC treatments.

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