The Journal of Infectious Diseases

MAJOR ARTICLE

Nucleos(t)ide Analogue Treatment for Patients With Hepatitis B Virus (HBV) e Antigen–Positive Chronic HBV Genotype C Infection: A Nationwide, Multicenter, Retrospective Study

Young Chang,[1,2,a] Won Hyeok Choe,[4,a] Dong Hyun Sinn,[5,a] Jeong-Hoon Lee,[1,2] Sang Hoon Ahn,[6] Hyewon Lee,[6] Jae-Jun Shim,[7] Dae Won Jun,[8] Soo Young Park,[9] Joon Yeul Nam,[1,2] Eun Ju Cho,[1,2] Su Jong Yu,[1,2] Dong Ho Lee,[3] Jeong Min Lee,[3] Yoon Jun Kim,[1,2] So Young Kwon,[4] Seung Woon Paik,[5] and Jung-Hwan Yoon[1,2]

[1]Department of Internal Medicine, [2]Liver Research Institute, and [3]Department of Radiology, Seoul National University College of Medicine, [4]Department of Internal Medicine, Konkuk University School of Medicine, [5]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, [6]Department of Internal Medicine, Yonsei University College of Medicine, [7]Department of Internal Medicine, Kyung Hee University School of Medicine, and [8]Department of Internal Medicine, Hanyang University College of Medicine, Seoul, and [9]Department of Internal Medicine, Kyungpook National University Hospital, Daegu, Korea

Background. Antiviral treatment for hepatitis B virus (HBV) e antigen (HBeAg)–positive chronic HBV infection is still controversial. We assessed whether antiviral treatment reduces the risk of liver disease progression in these patients.

Methods. This study included consecutive patients in 8 large-volume hospitals in Korea who tested positive for HBeAg and had an HBV DNA level of >20 000 IU/mL, an alanine aminotransferase (ALT) level of <40 IU/L, and no evidence of cirrhosis. The primary end point was the development of hepatocellular carcinoma (HCC), and the secondary end point was the development of cirrhosis.

Results. A total of 484 patients were included: 87 were in the antiviral treatment group, and 397 were in the control group. Baseline liver function was significantly more favorable for the control group. After matching for propensity score to overcome those differences, the antiviral treatment group had a significantly reduced risk for HCC (hazard ratio [HR], 0.234; log-rank $P = .046$) and cirrhosis (HR, 0.235; log-rank $P = .015$), compared with the control group. After balancing the baseline characteristics by using inverse probability weighting, antiviral therapy significantly decreased the risk of HCC (HR, 0.189; log-rank $P = .004$) and cirrhosis (HR, 0.347; log-rank $P = .036$).

Conclusion. Antiviral therapy for patients with HBeAg-positive chronic HBV infection and have a high HBV load reduces the risk of HCC, even if the ALT level is below the upper limit of normal.

Keywords. Immune-tolerant phase; antiviral treatment; hepatocellular carcinoma; liver cirrhosis.

Chronic hepatitis B virus (HBV) infection is a major global health problem. Globally, the number of chronically infected patients was about 240 million in 2005, and it has been increasing [1]. Individuals with HBV infection are at high risk of developing liver cirrhosis (LC) and hepatocellular carcinoma (HCC). According to recent studies, the HBV load is a strong risk predictor for both LC and HCC [2, 3], which means that patients with persistently high levels of HBV DNA have the highest risk of progression of liver disease.

A number of studies have reported that antiviral therapy with nucleos(t)ide analogues (NAs) might delay liver disease progression [4, 5]. For example, NA therapy was reported to reduce the risk of HCC development and recurrence [6–8]. Moreover, histological improvement of liver fibrosis or cirrhosis in patients with chronic hepatitis B (CHB) has been observed during long-term NA therapy [9, 10]. Long-term treatment with NAs, however, is expensive and involves high risks of adverse events and drug resistance. Therefore, the most important question regarding the management of CHB involves determining which patients need to be treated with NA therapy. Most international practice guidelines recommend starting treatment in patients with life-threatening liver disease and considering antiviral therapy in patients at the immune-clearance phase or the HBV e antigen (HBeAg)–negative phase of CHB [11–13]. It is controversial whether to treat the numerous patients with CHB who are outside the treatment guidelines, especially those with a high HBV DNA level and normal alanine aminotransferase (ALT) level (ie, individuals with HBeAg-positive chronic HBV infection), because those patients are usually asymptomatic and characterized by low incidences of liver inflammation and fibrosis [14]. Recent articles challenge the current treatment guidelines, however [15, 16]. The absence of serological markers of liver inflammation is not associated with absence of an HBV-specific T-cell response [17]. It has been suggested that HBV-specific immune responses already exist during HBeAg-positive chronic HBV infection, and the persistent immune destruction of infected hepatocytes in that phase is

Received 22 March 2017; editorial decision 15 September 2017; accepted 19 September 2017; published online September 23, 2017.

[a]Y. C., W. H. C., and D. H. S contributed equally to this article.

Correspondence: J.-H. Lee, MD, PhD, Department of Internal Medicine, Seoul National University Hospital, 101 Daehak-no, Jongno-gu, Seoul 03080, Korea (pindra@empal.com; JHLeeMD@gmail.com).

The Journal of Infectious Diseases® 2017;216:1407–14

DOI: 10.1093/infdis/jix506

comparable to that in the immune-clearance phase [18]. A high level of HBV DNA integration and clonal expansion of hepatocyte was reported among patients in the immune-tolerant phase [19].

In this study, we assessed the impact of NA therapy for patients with HBeAg-positive chronic HBV infection who have high HBV DNA levels but normal ALT levels in terms of development of HCC and LC.

MATERIALS AND METHODS

Study Population

This multicenter study retrospectively analyzed the outcomes of 484 consecutive patients with a diagnosis of HBeAg-positive CHB who had HBV DNA levels of >20 000 IU/mL and ALT levels of <40 IU/L. Patient data between January 2006 and March 2016 were reviewed. Patients were enrolled at one of 8 tertiary-care hospitals in Korea: Seoul National University Hospital, Konkuk University Hospital, Samsung Seoul Medical Center, Kyung Hee University Medical Center, Severance Hospital, Hanyang University Seoul Hospital, Kyungpook National University Hospital, and Asan Medical Center. Patients were excluded if they met any of the following criteria: confirmed LC diagnosis; prior diagnosis of any malignancy, including HCC; previous exposure to NA or interferon therapy; presence of antibodies to hepatitis C or D viruses; or receipt of prophylactic NA therapy because they were immunosuppressed. Study participants were categorized into 2 groups: the antiviral treatment group (n = 87) and the control group (n = 397). The treatment group consisted of patients who received NA therapy immediately after diagnosis of HBeAg-positive chronic HBV infection. Patients in the control group did not receive NA therapy; rather, they were followed regularly after receiving a diagnosis of HBeAg-positive chronic HBV infection. The control group received antiviral treatment once active hepatitis, LC, or HCC developed thereafter.

Patients in both groups were followed regularly, and select laboratory tests and liver imaging were performed according to treatment guidelines. Liver function tests, including those measuring levels of aspartate aminotransferase (AST), ALT, and HBV DNA (measured using real-time polymerase chain reaction), were performed every 2–6 months, depending on the patient's medical condition. Liver imaging, primarily ultrasonography and computed tomography, was performed every 6–12 months to monitor for the development of LC and HCC.

Study End Points

The primary end point was the development of HCC, and the secondary end point was the development of LC. The index date was defined as the date the was first received a diagnosis of HBeAg-positive chronic HBV infection. Clinical diagnosis of LC was determined on the basis of sonographic findings indicative of LC, such as a nodular, blunted liver edge with splenomegaly (length, >12 cm) accompanied by a low platelet count (<100 000 platelets/mL) or clinical signs of portal hypertension, including ascites, esophageal or gastric varices, and hepatic encephalopathy, as described previously [20, 21]. Two independent, experienced radiologists (J. M. L. and D. H. L.) reviewed all radiological images. In cases of disagreement, an additional independent, experienced radiologist reviewed the images, and a consensus was achieved among the 3 reviewers. HCC was diagnosed according to the European Association for the Study of the Liver guidelines [22]. Similar to the radiological diagnosis of LC, 3 independent, experienced radiologists reviewed all images, and an additional independent, experienced radiologist reviewed the images in cases of disagreement. If there was no clear radiological diagnosis of HCC, we obtained a liver biopsy specimen for histological diagnosis.

Statistical Analysis

Baseline characteristics were compared using a 2-sample *t* test or Wilcoxon rank sum test for continuous variables and a χ^2 test or Fisher exact test for categorical variables. A Cox proportional hazards model was used to identify and adjust for independent risk factors. Variables with a *P* value of <.05 in the univariate Cox regression analysis were input into the multivariate analysis. Propensity scores were calculated using logistic regression without considering interactions among covariates. Using the nearest neighbor method, we performed 1:1 propensity score (PS) matching. A caliper equal to standard deviations was used to reduce selection bias. Inverse probability weighting (IPW) based on propensity scores was performed to balance the baseline characteristics of the 2 groups. Kaplan-Meier plots were fitted after each statistical adjustment. The cumulative probabilities of events were compared using a log-rank test, and the hazard ratios (HRs) for events were estimated using univariate Cox regression analysis.

Differences with a *P* value of <.05 were considered statistically significant. All statistical analyses were performed using R, version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria). The MatchIt package and a survey package were used in R to perform PS matching and IPW, respectively.

Ethical Considerations

This study conformed to the ethical guidelines of the World Medical Association Declaration of Helsinki and was approved by the institutional review board of each participating hospital (ie, the Seoul National University Hospital Institutional Review Board, the Samsung Medical Center Institutional Review Board, the Asan Medical Center Institutional Review Board, the Severance Hospital Institutional Review Board, the Konkuk University Medical Center Institutional Review Board, the Kyung Hee University Hospital Institutional Review Board, the Hanyang University Seoul Hospital Institutional Review Board, and the Kyungpook National University Hospital Institutional Review Board). Written informed consent was waived because of the retrospective nature of the study and because there was no study-specific intervention beyond routine clinical care. Patient records were anonymized and deidentified prior to analysis.

RESULTS

Baseline Characteristics

Baseline characteristics of the study population are shown in Table 1. The majority of patients (347 of 484 [71.7%]) had an HBV DNA level exceeding 1.0×10^7 IU/mL (Supplementary Figure 1). While the demographic characteristics were similar between the 2 groups, results of baseline liver function tests differed significantly and was more favorable in the control group. The AST to platelet ratio index and the fibrosis 4 (FIB-4) index were calculated to compare the degree of hepatic fibrosis between groups. There were no significant differences between groups for those factors. PS matching and IPW were used to overcome differences in baseline liver function test results between the 2 groups. Baseline variables, including results of liver function tests, were well balanced following both PS matching and IPW, and no significant differences were observed between groups (Tables 2 and 3).

The overall median follow-up duration was 66.5 months (interquartile range [IQR], 23–80 months), with values of 71 months (IQR, 24–82 months) for the control group and 50 months (IQR, 42–66 months) for the treatment group. In the control group, 160 patients (40.3%) eventually received NA therapy within the follow-up period, whereas the remaining 237 patients did not require antiviral treatment. The mean interval between the index date and the time of NA therapy initiation in the control group was 30.5 months.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Control Group (n = 397)	Treatment Group (n = 87)	*P*
Age, y	41.5 ± 12.5	43.2 ± 13.0	.351
Sex			.606
Male	195 (49.1)	46 (52.9)	
Female	202 (50.9)	41 (47.1)	
HBV DNA level, log IU/mL	7.4 ± 1.2	7.3 ± 1.3	.909
HBeAg positive	397 (100)	87 (100)	1.000
BUN level, mg/dL	13.4 ± 6.6	14.3 ± 7.3	.602
Creatinine level, mg/dL	1.0 ± 0.6	1.0 ± 0.8	.871
Albumin level, g/dL	4.3 ± 0.3	4.0 ± 0.6	.006
Total bilirubin level, mg/dL	0.9 ± 0.4	1.2 ± 1.7	.441
Cholesterol level, mg/dL	189.1 ± 36.0	181.6 ± 48.0	.025
ALP level, IU/L	66.9 ± 27.7	76.8 ± 33.3	.022
AST level, IU/L	27.8 ± 10.1	30.6 ± 11.4	.005
ALT level, IU/L	26.8 ± 8.0	26.9 ± 7.9	.902
GGT level, IU/L	29.5 ± 41.0	42.2 ± 47.6	.009
Prothrombin time, INR	1.1 ± 0.1	1.1 ± 0.2	.471
Platelet count, $\times 10^3$ platelets/μL	199.5 ± 59.8	208.8 ± 59.3	.136
APRI	0.4 ± 0.3	0.4 ± 0.3	.170
FIB-4 index	1.4 ± 1.4	1.5 ± 1.3	.181

Data are no. (%) of subjects or mean value ± SD.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; APRI, aspartate aminotransferase to platelet ratio index; AST, aspartate aminotransferase; BUN, blood urea nitrogen; FIB-4, fibrosis 4; GGT, γ glutamyl transferase; HBeAg, hepatitis B virus e antigen; HBV, hepatitis B virus; INR, international normalized ratio; PT, prothrombin time.

Development of HCC and LC

After using multivariate analysis to adjust for several confounders that were significant risk factors for HCC development, the treatment group had a lower risk of developing HCC than the control group; however, the statistical significance was marginal (adjusted HR [aHR], 0.188; 95% CI, .030–1.186; *P* = .075; Table 4). The treatment group appeared to have a decreased risk of LC, but the difference between the 2 groups was not statistically significant (aHR, 0.382; 95% CI, .081–1.804; *P* = .225).

After PS matching, the treatment group showed a significantly lower risk of HCC (HR, 0.234; 95% CI, .050–1.104; log-rank *P* = .046; Figure 1A) and LC (HR, 0.235; 95% CI, .066–.833; log-rank *P* = .015; Figure 1B) than the matched control group. After balancing baseline liver function by using IPW, the risks of developing HCC (HR, 0.189; 95% CI, .052–.692; log-rank *P* = .004; Figure 2A) and LC (HR, 0.347; 95% CI, .095–1.270; log-rank *P* = .036; Figure 2B) were significantly lower for the treatment group, compared with the control group.

Subgroup Analysis Stratified by ALT Level

The upper limit of the normal ALT level was defined as 34 IU/L for men and 25 IU/L for women, rather than 40 IU/L, which is the suggested value for the Korean population [23]. A comparison of the end points between the 2 subgroups was performed. The baseline characteristics of the subgroups were largely similar, but several laboratory findings indicated that the treatment group had poorer liver function (Supplementary Table 1). Following IPW, the baseline variables were well balanced (Supplementary Table 2).

In multivariate analysis, the treatment group had a significantly lower risk of HCC than the control group (aHR, 0.037; 95% CI, .001–.973, *P* = .048; Supplementary Table 3) prior to performing IPW. Following IPW, the risk of developing HCC remained significantly lower for the treatment group (log-rank *P* = .003; Supplementary Figure 2).

Subgroup Analysis Stratified by FIB-4 Index

To more definitely exclude patients with possible advanced fibrosis, patients with a FIB-4 index of <3.25 were sorted. The treatment group maintained low adjusted hazards for developing HCC (aHR, 0.298; 95% CI, .036–2.468; *P* = .262; Supplementary Table 4) and LC (aHR, 0.742; 95% CI, .147–3.730; *P* = .717; Supplementary Table 5), similar to the entire study population.

Sensitivity Analysis Stratified by Age and FIB-4 Index

To minimize the influence of age and degree of hepatic fibrosis on the risk of HCC development, we stratified the subjects according to age and FIB-4 score, and calculated the HRs for HCC development of early antiviral treatment in each stratum. As shown in Supplementary Figures 3 and 4, the HRs were generally <1.0, indicating that early antiviral treatment consistently showed a protective effect against the development of HCC after controlling for strong risk factors, except for patients with a high probability of significant fibrosis (ie, those with a FIB-4 index

Table 2. Results of the Balancing Test Following Propensity Score Matching

Variable	Before Matching				After Matching			
	Control Group (n = 397)	Treatment Group (n = 87)	*P*	Standardized Difference	Control Group (n = 83)	Treatment Group (n = 83)	*P*	Standardized Difference
Propensity score	0.3 ± 0.2	0.2 ± 0.1	<.001	0.483	0.2 ± 0.2	0.2 ± 0.1	.216	0.144
Albumin level	4.0 ± 0.6	4.3 ± 0.3	.006	-0.369	4.1 ± 0.6	4.1 ± 0.5	.778	-0.083
Total bilirubin level	1.2 ± 1.7	0.9 ± 0.4	.441	0.177	1.0 ± 1.4	1.0 ± 0.5	.223	0.054
ALP level	76.8 ± 33.3	66.9 ± 27.7	.022	0.299	75.2 ± 31.9	74.7 ± 48.4	.924	0.014
AST level	30.6 ± 11.4	27.8 ± 10.1	.005	0.251	30.3 ± 11.4	31.2 ± 13.1	.863	-0.076
ALT level	26.9 ± 7.9	26.8 ± 8.0	.902	0.009	26.6 ± 7.9	27.8 ± 7.2	.366	-0.158
Prothrombin time, INR	1.1 ± 0.2	1.1 ± 0.1	.471	0.065	1.1 ± 0.1	1.1 ± 0.1	.330	-0.068
Platelet count	208.8 ± 59.3	199.5 ± 59.8	.136	0.158	210.6 ± 56.8	203.3 ± 78.3	.240	0.123

Data are mean value ± SD.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time.

of >3.25). Moreover, the protective effect was more apparent in patients with an older age and lower degree of fibrosis.

Subgroup Analysis Stratified by HBV DNA Level

Patients whose HBV DNA level was >1.0 × 10^7 IU/mL were sorted in both groups, and the end points were analyzed. The treatment group maintained low adjusted hazards for developing HCC (aHR, 0.613; 95% CI, .017–21.751; *P* = .788; Supplementary Table 6) and LC (aHR, 0.352; 95% CI, .023–5.510; *P* = .457; Supplementary Table 7).

Viral Suppression and HBeAg Seroconversion Rate

Over the observation period, the number of patients in the control group who received NA treatment according to current treatment guidelines gradually increased. Consequently, the cumulative incidence of viral suppression increased over time for both groups (Supplementary Figure 5). When comparing the rate of viral suppression between the 2 groups, the rate was significantly higher for the treatment group, compared with the control group (*P* < .001). The median suppression time was 17 months for the treatment group, compared with 71 months for the control group. The number of patients with HBeAg seroconversion was 57 of 397 (14.4%) in the control group and 15 of 82 (18.3%) in the treatment group. There was no significant difference in the rate of HBeAg seroconversion between the 2 groups (*P* = .106 by log-rank test; Supplementary Figure 6).

Pharmacoeconomic Analysis

On average, the treatment group received approximately 44.7 months of additional NA treatment. This additional treatment was associated with a 5.9% reduction in the incidence of HCC and a 15.0% reduction in the incidence of LC over the 120-month study period. Therefore, reducing the number of patients with incident HCC and LC by 1 in a cohort of 100 patients should require 7.7 months and 3.0 months, respectively, of additional NA treatment. Assuming that the relevant patients are treated with entecavir, the additional cost for treating patients with HBeAg-positive chronic HBV infection in Korea would be approximately $45 600 for LC and $117 000 for HCC (Supplementary Table 8).

DISCUSSION

Antiviral treatment was an independent, negative risk factor for HCC and LC in patients with CHB who had a high HBV DNA titer without active hepatic inflammation. It was demonstrated using various statistical methods, including multivariate analysis, PS matching, and IPW.

In general, the previous treatment guidelines recommend against initiating antiviral treatment for patients before the

Table 3. Results of the Balancing Test Following Inverse Probability Weighting

Characteristic	Control Group (n = 397)	Treatment Group (n = 87)	*P* (Unadjusted)	*P* (Adjusted)
Albumin level, g/dL	4.2 ± 0.5	4.2 ± 0.5	<.001	.318
Total bilirubin level, mg/dL	0.9 ± 0.4	0.9 ± 0.9	.099	.995
ALP level, IU/L	76.3 ± 64.7	70.2 ± 26.5	.009	.543
AST level, IU/L	29.2 ± 12.3	28.8 ± 9.3	.030	.810
ALT level, IU/L	26.9 ± 7.9	27.1 ± 7.6	.940	.859
Prothrombin time, INR	1.1 ± 0.1	1.1 ± 0.1	.564	.853
Platelet count, ×10^3 platelets/μL	205.6 ± 70.8	204.7 ± 51.5	.182	.922

Data are weighted mean ± weighted SD.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; PT, prothrombin time.

Table 4. Results of the Cox Proportional Hazards Model Evaluating the Development of Hepatocellular Carcinoma

	Univariate Analysis		Multivariate Analysis	
Variable	HR (95% CI)	*P*	HR (95% CI)	*P*
Albumin level, g/dL	0.196 (.117–.329)	<.001	0.433 (.159–1.183)	.103
Total bilirubin level, mg/dL	1.283 (1.076–1.530)	.005	1.109 (.680–1.810)	.678
ALP level, IU/L	1.010 (1.005–1.014)	<.001	1.014 (1.003–1.026)	.016
AST level, IU/L	1.077 (1.057–1.098)	<.001	1.022 (.988–1.058)	.211
ALT level, IU/L	1.039 (.987–1.095)	.144		
Prothrombin time, INR	41.517 (11.968–144.024)	<.001	1.612 (.070–37.284)	.766
Platelet count, $\times 10^3$ platelets/μL	0.968 (.959–.977)	<.001	0.978 (.968–.988)	<.001
Treatment group	0.673 (.201–2.251)	.521	0.188 (.030–1.186)	.075

Abbreviations: CI, confidential interval; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HR, hazard ratio; INR, international normalized ratio; PT, prothrombin time.

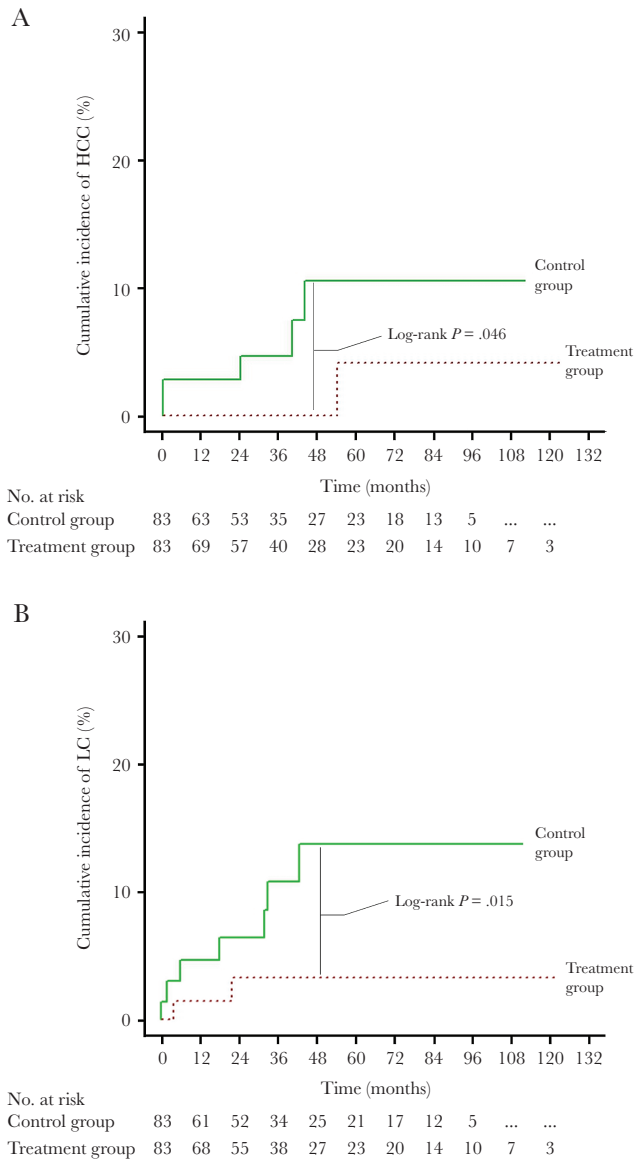

Figure 1. Kaplan-Meier plot of the incidence of liver related events following propensity score matching. *A*, The cumulative incidence of HCC in the treatment group is shown as a dashed line and the control group, a continuous line. *P* = .046 by a log-rank test. *B*, Cumulative incidence of LC in the treatment group is shown as a dashed line and the control group, a continuous line. *P* = .015 by a log-rank test.

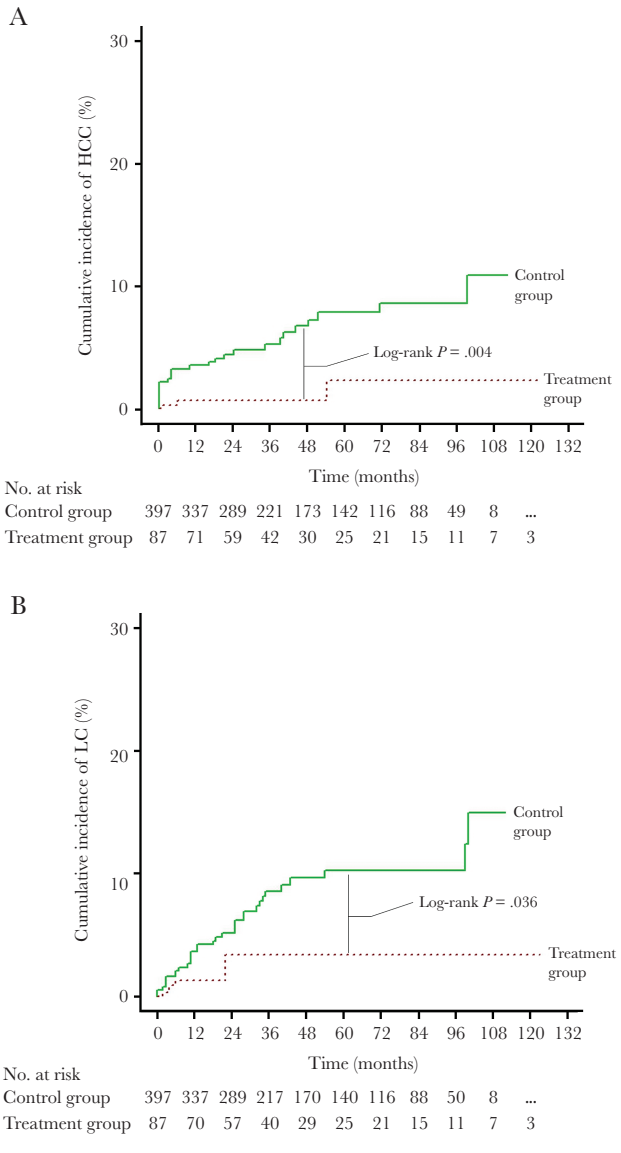

Figure 2. Weighted Kaplan-Meier plot of the incidence of liver related events following inverse probability weighting. *A*, Cumulative incidence of HCC in the treatment group is shown as a dashed line and the control group, continuous line. *P* = .004 by a log-rank test. *B*, Cumulative incidence of LC in the treatment group is shown as a dashed line and the control group, a continuous line. *P* = .036 by a log-rank test.

immune-clearance phase of CHB [11, 12], because HBeAg seroconversion is hard to achieve [24–26] and disease progression is considerably slow prior to the immune-clearance phase [18]. Several studies have suggested, however, that a normal ALT level does not always indicate minimal or no hepatic inflammation. In a clinicopathological study of 73 patients who were HBeAg positive with persistently normal ALT levels, 40% of the patients had significant liver fibrosis [27]. In another study, 27.8% of patients with CHB with a high viral load and persistently normal ALT levels had significant necroinflammation and fibrosis indicated by liver biopsy [28]. In a recent study in Hong Kong, significant necroinflammation was confirmed by histologic assessment in 22.5% of 40 patients who were HBeAg positive with normal ALT levels [29]. Taking those lines of evidence together, the ALT level does not accurately represent significant liver injury, and, furthermore, liver disease progresses consistently if there is active viral replication, even if the ALT level is persistently normal. In that context, it might be beneficial to suppress the HBV load to retard disease progression in patients with highly replicative CHB even if the ALT level is normal. There has been no previous study showing a clinical benefit of NA treatment in those patients. Our study showed, however, that NA treatment for such patients reduced the risk of developing HCC and LC significantly.

Our retrospective study was conducted in 8 large-volume hospitals in Korea, which has a single-payer national health insurance system. The initiation of NA treatment in such patients in our study cohort was largely determined by physicians, considering various factors, such as age, medical condition, economical condition, family history of HCC, occupational requirements, and the patients' preferences. As a result, the baseline characteristics of the 2 groups in our study were disparate, with markedly unfavorable characteristics in the treatment group, as expected, compared with the control group. We adjusted or balanced those variables by using 3 different statistical methods (ie, multivariate Cox regression analysis, PS matching, and IPW) in parallel, because the efficacy of NA therapy could be underestimated on account of the unfavorable conditions of the treatment group. After the adjustment, NA treatment was shown to protect against disease progression.

We assumed that the protective effects of NA therapy were mostly due to the impedance of hepatic inflammation by HBV suppression. High levels of circulating HBV trigger immune responses of the host that lead to hepatic inflammation [3]. Hence, hepatic inflammation occurs if there is active HBV replication, regardless of the phase of CHB. The accumulation of hepatic inflammation subsequently manifests as end organ damage: cirrhosis and HCC [3]. Viral suppression using NAs induces the regression of fibrosis [9, 10]. Moreover, the regressed fibrosis results in the reduction of clinical events of disease progression, including HCC [10]. The leading pathogenesis of HBV-related HCC is LC; however, there is another major pathway: HBxAg transactivation [30]. The suppression of the HBV load in the liver was suggested to lower hepatocarcinogenesis directly by reducing the HBx-initiating driving circuit [31].

The European Association for the Study of the Liver 2017 clinical practice guidelines suggest that the previously termed "immune-tolerant" phase be changed to the new nomenclature "HBeAg-positive chronic HBV infection," and they specify the upper limit of the normal range of ALT values as approximately 40 IU/L [32]. They recommend that patients with HBeAg-positive chronic HBV infection be treated if they are older than 30 years, regardless of the severity of liver histological lesions, or if they have a family history of HCC or cirrhosis. Our study results supported those expanded indications for antiviral treatment.

In Korea, genotype C HBV accounts for >98% of chronic HBV infections [33, 34] and is usually transmitted vertically, from mother to child [35, 36]. Genotype C–infected patients have delayed HBeAg seroconversion as compared to other genotypes [37, 38]. Hence, there is a much longer period of HBeAg-positive chronic infection in patients perinatally infected with genotype C HBV. This unique characteristic of genotype C HBV caused the older mean age of patients in our study, compared with that in other studies, whose patients were infected with other genotypes.

There are several concerns related to NA therapy in patients with CHB in the low-level inflammation stage. First, the response to NA treatment has been reported to be insufficient in patients with normal ALT levels, reflecting low-level inflammation. In our study, however, adequate HBV suppression was achieved after a long-term follow up period, the rate of which was comparable to that in a previous study [26]: 70.4% as compared to 66% at week 192. Because most of the involved patients received NA agents with a high genetic barrier, such as entecavir or tenofovir, no viral resistance was observed in the treatment group. The cost-effectiveness of long-term or lifelong NA treatment is another important issue. In the pharmacoeconomic analysis of our study, the cost-effectiveness of early NA therapy was quite reasonable. Because this study cohort was confined to adults chronically infected with HBV genotype C, the results should be applied only to similar populations. Since HCC and LC are rare in young age groups, it would be difficult to confirm the protective effects of early antiviral treatment in young patients. In terms of pharmacoeconomics as well, the number needed to treat among such patients would be larger than for our cohort population for the reason mentioned above, which suggests that it would be less cost-effective to treat those patients. The same applies to patients infected with HBV genotypes other than C.

There are several limitations in our study. The retrospective design is the main limitation. All of the patients in the 8 large institutions who received a diagnosis of CHB and met the inclusion criteria were enrolled without exception. Therefore, the participants should represent the population of interest. A second limitation is that the degrees of liver fibrosis were not precisely evaluated by biopsy or liver transient elastography. To make up for that shortcoming, we calculated several widely used fibrosis

markers, which verified that the majority of patients had a low probability of advanced fibrosis and that there were no differences in the degree of liver fibrosis between the 2 groups. In future prospective studies, a quantitative measure of the fibrosis degree should be obtained. A third limitation is that the sample size of the treatment group was relatively small. The Korean National Health Insurance Service does not pay for NA treatment for patients with HBeAg-positive CHB with high HBV DNA levels but ALT levels within 2 times the upper limit of normal if the patients have no HCC or LC. Patients outside of the reimbursement criteria must therefore be able afford the whole medical cost of NA treatment. As a result, the small sample size was inevitable in this study, even though we enrolled almost all patients who were received antiviral treatment during the immune-tolerant phase in Korea. Nonetheless, the efficacy of NA therapy in terms of the development of HCC and LC was supported with statistical significance. On the other hand, NA treatment that is paid for by a patient is closely related to a person's socioeconomic status (SES), and recent studies have demonstrated an association between SES and the incidence of HCC and LC [39, 40]. Accordingly, we have reviewed types of health insurance to determine the SES of the study population and verified that proportions of patients with the lowest income in the 2 groups were comparable. This result may indicate that, in most cases, physicians recommended the initiation early antiviral on the basis of the medical benefit to their patient, rather than their patient's SES.

Besides the aforementioned limitations, there still are several regrets in our study. Quantitative HBV surface antigen (HBsAg) titers were unfortunately not available for the majority of our study population because of the retrospective nature of our study. Also, the median follow-up duration was relatively short for determining the development of LC and HCC. In future prospective studies, it would be helpful to measure quantitative HBsAg titers, and prolonged follow-up might be needed to consolidate the long-term protective effects of early antiviral therapy on LC and HCC that we observed in this study.

In conclusion, early initiation of NA treatment for patients with CHB, before the immune-active phase, was associated with favorable clinical outcomes in terms of the development of HCC and LC.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Acknowledgments. J.-H. L. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. J.-H. L. conceived of and designed the study. W. H. C., D. H. S., J.-H. L., S. H. A., H. L., J.-J. S., D. W. J., S. Y. P., E. J. C., S. J. Y., D. H. L., J. M. L., Y. J. K., S. Y. K., S. W. P., and J.-H. Y. selected the study population. Y. C. and J. Y. N. collected and assembled the data. Y. C., W. H. C., D. H. S., and J.-H. L. analyzed and interpreted the data. Y. C. and J.-H. L. wrote the manuscripts. All authors approved the final manuscript.

Financial support. This work was supported by the Seoul National University Hospital Research Fund (grant 03-2016-0380) and by the Liver Research Foundation of Korea, as part of Bio Future Strategies Research Project.

Potential conflicts of interest. All authors: No reported conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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