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Risk Factors for Renal Functional Decline in Chronic Hepatitis B Patients Receiving Oral Antiviral Agents

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Abstract: Renal functional decline that is frequently seen during chronic hepatitis B (CHB) treatment can exert adverse effects on overall prognosis. It, however, is difficult to distinguish vulnerable patients who may experience renal dysfunction because most previous CHB studies were conducted in relatively healthy individuals. In this retrospective observational study, renal functional decline in CHB patients receiving oral antiviral agents for more than 6 months was analyzed and risk factors of chronic kidney disease (CKD) progression were determined.

Renal functional decline was defined when the estimated glomerular filtration rate (eGFR) decreased by more than 25% from baseline and rapid CKD progression was defined as eGFR decreased by more than 5 mL/min/1.73 m²/y among patients who experienced renal functional decline.

A total of 4178 patients were followed up for a median 23 months. Antiviral agents included lamivudine (17.0%), adefovir (3.7%), entecavir (70.4%), telbivudine (0.6%), tenofovir (4.0%), or clevudine (4.3%). Renal functional decline occurred in 706 (16.9%) patients. Based on multivariate Cox regression analysis, age, hypertension, diabetes, history of liver or kidney transplantation, underlying underlying CKD, and simultaneous administration of diuretics increased the hazard ratio for renal functional decline; however, clevudine reduced risk. The eGFR significantly increased over time in patients receiving telbivudine or clevudine compared with lamivudine. Among the 3175 patients followed up for more than 1 year, 407 (12.8%) patients experienced rapid CKD progression. Patients with rapid CKD progression showed lower serum albumin, higher total bilirubin, and prolonged prothrombin time compared with patients with stable renal function, but hepatitis B envelope antigen positivity and hepatitis B virus deoxyribonucleic acid level did not differ between the control and rapid CKD progression groups. Age, diabetes, kidney transplantation, underlying CKD, and simultaneous administration of diuretics were

identified as risk factors for rapid CKD progression, and clevudine showed a beneficial effect.

Age, hypertension, diabetes, liver or kidney transplantation, underlying CKD, and diuretics were identified as risk factors for renal functional decline. This study suggests that close monitoring of renal function and adequate management are required for CHB patients receiving antiviral agents with these risk factors.

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Abbreviations: CHB = chronic hepatitis B, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, HBeAg = hepatitis B envelope antigen, HBV DNA = hepatitis B virus deoxyribonucleic acid, HCC = hepatocellular carcinoma, HIV = human immunodeficiency virus, HR = hazard ratio, LC = liver cirrhosis, OR = odds ratio, RAS = renin-angiotensin system.

INTRODUCTION

Currently, there are 2 therapeutic options for the treatment of chronic hepatitis B (CHB), interferon and oral nucleos(t)ide analogues. For decades, oral antiviral agents have been widely used for treatment by virtue of their convenient daily regimen. These agents are confirmed to prevent the development of CHB-related death and hepatic complications including decompensated liver cirrhosis (LC) and hepatocellular carcinoma (HCC).^{1,2} On the contrary, there is no consensus regarding the discontinuation of treatment such that many patients continue treatment for life.³ Despite the merits of oral antiviral agents, there are concerns regarding long-term safety.

The adverse effect of antiviral agents on renal function is an important issue to be considered in CHB patients. Several previous studies have evaluated the safety as well as the efficacy of antiviral agents; however, there is a limitation in applying these results to clinical practice because most studies have been conducted in relatively healthy populations without other comorbidities.⁴⁻⁶ Adefovir is a well-known potential nephrotoxic drug that has dose-limiting tubular toxicity⁷ but the present recommended dose of adefovir was not shown to cause renal dysfunction in several studies.^{8,9} Tenofovir also showed similar features. In contrast with the nephrotoxic effect of tenofovir in human immunodeficiency virus (HIV) patients, no significant renal dysfunction was found in CHB patients.^{10,11}

In addition to oral antiviral agents, medical factors including comorbidities or other drugs may cause renal functional decline in CHB patients. Comorbidities, such as diabetes, hypertension, and underlying chronic kidney disease (CKD) could be important risk factors for aggravating renal function during treatment. Few reports, however, have analyzed the clinical impact of both antiviral agents and other comorbidities on renal function in CHB patients. Also, it is not understood

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whether severity of LC, presence of HCC, and frequently administered drugs with antiviral agents, such as renin–angiotensin system (RAS) blockers and diuretics, affect CKD progression. Renal functional decline is frequently seen in patients receiving antiviral agents for CHB, which may exert adverse impacts on overall prognosis.^{12,13}

To prevent renal impairment in CHB patients, a comprehensive analysis of several predicting factors affecting renal function, including comorbidities and drugs simultaneously administered with antiviral agents, liver disease status, and antiviral agents is needed. Because most previous studies were conducted in CHB patients with relatively good renal function, it is difficult to distinguish vulnerable patients who may experience renal functional decline in real practice. In this retrospective study, we thoroughly analyzed renal functional decline in CHB patients receiving oral antiviral agents focusing on both antiviral agents and other important medical factors, and determined the important risk factors of CKD progression during CHB treatment.

METHODS

Patients

A total of 8825 CHB patients who started oral antiviral treatment between January 2008 and December 2013 at Samsung Medical Center (a 2000-bed tertiary hospital in Seoul, South Korea) were recruited. Patients were classified into 6 groups according to the prescribed antiviral agent, including lamivudine, adefovir, entecavir, telbivudine, tenofovir, and clevudine. Only adefovir was allowed as a single or combination regimen in this study. Of those, 4647 patients were excluded based on the following criteria: 32 were ≤ 18 years of age; 36 and 18 were coinfecting with hepatitis C virus and HIV, respectively; 5 had transplant surgeries other than liver or kidney; 112 had end-stage renal disease requiring dialysis before enrollment; 601 and 100 were diagnosed as LC and HCC during the study periods, respectively; 1547 did not have baseline renal function within 1 month from starting antiviral agents; and 2196 were followed up less than 6 months (Figure 1).

After the prescription of antiviral agents, patients were followed up until renal replacement therapy, liver transplantation, patient death, change in antiviral agents, or loss to follow-up. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee, and the Institutional Review Board of Samsung Medical Center approved this study (IRB number: 201308117).

Data Collection

All data were collected from electronic medical records. The medical history included comorbidities, such as hypertension, diabetes, LC, HCC, and history of liver or kidney transplantation. The presence of HCC was defined as diagnosis of HCC within 1 year before enrollment. Information on drug history, including RAS blockers and diuretics, was also collected. Baseline laboratory data included serum creatinine, albumin, total bilirubin, alanine aminotransferase, fasting glucose, total cholesterol, uric acid, prothrombin time, hepatitis B envelope antigen (HBeAg), and hepatitis B virus deoxyribonucleic acid (HBV DNA). The presence of proteinuria was evaluated by urinalysis.

To evaluate renal function, serum creatinine levels were collected every 3 months and all patients had serum creatinine levels that were followed more than twice. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.¹⁴ The Chronic Kidney Disease Epidemiology Collaboration equation is as follows: $eGFR = 141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{age}} \times 1.018$ (if woman) $\times 1.159$ (if black), where Scr is serum creatinine, κ is 0.7 for women, and 0.9 for men, α is -0.329 for women and -0.411 for men, min indicates the minimum of Scr/ κ or 1, and max indicates the maximum of Scr/ κ or 1. All enrolled patients were Asian. Chronic kidney disease was defined as an eGFR lower than 60 mL/min/1.73 m² or proteinuria 1+ or higher than 1+ in urinalysis.

Outcomes

Renal functional decline was defined when eGFR decreased more than 25% from baseline and renal function did not recover until the end of follow-up. Recovered acute

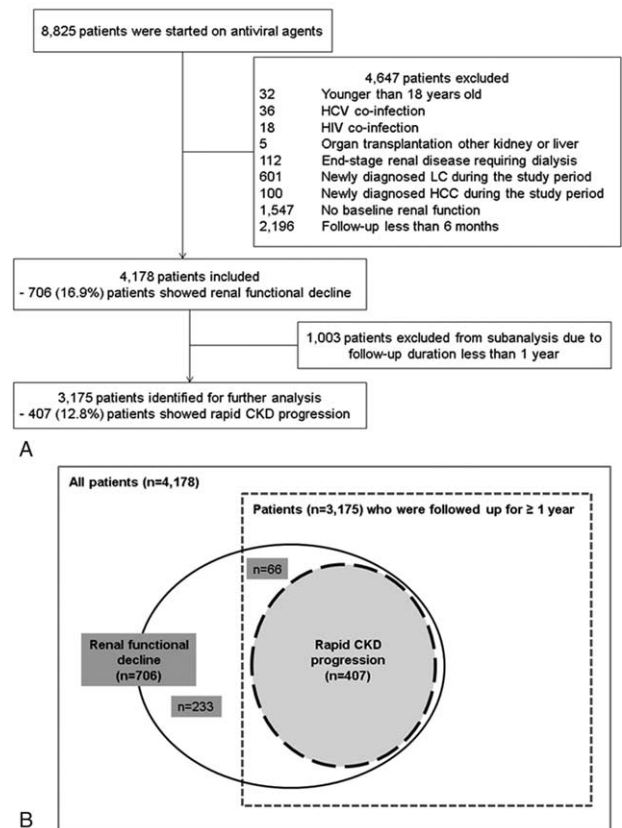


FIGURE 1. Study design and enrollment. **A**, A total of 4178 patients were included for renal functional decline analysis. Among patients who were followed up for more than 1 year, the rapid CKD progression group was compared with the control group whose renal function maintained stable. **B**, Renal functional decline occurred in 706 (16.9%) patients. In patients who were followed up for more than 1 year, 473 (14.9%) patients showed renal functional decline, of whom 407 (12.8%) patients showed rapid CKD progression and 66 (2.1%) patients showed only renal functional decline. CKD = chronic kidney disease, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HIV = human immunodeficiency virus, LC = liver cirrhosis.

kidney injury was not considered as renal functional decline. To determine the direct impact of antiviral agents on renal function, the rate of annual eGFR decline during the 3 years of CHB treatment were analyzed among patients without comorbidities, such as hypertension, diabetes, LC, HCC, history of transplantation, or administration of RAS blockers and diuretics. Finally, rapid CKD progression was analyzed, which was defined as an eGFR decrease by more than 5 mL/min/1.73 m²/y in patients experiencing renal functional decline. Both definitions of renal functional decline and rapid CKD progression were determined based on the definitions of CKD progression in the Kidney Disease: Improving Global Outcomes guidelines.¹⁵

Statistical Analysis

Continuous variables are expressed as the mean value ± standard deviation, or median (interquartile range) when the data were skewed. Data sets were compared using independent *t* test or analysis of variance. Categorical variables, expressed as a number (percentage), were analyzed using χ^2 tests. The Cox proportional hazard model was used to estimate hazard ratio (HR) for renal functional decline, and variables, including age, sex, presence of hypertension, diabetes, LC or HCC, CKD, history of liver or kidney transplantation, administration of RAS blockers or diuretics, and antiviral agents were included in multivariate analysis. Lamivudine was used as the reference in comparison between antiviral agents. Among patients without comorbidity, the rate of annual eGFR decline depending on the antiviral agent was analyzed using the generalized estimating equation. Finally, rapid CKD progression was driven by individual eGFR slope, which was calculated from linear regression analysis, and then logistic regression analysis was performed to obtain the odds ratio (OR) in univariate and multivariate analyses. Multivariate OR was adjusted by age, sex, presence of hypertension, diabetes, LC or HCC, CKD, history of liver or kidney transplantation, administration of RAS blockers or diuretics, and antiviral agents as well as baseline eGFR. All analyses were performed using SAS 9.4 (SAS institute, Cary, NC, USA). A *P* value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

A total of 4178 CHB patients receiving oral antiviral agents were recruited. There were 2892 (69.2%) men and 1286 (30.8%) women. The mean age was 51 ± 11 years and the median duration of follow-up was 23 (12, 39) months. The prevalence of LC and HCC was 49.2% and 32.0%, respectively. This study included 162 (3.9%) liver transplant recipients and 12 (0.3%) kidney transplant recipients. Among all patients, 124 (3.0%) patients were defined as CKD.

Patients were classified into 6 groups: 712 (17.0%) lamivudine, 155 (3.7%) adefovir, 2942 (70.4%) entecavir, 23 (0.6%) telbivudine, 167 (4.0%) tenofovir, and 179 (4.3%) clevudine (Table 1). The majority of patients were treated with entecavir, and the duration of follow-up was the shortest in the tenofovir group.

Risk Factor Analysis Depending on Comorbid Conditions

Of 4178 patients, 706 (16.9%) experienced renal functional decline during CHB treatment (Figure 1). A risk factor analysis for renal functional decline depending on comorbid conditions was performed (Table 2). Age and comorbidities such as hypertension and diabetes were significant predicting factors for renal functional decline in both univariate and multivariate analyses (HR 1.03, 1.42 and 1.75, *P* < 0.001, *P* = 0.002 and *P* < 0.001, respectively, in multivariate analysis). LC was a significant factor before adjustment (HR 1.14, *P* < 0.001), but was not after adjustment (*P* = 0.09). On the contrary, HCC did not exert an adverse impact on renal function. A history of liver or kidney transplant was a considerable risk factor for renal impairment during CHB treatment (HR 2.19 and 3.47, *P* < 0.001 and *P* = 0.001, respectively, in multivariate analysis). Presence of underlying CKD also showed an adverse impact on renal function before and after adjustment (HR 1.81 and 1.99, respectively, both *P* < 0.001).

TABLE 1. Baseline Characteristics According to Oral Antiviral Agents

	Lamivudine (N = 712)	Adefovir (N = 155)	Entecavir (N = 2,942)	Telbivudine (N = 23)	Tenofovir (N = 167)	Clevudine (N = 179)
Observation duration, mo	15 (8, 31)	30 (17, 48)	27 (15, 42)	12 (6, 16)	9 (7, 11)	15 (10, 23)
Age, y	51.8 ± 11.0	50.6 ± 10.7	51.1 ± 10.5	51.4 ± 12.7	49.6 ± 11.8	51.2 ± 10.6
Male	426 (59.8)	111 (71.6)	2,106 (71.6)	11 (47.8)	104 (62.3)	134 (74.9)
Hypertension	148 (20.8)	21 (13.5)	524 (17.8)	3 (13.0)	13 (7.8)	23 (12.8)
Diabetes mellitus	123 (17.3)	21 (13.5)	560 (19.0)	7 (30.4)	16 (9.6)	28 (15.6)
LC	212 (29.8)	67 (43.2)	1,598 (54.3)	5 (21.7)	60 (35.9)	114 (63.7)
HCC	117 (16.4)	55 (35.5)	1,045 (35.5)	8 (34.8)	30 (18.0)	81 (45.3)
Liver transplantation	0 (0.0)	1 (0.6)	161 (5.5)	0 (0)	1 (0.6)	0 (0)
Kidney transplantation	4 (0.6)	0 (0)	8 (0.3)	0 (0)	0 (0)	0 (0)
CKD	28 (3.9)	8 (5.2)	130 (4.4)	0 (0)	10 (6.0)	3 (1.7)
Use of RAS blockers	82 (11.5)	14 (9.0)	265 (9.0)	2 (8.7)	6 (3.6)	179 (6.7)
Use of diuretics	153 (21.5)	28 (18.1)	728 (24.7)	3 (13.0)	19 (11.4)	55 (30.7)

Continuous variables are expressed as mean value ± standard deviation or median (interquartile range) when data are skewed, and categorical variables are expressed as number (percentage).
 CKD = chronic kidney disease, HCC = hepatocellular carcinoma, LC = liver cirrhosis, RAS = renin–angiotensin system.

TABLE 2. Risk Factors for Renal Functional Decline Depending on Underlying Conditions

	Univariate Analysis		Multivariate Analysis*	
	HR (95% CI)	P	HR (95% CI)	P
Age, per y	1.02 (1.01, 1.03)	<0.001	1.03 (1.02, 1.04)	<0.001
Male	0.97 (0.82, 1.14)	0.68	1.11 (0.94, 1.32)	0.23
Hypertension	2.03 (1.72, 2.39)	<0.001	1.42 (1.13, 1.78)	0.002
Diabetes mellitus	2.80 (2.39, 3.27)	<0.001	1.75 (1.45, 2.11)	<0.001
LC	1.14 (1.15, 1.55)	<0.001	0.85 (0.71, 1.03)	0.09
HCC	1.10 (0.94, 1.28)	0.25	0.88 (0.74, 1.04)	0.13
Liver transplantation	3.64 (2.89, 4.60)	<0.001	2.19 (1.65, 2.91)	<0.001
Kidney transplantation	5.14 (2.56, 10.32)	<0.001	3.47 (1.67, 7.19)	0.001
CKD	1.81 (1.36, 2.43)	<0.001	1.99 (1.47, 2.70)	<0.001
Use of RAS blockers	1.76 (1.42, 2.17)	<0.001	0.96 (0.72, 1.28)	0.78
Use of diuretics	2.68 (2.30, 3.11)	<0.001	1.96 (1.65, 2.33)	<0.001

Values are based on Cox proportional hazard model for renal functional decline.

CI=confidence interval, CKD=chronic kidney disease, HCC=hepatocellular carcinoma, HR=hazard ratio, LC=liver cirrhosis, RAS=renin-angiotensin system.

*Adjusted by age, sex, presence of hypertension, diabetes, LC, HCC, or CKD, history of liver or kidney transplantation, use of RAS blockers or diuretics, and antiviral agents.

Risk Factor Analysis Depending on Medication

The association between RAS blockers or diuretics and renal functional decline was evaluated (Table 2). RAS blockers were related with increased risk of renal functional decline before adjustment, but it was not significant after adjustment by variables including hypertension ($P < 0.001$ and $P = 0.78$, respectively). The administration of diuretics, however, was associated with renal functional decline in both univariate and multivariate analyses (HR 2.68 and 1.96, respectively, both $P < 0.001$).

The association between antiviral agents and renal functional decline was also analyzed using lamivudine as reference in both univariate analysis and multivariate analysis (Table 3). Entecavir showed a renoprotective effect before adjustment (HR 0.76, $P = 0.005$); however, the effect was not statistically significant in multivariate analysis (HR 0.86, $P = 0.16$). Adefovir did not correlate with renal functional decline whereas clevudine showed a protective effect on renal function (HR 0.36, $P = 0.004$).

The direct impacts of antiviral agents on renal function were evaluated among patients without comorbid conditions. There were 1064 patients who did not have comorbidities: 254 in the lamivudine, 42 in the adefovir, 622 in the entecavir, 10 in the telbivudine, 86 in the tenofovir, and 50 in the clevudine groups. Figure 2 shows the annual eGFR changes according to antiviral agent. The eGFR in the lamivudine, adefovir, entecavir, and tenofovir groups decreased by a rate of -1.0 , -1.8 , -1.2 , and -0.5 mL/min/1.73 m²/y, respectively (Figure 2A). On the contrary, eGFR in the telbivudine and clevudine groups increased by a rate of 3.9 and 1.5 mL/min/1.73 m²/y (Figure 2A). Furthermore, the rate of annual eGFR decline depending on antiviral agent was compared (Figure 2B). Annual change of eGFR in the clevudine group was positive compared with the lamivudine group ($P = 0.01$). Telbivudine also showed a renoprotective effect in this analysis ($P = 0.005$).

TABLE 3. The Association of Oral Antiviral Agents with Renal Functional Decline

	Univariate Analysis		Multivariate Analysis*	
	HR (95% CI)	P	HR (95% CI)	P
Lamivudine	Reference		Reference	
Adefovir	0.72 (0.48, 1.08)	0.11	0.94 (0.62, 1.43)	0.77
Entecavir	0.76 (0.63, 0.92)	0.005	0.86 (0.69, 1.06)	0.16
Telbivudine	0.63 (0.16, 2.56)	0.52	0.80 (0.20, 3.26)	0.76
Tenofovir	1.03 (0.63, 1.70)	0.90	1.62 (0.98, 2.69)	0.06
Clevudine	0.30 (0.15, 0.59)	<0.001	0.36 (0.18, 0.72)	0.004

Values are based on Cox proportional hazard model for renal functional decline.

CI=confidence interval, CKD=chronic kidney disease, HCC=hepatocellular carcinoma, HR=hazard ratio, LC=liver cirrhosis, RAS=renin-angiotensin system.

*Adjusted by age, sex, presence of hypertension, diabetes, LC, HCC, or CKD, history of liver or kidney transplantation, and use of RAS blockers or diuretics.

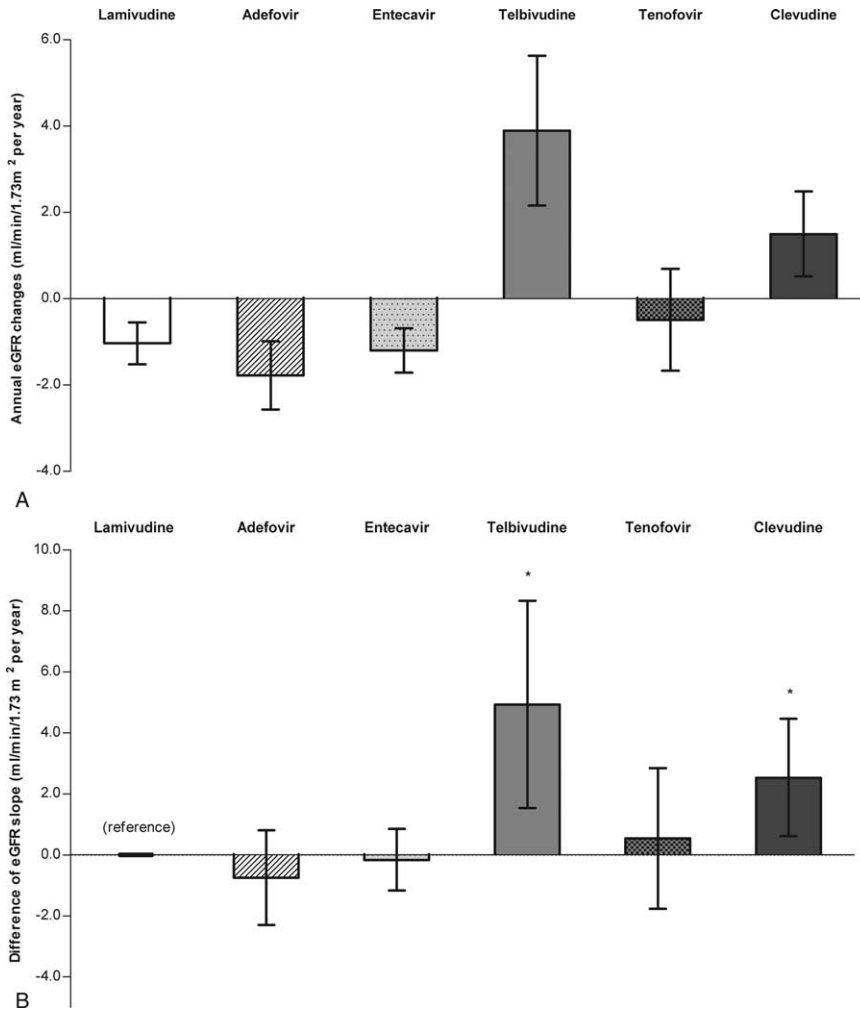


FIGURE 2. Annual eGFR changes according to the antiviral agents in CHB patients without comorbidities. A, The overall eGFR in patients treated with lamivudine, adefovir, entecavir, and tenofovir gradually decreased, whereas eGFR in patients treated with telbivudine and clevudine increased. B, The rate of annual eGFR decline depending on the antiviral agents was compared using lamivudine as the reference. Compared with lamivudine, annual change of eGFR in the clevudine and telbivudine groups was positive by 2.5 mL/min/1.73 m²/y and 4.9 mL/min/1.73 m²/y, respectively ($P=0.01$ and $P=0.005$). eGFR = estimated glomerular filtration rate * $P < 0.05$ compared with lamivudine.

Rapid Chronic Kidney Disease Progression

We conducted further analysis regarding rapid CKD progression among 3175 patients who were followed up for more than 1 year. Renal functional decline was found in 473 (14.9%) patients, of whom 407 (12.8%) patients were classified as rapid CKD progression and the remaining 66 (2.1%) patients only experienced renal functional decline. Patients in the rapid CKD progression group were compared with the other patients as the control group (Tables 4 and 5). Age, sex, and presence of HCC did not differ between the 2 groups. The prevalence of hypertension, diabetes, LC, and underlying CKD, however, was higher in the rapid CKD progression group ($P < 0.001$, $P < 0.001$, $P = 0.03$, and $P = 0.04$, respectively). The rapid CKD progression group included more patients with liver or kidney transplants compared with the control group (both $P < 0.001$). Administration of RAS blockers and diuretics together with antiviral agents was also more prevalent in the rapid CKD progression group ($P = 0.001$ and $P < 0.001$).

Laboratory results were compared between the control and rapid CKD progression groups (Table 5). Serum albumin level was significantly lower ($P < 0.001$), and total bilirubin was higher in the rapid CKD progression group ($P < 0.001$). Alanine aminotransferase, however, was not different ($P = 0.11$). Prothrombin time in the rapid CKD progression group was more prolonged than in the control group ($P = 0.009$). Levels of glucose, uric acid, and total cholesterol also showed differences ($P = 0.002$, $P < 0.001$, and $P < 0.001$, respectively). HBeAg positivity and HBV DNA level, however, did not differ between the groups ($P = 0.51$ and 0.77 , respectively). Although baseline eGFR in the rapid CKD progression group was higher compared with the control group, eGFR decreased more rapidly ($P < 0.001$).

Logistic regression analysis was conducted to identify risk factors of rapid CKD progression (Figure 3). Age, underlying diabetes mellitus, and diuretics were risk factors for rapid CKD progression (OR 1.04, 1.74, and 1.93, respectively, all

TABLE 4. Baseline Characteristics of Control and Rapid Chronic Kidney Disease Progression Groups

	Control (N = 2768)	Rapid CKD Progression (N = 407)	P
Age, y	50.7 ± 10.7	51.8 ± 10.2	0.05
Male	1970 (71.2)	288 (70.8)	0.87
Hypertension	462 (16.7)	108 (26.5)	<0.001
Diabetes mellitus	422 (15.2)	131 (32.2)	<0.001
LC	1408 (50.9)	230 (56.5)	0.03
HCC	913 (33.0)	142 (34.9)	0.45
Liver transplantation	101 (3.6)	37 (9.1)	<0.001
Kidney transplantation	4 (0.1)	5 (1.2)	<0.001
CKD	110 (4.0)	25 (6.1)	0.04
Use of RAS blockers	249 (9.0)	57 (14.0)	0.001
Use of diuretics	553 (20.0)	159 (39.1)	<0.001

Continuous variables are expressed as mean value ± standard deviation and categorical variables are expressed as number (percentage). CKD = chronic kidney disease, HCC = hepatocellular carcinoma, LC = liver cirrhosis, RAS = renin-angiotensin system.

$P < 0.001$). Although hypertension and liver transplantation were not significant factors ($P = 0.07$ and 0.05 , respectively), kidney transplantation and underlying CKD were identified as strong risk factors for rapid CKD progression (OR 16.91 and 4.59, respectively, both $P < 0.001$). Analysis regarding antiviral agents showed that clevudine had a renoprotective effect compared with lamivudine (OR 0.17, $P = 0.001$).

DISCUSSION

Our retrospective study with a large number of patients thoroughly investigated risk factors of renal impairment during CHB treatment with oral antiviral agents. In this study, 16.9% of patients underwent renal functional decline, and 12.8% of patients experienced rapid CKD progression. Comorbidities, such as hypertension, diabetes, and underlying CKD as well as aging were identified as significant risk factors for renal functional decline. Moreover, this study demonstrated that patients who underwent liver or kidney transplants were predisposed to renal impairment. We also evaluated the impacts of the

simultaneous administration of RAS blockers or diuretics on renal function. Administration of either drug together with antiviral agents was associated with renal functional decline, although the risk of RAS blockers was neutralized after adjustment for hypertension. Patients with rapid CKD progression showed lower albumin levels, higher total bilirubin levels, and increased prolonged prothrombin time compared with patients with stable renal function; however, baseline HBV DNA levels and HBeAg positivity did not differ between the groups. Among the oral antiviral agents, including lamivudine, adefovir, entecavir, telbivudine, tenofovir, and clevudine, clevudine had a protective effect on renal function compared with lamivudine. Telbivudine might have a potential benefit on renal function although this needs to be verified through further studies that include a sufficient number of patients.

Renal function is an important prognostic factor in CHB patients similar to how the prognostic model for predicting survival in cirrhosis includes serum creatinine.¹³ In a cross-sectional study, Amet et al¹⁶ investigated the prevalence of

TABLE 5. Laboratory Results in Control and Rapid Chronic Kidney Disease Progression Groups

	Control (N = 2768)	Rapid CKD Progression (N = 407)	P
Albumin, g/dL	4.1 ± 0.5	3.8 ± 0.7	<0.001
Total bilirubin, mg/dL	0.8 (0.6, 1.1)	1.0 (0.6, 1.9)	<0.001
Alanine aminotransferase, U/L	49.0 (29.0, 98.5)	50.5 (30.0, 149.5)	0.11
Prothrombin time, INR	1.07 (1.01, 1.14)	1.10 (1.02, 1.23)	0.009
Glucose, mg/dL	110.3 ± 44.9	121.3 ± 57.5	0.002
Uric acid, mg/dL	4.9 ± 1.4	4.3 ± 1.6	<0.001
Total cholesterol, mg/dL	167.7 ± 38.6	157.3 ± 46.8	<0.001
HBeAg positivity	859 (54.2)	97 (51.6)	0.51
Log HBV DNA, log(IU/mL)	5.24 (3.28, 6.62)	5.12 (3.30, 6.43)	0.77
Serum creatinine, mg/dL	0.88 ± 0.27	0.78 ± 0.30	<0.001
eGFR, mL/min/1.73 m ²	99.0 ± 21.0	118.9 ± 37.4	<0.001
Annual eGFR change, mL/min/1.73 m ² /y	-1.2 (-4.2, 2.8)	-12.0 (-21.6, -7.6)	<0.001

Continuous variables are expressed as mean value ± standard deviation or median (interquartile range) when data were skewed, and categorical variables are expressed as number (percentage).

CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, HBeAg = hepatitis B envelope antigen, HBV DNA = hepatitis B virus-deoxyribonucleic acid, INR = international normalized ratio.

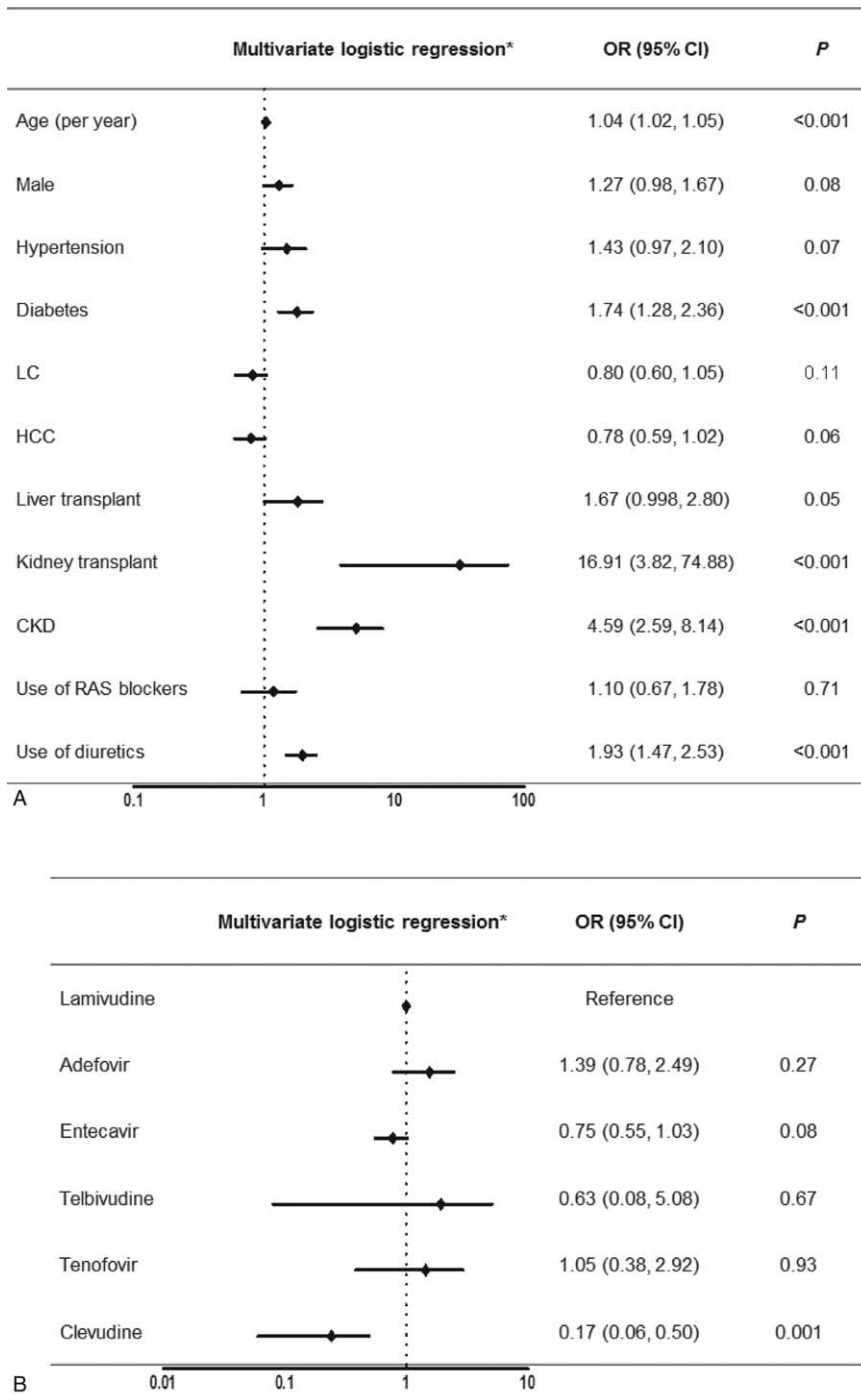


FIGURE 3. Risk factors for rapid CKD progression. A, Age and diabetes significantly increased odds ratio. Patients with a history of kidney transplantation and underlying CKD were more vulnerable for renal functional decline during CHB treatment. The use of diuretics was also associated with rapid CKD progression. B, The association between antiviral agents and rapid CKD progression was analyzed using lamivudine as the reference. Multivariate logistic regression analysis showed that clevudine had a renoprotective effect compared with lamivudine. CI = confidence interval, CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, HCC = hepatocellular carcinoma, LC = liver cirrhosis, OR = odds ratio, RAS = renin-angiotensin system. *Adjusted by age, sex, presence of hypertension or diabetes, LC, HCC, underlying CKD, history of liver or kidney transplantation, simultaneous administration of RAS blockers or diuretics, antiviral agents, and baseline eGFR.

renal abnormalities in CHB patients and reported that 64.6% were found to have kidney disease by international definition; therefore, they emphasized the necessity for regular monitoring of renal function. In addition, a recent analysis in Taiwan found that hepatitis B virus infection was a significant risk factor for end-stage renal disease.¹⁷ Nevertheless, a comprehensive longitudinal analysis for renal functional deterioration in CHB patients receiving antiviral agents that is clinically applicable has not been performed to date. Renal outcomes in a large number of CHB patients followed up for median 23 months were evaluated using 2 different approaches of renal functional decline and rapid CKD progression. Analysis of renal functional decline identified risk factors for renal impairment. Moreover, further analysis of rapid CKD progression showed direct and intuitive impacts of variables on the rate of eGFR change. As shown in our analyses, several comorbid conditions are prevalent in CHB patients and can affect renal function over the period of CHB treatment with antiviral agents. These results suggest important clinical implications and the need for a thorough evaluation of both renal function and risk factors before and during treatment with oral antiviral agents.

In this study, the known risk factors of CKD progression, such as diabetes, hypertension, and underlying CKD were confirmed to aggravate renal function in CHB patients as well. Diabetes was already reported as a significant risk factor for aggravating liver function as well as renal function, and furthermore it increases mortality in liver disease.^{18,19} Nevertheless, treatment of hypertension and diabetes in patients with liver disease is a complicated issue. RAS blockers and diuretics are widely used in patients with hypertension or diabetes,²⁰ but simultaneous administration of RAS blockers or diuretics was identified as a risk factor for renal functional decline in this study even when statistical significance was neutralized after adjustment for hypertension. RAS blockers may facilitate renal functional decline in CHB patients with increased RAS activity, especially in advanced LC.²¹ Based on previous reports and our results, we believe that the simultaneous prescription of RAS blockers or diuretics with antiviral agents should be reevaluated considering changes in renal function, blood pressure, volume status, and proteinuria in CHB patients, especially with LC features.

Severity of liver disease and presence of HCC were also evaluated in the study. The patients who were newly diagnosed with LC or HCC during the study period were excluded because potential confounders such as radiocontrast agents for computed tomography or transarterial chemoembolization and surgery may be more frequently encountered. In addition, a new diagnosis of LC or HCC implies a change in primary liver disease status, which is an important baseline characteristic. Therefore, patients who were newly diagnosed with LC or HCC during the study period were excluded to minimize confounders and avoid substantial changes in baseline characteristics. LC and HCC were not predictors for renal functional decline in our analyses. Rather, relatively decreased HR was identified in multivariate analyses, which can be explained because serum creatinine levels in patients with decreased hepatic function can be overestimated because of decreased hepatic production of creatine and muscle wasting.²² On the contrary, the rapid CKD progression group showed a progressive decline of eGFR despite an initial high level of eGFR. Markers reflecting the severity of liver disease, such as low albumin, high total bilirubin, prolonged prothrombin time, and the simultaneous administration of diuretics were more frequent in the rapid CKD progression group compared with the control group. Decreased

uric acid and cholesterol levels found in the rapid CKD group also might be associated with the severity of hepatic dysfunction.^{23,24} Renal functional decline in LC is represented by type 2 hepatorenal syndrome, which is caused by the consequence of refractory ascites.²⁵ We believe that if hepatic dysfunction progresses in CHB patients, these patients are more prone to renal functional decline. HBV DNA levels and HBeAg positivity, however, did not correlate with rapid renal functional decline. Mauss et al⁶ also showed that HBV DNA levels were not associated with both baseline eGFR and changes in eGFR. Our data suggest that overall liver function rather than HBV DNA or HBeAg exerts greater substantial influence on renal functional changes in CHB patients receiving antiviral agents.

In our study, patients with a previous history of liver or kidney transplants were vulnerable for renal functional decline. Renal dysfunction is highly prevalent and has a significant impact on mortality in patients receiving liver transplants, similar to those receiving kidney transplantation.^{26,27} Renal dysfunction is caused by multiple factors, including immunosuppressive drugs, especially calcineurin inhibitors, comorbid conditions, such as hypertension or diabetes, and pretransplant kidney disease.²⁸ Therefore, several risk factors should be identified and managed well in CHB patients taking antiviral agents after liver transplants to preserve renal function.

The impacts of oral antiviral agents on renal function were analyzed by 3 different approaches in this study, and all analyses showed similar results. A notable finding was that the nephrotoxicity of adefovir was not significant. Although several studies showed renal impairment related with adefovir,^{29–31} others reported renal safety at the current adefovir dosage, similar to our results.^{8,9} At our center, the usual adefovir dosage for patients with normal renal function is 10 mg/d, and the dosage is correctly adjusted by eGFR following guideline recommendations.³² Our results might also be related to the definition of renal functional decline, because adefovir-induced nephropathy is reversible.⁴ Recovery of renal function after eGFR decline was not defined as a renal event in this study. We also found that tenofovir is safe, similar to a previous study^{11,33} although our observation period for tenofovir was shorter than that of other agents. Clevudine showed a favorable effect on renal function compared with lamivudine. Although the renal impact of clevudine has not had much attention, a high frequency of resistance and associated myopathy make it difficult for clevudine to be the first-line therapy.^{34,35} Despite the small number of patients, we found that eGFR in telbivudine group significantly increased over time. This result is in accordance with recent reports that showed improvement of renal function in CHB patients with telbivudine.^{36,37}

There are some limitations to this study. First, because of the retrospective real-life cohort design, several baseline characteristics, especially group size and observation duration, were not evenly distributed according to each group. Telbivudine and tenofovir were introduced recently in Korea; therefore, the number of patients receiving these drugs was relatively small. Size differences were also seen in patients with a history of liver or kidney transplants. We, however, analyzed the impacts of antiviral agents on renal function using three different methods and all showed similar results. In addition, because our study focused on baseline predicting factors including comorbidities and antiviral agents, the correlation between treatment response and renal function was not analyzed. Results from the rapid CKD progression group, however, support that conservation of liver function indirectly contributes to preserve renal function. A previous study also reported that CHB

treatment with antiviral agents has beneficial effects on renal function compared with untreated CHB patients.⁶

Despite these limitations, several risk factors of renal functional decline, such as age, comorbidities of hypertension and diabetes, previous history of liver or kidney transplantation, and underlying CKD were identified in our study with a large number of CHB patients. Concomitant administration of RAS blockers or diuretics was also identified as a risk factor for renal impairment. Furthermore, our study confirmed that severe hepatic dysfunction may enhance renal functional deterioration. Among the oral antiviral agents, clevudine was found to be relatively safe for renal function compared with lamivudine. In addition, telbivudine might have a favorable effect on renal function although the number of patients in telbivudine group was small. These findings have substantial clinical implications to physicians treating CHB patients using antiviral agents. To prevent renal functional decline and retard CKD progression in CHB patients receiving oral antiviral agents, a multidisciplinary approach by both hepatologists and nephrologists is required for the adequate management of several risk factors.

REFERENCES

- Papatheodoridis GV, Lampertico P, Manolakopoulos S, et al. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol*. 2010;53:348–356.
- Zhang QQ, An X, Liu YH, et al. Long-term nucleos(t)ide analogues therapy for adults with chronic hepatitis B reduces the risk of long-term complications: a meta-analysis. *Virology*. 2011;8:72.
- Shouval D, Lai CL, Chang TT, et al. Relapse of hepatitis B in HBeAg-negative chronic hepatitis B patients who discontinued successful entecavir treatment: the case for continuous antiviral therapy. *J Hepatol*. 2009;50:289–295.
- Fontana RJ. Side effects of long-term oral antiviral therapy for hepatitis B. *Hepatology*. 2009;49:S185–195.
- Fung J, Seto WK, Lai CL, et al. Extrahepatic effects of nucleoside and nucleotide analogues in chronic hepatitis B treatment. *J Gastroenterol Hepatol*. 2014;29:428–434.
- Mauss S, Berger F, Filmann N, et al. Effect of HBV polymerase inhibitors on renal function in patients with chronic hepatitis B. *J Hepatol*. 2011;55:1235–1240.
- Marcellin P, Chang TT, Lim SG, et al. Adefovir dipivoxil for the treatment of hepatitis B e antigen-positive chronic hepatitis B. *N Engl J Med*. 2003;348:808–816.
- Izzedine H, Hulot JS, Launay-Vacher V, et al. Renal safety of adefovir dipivoxil in patients with chronic hepatitis B: two double-blind, randomized, placebo-controlled studies. *Kidney Int*. 2004;66:1153–1158.
- Manolakopoulos S, Striki A, Deutsch M, et al. Long-term adefovir plus lamivudine therapy does not decrease creatinine clearance in HBeAg-negative chronic hepatitis B patients. *Liver Int*. 2011;31:1525–1532.
- Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med*. 2008;359:2442–2455.
- Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology*. 2011;140:132–143.
- Llach J, Gines P, Arroyo V, et al. Prognostic value of arterial pressure, endogenous vasoactive systems, and renal function in cirrhotic patients admitted to the hospital for the treatment of ascites. *Gastroenterology*. 1988;94:482–487.
- Fernandez-Esparrach G, Sanchez-Fueyo A, Gines P, et al. A prognostic model for predicting survival in cirrhosis with ascites. *J Hepatol*. 2001;34:46–52.
- Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604–612.
- Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney Int*. 2013;3(Suppl):1–150.
- Amet S, Bronowicki JP, Thabut D, et al. Prevalence of renal abnormalities in chronic HBV infection: the HARPE study. *Liver Int*. 2015;35:148–155.
- Chen YC, Su YC, Li CY, et al. A nationwide cohort study suggests chronic hepatitis B virus infection increases the risk of end-stage renal disease among patients in Taiwan. *Kidney Int*. 2015;87:1030–1038.
- Huo TI, Wu JC, Lee PC, et al. Diabetes mellitus as a risk factor of liver cirrhosis in patients with chronic hepatitis B virus infection. *J Clin Gastroenterol*. 2000;30:250–254.
- Bianchi G, Marchesini G, Zoli M, et al. Prognostic significance of diabetes in patients with cirrhosis. *Hepatology*. 1994;20:119–125.
- Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension*. 2003;42:1206–1252.
- Henriksen JH, Moller S. Liver cirrhosis and arterial hypertension. *World J Gastroenterol*. 2006;12:678–685.
- Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med*. 1999;341:403–409.
- Decaux G, Mols P, Naeije R, et al. Hypouricemia in cirrhosis reflects hemodynamic alterations. *Metabolism*. 1984;33:750–753.
- Halsted CH. Nutrition and alcoholic liver disease. *Semin Liver Dis*. 2004;24:289–304.
- Guevara M, Arroyo V. Hepatorenal syndrome. *Expert Opin Pharmacother*. 2011;12:1405–1417.
- Sharma P, Welch K, Eikstadt R, et al. Renal outcomes after liver transplantation in the model for end-stage liver disease era. *Liver Transpl*. 2009;15:1142–1148.
- Lee JP, Heo NJ, Joo KW, et al. Risk factors for consequent kidney impairment and differential impact of liver transplantation on renal function. *Nephrol Dial Transplant*. 2010;25:2772–2785.
- Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003;349:931–940.
- Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B for up to 5 years. *Gastroenterology*. 2006;131:1743–1751.
- Ha NB, Ha NB, Garcia RT, et al. Renal dysfunction in chronic hepatitis B patients treated with adefovir dipivoxil. *Hepatology*. 2009;50:727–734.
- Vigano M, Lampertico P, Lavarone M, et al. High risk of renal impairment during long-term adefovir and lamivudine combination therapy in patients with lamivudine-resistant chronic hepatitis B. *J Hepatol*. 2009;50:S338–S339.
- European Association For The Study Of The Liver. EASL clinical practice guidelines: management of chronic hepatitis B virus infection. *J Hepatol*. 2012;57:167–185.
- Gish RG, Clark MD, Kane SD, et al. Similar risk of renal events among patients treated with tenofovir or entecavir for chronic hepatitis B. *Clin Gastroenterol Hepatol*. 2012;10:941–946.

34. Seok JI, Lee DK, Lee CH, et al. Long-term therapy with clevudine for chronic hepatitis B can be associated with myopathy characterized by depletion of mitochondrial DNA. *Hepatology*. 2009;49:2080–2086.
35. Choung BS, Kim IH, Jeon BJ, et al. Long-term treatment efficacy and safety of clevudine therapy in naive patients with chronic hepatitis B. *Gut Liver*. 2012;6:486–492.
36. Wang Y, Thongsawat S, Gane EJ, et al. Efficacy and safety of continuous 4-year telbivudine treatment in patients with chronic hepatitis B. *J Viral Hepat*. 2013;20:e37–e46.
37. Gane EJ, Deray G, Liaw YF, et al. Telbivudine improves renal function in patients with chronic hepatitis B. *Gastroenterology*. 2014;146:138–146.