Efficacy and safety of Entecavir for Hepatitis B virus-associated Glomerulonephritis with renal function insufficient

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Research Article

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Abstract

Background HBV-GN is one of the most common secondary kidney diseases in China. Entecavir is one of the first-line antiviral nucleoside drugs at present, which can also effectively apply to antiviral therapy for HBV-GN.

Objective The retrospective study to explore whether the entecavir is efficacy and safety for the treatment of Hepatitis B virus-associated glomerulonephritis(HBV-GN) with renal function insufficient.

Methods We screened patients diagnosed with HBV-GN in The Affiliated Hospital of Qingdao University, elevated serum creatinine at 130umol/l ~ 250umol/l. Group 1 (30 patients) was given entecavir as antiviral treatment. Group 2 (28 patients) was treated with angiotensin II receptor blocker (ARB). The changes of renal function and the possible influencing factors were observed, with a mean follow-up time of 36 months.

Results Baseline demographic and clinical parameters were not different between the 2 groups. For both cohorts, serum creatinine levels were increased gradually and the levels of eGFR declined progressively during the follow-up. At the end of the follow-up, serum creatinine levels in group 1 (t = 1.64, P = 0.1) and in group 2 (t = 4.35, P = 0.001) were considered statistically significant compared to baseline creatinine. The levels of eGFR in group 1 (t = 2.37, P = 0.0018) and in group 2 (t = 4.35, P = 0.001) were considered statistically significant compared to baseline eGFR. Comparison between the two groups showed that the elevated serum creatinine level and reduction in the level of eGFR were significantly lower in group 1 (t = 2.67, P = 0.008) than in group 2 (t = 2.76, P = 0.006), which were considered statistically significant. At the same time, cumulative renal survival, using end-stage renal disease (ESRD, eGFR < 15ml/min) as the primary renal endpoint, was 96.7% in group 1 and 67.9% in group 2 respectively (P = 0.005). Meanwhile, urine protein excretion was significantly decreased in both groups compared with baseline values, group 1 (t = 5.74, P = 0.001) and group 2 (t = 4.27, P = 0.001), while no significant difference was found(P = 0.370)in both groups. We performed a multivariate Cox regression analysis required eGFR < 15ml/min as the primary end point, then we found that the entecavir treatment and remission of proteinuria were the protective factors of renal function impairment, while the lower baseline eGFR was the risk factor of the progression of ESRD.

Conclusion Entecavir treatment slows the progression of renal function impairment in HBV-GN, meanwhile, entecavir shows a significantly renal protective effect.

Introduction

China is a country with high incidence of Hepatitis B virus (HBV) infection currently [1], HBV-GN is also one of the most common secondary kidney diseases in China[2]. Long-standing HBV infection increases the risk of extrahepatic complications, especially aggravation of renal injury[3]. Some patients were diagnosed with renal function impairment or eGFR declination at the first visit, which will lead to ESRD without timely intervention therapy. Entecavir is one of the first-line antiviral nucleoside drugs at present,

which can also effectively apply to antiviral therapy for HBV-GN. However, entecavir and tenofovir alafenamide (TAF) are recommended for routine use at present[4]. Additionally, entecavir also showed a high safety to kidney. Many global guidelines of chronic Hepatitis B (CHB) recommended it as the first-line treatment for HBV patients with renal dysfunction[5,6]. For the safety of entecavir treatment in kidney, most of the current studies have focused on patients with HBV and renal function impairment. They showed that entecavir was not associated with an increased risk of kidney injury. As for patients who were diagnosed with HBV-GN leading to renal dysfunction, whether entecavir has a protective effect in kidney or delays renal function impairment has not been previously reported in clinical study. However, in the previous studies, we found that antiviral treatment was associated with significant reduction in proteinuria in HBV-GN patients with normal renal function. Therefore, we recruited HBV-GN patients with renal dysfunction and tested their clinical indicators after entecavir treatment. Then they would be compared with those in the control group in order to explore entecavir protective effect in HBV-GN patients with renal dysfunction.

Materials And Methods

1.1 Patient selection

All HBV-GN patients who presented from 2006 leading up to 2016 with elevated serum creatinine not currently on antiviral therapy were included. Subjects with secondary renal disease such as diabetes mellitus and systemic lupus erythematosus (SLE), hematologic malignancies or solid tumors, Hepatitis B liver fibrosis or cirrhosis and Hepatitis B-related HCC were excluded from the analysis. Finally, 30 patients (group 1) were treated with entecavir, 28 patients (group 2) were only treated with ARB and other antihypertensive drugs. The present study was approved by the Ethics Committee of The Affiliated Hospital of Qingdao University.

All patients visited with elevated serum creatinin levels (130umol/l~250umol/l), eGFR was determined with CKD–EPI equation between 59 and 17 mL/min. Due to patients showed a rise in serum creatinine and a decline in eGFR, patients did not receive glucocorticoid or immunosuppressant treatment. Patients in both cohorts were treated with an angiotensin II receptor blockers (ARB) with or without additional antihypertensive agents to achieve a blood pressure target of below 130/85 mmHg. All patients had varying levels of proteinuria, some of whom presented with hematuria. The dose of entecavir was adjusted according to the eGFR, eGFR≥50ml/min, 0.5mg/d; 30ml/min≤eGFR≤49ml/min, 0.25mg/d; 10ml/min≤eGFR≤29ml/min, 0.15mg/d. Complete remission of proteinuria was defined as a value for 24 hours urinary protein excretion that was below 0.5g; partial remission was defined as a decline in urinary protein excretion by 50% or more over baseline value but the absolute amount of proteinuria was over 0.5 g/d(Table 1).

After a 3 years follow-up, we observed the changes including the improvement and the progression of renal functions of participants in 2 groups and the number of patients progressed to ESRD. We also observed the effects of blood pressure, proteinuria, baseline of eGFR, HBV replication, renal pathological

stage and HBeAg seroconversion on renal function. CKD5 comprised patients with ESRD (stage 5 of CKD with eGFR <15 ml/min).

Table 1 Baseline demographic and clinical characteristics in subjects with HBV-GN

Variables	Group 1 (N=30)	Group 2 (N=28)	P-value	t/X^2
Age, y	53.10±9.06	53.36±8.21	0.910	0.11
Gender, M:F	21:9	19:9	0.860	0.03
SBP, mmHg	155±20	158±18	0.599	0.53
DBP, mmHg	90±8	92±6	0.393	0.86
Urine protein excretion, g/day	2.88±1.04	2.80±0.99	0.785	0.27
Presence of microscopic hematuria, %	27 (90.00)	25 (89.29)	-	0.08
Scr, umol/L	184.00±35.04	181.64±35.06	0.799	0.26
ALB, g/L	32.33±5.86	32.57±5.30	0.872	0.16
Serum C3, g/L	1.21±0.32	1.23±0.36	0.866	0.17
HBsAg-positive, %	30 (100.00)	28 (100.00)	-	-
HBeAg-positive, %	24 (80.00)	22 (78.57)	0.893	0.02
Serum HBV DNA (log10) copies/mL	5.11±0.99	5.20±1.00	0.758	0.31
Stage of MN				
I or II, %	5 (16.67)	4 (14.29)	-	0.06
III or IV, %	22 (73.33)	21 (75.00)		
Hypertension, %	24 (80.00)	22 (78.57)	0.893	0.02
Received entecarvir, %	30 (100.00)	0	-	-
Received ARB, %	30 (100.00)	28 (100.00)	-	-

1.2 Renal pathological examination of HBV-GN

Renal pathological examination was also implemented for all patients. Kidney pathological specimens were collected and processed for immunofluorescence evaluation, which showed HBV antigens deposition and meet the diagnostic criteria of HBV-GN(Figure 1).

1.3 Statistics

SPSS 22.0 statistical software was applied for data processing. Measurement data were presented as mean ± standard deviation (SD). Rank sum test was used for continuous variables. All categorical variables were compared between groups using χ2 test. Comparisons between multiple groups were performed by one-way analysis of variance (ANOVA). Comparisons between two groups were carried out using t-test. The counting data were tested by a chi-square test. Kaplan-Meier survival analysis was applied to calculate the patient cumulative survival rates. Multivariate cox regression was used to analyze whether the baseline eGFR of patients, 24 hour urine protein excretion, pathological type, quantification of HBV-DNA, type of HBV antigen deposition or HBeAg seroconversion may each predict renal function. *P* values of <0.05 were used to identify statistically significant differences.

Results

All patients in both groups achieved target blood pressure control within 6 months of diagnosis, using ARB with or without additional antihypertensive agents(Figure 2).

In group 1, the patients were followed up for 3 years. There was significant reduction of 24-hour urine protein excretion from 6 months of starting entecavir treatment. The average urinary protein excretion was 1.78 g/24 hours at 36 months, which was statistically significant when compared to baseline($t = 5.74$, $P = 0.001$)(Figure 3); 11 patients went into complete or partial remission after entecavir treatment, the remission rate was 36.7%. There was also a concomitant increase in serum creatinine levels and a decline in eGFR levels. At 36 months, serum creatinine levels increased when compared with the baseline levels, although the difference was not statistically significant($t = 1.64$, $P = 0.1$)(Figure 4). But the difference in eGFR was statistically significant for comparison with baseline($t = 2.37$, $P = 0.018$)(Figure 4). Serum HBV DNA fell below 10^3/ml detection threshold in the 18 patients within the 6 months of treatment, and all the patients, serum HBV DNA values fell below 10^3/ml within the 12 months of treatment. 24 patients were HBeAg-positive before treatment, 7 patients cleared HBeAg after treatment, in addition, 15 patients seroconverted to anti-HBe. Entecavir was well tolerated in all subjects and not associated with any adverse drug effect and drug resistance.

In group 2, the average urinary protein excretion was 2.11 g/24 hours at 36 months, which was statistically significant when compared to baseline($t = 4.27$, $P = 0.001$)(Figure 3); 6 patients went into complete or partial remission after entecavir treatment, the remission rate was 21.4%. There was also a concomitant increase in serum creatinine level and a decline in eGFR levels. At 36 months, serum creatinine levels increased when compared with the baseline levels($t = 4.35$, $P = 0.001$)(Figure 3), eGFR levels decreased when compared with the baseline levels($t = 4.35$, $P = 0.001$)(Figure 5), and the difference was statistically significant. There was no change in the levels of HBV DNA replication and HbeAg expression in patients.

The cumulative 3-year renal survival was 96.7% in group 1 and 67.9% in group 2 ($P = 0.005$, log-rank test) (Figure 6). Treatment with entecavir was associated with a 28% reduction in the actual risk of progression to ESRD within 3 years. Hepatic decompensation, cirrhosis or malignancy was not observed during follow-up in both groups.

Discussion

China is among the countries with the highest prevalence of HBV infection[8], meanwhile, chronic kidney disease is also one of the most important public health problem in our country. The epidemiological data of China in 2012 suggest that about 120 million cases of chronic kidney disease (CKD) were diagnosed worldwide [9]. Whether clinical or laboratory studies, the results showed an association between HBV and CKD. HBV infection may cause kidney damage, however, it is also a risk factor to kidney dysfunction[10,11]. The results from the Chinese Center for Disease Control and Prevention(CDC) of the epidemiology of Hepatitis B survey in those aged 1~29 years in China showed that HBsAg positivity in people aged 1–4 years, 5–14 years and 15–29 years was 0.32%, 0.94% and 4.38%, however, the data

decreased by 96.7%, 91.2% and 55.1% when compared to 1992, respectively. The prevalence of the HBsAg is estimated to be 5%□6% of the general population currently, the number of chronic HBV infected patients is approximately 70 million, 20~30 million of whom were diagnosed with CHB[13]. The occurrence of kidney disease in patients who were positive for serum HBsAg was evaluated, which suggested that 64.6% patients have been accompanying chronic kidney diseases[14]. Furthermore, a recent large epidemiological survey showed that chronic hepatitis B patients significantly increased the risk of chronic kidney disease, which is increased by 37% in surface antigen positive patients when compared to surface antigen negative patients. Males were identified to be at greater risk by 77%[15]. A single-center cross-sectional study by Ning et al[16] indicated that among 1985 patients received antiviral therapy, 7.9% of whom were diagnosed with chronic kidney disease. At the same time, the diagnosis of HBV infection with renal disease not only acutely affects the prognosis of patients, but also increases the risk of death[17]. The incidence of HBV-GN was 3%-5%[18], renal pathology was needed in diagnosis, so exact incidence was unclear.

Currently, entecavir is the first-line nucleoside (acid) antiviral drug for use for the treatment of HBV, the preferred use of entecavir could be recommended for Hepatitis B patients with renal dysfunction according to 2017 European Association for the Study of the Liver(EASL) and 2018 the American Association for the Study of Liver Diseases(AASLD), in addition, the use of entecavir was also recommended by the guidelines of Chinese prevention and treatment for CHB (2019 vision)[19]. The use of entecavir cause renal tubular impairment was observed in only one case from the published literature[20], so we speculated that entecavir had a high renal safety.

In a retrospective study, Suzuki et al [21] found that the use of entecavir in Hepatitis B patients with renal failure even requiring dialysis did not worsen kidney function. Tsai et al[22] found that no significant change was seen in the eGFR levels of 233 CHB patients after 44 months of entecavir treatment. The above researches were designed to patients with HBV and renal dysfunction or observing the changes of renal function. However, there has been less research in renal function damage which had been caused by HBV-GN, therefore, this study further explored the renal protection of entecavir in HBV-GN.

In previous studies, we found that urinary protein excretion decreased in HBV-GN patients after antiviral therapy[7], for HBV-GN patients with renal dysfunction, the focus of this study was whether entecavir slowed the progression of renal function impairment to protect kidney function. Our findings for HBV-GN patients with renal dysfunction suggested that creatinine levels of patients increased compared to baseline after entecavir treatment, but at the 6th, 12th, 24th, 36th month follow-ups when compared with the control group, the elevated levels of serum creatinine and the rate of decreased eGFR were significantly lower. ESRD was defined as an eGFR <15 mL/min and needed renal replacement therapy, so the renal survival rates of patients were analyzed further by K–M survival analysis. The renal survival rates of patients were higher than those of the control group after entecavir treatment. The above results can be expressed by which the treatment with entecavir slowed the progression of renal function impairment and had a protective effect on kidney.

To further analyze the mechanism of action of entecavir on renal protection, in our research, we firstly found that there was a clear decrease in the serum HBV DNA levels of patients after antiviral therapy. After following up for one year, their HBV DNA levels were decreased to the lower limit of laboratory testing. In our previous studies, the levels of HBV DNA were closely related to clinical prognosis of HBV-GN. 22 patients achieved HBeAg negative and seroconversion after antiviral therapy, which was a critical link in the antiviral treatment of CHB, as well as in the treatment of HBV-GN. Second, proteinuria was reduced in both groups after the treatment, it was a more significant decline after antiviral therapy although the difference was not statistically significant. And the group receiving antiviral treatment achieved a higher proteinuria remission rate. Therefore, the decline of HBV DNA in serum, the HBeAg seroconversion and the remission rate of urinary protein are the possible molecular mechanisms of retarding the deterioration of renal function. Through the multivariate Cox regression, studies suggested that the antiviral therapy and the remission of urinary protein excretion were protective factors for kidney function. In addition, the lower baseline eGFR was the risk factor of the progression of ESRD(Table 2). Entecavir treatment improves renal outcome in HBV-GN and shows a significantly renal protective effect. Randomized studies in a larger cohort of patients and a long-term observation are needed to validate this important issue.

Table 2 Multivariable COX regression analysis for predictors of ESRD

Variables	HR (95% CI)	*P*-value
Baseline eGFR	19.415 (6.136, 61.427)	<0.001
Entecavir		
No	1.00	
Yes	0.479 (0.230, 0.996)	0.049
Remission		
No	1.00	
Yes	0.276 (0.097, 0.780)	0.015

Declarations

Ethics approval and consent to participate

Approval was granted by The Affiliated Hospital of Qingdao University. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was obtained from all individual participants included in the studies.

Consent for publication

Informed consent was obtained from all individual authors included in the studies.

Availability of data and material

All data generated or analyzed during this study are included in this article.

Competing interests

The authors declare no conflicts of interest.

Finding

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Authors' contributions

Conceptualization: YU Yani, XU Lingyu and XU Ting; clinical study information: ZHANG Wei and ZHAO Long; formal analysis and investigation: YANG Chengyu; writing—original draft preparation: YU Yani, XU Lingyu and XU Ting; writing—review and editing: YU Yani, XU Lingyu, BU Quandong, XU Yan J and JIANG Wei.

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Figures

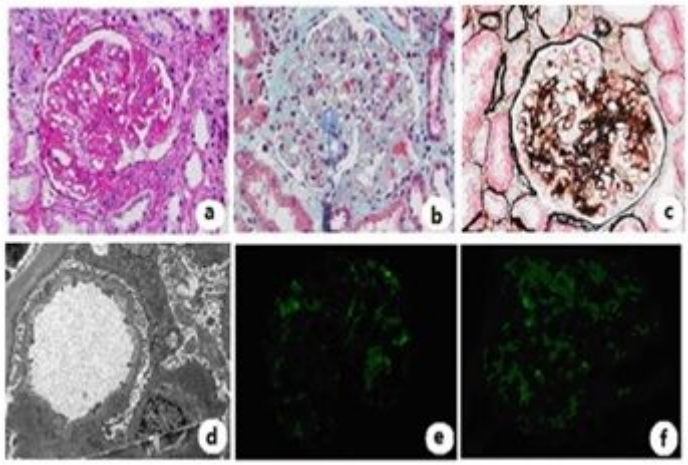


Figure 1

Pathology of HBV-GN. (A) PAS stain (×400). (B) Masson stain (×400). (C) PASM stain (×400). (D) electron microscopy (×10000). (E) IF staining for HBsAg (×400). (F) IF staining for HBeAg (×400).

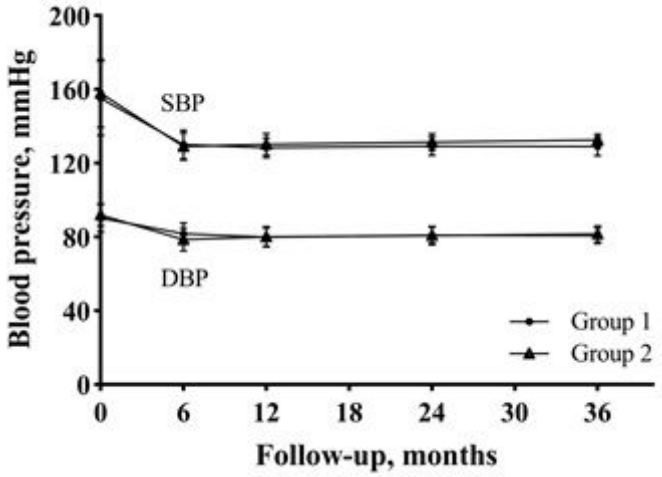


Figure 2

Blood pressure control during follow-up.

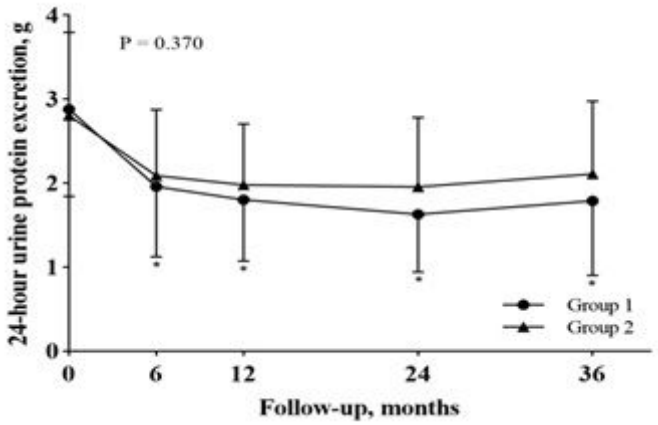


Figure 3

Change in urinary protein excretion rates in Entecavir-treated (group 1) and control subjects (group 2). Results are expressed as mean ± SD. ∗P < 0.05 vs. baseline values. P = 0.370 vs. the corresponding time point in group 1.

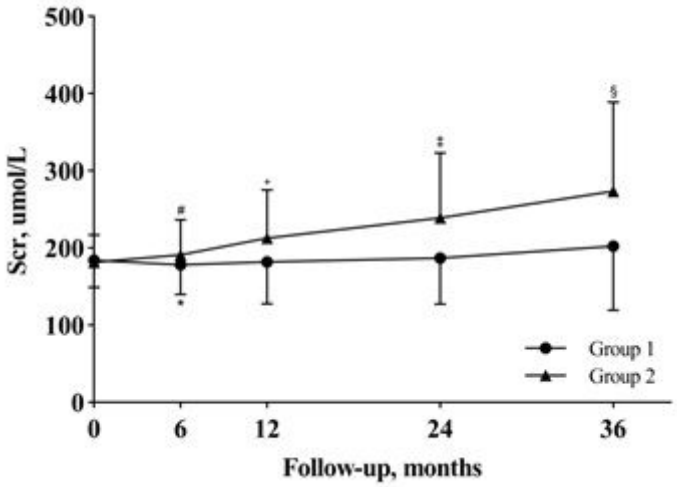


Figure 4

Change in Scr in Entecavir-treated (group 1) and control subjects (group 2). Results are expressed as mean ± SD. ∗P = 0.018 vs. baseline values. #P = 0.286, +P = 0.034, ‡P = 0.012, §P = 0.008, vs. the corresponding time point in group 1.

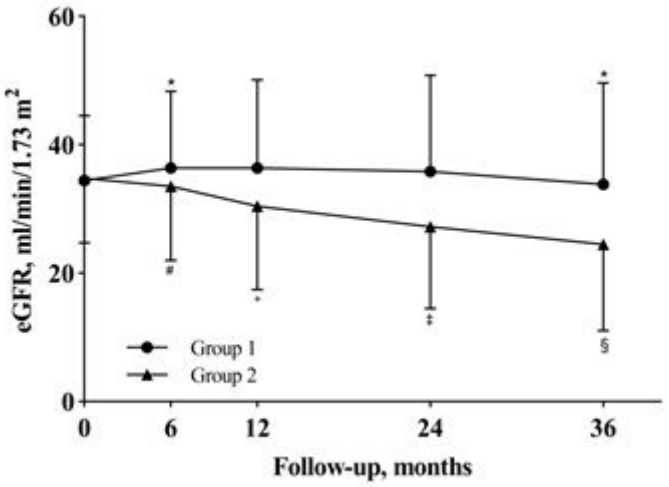
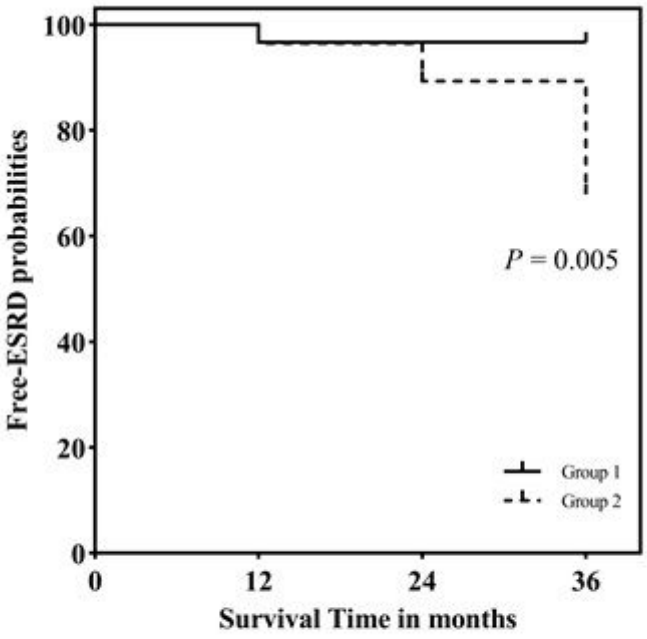


Figure 5

Change in eGFR in Entecavir-treated (group 1) and control subjects (group 2). Results are expressed as mean ± SD. ∗P < 0.05 vs. baseline values. #P = 0.297, +P = 0.055, ‡P = 0.009, §P = 0.006, vs. the corresponding time point in group 1.



No. at risk

Group 1:	30	29	29	29
Group 2:	28	27	25	19

Figure 6

Kaplan-Meier analysis of renal survival in patients who received (solid line) and did not receive (dotted line) entecavir treatment for HBV-GN.