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Efficacy of entecavir in treating hepatitis B virus-associated membranous nephropathy

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ABSTRACT

Objective: hepatitis B virus-associated membranous nephropathy (HBV-MN) is the most common pathological type of hepatitis B virus-associated glomerulonephritis. This study evaluated the efficacy of entecavir antiviral therapy for HBV-MN patients due to the intolerable side effects of interferon-alpha and high incidence rate of drug-resistance in lamivudine therapy.

Method: thirty-two patients with HBV-MN were identified by biopsy and treated with entecavir for 52 weeks. These patients were followed up to evaluate outcomes of entecavir-treatment. Descriptive statistics were used to summarize patient demographics and treatment outcomes.

Results: entecavir treatment reduced 24-h urinary protein excretion. The total probability of partial proteinuria and complete remission at 24 and 52 weeks was 53.1 and 78.1 %, respectively. A decrease of circulating HBV-DNA was observed in all patients

with active HBV replication. The significant decrease of 24-h urinary protein began at 12 weeks, as early as the decrease of serum HBV-DNA level. The serum HBV DNA titers at baseline and after 52 weeks of treatment were 4.3 ± 2.8 log_{10} and 2.3 ± 1.7 log_{10}, respectively. Meanwhile, eGFR increased from 100.3 ± 20.5 ml/min/1.73 m^2 at baseline to 107.7 ± 15.9 ml/min/1.73 m^2 after 52 weeks of treatment. The serum alanine aminotransferase level (ALT) gradually decreased to normal during entecavir antiviral treatment.

Conclusions: entecavir treatment in HBV-MN patients was carefully described. Complete remission and HBV replication suppression were induced by entecavir treatment in HBV-MN patients. Patients with high serum creatinine (Scr), ALT and low eGFR levels benefit more from entecavir treatment. Entecavir therapy is well tolerated by patients and no adverse reactions were observed.

Keywords: Hepatitis B virus-associated membranous nephropathy. Entecavir. Proteinuria. eGFR.

INTRODUCTION

Hepatitis B virus (HBV) infection can cause not only liver diseases but also a spectrum of extrahepatic diseases such as HBV-associated glomerulonephritis (HBV-GN). This is one of the most common secondary glomerulonephrites, after lupus nephritis (1). The most common histological type of HBV-GN is membranous nephropathy (MN) (2). Although MN progresses slowly and presents a relatively high spontaneous remission rate in children, the existing data suggested that there is another scenario in adults (2,3). The course of HBV-MN in adults in HBV endemic areas is not optimistic. Nearly 30 % of the HBV-MN adult patients developed end-stage renal disease (renal failure) and approximately 10 % would require kidney replacement therapy (2,4,5). Thus, an effective therapeutic regimen that not only attenuates proteinuria but also inhibits HBV replication is needed for adult patients with HBV-MN.

Currently, the common antiviral drugs include interferon or nucleoside/nucleotide analogues such as lamivudine, telbivudine, adefovir dipivoxil, entecavir, as well as tenofovir-based agents, TDF and TAF. It has been suggested that antiviral therapy might attenuate proteinuria in patients with HBV-MN (6-8). However, there is no consensus on the optimal strategy of treatment for HBV-MN. Two major reasons limited the clinician's choice. The first reason is that most of the antiviral drugs are not suitable for patients with abnormal hepatic function or impaired renal tubular function. For example, interferon-alpha treatment increases the risk of decompensation in patients with advanced cirrhosis (3,9). Adefovir is limited in renal impaired patients due to its tubular toxicity. Furthermore, resistant mutant virus strains develop after long-term treatment with nucleoside analogs. HBV-MN cannot be treated after the resistance occurs due to the high incidence of lamivudine and telbivudine resistant-HBV mutant (10). Thus, it is reasonable to try monotherapy with new nucleotide analogues or in combination with other types of drug for HBV-MN.

Some case reports have shown that entecavir was effective in both antiviral and abrogating proteinuria, including lamivudine-resistant strains (10-13). Thus, it might be a reasonable candidate. However, no data have shown whether entecavir benefits HBV-MN patients by the multiple-case study. Our previous research has shown that tacrolimus (TAC) combined with entecavir effectively induced remission of HBV-MN with nephrotic syndrome, without enhancing viral replication in Chinese adults (14). The working mechanism of TAC is the inhibition of HBV entry into hepatocytes through targeting of the candidate HBV receptor, sodium taurocholate cotransports polypeptide (NTCP) (15-16). This combination of entecavir and TAC was unsuitable for HBV-MN patients without nephrotic syndrome or renal tubulointerstitial lesions. Thus, it is still important to determine the efficacy of entecavir monotherapy on HBV-MN patients.

PATIENTS AND METHODS

Patients

Data from 32 patients admitted to the Guangdong General Hospital from January 2010 to December 2013 were retrospectively studied. The inclusion criteria were: a) age from 18 to 70 years; b) all HBV-GN cases with biopsy-proven MN; c) evidence of chronic HBV infection based on the presence of HBsAg, HBeAg or HBV DNA in serum; d) an estimated glomerular filtration rate (eGFR) > 50 ml/min/1.73 m^2 according to the Chronic Kidney Disease Epidemiology Collaboration (CKD- EPI) formula; and e) no immunosuppressor or antiviral drug intake before treatment. The exclusion criteria included a diagnosis of idiopathic MN, severe hepatitis, decompensated cirrhosis, liver cancer, malignancy, diabetes mellitus, severe infections or any other systemic disease known to be associated with secondary MN.

Clinical data including Scr, eGFR, 24-h excretion of urine protein, serum albumin, serum HBV-DNA, percentage of active HBV replication, serum HBsAg, HBeAg, HBsAb, HBeAb, HBcAb, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were collected from all patients. Active HBV replication was defined as HBsAg positive and/or serum HBV DNA positive.

The study protocol was in accordance with the ethical guidelines of the Declaration of Helsinki amended in 2008 and approved by the Guangdong General Hospital's Ethics Committee. All patients provided written informed consents.

METHODS

Diagnosis of HBV-MN

HBV-GN is confirmed by the concurrence of the following indications: a) HBV antigen observed in serum (inactive carriers were included); b) renal biopsy showed glomerulonephritis without other types of secondary nephritis; and c) HBV antigen presented in the kidney, which is required for the diagnosis of HBV-GN.

The determination of HBV-associated MN was based on histological measurements with light, immunofluorescence and electron microscopy. Renal tissue samples were routinely processed and stained with hematoxylin-eosin, periodic acid-Schiff, Masson's trichrome, Jones's silver and Congo red stains. For direct immunofluorescence, frozen

sections of the fresh tissue samples were stained with antisera against human C3, C4, C1q, IgA, IgM, IgG and fibrinogen. HBV-specific antigens were assessed by indirect immunofluorescence using a rabbit polyclonal antibody against HBcAg and monoclonal antibodies against HBeAg and HBsAg, as previously described (18). Two renal pathologists performed histologic grading of MN and did not have knowledge of the patients' clinical status.

Serum DNA levels were determined using the polymerase chain reaction (PCR). Other serum HBV markers, including HBsAg, HBeAg, HBsAb, HBeAb and HBcAb, were detected using the enzyme-linked immunosorbent assays (ELISA). The low limitation of HBV DNA tittering assay is 500 cp/ml and HBV DNA < 500 cp/ml was considered as undetectable.

Entecavir treatment

All the HBV-MN patients took 0.5 mg/day entecavir (Sino American Shanghai Squib Pharmaceutical Ltd.) and were followed-up for 52 weeks. All patients were instructed to maintain the same dosage of angiotensin receptor blockers (ARB) or angiotensin-converting enzyme inhibitors (ACEI) as before enrollment. The patients achieved a blood pressure target of below 130/85 mmHg, with or without additional antihypertensive agents.

Outcome measures

The primary outcome variable was the number of patients who attained a complete or partial remission (CR or PR). CR was defined as < 0.5 g/24 h proteinuria or lower, plus stable renal function (eGFR > 50 ml/min/1.73 m^2). PR was defined as urinary protein < 3.5 g/24 h and/or 50 % lower than the baseline value, plus stable renal function. Treatment failure (NR) was defined as the persistence of 24 h urinary protein that exceeded 50 % over the baseline level, or unchanged 24 h urinary protein. Secondary outcome variables included serum creatinine level, serum HBV DNA level and serum ALT level. The HBV DNA level was detected at baseline and time points of 12, 24 and 52 weeks after treatment. Other parameters were evaluated at baseline and eight, 12, 24,

36 and 52 weeks after treatment.

Safety analysis, including at least one safety assessment, was performed in all enrolled patients who received entecavir since the treatment began. Safety assessment included an evaluation of adverse events and laboratory abnormalities.

Statistical analysis

The frequencies of categorical variables are presented as a percentage. The measured variables are shown as the mean ± SD (standard deviation) or median (interquartile range). The quantitative data, before and after treatment, were analyzed using the paired student *t*-test or Wilcoxon signed-rank test with two-tails. p-values less than 0.05 were considered as statistically significant. The statistical analysis was performed using SAS9.2.

RESULTS

General characteristics

The baseline demographic, clinical, and laboratory characteristics of the 32 patients are shown in table 1. There was no statistically significant difference for the baseline demographic, clinical and laboratory characteristics between the 52 weeks remission *versus* non-remission groups. Before treatment, HBV markers (serum HBsAg, HBeAg, or HBV-DNA) were positive among all the patients and 65.6 % of the patients had active viral replication. Nine patients had nephrotic syndrome (proteinuria > 3.5 g/24 h). Five patients had abnormal serum alanine aminotransferase (ALT ≥ 1.5 times of the upper limit of normal range). With regard to eGFR grade, eight of 32 patients had a low renal filtration rate and one patient was diagnosed with stage 3 chronic kidney disease (CKD), other patients had a normal eGFR.

The rate of partial or complete remission induced by entecavir

Complete and partial remission of proteinuria at different time points after entecavir treatment are shown in figure 1. The percentages of proteinuria remission (PR + CR)

were 53.1 %, 68.8 % and 78.1 % at 24, 36 and 52 weeks, respectively (Fig. 1A). The urinary protein level was significantly lower after 12 weeks of entecavir treatment and remission was maintained until 52 weeks of treatment were completed (Fig. 1B). Urinary protein decreased from 2.88 g/24 h (95 % CI: 2.2-3.6) at baseline to 2.1 g/24 h (95 % CI: 1.6-2.7) ($p < 0.05$) at week 12, 1.5 g/24 h (95 % CI: 1.1-2.0) ($p < 0.05$) at week 24, 1.2 g/24 h (95 % CI: 0.8-1.6) ($p < 0.05$) at week 36 and 0.92 g/24 h (95 % CI: 0.6-1.2) at week 52 ($p < 0.05$). After 52 weeks of treatment, 12 patients (37.5 %) excreted normal urinary protein (< 0.5 g) in 24 hrs.

Repaired renal function by entecavir treatment

There was no significant change in Scr levels during antiviral therapy, as the Scr levels of most of the patients were normal (Fig. 2A). With regard to subpopulations, the Scr levels of Q1 and Q2 were similar during the 52 weeks of treatment. However, the Scr level of Q3 decreased from 92.0 µmol/l at 36 weeks to 79.5 µmol/l at 52 weeks. Furthermore, the greatest Scr decrease occurred from an abnormal 131.0 µmol/l at 36 weeks to a normal 98.0 µmol/l at 52 weeks (data not shown). This means the high Scr population benefit more from the entecavir treatment. None of the patients had progressed to end-stage renal disease at the end of treatment.

Improvement of eGFR from baseline to 52 weeks is shown in figure 2B. The average eGFR tends to increase during treatment. The eGFRs were 101.2 ± 21.8, 105.8 ± 17.2, and 107.7 ± 15.9 ml/min/1.73 m^2 at weeks 24, 48 and 52 of entecavir antiviral treatment, respectively. Compared to the baseline, eGFR significantly increased from 100.3 ± 20.5 ml/min/1.73 m^2 at baseline to 107.7 ± 15.9 ml/min/1.73 m^2 at 52 weeks ($p < 0.05$). Patients with lower eGFR will benefit more from entecavir treatment (data not shown).

Changes of liver function

After entecavir antiviral treatment, the serum HBV DNA titer was significantly decreased in 21 patients with active HBV replication (Fig. 3A). The mean levels of serum HBV DNA

titers are 4.25, 2.87, 2.43 and 2.25 $\log_{10}$ IU/ml at 0, 12, 24 and 52 weeks after treatment. Circulating HBV DNA levels even fell below the detection threshold in six out of 21 patients (28.6 %) at week 24, and in nine of 21 patients (42.9 %) at week 52. After 52 weeks of entecavir antiviral treatment, four of 12 (33.3 %) persistent viremia patients presented complete proteinuria remission and five of nine (55.6 %) HBV DNA seroconversion patients presented complete proteinuria remission. There was no significant difference between the persistent viremia patients and seroconversion patients, which may be due to the limited sample size. HBeAg or HBsAg seroconversion was not observed during treatment.

The serum ALT levels decreased to normal levels in five patients with abnormal ALT. The mean value of serum ALT level decreased from 34.2 ± 29.9 U/l (95 % CI: 23.4-45.0) at baseline to 21.2 ± 6.4 U/l (95 % CI: 18.8-23.5) at the end of therapy ($p < 0.05$) (Fig. 3B). After 24 weeks of therapy, the ALT level was significantly lower than that before treatment. In addition, patients with relatively high ALT levels benefit more from entecavir treatment.

Adverse events during the therapy of entecavir

Twelve patients suffered from persistent viremia after 52 weeks of treatment. Hepatic decompensation or malignancy was not observed during follow-up. No adverse effects of entecavir were found in any patient during the treatment period.

DISCUSSION

Membranous nephropathy is the most common pathological type of hepatitis B virus-associated glomerulonephritis (2). Antiviral drugs are highly recommended for HBV-GN as the first choice in the current therapeutic guidelines. It has been suggested that lamivudine treatment might improve renal function in HBV-MN patients (17). The widespread and long-term application of lamivudine was limited in the clinical use due to the high incidence rate of lamivudine resistant-mutant in HBV strains and the outstanding recurrence of proteinuria (17,18). Yan Z et al. reported that telbivudine

might alleviate proteinuria and protect renal function (7). However, the frequency of telbivudine resistant-mutants is also high (10). Although adefovir and tenofovir can both inhibit HBV replication and induce the remission of proteinuria (19), their potential nephrotoxicity has limited their clinic use for patients with HBV-GN (20). Therefore, new nucleoside analogues such as entecavir could be considered as an alternative rescue therapy of lamivudine or interferon when drug-resistance occurs in HBV-MN patients.

Entecavir is a new type of antiviral drug and has been used to treat chronic hepatitis B since 2005. It has been used as the first-line agent for the treatment of naïve chronic hepatitis B patients for more than ten years due to its strong HBV inhibitory effect and low rate of inducing resistance (21-23). In addition, entecavir can reduce inflammation, necrosis and fibrosis of the kidney tissues (19). Meanwhile, it has been reported in some case reports that entecavir monotherapy or in combination with prednisolone can significantly attenuate proteinuria and maintain a complete remission in HBV-MN (7,12). However, no study has focused on the dynamic change of renal function in HBV-MN patients treated with entecavir.

In this study, we retrospectively analyzed 32 HBV-MN patients with entecavir monotherapy. The results showed that entecavir antiviral therapy could improve the outcome of patients with HBV-MN. A significant reduction of 24-h urinary protein appeared after as soon as 12 weeks of treatment. A high remission rate (78 %) was achieved (25 out of 32 HBV-MN patients) at the end of treatment, compared with a 60 % remission in patients treated with lamivudine (19) and 73 % remission with adefovir treatment (24) in other studies. Our results supported the hypothesis that antiviral drugs could benefit HBV-GN patients (3,6,17). In this study, our data showed that entecavir was one of the best choices for treating HBV-MN due to its high efficacy and safety.

To date, there are some hypotheses that explain the possible pathogenesis of HBV-GN: (a) HBV directly infects renal cells, resulting in kidney damage (24,25); b) HBV antigen-antibody complexes are generated (circulating immune complexes and/or original site immune complexes) and deposit in the glomeruli (26); and c) HBV infection induces

autoimmune injury. Our results showed that entecavir was very active in the inhibition of HBV replication. Serum HBV DNA level decreased in all 21 patients with active HBV replication and HBV DNA in blood could not be detected in nine cases by week 52. This reduction of the HBV DNA level did not correlate with the remission of proteinuria. Thus, indirectly supporting the hypothesis that immune complex deposits induce kidney damage or HBV causes autoimmune injury in addition to the fact that the kidney is directly infected by HBV. Furthermore, this result may be related to HBV genotype or the duration of HBV infection. Previous studies have shown that entecavir results on serological conversion of HBeAg after 13 months of treatment (21). However, no serological conversion of HBeAg was observed in our study, which may be due to the short follow-up time. In addition, entecavir-resistance virus and severe side effects were not observed in our study.

As a result of inhibiting HBV replication, ALT levels significantly decreased after 24 weeks of entecavir therapy. The early stage of the liver disease means that the ALT levels are normal in all patients before treatment. However, a decrease in the ALT level still indicated that liver function could benefit from entecavir therapy.

One limitation of our study is the absence of a control group. Thus, raising the issue that some of these patients may have improved, regardless of antiviral therapy. Our Ethics Committee did not authorize an untreated control group, thus we were unable to use a control arm. As indicated in the current reference (27), spontaneous remission may occur in young patients but rarely in adults. Thus, entecavir treatment was considered as the main effect on HBV MN in this study.

CONCLUSION

This study has demonstrated the beneficial effects of entecavir therapy on HBV-MN in Chinese adult patients, such as a significant proteinuria remission. Patients with higher Scr or ALT levels or a lower eGFR level can benefit more from entecavir therapy. Our results suggest that entecavir could be an effective mono-treatment as a first-line antiviral agent for adult patients with HBV-MN. A large prospective cohort study is

needed to further confirm the conclusion of our study and explore the potential role of entecavir as a monotherapy for HBV-MN.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Ethical approval was given by the Ethics Committee of Guangdong Provincial People's Hospital, Guangzhou, China. All patients gave their written informed consent.

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AUTHOR'S CONTRIBUTION

LW and ZY contributed to the study conception and design. All authors collected the data and performed the data analysis. All authors contributed to the interpretation of the data and the completion of figures and tables. All authors contributed to the drafting of the article and final approval of the submitted version.

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Table 1. Demographic, clinical and laboratory characteristics of patients at baseline

Variables	*All* *n = 32*	*Partial/complete remission (at 52 weeks)* *n = 25*	*No remission (at 52 weeks)* *n =7*	*p values*
Age(years), mean ± sd	39.72 ± 12.14	41.24 ± 12.79	42.00 ± 15.26	0.895
Age grade, n (%)				0.75
< 40	14 (43.75)	10 (40.00)	4 (57.14)	
40-50	11 (34.38)	9 (36.00)	2 (28.57)	
> 50	7 (21.88)	6 (24.00)	1 (14.29)	
Gender, n (%)				0.669
Male	18 (56.25)	15 (60.00)	3 (42.86)	
Female	14 (43.75)	10 (40.00)	4 (57.14)	
sCr (μmol/l), median (IQR)	74 (51.50, 85.50)	72.92 ± 22.74	69.43 ± 21.58	0.719
eGFR (ml/min·1.73 m^2), mean ± sd	100.27 ± 19.82	100.08 ± 20.67	101.11 ± 21.58	0.909
eGFR grade				0.48
> 90	23 (71.87)	19 (76.00)	4 (57.14)	
60-90	8 (25.00)	5 (20.00)	3 (42.86)	
50-60	1 (3.13)	1 (4.00)	0 (0.00)	
Baseline urinary protein (g/24 h), median (IQR)	2.69 (1.15, 3.77)	3.19 ± 2.14	1.78 ± 0.79	0.079
Baseline serum albumin (g/l), mean ± sd	28.40 ± 8.24	28.95 ± 8.00	26.67 ± 9.41	0.533
Serum HBV DNA (log_{10}), median (IQR)	4.11 (1.00, 7.02)	4.36 ± 2.62	3.85 ± 3.57	0.745
Active HBV replication, n (%)	21 (65.6)	18 (72.00)	3 (42.86)	0.197
HBsAg-positive, n (%)	24 (75)	19 (76.00)	5 (71.43)	1
HBeAg-positive, n (%)	15 (46.9)	13 (52.00)	2 (28.57)	0.4
ALT (U/l), median (IQR)	22 (15.00, 41.00)	36.76 ± 32.16	24.86 ± 19.05	0.316

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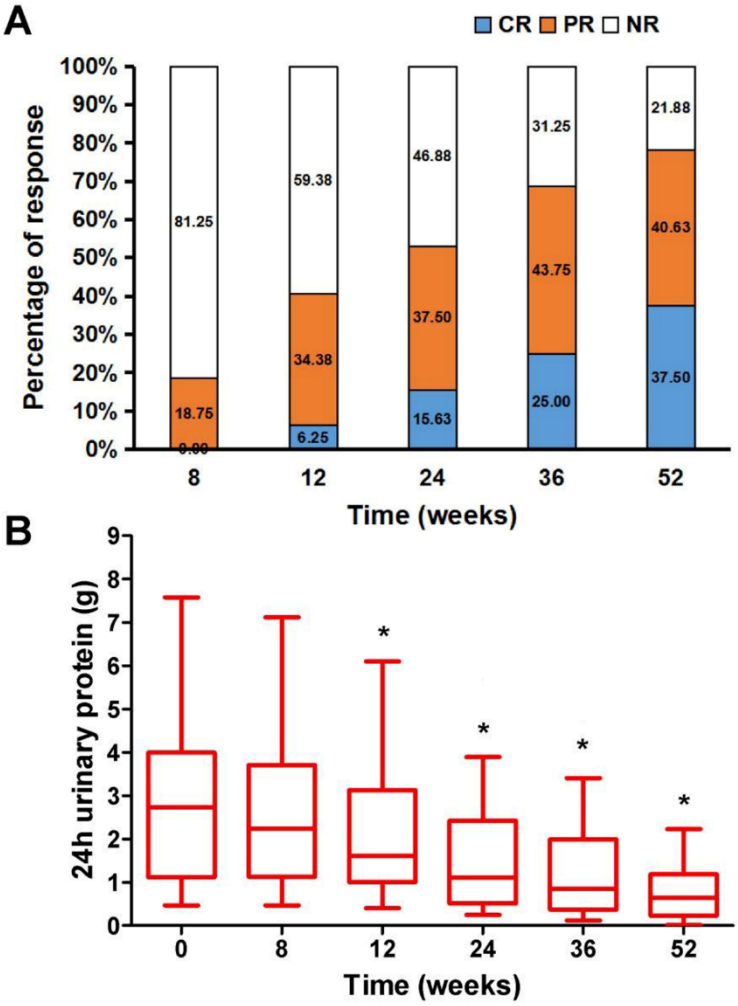

Fig. 1. Improved urinary protein level, suggesting renal function repair after entecavir treatment. A. The percentage of proteinuria remission is shown. CR: complete remission; PR: partial remission; NR: no response. B. Urinary protein levels at 24 hours are plotted. *$p < 0.05$, compared with the baseline value.

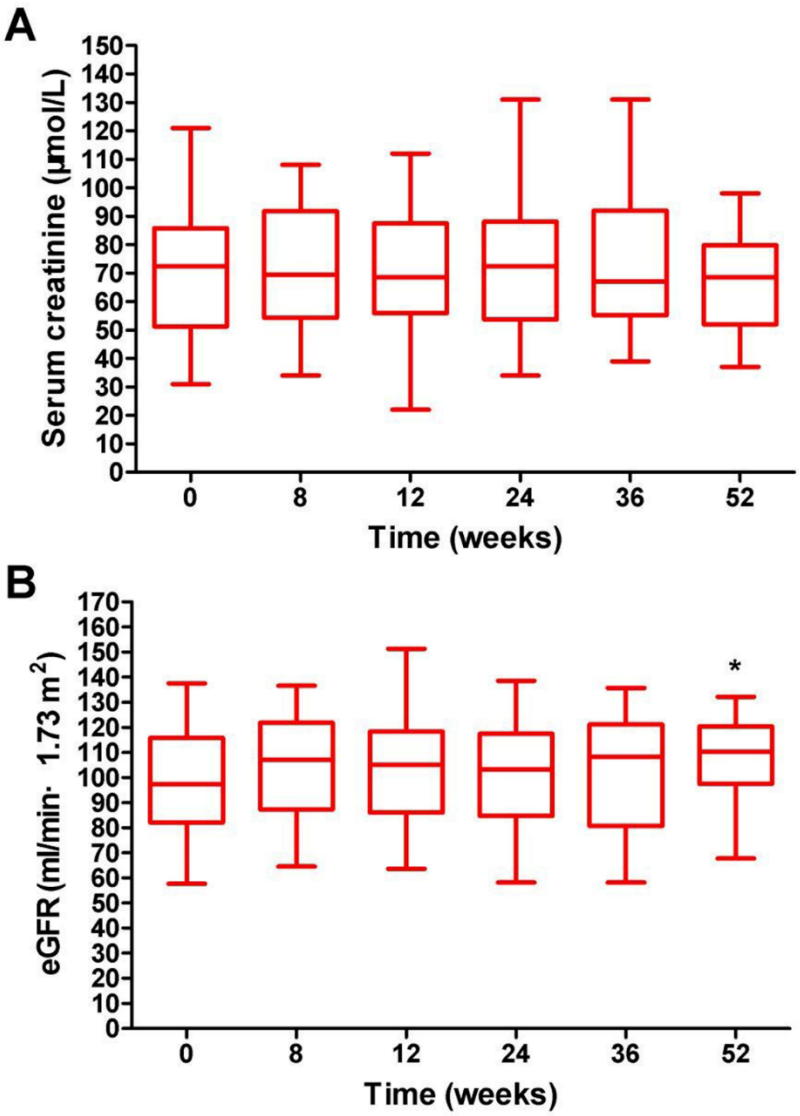

Fig. 2. Serum creatinine level and eGFR. A. There were no significant changes in the serum creatinine level. B. eGFR gradually increased during treatment. *p < 0.05, compared with the baseline value.

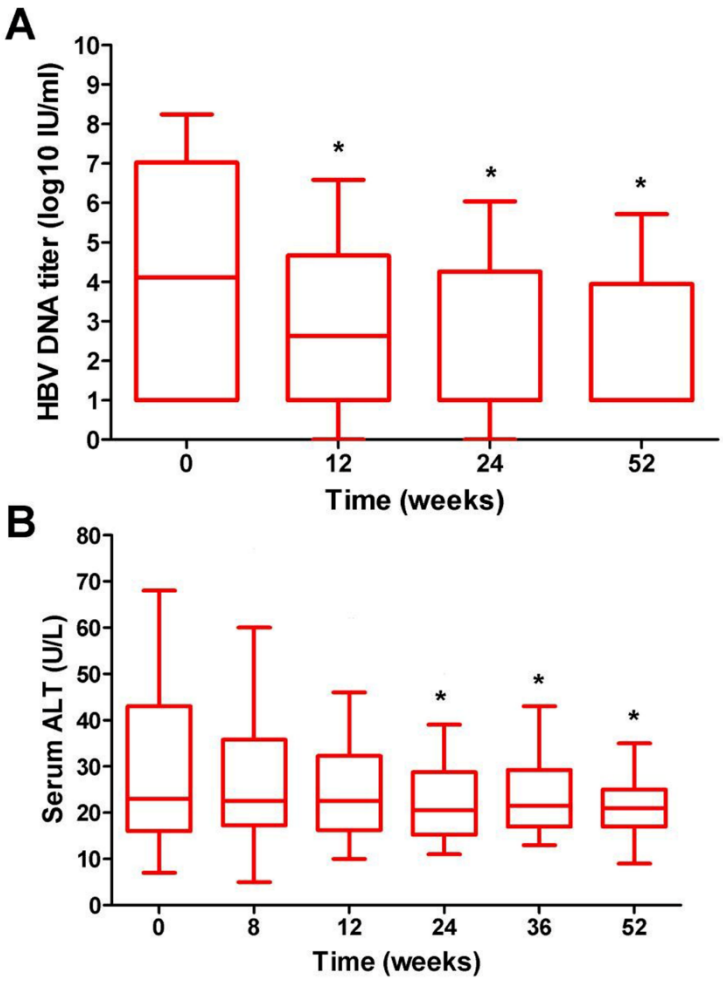

Fig. 3. Serum HBV DNA and ALT levels. A. The HBV DNA level was determined by HBV DNA titers. HBA DNA replication was strongly inhibited by entecavir. B. ALT level was assayed for liver function. The ALT level decreased after 24 weeks of treatment as a result of a decreased viral replication after entecavir treatment. *p < 0.05, compared with the baseline value.