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Effectiveness of telbivudine antiviral treatment in patients with hepatitis B virus-associated glomerulonephritis

A 104-week pilot study

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Abstract

The aim of this study was to evaluate clinical efficacy of telbivudine in treatment of hepatitis B virus-associated glomerulonephritis (HBV-GN).

A total of 43 HBV-GN patients combined with chronic hepatitis B were treated with telbivudine for 104 weeks. Serum levels of HBV DNA viral load, HBeAg, HBeAb, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Cr), and 24-hour urinary protein were evaluated after telbivudine treatment of 12, 24, 52, 76, and 104 weeks. Estimated glomerular filtration rate (eGFR) was calculated at baseline, 24 weeks, 52 weeks, and 104 weeks of treatment, respectively. Complete remission (CR) was defined as urinary protein <0.3 g/day, with normal ALT, AST, Cr, and eGFR. Criteria for partial remission include: 24-hour urinary protein excretion decreased by >50% compared with baseline level, and ALT and AST decreased >50%.

Proteinuria level gradually decreased in patients with HBV-GN after telbivudine treatment. The percentages of PR + CR were 90.7% and 95.3%, respectively, at 52 and 104 weeks. Compared to baseline, eGFR were significantly increased from 69.2 ± 23.1 mL/min/1.73 m^2 to 116.2 ± 26.3 mL/min/1.73 m^2 at 104 weeks of treatment. Multivariate analysis indicated that baseline HBV DNA viral load (odds ratio [OR] = 1.19, 95% confidence interval [CI] 1.11–2.19, $P = .02$) and baseline urinary protein (OR = 1.08, 95% CI 1.04–2.44, $P = .03$) were independent risk factors associated with CR after telbivudine treatment among patients with HBV-GN.

Our study demonstrates that telbivudine can be used to treat HBV-GN and effectively improve eGFR in these patients.

Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, CK = Creatine kinase, CR = complete remission, Cr = creatinine, GFR = glomerular filtration rate, HBcAb = hepatitis B core Antibody, HBeAb = hepatitis B e antibody, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HBV-GN = hepatitis B virus-associated glomerulonephritis, HBeAg = hepatitis B e antigen, PR = partial remission.

Keywords: antiviral treatment, hepatitis B virus, hepatitis B virus associated glomerulonephritis, nephrotic syndromes, telbivudine

1. Introduction

Chronic hepatitis B virus (HBV) infection occurs worldwide and is associated with increased risk of extrahepatic diseases, end-stage liver disease, cirrhosis, and hepatocellular carcinoma.[1,2] Hepatitis B virus-associated glomerulonephritis (HBV-GN) is one of the most important HBV-related extrahepatic disease and most common secondary immune complex glomerulonephritis induced by HBV. Most HBV-GN patients present nephrotic syndrome with mild to moderate proteinuria. Although spontaneous remission of HBV-GN has been reported in pediatric cases,[3] treatment in adult HBV-GN patients is not as successful as in children.[4] Approximately, 30% of adult patients with HBV-GN may develop into end-stage renal disease including renal failure, and renal replacement will be required in 10% of these patients.[5] Treatment options of HBV-GN are still limited and there is no consensus recommended worldwide, especially for adult patients.

Some patients with nephritic syndrome are treated with immunosuppressive agents. However, treatment with immunosuppressive agents like glucocorticoids is controversial for HBV-GN patients because of their inhibition of the immune system and potential activation of latent HBV, leading to active HBV replication and aggravation of renal lesions. For HBV-GN patients, antiviral drugs might be a favorable treatment option, as these drugs can inhibit HBV replication, thereby protecting liver functions and relieving the symptoms of kidney. It has been demonstrated that antiviral therapy promotes the clearance of HBV and abrogates the co-existing renal disease[6].

Telbivudine is an antiviral drug with high Hepatitis B e Antigen (HBeAg) to HBe antibody (HBeAb) seroconversion rate.[7] It has been reported that telbivudine has protective effect on compromised glomerular filtration rate (GFR) in HBV-infected

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The authors report no conflicts of interest.

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patients.[6,8–11] However, few studies have been carried out to investigate the effects of telbivudine in the treatment of HBV-GN patients for a long period. Here, we report the 104-week outcomes in 43 HBV-GN patients receiving telbivudine, and provide medical evidences of telbivudine antiviral treatment in patients with HBV-GN.

2. Materials and methods

2.1. Subjects

From February 2011 to February 2013, a total of 43 adult HBV-GN patients (29 males and 14 females, age range 20~52 years, average age 35.5 ± 10.9 years) were enrolled from No. 6 People's Hospital of Qingdao. The demographic and baseline characteristics were shown in Table 1.

Patients with HBV-GN aged 16 to 61 years were enrolled in our study. Diagnostic criteria for HBV-GN in this study are as follows: the presence of a serum HBV antigen; the diagnosis of glomerulonephritis with the exclusion of other types of secondary nephritis; and the presence of renal HBV antigen. Patients were excluded if they: patients with severe hepatitis, decompensate cirrhosis, liver cancer, and patients who had developed end-stage renal diseases; subjects who had used other antiviral drugs before the treatments; patients accompanied HCV, HIV and other chronic viral infections, autoimmune hepatitis, systemic lupus erythematosus, and other autoimmune diseases; and patients with family history of myopathy or myopathy. All 43 patients completed the 104-week treatment and follow-up.

This study protocol followed the ethical guidelines of the Declaration of Helsinki amended in 2008 and was approved by the Ethics Committee of No. 6 People's Hospital of Qingdao.

2.2. Laboratory tests

Serum levels of HBV DNA, hepatitis B surface antigen (HBsAg), hepatitis B surface Antibody (HBsAb), HBeAg, HBeAb, hepatitis B core antibody(HBcAb), alanine aminotransferase(ALT), aspartate aminotransferase(AST), and serum creatinine(Cr) were measured in the clinical lab of No. 6 People's Hospital of Qingdao. Creatine kinase(CK), CK-MB, and 24-hour urinary protein changes were tested at enrollment and 12, 24, 52, 76, and 104 weeks of treatment. GFR at baseline, 24 weeks, 52, and 104 weeks of treatment were measured. (2) Unexplained fatigue, muscle pain, other symptoms and abnormal indicators were observed and recorded during treatment and follow-up. Specialized physicians are responsible for guiding medication adjustment during treatment.

Table 1

Demographic and baseline characteristics by groups.

Variables	
Sample size	43
*Age, y	35.5 ± 10.9
Sex (M/F)	29/14
*ALT, U/L	210.9 ± 55.6
*AST, U/L	161.0 ± 44.4
*HBV DNA level, (log_{10}IU/mL)	5.2 ± 2.2
*Creatinine, μmol/L	112.5 ± 32.4
*Urinary protein, g/day	5.2 ± 2.2
*eGFR, mL/min/1.73 m^2	69.2 ± 23.1

ALT = alanine aminotransferase, AST = aspartate aminotransferase, eGFR = estimated glomerular filtration rate, HBV = hepatitis B virus.
* Expressed as mean ± standard deviation.

2.3. Antiviral Treatment

All patients enrolled in our study received telbivudine (Beijing Novartis Pharmaceutical Co., Ltd.) for 0.6 g/day. Patients were followed-up for 104 weeks in our study. To evaluate the efficacy of telbivudine in patient with HBV-GN, immune-suppressants were not used during treatment.

2.4. Efficacy endpoints and safety analysis

The primary efficacy endpoint was the proportion of patients who experienced with complete or partial remission (CR or PR). Criteria for CR include: urinary protein <0.3 g/day, stable renal function, and normal liver functions (as indicated by normal ALT and AST). Criteria for partial remission include: 24-hour urinary protein excretion decreased by >50% compared with baseline level, and ALT and AST decreased >50% compared with baseline level.

Secondary efficacy endpoint measures included mean serum HBV DNA decreased and the proportions of patients with HBeAg loss or seroconversion, virologic breakthrough, primary nonresponse, and genotypic resistance.

Safety analysis included all patients who enrolled and received study medication and had at least 1 safety assessment since the baseline. Safety assessment included assessment of adverse events and laboratory abnormalities.

2.5. Statistical analysis

Continuous variables were expressed as mean and standard deviation, and categorical variables were expressed as percentages. HBV DNA viral load in our study were expressed in logarithmic units (log_{10}IU/mL). The χ^2 test and t test were applied when they are appropriate. The statistical significance of all tests was set as $P < .05$ by 2-tailed tests. Data analyses and quality control procedures were performed using SPSS for Windows, version 13.0 (SPSS Inc. 233 South Wacker Drive, 11th Floor, Chicago, IL).

3. Results

3.1. Effects of telbivudine on complete and partial remission rate

Complete and partial remission rates at different time after treatment were shown in Figure 1. At 12 weeks, telbivudine

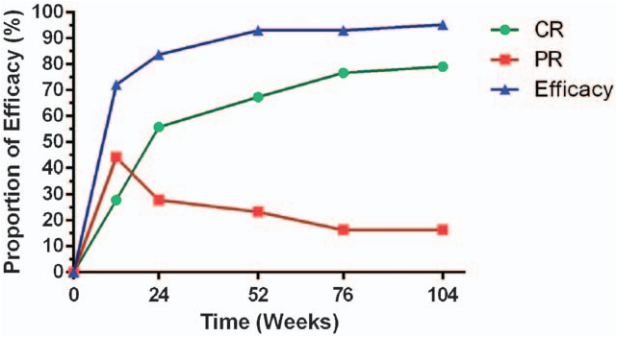

Figure 1. Proportion of proteinuria remission in patients with hepatitis B virus-associated glomerulonephritis during Telbivudine treatment. At week 12, telbivudine treatment was associated with significant reduction in proteinuria and with prolonged period of treatment. The percentages of proteinuria remission (PR + CR) were 83.7%, 90.7%, 95.3% at week 24, 52, and 104, respectively. At week 104, a total of 34 (79.1%) patients with urinary protein <0.3 g/day. CR = complete remission, PR = partial remission.

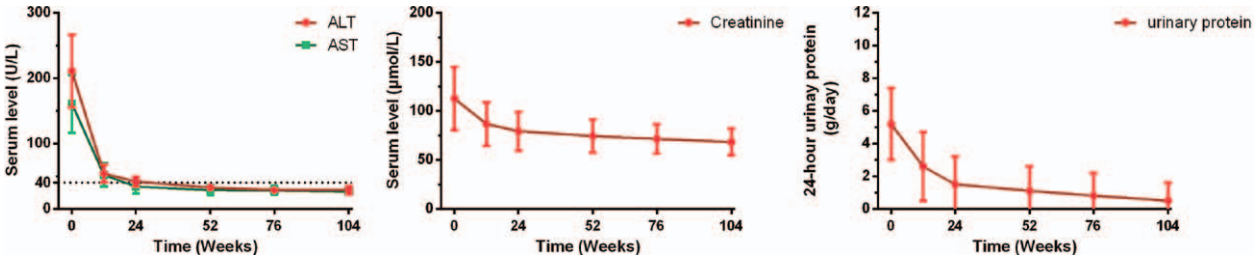

Figure 2. Dynamic changes of ALT/AST, serum creatinine, and level of urine protein ALT and AST levels were significantly decreased after telbivudine treatment. The respective level of ALT/AST were 210.9±55.6/161.0±44.4, 53.9±13.5/51.9±17.6, 41.8±7.6/34.1±10.1, 32.7±4.8/28.5±7.9, 28.9±5.5/28.2±6.8, 28.6±6.2/26.0±5.6 U/L at week 0, 12, 24, 52, 76, and 104 (all $P<.001$). The creatinine levels were 112.5±32.4, 86.5±22.2, 79.2±19.7, 74.2±16.9, 71.4±14.9, 68.3±13.7 umol/L (all $P<.001$). The 24-hour urinary protein were 5.2±2.2, 2.6±2.1, 1.5±1.7, 1.1±1.5, 0.8±1.4, and 0.5±1.1, respectively, after telbivudine antiviral treatment at week 0, 12, 24, 52, 76, and 104 (all $P<.001$). ALT = alanine aminotransferase, AST = aspartate aminotransferase.

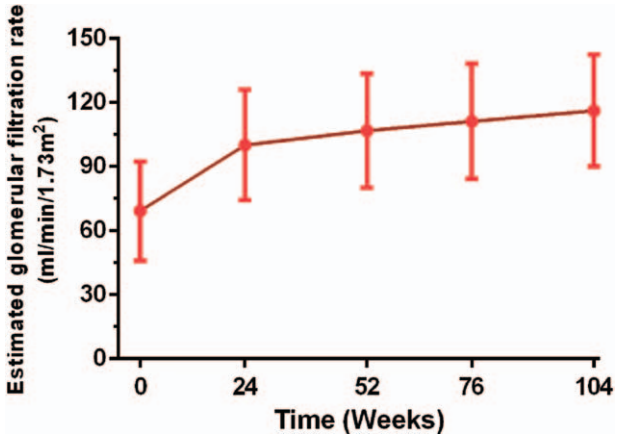

Figure 3. Dynamic change of eGFR after telbivudine treatment. The average level of eGFR increases with telbivudine treatment. The respective eGFRs were 69.2±23.1, 100.1±25.9, 106.8±26.7, 111.2±27.0 and 116.2±26.3 at week 0, 24,52, 76, and 104 after telbivudine antiviral treatment ($P<.001$).

treatment was associated with significant decreased in proteinuria and with prolonged period of treatment, the curative effect was remarkable. The percentages of proteinuria remission (PR + CR) were 83.7%, 90.7%, 95.3% at 24, 52, and 104 weeks, respectively. At 104 weeks, levels of urinary protein in 34 (79.1%) patients dropped <0.3 g/day.

ALT, AST, and serum creatinine levels were significantly decreased after telbivudine treatment. In addition, significantly decreased in proteinuria was observed. As shown in Figure 2, urine protein in 41 patients returned to normal at 76 weeks. Only 2 patients had mildly elevated urine protein level at 104 weeks.

3.2. Improvement of eGFR by telbivudine treatment

Dynamic Changes in eGFR from baseline to 104 weeks of telbivudine treatment were shown in Figure 3. After 24 weeks of treatment, eGFR increased significantly to 100.1±25.9 mL/min/1.73 m^2 ($P<.001$). The average level of eGFR continued to increase with longer period of treatment. The respective eGFRs were 106.8±26.7, 111.2±27.0, and 116.2±26.3 at week 52, 76, and 104 after telbivudine antiviral treatment.

3.3. Antiviral efficacy of telbivudine treatment

After antiviral treatment with telbivudine, HBV DNA viral load was decreased in patients with HBV-GN, as shown in Figure 4, with HBV DNA viral load of 5.2±2.2, 4.2±1.2, 3.2±1.6, 2.6±1.3, 2.1±1.2, and 1.2±0.9 $\log_{10}$ IU/mL, respectively at week 12, 24, 52, 76, and 104. Serum HBeAg was eliminated in some

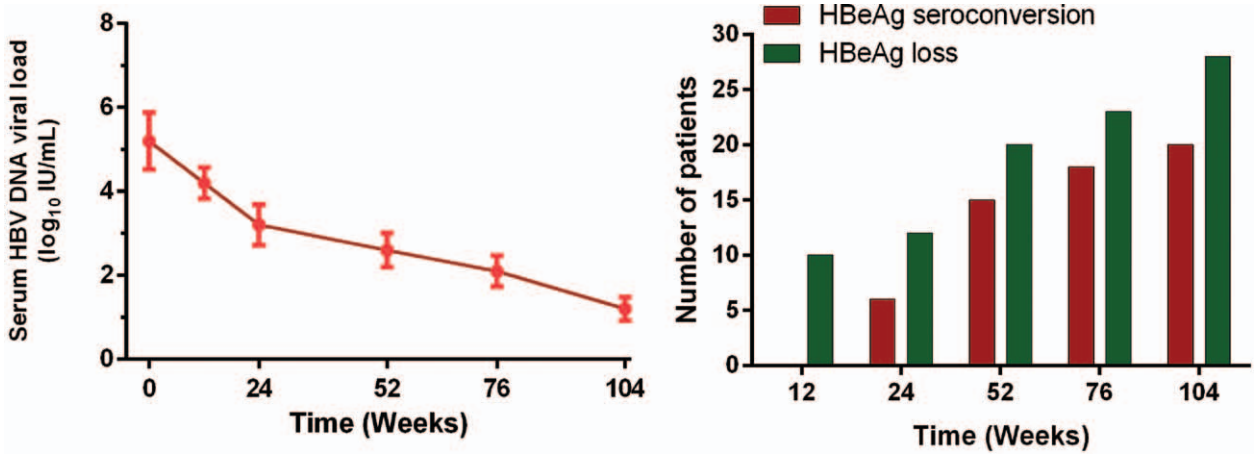

Figure 4. Efficacy of telbivudine on HBV among patients with hepatitis B virus-associated glomerulonephritis (HBV-GN). HBV DNA viral load were decreased in patients with HBV-GN with viral load of 5.2±2.2, 4.2±1.2, 3.2±1.6, 2.6±1.3, 2.1±1.2, and 1.2±0.9 $\log_{10}$ IU/mL, respectively, at week 12, 24, 52, 76, and 104. HBeAg loss rates were 27.9%, 46.5%, 53.4%, and 65.1% at 24, 52, 76, and 104 weeks, respectively. HBeAb seroconversation rates were 14%, 34.9%, 41.9%, and 46.5% at 24, 52, 76, and 104 weeks, respectively. HBeAg = hepatitis B e antigen, HBV = hepatitis B virus.

Table 2

Baseline variables associated with complete remission.

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Sex	1.14	0.88–1.47	0.32			
Age	0.98	0.97–0.99	0.04			
ALT level	0.98	0.74–1.3	0.91			
AST level	1.17	0.95–1.43	0.14			
HBV DNA levels	1.65	1.18–2.31	0.003	1.47	1.02–2.11	0.02
Creatinine level	0.87	0.68–1.11	0.26			
Urinary protein	2.57	2.14–3.13	<0.001	1.71	1.17–2.51	0.01
eGFR level	1.52	1.02–2.28	0.03			

ALT = alanine aminotransferase, AST = aspartate aminotransferase, CI = confidence interval, eGFR = estimated glomerular filtration rate, HBV = hepatitis B virus, HR = hazard ratio.

patients. HBeAg loss rates were 27.9%, 46.5%, 53.4%, and 65.1% at 24, 52, 76, and 104 weeks, respectively. HBeAb seroconversation rates were 14%, 34.9%, 41.9%, and 46.5% at 24, 52, 76, and 104 weeks, respectively, as shown in Figure 4.

3.4. Univariate and multivariate analysis for CR

To the analysis of independent factors associated with CR, we performed multivariate Cox regression analysis to identify the predictive factors associated CR at week 104. Univariate results indicated that age, baseline HBV DNA levels, baseline urinary protein, and baseline eGFR level were risk factors to develop CR at week 104. Multivariate analysis indicated that only baseline HBV DNA viral load and baseline urinary protein were independent risk factors associated with CR after telbivudine treatment among patients with HBV-GN, as shown in Table 2.

3.5. Adverse events during telbivudine treatment

During the treatment, persistent viremia was observed in 5 patients. Those patients admitted with poor adherence with telbivudine during follow-up, and 3 of them identified with genotype telbivudine resistance. Serum level of CK and CK-MB had no significant change before and after treatment. Only 1 male patient developed transient mildly elevated CK at 12 weeks of treatment and the CK level in this patient returned spontaneously to normal level 4 weeks later. During the treatment, no fatigue, muscle pain, and other adverse reactions were observed.

4. Discussion

Chronic HBV infections pose a serious threat to human's health and incidence of HBV infection is very high in some Asian countries.[12–17] HBV-GN is a common complication of HBV infection. Currently, HBV-GN is considered as a chronic latent disease and patients present with the nephrotic syndromes. Some patients present with mild to moderate proteinuria and hematuria. In this study, 43 patients were enrolled and most of them had no typical clinical manifestations of chronic nephritis. Most of them were diagnosed with nephritis in the usual examination. The specific onset time was not clear. Only 2 patients came to our hospital because of swelling of the eyelids, prominent fatigue, and suspected nephritis. The main pathogenesis of HBV-GN is probably that viruses infect kidney cells and HBV antigen–antibody complexes deposit in the glomeruli, resulting in immunological injury.[18] Accordingly, anti-HBV drugs could be effective regimen in the treatment of HBV-GN. Some studies have shown that antivirals are effective in HBV-GN patients as they can inhibit HBV DNA replication, clear the viral antigens, alleviate proteinuria and protect renal function.[19–22]

There is no standardized recommendation of antiviral drugs for HBV-GN to date. Lamivudine is the first antiviral drug used to treat HBV-GN patients. Tang et al[23] reported that lamivudine can improve the remission rate of proteinuria and inhibit HBV DNA replication. However, clinical application of lamivudine is limited because of the high resistant rate and recurrence of proteinuria after treatment.[24] Entecavir can also effectively inhibit the HBV-DNA replication and improve the remission rate of proteinuria with low resistant rate. However, most patients cannot afford it because of its high cost. Adefovir, dipivoxil, and tenofovir are phosphonate nucleotide analog of adenosine, which can inhibit viral polymerases and causes DNA chain termination. However, the concern for potential nephrotoxicity has limited their use in patients with HBV-GN. A meta-analysis conducted by Fabrizi et al[25] showed that interferon was safe and effective, and that the proteinuria remission rate reached 50%. However, the widespread application of interferon was limited in clinics because of its high economic burden and adverse reactions. Therefore, more affordable drugs with fewer side effects should be further explored for the treatment of HBV-GN.

Telbivudine, an effective antiviral drug, has attracted more and more clinical attention because of its higher HBeAg to HBeAb seroconversion rate and its potentially favorable effect on glomerular filtration rate. Seroconversion of HBeAg to HBeAb is considered to be a favorable prognostic predictor for HBV-GN, as it indicates that the deposition of glomerular immune complex is decreasedor eliminated. In GLOBE Phase III study, HBeAg loss was achieved in 41% of patients treated with telbivudine as compared with 32% of patients treated with lamivudine, and 36% of patients in the telbivudine group achieved seroconversion to HBeAb as compared with 27% in the lamivudine group.[26] In Chinese Phase III trial patients, the seroconversion rate was 29% in the telbivudine group compared with 20% in the lamivudine group after 2 years of treatment.[27] All kinds of studies suggest that both the innate and adaptive immune responses contribute to high seroconversion rate during telbivudine treatment through modulation of the function and/or expression of CD4+/CD8+T cells, TH1/TH2, Treg, PD-1/PD-L1, TH17, interleukin-21, and Follicular helper T cell (TFH).[28–30] In our study, HBeAg was eliminated in 28 (65.1%) patients at 104 weeks of treatment. Among these patients, 20 (46.5%) patients developed HBeAb. All of these patients achieved CR or PR at 104 weeks, indicating that development of anti-HBeAg antibodies and HBeAg clearance are associated with remission of proteinuria.[31,32] These results also support the theory that immune complex deposition plays a central role in pathogenesis of HBV-GN.

Another important finding of this study is that telbivudine has protective effect on renal functions. Serum creatinine levels decreased to some extent in the group of patients at 24 weeks and returned to the normal level with the extension of treatment. After 104 weeks' treatment, eGFR levels were significantly increased and 24-hour urinary protein quantitation was significantly decreased compared with baseline levels. We believe that the mechanisms may involve: telbivudine can inhibit HBV replication, and reduce serum levels of HBeAg, HBsAg and other HBV antigens, especially in nephridial tissue, thereby alleviating the HBV immunity mediated renal injury; telbivudine has immunomodulatory effect and it may improve the glomerular filtration rate independent of antiviral role, which still needs further study. Pipili et al[33] recommended that telbivudine was one of the preferred therapeutic options for patients with any renal dysfunction.

Whether the efficacy of telbivudine to patients with HBV-GN is superior to other anti-HBV agents is an interesting and important question. There are 5 anti-HBV agents including lamivudine, telbivudine, adefovir, entecavir, and tenofovir. Among them, lamivudine is not recommended because of its low resistance barrier. Adefovir and tenofovir cannot be used in HBV-GN patients because of their apparent nephrotoxicity. Therefore, only telbivudine and entecavir are recommended by the APASL guidelines for patients with HBV-GN. Although telbivudine has potent antiviral effects and renal protective effects, its resistance barrier is lower than that of entecavir. Although entecavir has a strong antiviral effect and a high resistance barrier, entecavir does not have renal protection function according to the latest report. The glomerular filtration rate of patients who treated with entecavir is gradually and slowly decreasing. For telbivudine, whether renal protection outweighs the low resistance barriers is a key issue that requires further prospective studies to confirm.

In our study, the HBV DNA viral loads at baseline were relatively low with only 5.2 ± 2.2 log10 IU/mL, whereas the ALT levels were relatively high with 210.9 ± 55.6 U/L. Studies have reported that high HBV viral load and low ALT level at baseline were independent risk factors associated with HBV viral resistance. In addition, according to studies reported before and the result of our study, high HBV DNA viral load is also the risk factor associated with CR in patients with HBV-GN that may explain the reason why the resistance rate is relatively lower and CR rate relatively high in our study.

The therapeutic effects on HBV-GN patients were mainly achieved by application of telbivudine because of its antiviral and immune regulatory efficacies. It should be noted that glycyrrhizin preparations administered to patients in this study can also protect liver and renal functions and exert anti-inflammatory effects. There were no significant adverse reactions observed during the treatment.

5. Conclusion

In conclusion, despite of the limited sample size, the study showed that telbivudine is a favorable therapeutic option for the treatment of HBV-GN in Chinese patients and further studies with larger sample size will be needed to validate our finding.

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