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CLINICAL STUDY

Efficacy of adefovir dipivoxil combined with a corticosteroid in 38 cases of nephrotic syndrome induced by hepatitis B virus-associated glomerulonephritis

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Abstract

Objective: To investigate the treatment efficacy of adefovir dipivoxil combined with a corticosteroid on hepatitis B virus-associated glomerulonephritis (HBV-GN). *Methods*: A total of 38 patients with nephrotic syndrome induced by HBV-GN were treated for 36 weeks between 2010 and 2012. *Results*: The efficacy analysis showed that 11 patients achieved complete remission and 17 patients achieved partial remission, and the effective remission rate was 73.7%. In addition, 10 patients achieved no remission. *Conclusions*: Adefovir dipivoxil combined with corticosteroids has a certain efficacy on the HBV-GN and displays few adverse reactions. A large sample, randomized double-blind controlled study and long-term follow-up are needed to verify the efficacy of adefovir dipivoxil combined with corticosteroids.

Keywords

Antiviral agents, corticosteroid, efficacy, hepatitis B virus-associated glomerulonephritis, nephrotic syndrome

History

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Introduction

Hepatitis B virus-associated glomerulonephritis (HBV-GN) is a secondary immune complex glomerulonephritis that is induced by HBV and is the most common complication of HBV patients. The clinical features of HBV-GN are insidious onset, hematuria and albuminuria. Certain HBV-GN patients either present with nephrotic syndrome or even renal failure. Treating HBV-GN is a tough problem because the pathogenesis of HBV-GN is unclear, and there is no unified treatment principle worldwide. For the patients with nephrotic syndrome induced by HBV-GN, the concept of combining corticosteroids with antiviral therapy is still controversial. In our study, adefovir dipivoxil combined with a corticosteroid was used as a treatment for HBV-GN; a favorable result was obtained, thus providing a basic therapeutic regimen for HBV-GN.

Patients and methods

From October 2010 to March 2012, a total of 38 patients (23 males and 15 females; age range 20–50 years; average age 32.5 ± 12.6 years) with HBV-GN were treated in the Xiangya Hospital. The duration was 2–8 weeks, and the mean duration was 5 ± 1.2 weeks. This study was approved by Institutional Review Board of the Xiangya Hospital of Central South University, and an informed consent was obtained from all patients.

Inclusion criteria

(1) Evidence of chronic HBV DNA in the serum and chronic hepatitis were determined by liver biopsy. (2) Glomerulonephritis was diagnosed and other secondary glomerulopathies, such as lupus nephritis, was excluded. (3) HBV antigen was discovered in the renal pathological section.

Renal histopathological examination

Histological changes were observed by routine HE, PAS and Masson staining. IgG, IgA, IgM, C3, C4, HBsAg and HBcAg were tested by immunohistochemistry.

Methods

All 38 patients received adefovir dipivoxil (10 mg/d) combined with prednisone ($1\ mgkg^{-1}\ d^{-1}$). The dose of prednisone was slowly reduced eight weeks later (10% of the total dose was reduced once every two weeks), and the combined therapy lasted for 36 weeks. Other cytotoxic drugs or immunosuppressants were not used during the treatment period. HBV-DNA, HBeAg, serum creatinine, 24-hour urinary protein quantity, serum albumin, cholesterin, triglyceride, blood urea nitrogen and alanine aminotransferase were tested in the 8th, 12th, 24th and 36th weeks, respectively.

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Efficacy observation

(1) Complete remission: the 24-hour urinary protein quantity was less than 0.3 g/d; the levels of serum albumin, blood urea nitrogen, serum creatinine and alanine aminotransferase were in the normal range. (2) Partial remission: the 24-hour urinary protein quantity decreased more than 50% of the pre-therapy level. (3) No remission: laboratory results and symptoms showed no improvement.

Statistical analysis

Data were recorded as the mean ± SD and analyzed by paired *t*-tests. A p value of less than 0.05 was considered to be statistically significant.

Results

Efficacy analysis

There were no adverse reactions in the 38 patients during the treatment period. In the 38th week, the titer of HBV-DNA was reduced to 20%, and the HBeAg-negative rate was 21%. Of the 38 patients, 11 patients achieved complete remission, 17 patients achieved partial remission and the effective rate was 73.7%; 10 patients achieved no remission (Table 1). The follow-up of one patient was aborted due to a concurrent infection.

Laboratory examination

At 8, 12, 24 and 36 weeks, the levels of serum creatinine, serum albumin, cholesterin, triglyceride, blood urea nitrogen, 24-hour urinary protein quantity and alanine aminotransferase improved compared with those measured at pre-therapy ($p < 0.05$) (Table 2).

Renal histopathological examination

Membranous nephropathy was observed in 19 patients (50.0%), membranoproliferative nephritis in 11 patients (28.9%) and mesangial proliferative nephritis in 8 patients (21.1%). HBV antigen in the renal tissue attained 100% detection rate. Twenty-three patients tested positive for both HBsAg and HBcAg; 15 patients tested positive for HBsAg. In patients with membranous nephropathy, HBsAg and HBcAg were mainly deposited below the capillary epithelium in line-like, granular shapes and as lumps. In patients with membranoproliferative nephritis, HBsAg and HBcAg were mainly deposited in the mesangial region and the glomerular capillary wall in diffuse granular shapes. In patients with mesangial proliferative nephritis, HBsAg and HBcAg were mainly deposited in the mesangial region.

Table 1. Efficacy analysis of different histopathological types.

Histopathological type	Cases	Complete remission	Partial remission	No remission	Effective rate (%)
MN	19	5	8	6	68.4
MPGN	11	4	4	3	72.7
MsPGN	8	2	5	1	87.5
Total	38	11	17	10	73.7

Discussion

China has a high incidence of HBV infection, which gives rise to a high incidence of HBV-GN, and the incidence rate in the males is higher than that in females. The clinical manifestations of HBV-GN are varied and similar to that of the same pathological type of primary glomerulonephritis. According to the data from renal biopsies from some parts of China, HBV-GN, which accounted for approximately 2.5% of the patients who underwent renal biopsies,[1] was a common secondary glomerulopathy. The possible pathogenesis of HBV-GN is as follows: (1) the viruses infect kidney cells, resulting in kidney damage. The existence of HBV-DNA in the kidney tissues has been confirmed by the modern molecular biological techniques. Lai[2] found HBV-DNA in the kidney tissues of parts of IgA patients, which was considered to be associated with disease progression. (2) HBV antigen–antibody complexes (circulating immune complexes and/or original site immune complexes) deposit in the glomeruli, resulting in immunological injury and participate in the immunopathogenesis of HBV-GN.[3] (3) Autoimmune injury induced by HBV infection: researchers found that HBV appeared to be a trigger for the patients to produce a variety of autoantibodies, such as DNA antibodies, anti-cytoskeletal components antibodies, anti-smooth muscle antibodies and anti-liver-specific lipoprotein antibodies. (4) Immunodeficiency: HBV weakens the function of the mononuclear macrophage system, which gives rise to the decreased scavenging ability of immunological substances in the blood circulation, resulting in increased immune complexes in the glomeruli.

HBV-GN contains several pathological types; membranous nephropathy is the most common pathological type, followed by mesangial proliferative nephritis and membranoproliferative nephritis. The less aggressive pathological types include IgA nephropathy, minimal change disease, crescentic glomerulonephritis and focal segmental glomerulosclerosis.[4]

There is no standardized effective treatment for HBV-GN to date. Lamivudine, a type of cytosine nucleoside analogue, can effectively suppress RNA reverse transcriptase. A study

Table 2. Laboratory examination of 38 patients with HBV-GN before and after treatment.

Time	24 hours urinary protein quantity (g)	Serum albumin (g/L)	Triglyceride (mmol/L)	Cholesterin (mmol/L)	Blood urea nitrogen (mmol/L)	Serum creatinine (μmol/L)	Alanine aminotransferase (U/L)
Pretherapy	5.53 ± 3.5	28.12 ± 5.45	3.08 ± 1.34	7.47 ± 2.16	7.45 ± 1.38	135.06 ± 74.1	64.35 ± 20.16
8th week	3.12 ± 1.24*	32.01 ± 4.62*	2.76 ± 1.18*	6.24 ± 1.75*	6.79 ± 1.02	105.46 ± 38.5	63.16 ± 15.98
12th week	2.87 ± 1.45*	34.25 ± 3.19*	2.19 ± 1.08*	5.69 ± 1.44*	6.70 ± 1.05	94.33 ± 34.1	62.05 ± 14.79
24th week	1.98 ± 1.12*	38.04 ± 2.36*	2.11 ± 0.83*	5.54 ± 1.35*	6.67 ± 1.13	87.34 ± 21.4	59.04 ± 15.11
36th week	1.64 ± 0.83*	38.36 ± 2.51*	2.02 ± 0.76*	5.25 ± 1.04*	6.53 ± 1.24	85.07 ± 20.6	49.16 ± 7.35

Notes: *Indicates a statistically significant $p < 0.05$.

by Tang et al.[5] showed that 10 patients who were positive for HBsAg and membranous nephropathy, which was confirmed by renal biopsy, presented with a nephrotic syndrome and underwent treatment with lamivudine. The complete remission rates of 40% and 60% were attained in the 6th and 12th months, respectively; but the widespread application of lamivudine was limited in clinics due to its high tolerance and low HBeAg-negative rate.[6]

A meta-analysis of the efficacy and the safety of an interferon for the treatment of HBV-GN was conducted by Fabrizi et al.[7] The results showed that the interferon was safe and effective, and that the proteinuria remission rate reached 50%, but the widespread application of lamivudine was limited in clinics due to its high economic burden and adverse reactions.

Entecavir, a new type of anti-HBV medicine, can effectively inhibit the HBV-DNA replication; depress the serum levels of transaminase; and improve the inflammation, necrosis and fibrosis of the kidney tissues. However, most patients cannot afford entecavir due to its high cost.

Adefovir dipivoxil is an oral prodrug of adefovir, an acyclic nucleoside phosphonate analogue of adenosine monophosphate that is actively transported into mammalian cells, where it is converted by host enzymes to adefovir diphosphate. Adefovir diphosphate inhibits viral polymerases and causes DNA chain termination.[8] Study of Li et al.[9] showed that the adefovir dipivoxil was effective and safe for the treatment of HBV-GN. The titer of HBV-DNA in 76 patients was reduced significantly, and the replication of the HBV-DNA was inhibited well.

In our study, adefovir dipivoxil combined with corticosteroids was used for the treatment of HBV-GN presenting as nephrotic syndrome, which can both inhibit the renal immunological injury and decrease the replication of viruses. Our results showed that the effective rate was 74%, which was better than that of a single interferon or lamivudine for the treatment of HBV-GN. Statistical analysis of the efficacy among different pathological types of HBV-GN showed no significant difference ($p > 0.05$), which may be due to the small size of the sample. After the combined therapy, laboratory examination showed that the levels of the 24-hour urinary protein quantity were decreased and the levels of serum albumin were significantly improved. Significant differences were observed compared to the pretreatment levels, and no adverse reactions were observed after long-term medication. Adefovir dipivoxil has a relatively low drug resistance and is suitable for long-term use. Adefovir dipivoxil combined with corticosteroids has a certain efficacy on the HBV-GN presenting as nephrotic syndrome and displays few adverse reactions. Due to the small sample size in our study, a large sample, randomized double-blind controlled study and long-term follow-up are needed to verify the efficacy of adefovir dipivoxil that is combined with corticosteroids.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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