

The curative effect of adefovir dipivoxil treating HBeAg negative chronic hepatitis B and treating HBeAg positive chronic hepatitis B combining interferon α -2b

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Abstract: This study aimed to research the efficiency of adefovir dipivoxil in hepatitis B e antigen (HBeAg)-negative chronic hepatitis B treatment and in combination with α -2b interferon in the treatment of HBeAg-positive chronic hepatitis B. A total of 102 cases of adult patients with HBeAg chronic hepatitis B were selected for testing. HBeAg negative chronic hepatitis B patients took 10mg adefovir dipivoxil capsules once daily, while positive chronic hepatitis B patients were randomly divided into either a treatment group or a control group. The treatment group was administered with 10mg adefovir dipivoxil capsules, 1 time daily, and injected with 5 million U Recombinant Human Interferon α -2b through muscle every other day. The control group was treated with 10mg adefovir dipivoxil capsules, 1 time per day. We examined alanine aminotransferase (ALT) normalization and the Hepatitis B Virus (HBV)-DNA negative rate (undetectable rate), as well as, HBeAg / hepatitis B e antibody (HBeAb) sero-conversion rate to detect treatment effects. The results proved that after 6 months of medication therapy, the ALT normalization rate was 49.9%, and the HBV-DNA negative conversion rate was 54.3%. 18 months into the treatment, showed an ALT normalization rate of 73.2%, while the HBV-DNA negative conversion rate grew to 76.8%. The use of adefovir dipivoxil treatment of the negative chronic HBV has a certain extent combined with α -2b Interferon therapy in treatment of HBeAg positive chronic hepatitis B. After a 48-week observation period, ALT normalization and HBV-DNA rate could not be measured, HBeAg/HBeAb sero-conversion rose higher, indicating that the treatment of the combined drugs is more efficient than taking adefovir dipivoxil by itself, and the data were comparable with the control group ($P < 0.05$). Thus adefovir dipivoxil can greatly improve the restrain function to HBV-DNA, and improve the immunity and control ability of the body, with obvious short-term effects, in combination with Interferon.

Keywords: adefovir dipivoxil; interferon α -2b; HBeAg negative chronic hepatitis B; HBeAg positive chronic hepatitis B

INTRODUCTION

Anti-virus treatment is the key of chronic hepatitis B treatment. Anti-virus drugs externally applied for treating chronic hepatitis B are mainly interferon and nucleoside analogue. To be specific, the drugs include normal interferon α , pegylation interferon α -2a, lamivudine, adefovir dipivoxil, entecavir and telbivudine etc. Adefovir dipivoxil and interferon α -2b are the nationally recognized anti-virus drugs of hepatitis B (Ni and Lu 2010; Yu *et al.*, 2011).

Adefovir dipivoxil, a novel oral antiviral drug, can transform into diphosphate adefovir dipivoxil with pharmacological activity *in vivo* which can effectively inhibit replication of hepatitis B virus (HBV) by competing for deoxyadenosine triphosphate; less drug resistance produced after oral administration is its best advantage (Liu *et al.*, 2011). Interferon or nucleotide analogues are usually used in antiviral treatment clinically; however, combined treatment is recommended as treatment applying interferon only shows up low response rate and moreover, long term use of nucleotide analogues are more likely to induce virus vibration and

thus affect curative (Sellrie *et al.*, 2014 and Wu *et al.*, 2004).

HBeAg negative chronic hepatitis B as a special clinical type can apply different prognosis judgment methods and therapies. *Guide to Prevention and Treatment of Chronic Hepatitis B* suggests treating it with interferon or nucleotide analogues such as entecavir, and moreover, *European Practice Guide to Treatment of Chronic Hepatitis B* released in 2009 proposed to take HBV DNA response, hepatitis B surface antigen (HbsAg) disappearance and serological conversion as the ideal objective of chronic hepatitis B treatment (EASL, 2009). Thus this study tried to explore the efficiency of adefovir dipivoxil in treating HBeAg negative chronic hepatitis B and in combination with interferon α -2b in treating HBeAg positive chronic hepatitis B.

MATERIALS AND METHODS

General materials

A total of 102 adult HBeAg chronic hepatitis B patients admitted in our hospital from May 2012 to December 2014 were selected. Among them, 40 were diagnosed as negative chronic hepatitis B patients, with ALT of 73 U/L to 204U/L (mean 118 \pm 12 U/L); HBV-DNA was

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determined as 1×10^3 - 10^5 copy/ml (mean 2.38×10^5 copy/ml). The patients who took interferon or any other immunoregulator in the last half year, who had received organ or marrow transplantation, who had been treated with nucleoside analog for more than 12 weeks were excluded. Besides, patients of viral hepatitis such as hepatitis C, alcoholic hepatitis, drug hepatitis and autoimmune hepatitis were also excluded. Sixty-two patients were diagnosed as positive chronic hepatitis B. All the patients satisfied the following conditions: (1) hepatitis B surface antigen (HBsAg) (+), HBeAg (+) > 6 months; (2) HBV-DNA $\geq 10^5$ copy/ml; (3) ALT level is twice to ten times of normal level; other hepatitis such as viral hepatitis, alcoholic hepatitis, drug hepatitis, autoimmune hepatitis were excluded, and all the selected patients had no family history of hepatitis B and has not taken other antiviral drugs or immunoregulator during the latest half year. Patients of diabetes, kidney disease and thyroid disease were excluded. The diagnosis above all meets the clinical criteria of Guideline for Chronic Hepatitis B Prevention and Treatment of 2010 (Ji and Li 2010). This study has approved by the ethics committee in our hospital, and all the patients and their relatives have agreed to the treatment above and signed the informed consent.

Materials grouping

Those 62 patients with positive chronic hepatitis B were divided into two groups according to the illness condition and the patients' wishes. The treatment group consisting of 32 patients was treated with adefovir dipivoxil combined with interferon α -2b, and the control group consisting of 30 patients was treated with adefovir dipivoxil only. Patients who were 18 years over, had HBV-DNA no less than 1×10^5 copy/mL and ALT between 80U/L and 1,000U/L in one month before treatment and have developed HbsAg and HBeAg positive for more than six months were included in the study. In addition, those who has taken interferon, lamivudine, adefovir and thymosin in one year and developed glucose-6-phosphate dehydrogenase (G6PD) defect, hyperthyroidism, hepatocellular carcinoma, liver cirrhosis associated with severe fat liver or associated with other severe diseases such as unstable diabetes, other malignant tumors and autoimmune disease were all excluded.

Therapeutic method

Forty HBeAg negative chronic hepatitis B patients were treated with 10mg adefovir dipivoxil capsule (Chia Tai Tianqing Pharmacy Group Co., LTD, Jiangsu, China), 1 time daily and then observed for 1.5 years; HBeAg positive chronic B patients were treated with 10 mg adefovir dipivoxil capsule, 1 time daily, and 5 million intramuscular recombinant human interferon α -2b every other day; control group was treated with 10 mg adefovir dipivoxil, 1 time daily and the treatment lasted for 48 weeks. Both two groups received liver protection

treatment applying glutathione, ailymarin and diammonium glycyrrhizinate, etc.

Detection method

HBeAg negative chronic hepatitis B patients received conventional detection of liver function during the treatment of adefovir dipivoxil, in the mean time, serum marker of HBV was detected applying enzyme linked immunosorbent assay and HBV-DNA was detected reagent made by Da'an Gene and fluorescent quantitative polymerase chain reaction. In HBeAg positive chronic hepatitis B group, HBV-DNA and HBeAg negative conversion (serous HBV-DNA negative conversion: concentration $< 1.0 \times 10^3$ copy/ml) was detected applying polymerase chain reaction, and the untoward effect was observed.

Curative effect evaluation

In HBeAg negative treatment group, the ALT normalization rate and HBV-DNA uncertainty rate was evaluated every 6 months since the treatment started. The evaluation criteria of 62 patients in positive chronic hepatitis B group were: ALT normalization rate; HBV-DNA uncertainty rate; HBeAg/HBeAb serum conversion rate.

Safety evaluation

Safety evaluation, i.e., record and assessment of adverse event, serious adverse event, laboratory detection value abnormality and off case was carried out at the end of 24th week (middle stage evaluation) and 48th week (terminal evaluation). Fig. 1 is the follow up process.

STATISTICAL ANALYSIS

SPSS 20.0 statistical software was used for data processing. Measurement data conforming to normal distribution adopted description, while the comparison between two groups used independent sample test. Measurement data not conforming to normal distribution was described by median and scope and verified by rank sum test. Enumeration data was described by cases (percentage) and statistical results were processed by t test. Logistic analysis was used in multi-factor analysis. Two-sided test was used as the statistical test method. Difference was considered to have statistical significance if $P < 0.05$.

RESULTS

Clinical data

Patients were divided into treatment group and control group. In treatment group, there were 18 male and 14 female, with age ranging from 25~58 years (average 41.5 ± 12.6 years) and average disease course of 5.1 ± 2.7 years; while control group included 13 male and 17 female whose age was ranged from 23 to 55 years

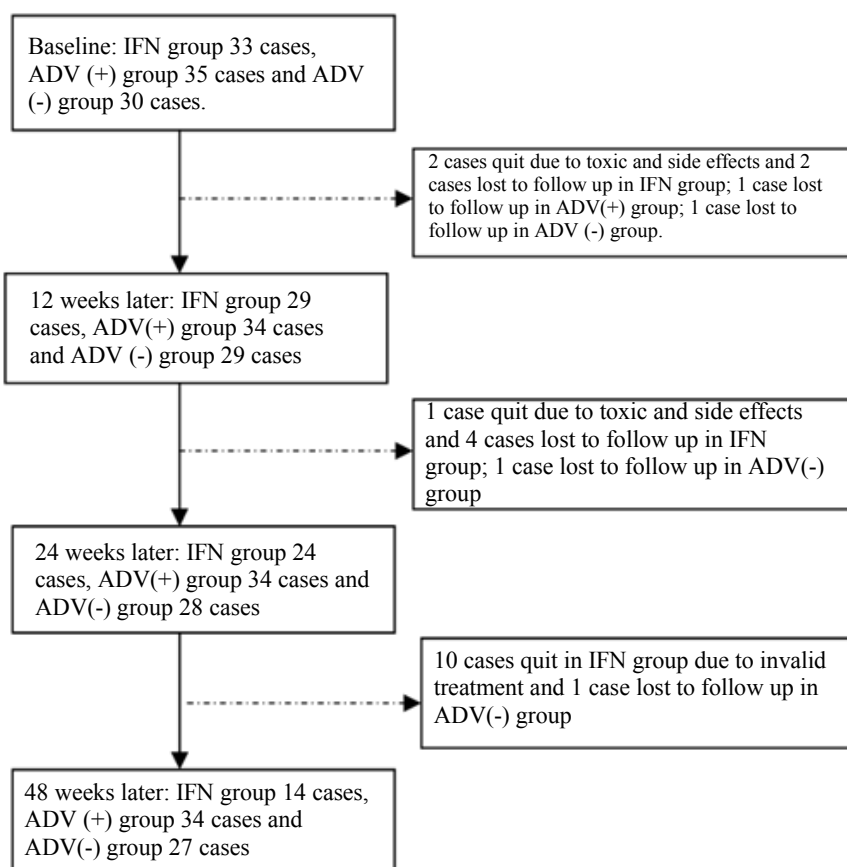


Fig. 1: Flow of treating chronic hepatitis B with interferon α -2a and adefovir dipivoxil

(average 40.3 ± 11.8 years) and whose average disease course was 5.8 ± 1.9 years. Gender, age, disease course and disease condition were not statistically significant between two groups; thus they were comparable.

Curative effect of Adefovir dipivoxil treating HBeAg negative chronic hepatitis B

Virological and biochemical response situation during the treatment of HBeAg negative chronic hepatitis B patients is shown in table 1. The table shows that as the treatment went on, the liver function of HBeAg negative chronic hepatitis B patients treated with adefovir dipivoxil gradually turned to be normal, and meanwhile HBV-DNA negative conversion rate also gradually increased, which suggested that adefovir dipivoxil had a good short-term curative effect in treating HBeAg negative chronic hepatitis B. Furthermore, during the treatment, no severe untoward effect such as kidney function injure related with adefovir dipivoxil was found, and the tolerance of the patients was fine.

Curative effect of adefovir dipivoxil treating HBeAg positive chronic hepatitis B combining interferon α -2b

Comparison of clinical effect: compared with control group of the corresponding period, the ALT normalization

rate of each detecting point of treatment group had no statistical significance ($P > 0.05$); HBV-DNA uncertainty rate at different detecting points had statistical significance ($P < 0.05$); HBeAg/HBeAb serum conversion rate was not statistical significance at the 12th week during the treatment, but was statistically significant at 24th, 36th and 48th week ($P < 0.05$); the HBV-DNA uncertainty rate and HBeAg/HBeAb serum conversion rate of treatment group was distinctly higher than control group. Details are shown in table 2.

Untoward effect: in treatment group, symptoms of fever and muscular soreness happened to 90.6 % of the patients during the first day of treatment, and body temperature became normal and the muscular soreness remitted or disappeared within 6 days; 46.9 % patients were found with reduced leukocyte or blood platelet, and 24 weeks after treatment, the situation turned to be normal; 3.1 % patients were found with slightly abnormal thyroid function, and without special treatment, the function turned to be normal as well in reexamination; no patients stopped taking drugs due to untoward effects. No obvious untoward effects were found in adefovir dipivoxil group (control group).

Table 1: Comparison of virological and biochemical response situation during the treatment of adefovir dipivoxil (%)

HBeAg negative chronic hepatitis B group	Treatment duration	ALT normalization rate	HBV-DNA negative conversion rate
	6 months	49.9	54.3
	12 months	58.7	63.9
	18 months	73.2	76.8

Table 2: Comparison of curative effect between treatment group and control group

Time	Group	ALT normalization rate	HBV-DNA uncertainty rate	HBeAg/HBeAb serum conversion rate	p value
12 weeks later	Treatment group (n=32)	23(71.9)	11(34.4)*	12(37.5)	0.032
	Control group (n=30)	19(63.3)	4(13.3)*	4(13.3)*	
24 weeks later	Treatment group (n=32)	27(84.4)	21(65.6)*	14(43.8)*	0.015
	Control group (n=30)	21(70.0)	9(30.0)*	5(16.7)*	
36 weeks later	Treatment group (n=32)	28(87.5)	23(71.9)*	16(50.0)*	0.026
	Control group (n=30)	24(76.7)	11(36.7)*	6(20.0)*	
48 weeks later	Treatment group (n=32)	30 (93.8)	25 (78.1)*	18 (56.3)*	0.038
	Control group (n=30)	26(86.7)	13(43.3)*	7(23.3)*	

Note: * P<0.05, compared to control group in the same period; the critical value of HBV-DNA quantitative determination was 1,000 copies/mL.

DISCUSSION

It has been proved in the present study that, virus load and HBeAg seroconversion rates were improved significantly in treatment with interferon in combination with adefovir dipivoxil compared to single drug treatment. This research compared the curative effect of the combination of adefovir dipivoxil and interferon in the treatment of HBeAg positive chronic hepatitis B and single use of adefovir dipivoxil in the treatment of HBeAg negative chronic hepatitis B. Adefovir dipivoxil, a compound of adenine and phosphate, rapidly transforms into activated adefovir when orally taken. Its function mechanism is to constantly restrain the replication of HBV by restraining the activity of HBV-DNA polymerase, thus exhaust the covalently closed circular DNA (cccDNA) within the body and resist the virus (Chen *et al.*, 2013; Qaqish *et al.*, 2003; Shahabadi *et al.*, 2014). Interferon α -2b with both immune regulation and anti-virus effect can, on the one hand, improve the specificity of virus and function of non-specific cell, and on the other hand, generate several kinds of antiviral protein through signal path of interferon to act on steps such as HBV replication and transcription (Sulkowski *et al.*, 2004; Freund *et al.*, 1988; Tansel *et al.*, 2006; Badkar *et al.*, 2007). These two drugs have different function mechanisms and combination of them can produce coordination or superimposed effect, improve antiviral effect and lower drug resistance risk.

The results of this research showed at the 12th, 24th, 36th and 48th week after the application of the combination of adefovir dipivoxil and interferon α -2b, HBV-DNA uncertainty rate was obviously higher than the group

treated with adefovir dipivoxil only in the same period, and the difference had statistical significance (P<0.05). At the 24th, 36th and 48th week after the treatment, the HBeAg/HBeAb serum conversion rate was also distinctly higher than the group treated with adefovir dipivoxil only, and the difference was of statistical significance (P<0.05). The above results suggested the combination treatment could better restrain HBV-DNA and greatly improve immune and control ability of the body, with evident short-term curative effect. The untoward effects of interferon mainly include short-term fever, muscular soreness and transient marrow suppression, and slight thyroid function abnormality which are barely happened; Adefovir dipivoxil has been verified to have renal toxicity which is not obvious in this research. In this research, the renal toxicity of combination treatment group has not increased distinctly and there was no untoward effect in both treatment group and control group, which suggested that the combination of adefovir dipivoxil and interferon has high security in the treatment of treating chronic hepatitis B. But in this study, the sample size was small and the observation time was short; therefore, long-term curative effect and safety of treatment with adefovir dipivoxil combined with interferon α -2b should be studied with a large size of samples and long time follow up for further observation in the future. Besides, this research evaluated the anti-virus effect of adefovir dipivoxil in treating HBeAg negative chronic hepatitis B by measuring the quantification variation of HBV-DNA and ALT normalization rate during the treatment and revealed that adefovir dipivoxil only could to some extent restrain the negative chronic HBV. This study proved that treating HBeAg positive chronic hepatitis B with

interferon α -2b in combination with adefovir dipivoxil could remarkably improve curative effect by restraining duplication of HBV to the largest extent and accelerating HBeAg negative conversion.

CONCLUSION

In short, adefovir dipivoxil has a certain effect, and can restrain virus replication when treating HBeAg negative chronic hepatitis B. Besides, adefovir dipivoxil combined with interferon α -2b has better effect than single use of adefovir dipivoxil, in the treatment of HBeAg positive chronic hepatitis B.

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