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Original Article

Study on comparison of efficacy of entecavir and adefovir dipivoxil in treatment of hepatitis B cirrhosis

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Abstract: Objective: To compare the therapeutic effect between entecavir (ETV) and adefovir dipivoxil (ADV) in patients with hepatitis B cirrhosis. Methods: A total of 83 patients with hepatitis B cirrhosis were included in this study. The patients were assigned into the ETV group (n=42) and the ADV group (n=41). All patients received routine treatment. Patients in the ETV group were treated with entecavir, while those in the ADV group were treated with adefovir dipivoxil. The curative time was for one year. The observed indicators in terms of therapeutic effect were: HBV DNA negative conversion rate, HBeAg negative conversion rate, life quality, hepatic fibrosis and inflammatory factors were all compared between the ETV group and ADV group. Results: At the end of treatment, the total effective rate in the ETV group was remarkably higher (83.33% vs 63.41%), with a significant difference in contrast to the ADV group (P=0.039). Compared with the ADV group, the HBV DNA negative conversion rate (65.85% vs 88.10%) and HBeAg negative conversion rate (12.20% vs 30.95%) of the ETV group were significantly higher (all P<0.05). In contrast to the ADV group, the serum levels of PC III, IV-C, LN, HA and TNF-α at the end of treatment in the ETV group were significantly decreased, and the QLQ-C30 score and serum IL-10 level were significantly increased (P<0.001). Conclusion: Compared with adefovir dipivoxil, entecavir has obvious advantages with better therapeutic effects, higher HBV-DNA negative conversion rate and HBeAg negative conversion rate, better results in life quality, and fewer responses of hepatic fibrosis and inflammation.

Keywords: Hepatitis B cirrhosis, entecavir, adefovir dipivoxil, treatment effect

Introduction

Hepatitis B virus is the most common hepatitis virus that leads to chronic liver cirrhosis. It is characterized by distortion and destruction of normal liver architecture. According to an epidemiological survey, 5-year survival rates of patients with compensated cirrhosis and decompensated cirrhosis were 84% and 14%, respectively [1]. Moreover, it was reported that cirrhosis is the greatest cause of liver cancer, with about 70%-90% of liver cancer developing form liver cirrhosis [2]. Many studies reported that antiviral agents were able to control viral replication, improve liver function, and reduce the development of decompensated cirrhosis and liver cancer [3, 4]. The selection of appropriated antiviral agents for patients with hepatitis B cirrhosis plays an important role in the recovery of life quality and long-term prognosis [5].

Adefovir dipivoxil, as a kind of antiviral drug, belongs to the class of nucleoside drugs. It is widely used in clinical practice and works through inhibiting reverse transcriptase and reducing the activity of DNA polymerase [6]. It is reported that adefovir dipivoxil has a good effect in the process of anti-HBV [7]. Akuta et al. [8] reported that Adefovir dipivoxil is an effective rescue treatment for lamivudine-resistant Hepatitis B virus. However, in the years since its launch, clinical resistance to Adefovir dipivoxil has occurred. During long-term antiviral therapy, Adefovir dipivoxil has an impact on renal function and can lead to proximal renal tubular toxicity as reflected by elevated creatinine levels and hypophosphatemia [9, 10]. Recently, Entecavir, which is a nucleoside analogue of 2'-deoxyguanosine has been applied by more and more gastroenterologist to treat hepatitis B virus. However, reports on its therapeutic effect are inconsistent [11, 12]. The

question remains, is it safe and efficacious to select entecavir as the first-line agent for patients with chronic hepatitis B and compensated liver cirrhosis [13]? So far, it still remains that there is no effective clinical evidence on this topic. In addition, there are few reports on the comparison of therapeutic effects between Adefovir dipivoxil and Entecavir in the treatment of hepatitis B cirrhosis. In this context, this clinical trial was designed to investigate the difference in efficacy between entecavir and adefovir dipivoxil in patients with chronic hepatitis B and compensated liver cirrhosis in term of total effective rate, HBV DNA negative conversion rate, HBeAg negative conversion rate, life quality, hepatic fibrosis and inflammatory factors. This study is important to provide experimental evidence for developing new ideas in the clinical treatment of hepatitis B cirrhosis.

Materials and methods

Subjects

Patients admitted to the Gastroenterology Department of the Central Hospital of Minhang District, Shanghai for hepatitis B cirrhosis from January 2016 to May 2018 were enrolled in this study. This experiment was approved by the Ethics Committee of our hospital, and all the included patients or their families signed the informed consent.

Inclusion criteria: (1) patients aged 18-65 years old and met the diagnostic criteria for hepatitis B cirrhosis [14]; (2) patients who did not undergo anti-HBV treatment before this study began; (3) serological tests showed that HBeAg and HBV DNA were positively expressed; (4) the included patients actively cooperated with the performance of this study and clinical data was complete.

Exclusion criteria: (1) the related symptoms of decompensated cirrhosis such as upper gastrointestinal hemorrhage and ascites; (2) serious dysfunction of important organs such as the heart, lung, kidney, and brain; (3) malignant tumor diseases such as liver cancer, other chronic hepatitis such as Hepatitis C and autoimmune hepatitis, other liver cirrhosis such as alcoholic hepatitis and fatty liver; (4) allergic reaction to entecavir or adefovir dipivoxil drugs; (5) cognitive impairment; (6) antiviral drugs used before; (7) pregnant and nursing women.

According to the inclusion criteria and exclusion criteria, 90 patients with hepatitis B cirrhosis were recruited in this study, and the clinical trial data were retrospectively analyzed. Based on the treatment methods, these patients were divided into the entecavir group (ETV group) and adefovir dipivoxil group (ADV group) (45 patients in each group). Patients in the ETV group were treated with entecavir, while patients in the ADV group were treated with adefovir dipivoxil. In the course of the experiment, if the patients developed significant complications such as myositis, metabolic acidosis and rhabdomyolysis, they were withdrawn from the study.

Treatment methods

All the included patients underwent symptomatic therapy such as low-fat high-quality protein diets, jaundice reduction, liver protection, and maintenance of electrolyte and acid-base balance. Patients in the ETV group received Entecavir (GlaxoSmithKline Pharmaceutical Co., Ltd.) at a dose of 0.5 mg once a day, while patients in the ADV group received adefovir dipivoxil (GlaxoSmithKline Pharmaceutical Co., Ltd.) for anti-HBV treatment. The dose of adefovir dipivoxil was 10 mg once a day. The length of treatment was one year.

Observed indexes

Comparison of treatment effects between two groups: At the end of treatment, the therapeutic effects of patients in two groups were evaluated. The judgement standards were as follows [15]: Significant effect: clinical symptoms basically disappeared and the function of the liver recovered to normal; Effectivity: clinical symptoms were remarkably relieved, and the function of the liver recovered more than 50% in contrast to that before treatment; No effect: clinical symptoms did not improve and the function of the liver recovered less than 50% in contrast to that before treatment. The total effective rate of therapy was calculated based on the following method: total effective rate of therapy = (1 - number of patients with no effect/total number of patients) × 100%.

Table 1. Comparison of general information between two groups

Group	ETV group (n=42)	ADV group (n=41)	t/χ^2	P
Male/Female (n)	20/22	23/18	0.597	0.440
Age (years)	50.21±3.34	51.42±3.94	1.511	0.135
BMI (kg/m^2)	21.35±1.22	20.91±1.08	1.738	0.086
Course of disease (years)	6.12±0.85	6.31±0.72	1.098	0.276
Serum albumin (g/L)	27.91±2.80	27.76±2.64	0.251	0.803
PTA (%)	46.12±7.25	46.41±7.53	0.179	0.859
Diabetes (n)	5	7	0.448	0.503
Hypertension (n)	9	7	0.253	0.615
Hyperlipidemia (n)	6	8	0.404	0.525
Child-Pugh classification (n)				
A	20	18	0.457	0.796
B	17	16		
C	5	7		

Note: BMI: Body mass index; PTA: Prothrombin activity; ETV: Entecavir; ADV: Adefovir dipivoxil.

Comparison of HBV DNA negative conversion rate and HBeAg negative conversion rate between two groups: At the end of treatment, the level of HBV DNA was examined based on the instructions of HBV DNA fluorescence quantitative PCR Kits (Thermo Fisher Company, USA) by ABI 7500 fluorescence quantitative PCR instrument (Applied Biosystems Company, USA). The HBV DNA negative conversion rate was calculated according to the following method: HBV DNA negative conversion rate = Number of patients with HBV DNA negative conversion/total number of patients × 100%. The level of HBeAg was detected based on the instructions of enzyme immunoassay Kits (Abbott Company, USA) by the fully automated AXSYM System immunoanalyzer (Abbott Company, USA). The HBeAg negative conversion rate was calculated according to the following formula: HBeAg negative conversion rate = Number of patients with HBeAg negative conversion/total number of patients × 100%.

Comparison of Quality Life Questionnaire Core 30 (QLQ-C30) scores between two groups: The QLQ-C30 scale was applied to evaluate life quality of patients in both groups before treatment and at the end of treatment [16]. There were 30 questions in the QLQ-C30 scale including five items regarding physiological function, cognitive function, role function, social function and emotional function. A lower score suggests lower life quality.

Comparison of indicators of hepatic fibrosis between the two groups: 5 mL of venous blood was drawn from patients before treatment and at the end of treatment, and centrifuged at 3000 r/min for 15 min. Then, the serum was isolated and stored at -20°C. The levels of serum hyaluronidase (HA), laminin (LN), IV type collagen (IV-C), and procollagen type III (PC III) were measured by radioimmunoassay according to the instructions of radioimmunoassay Kits (Oriondiagnostica, Finland).

Comparison of tumor necrosis factor-α (TNF-α) and interleukin-10 (IL-10) between two groups: The levels of serum TNF-α and IL-10 were detected in patients before treatment and at the end of treatment. The ELISA Kits (R&D science, USA) were used to examine the levels of serum TNF-α and IL-10. The assays were conducted strictly following the operating instructions on the Kits.

Statistical analysis

The data of this research was analyzed using SPSS software (IBM, USA), version 22.0. Measurement data were presented as Mean ± standard deviation (SD). The comparisons between two groups were performed by independent samples t-tests, while the comparisons before and after treatments were performed using paired t-tests. Enumeration data were expressed in the form of case/percentage [n (%)]. The comparisons between two groups were conducted using chi square tests. $P< 0.05$ was considered as a statistically significant difference.

Results

Basic data of patients

Table 1 shows that there were no significant differences regarding sex, age, body mass index, course of disease, Serum albumin, prothrombin activity, Child-Pugh classification and underlying diseases between the ETV group and ADV group (all $P>0.05$), and as such they

Table 2. Comparison of therapeutic effect between two groups

Group	No effect (cases)	Effectivity (cases)	Significant effect (cases)	Total effective rate (%)
ETV group (n=42)	7	12	23	83.33
ADV group (n=41)	15	9	17	63.41
X^2				4.226
P				0.039

Note: ETV: Entecavir; ADV: Adefovir dipivoxil.

Table 3. Comparison of HBV DNA negative conversion rate and HBeAg negative conversion rate [n (%)]

Group	HBV DNA negative conversion rate	HBeAg negative conversion rate
ETV group (n=42)	37/42 (88.10%)	13/42 (30.95%)
ADV group (n=41)	27/41 (65.85%)	5/41 (12.20%)
X^2	5.814	4.298
P	0.016	0.038

Note: ETV: Entecavir; ADV: Adefovir dipivoxil.

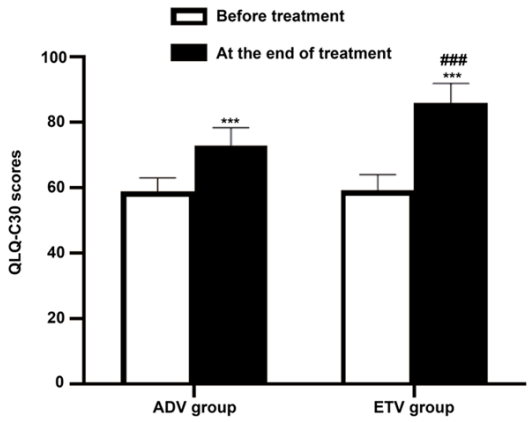

Figure 1. Comparison of QLQ-C30 scores between two groups. Compared with the same group before treatment, ***P<0.001, compared with ADV group, ###P<0.001. Note: QLQ-C30: Quality life questionnaire core 30; ETV: Entecavir; ADV: Adefovir dipivoxil.

were comparable. During the period of treatment, there was one patient lost to follow-up and two patients whi withdrew from the trial due to liver cancer in the ETV group. In the ADV group, there were 2 patients lost to follow-up and two patients who withdrew from this research due to death and decompensated liver cirrhosis. Oveall, there were 42 patients in ETV group and 41 patients in ADV group. There was no significantly statistical differences for basic information between two groups.

Therapeutic effect

At the end of treatment, the total effective rate of treatment in the ETV group was 83.33% (35/42), while the total effective rate of therapy in the ADV group was 63.41% (26/41). A significant difference in total effective rate of treatment was found between two groups (P=0.039), as shown in **Table 2**.

HBV DNA negative conversion rate and HBeAg negative conversion rate

As seen in **Table 3**, at the end of treatment, the HBV DNA negative conversion rate was 88.10% (37/42) in the ETV group and 65.85% (27/41) in the ADV group. There was a significant difference between the two groups (P=0.016). The HBeAg negative conversion rate of patients in ADV group was remarkably lower than that in ETV group (12.20% vs 30.95%), a significant difference was found (P=0.038).

Life quality

QLQ-C30 scores differed insignificantly between the ADV group and ETV group before treatment (58.72±4.25 vs 59.16±4.81, P> 0.05); the corresponding scores in both groups at the end of treatment were significantly higher than those before treatment (all P<0.001). At the end of treatment, QLQ-C30 scores in the ETV group was considerably higher than that in the ADV group, and there was a statistically significant difference (72.85±5.46 vs 85.73±6.15, t=10.080, P<0.001), as shown in **Figure 1**.

Indicators of hepatic fibrosis

There were not significant differences found for the serum levels of PC III, IV-C, LN and HA before treatment between two groups. The serum levels of PC III, IV-C, LN and HA at the end of treatment in the ADV group and ETV group were significantly lower than those before treatment (all P<0.001). At the end of treatment, patients in the ETV group had sig-

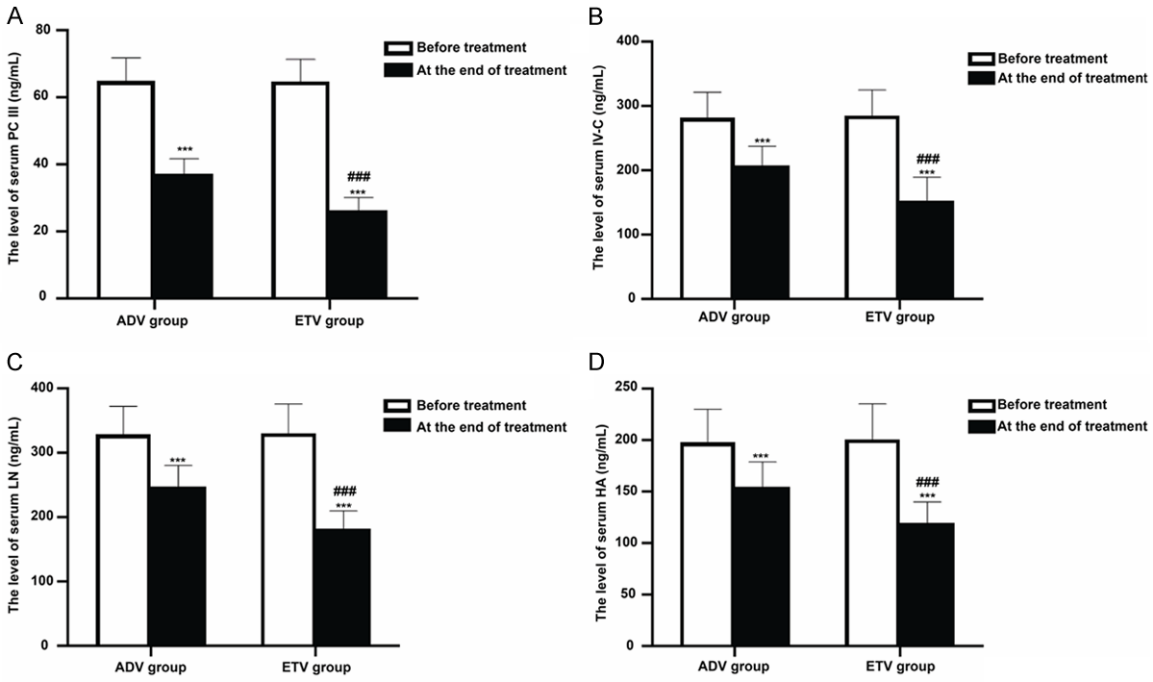

Figure 2. Comparison of hepatic fibrosis indexes between two groups. A: The level of serum PC III; B: The level of serum IV-C; C: The level of serum LN; D: The level of serum HA. Compared with the same group before treatment, ***P<0.001, compared with ADV group, ###P<0.001. Note: PC III: Procollagen type III; IV-C: IV type collagen; LN: Laminin; HA: hyaluronidase; ETV: Entecavir; ADV: Adefovir dipivoxil.

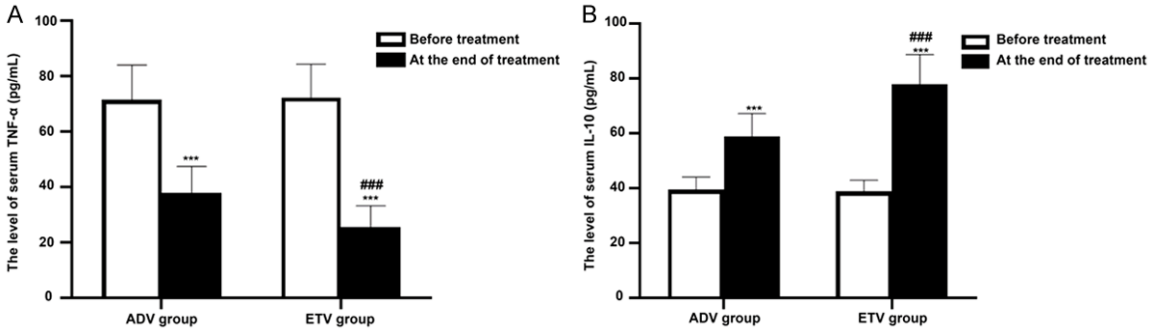

Figure 3. Comparison of inflammatory factors between two groups. A: The level of serum TNF-α; B: The level of serum IL-10. Compared with the same group before treatment, ***P<0.001, compared with ADV group, ###P<0.001. Note: TNF-α: Tumor necrosis factor-α; IL-10: Interleukin-10; ETV: Entecavir; ADV: Adefovir dipivoxil.

nificantly lower serum levels of PC III, IV-C, LN and HA than those in the ADV group (all P<0.001), as shown in **Figure 2**.

Serum levels of TNF-α and IL-10

As shown in **Figure 3**, there was no significant difference in the serum levels of TNF-α and IL-10 between the ADV group and the ETV group before treatment (P>0.05). The TNF-α level at the end of treatment in both groups was significantly lower than those before treatment, while the IL-10 level at the end of treatment in both groups was remarkably higher than those before treatment, and the differences were statistically significant (all P< 0.001). In addition, the TNF-α level at the end of treatment in the ETV group was markedly lower than that in the ADV group, while the IL-10 level at the end of treatment in ETV was obviously higher than that in the ADV group, and there were statistically significant differences (all P<0.001).

Discussion

Hepatitis B cirrhosis is a common chronic infectious disease with high morbidity and mortality rate, and as such it seriously influences the life quality and physical and mental health of these patients. Increasing evidence has been found to show that the suppression of hepatitis B virus replication could result in alleviation of hepatic necroinflammation and fibrosis, and consequently improvement of liver function in patients with hepatitis B cirrhosis [17]. It is confirmed that antiviral treatment is associated with improved clinical outcomes [18]. Currently, the first choice of antiviral agents for treatment of hepatitis B cirrhosis is still being discussed and the challenges that must be dealt with by gastroenterologist are also relevant.

There are many antiviral agents for therapy of hepatitis B cirrhosis. Adefovir dipivoxil, is a kind of acyclic analog of 5'-monophosphate deoxyadenosine and it is widely used in the clinic, especially in less economically developed regions because of its easy availability and low cost [19]. Adefovir dipivoxil, as a typical antiviral drug, converts into adefovir diphosphate by phosphorylation, and then is integrated into the HBV DNA resulting in termination of the DNA chain length, and finally produces an antiviral effect by competing with dCTP. Shi et al. [20] reported that in contrast to lamivudine, Adefovir dipivoxil has obvious antiviral effects and lower incidence of induced drug resistance. The results of this research showed that the total effective rate of Adefovir dipivoxil in treatment of hepatitis B cirrhosis was 63.41%. The HBV DNA negative conversion rate and HBeAg negative conversion rate could reach 65.85% and 12.2%, respectively. The above results were similar with Feng et al.'s report [21]. Compared with before treatment, Adefovir dipivoxil can remarkably improve life quality of patients, which was basically in accordance with the results reported by Shepherd et al. [22]. In addition, other studies reported that Adefovir dipivoxil treatment can increase the immunity of Th1/Th2 cells in patients with chronic hepatitis B [23] and the levels of the serum markers of hepatic fibrosis decreased significantly after Adefovir dipivoxil in hepatitis B cirrhosis patients within a decompensation period [24]. This study also reported that compared with those prior to the treatment, Adefovir dipivoxil treatment could increase the level of serum IL-10, and decrease the levels of TNF-α and hepatic fibrosis indicators such as PC III, IV-C, LN and HA for chronic hepatitis B patients with cirrhosis in the compensation period.

In order to find the best antiviral effects, Entecavir was selected as the subject in this study. So far, no statistical conclusion has been drawn on the effect of Entecavir in patients with hepatitis B cirrhosis in contrast to Adefovir dipivoxil. Entecavir is a nucleoside analogue, and it is rapidly phosphorylated into the active intracellular 5'-triphosphate form which reduces replication of hepatitis B virus. It was reported that Entecavir 1.0 mg once daily was obviously more effective than lamivudine 100 mg once daily after one year in lamivudine-refractory, HBeAg-positive patients [25]. Moreover, many studies showed that Entecavir treatment remarkably decrease liver cancer risk compared with no treatment in patients with hepatitis B virus [26]. Kara et al. reported that Entecavir treatment was not significantly associated with change of glomerular filtration rate in patients with chronic hepatitis B [27]. In this study, the results showed that Entecavir was more effective than Adefovir dipivoxil in patients with hepatitis B cirrhosis. This may be because Entecavir can rapidly inhibit hepatitis B virus replication, help to decrease the production of hepatitis cells and transfer to normal hepatocytes, ultimately improving the liver function. Moreover, in contrast to the ADV group, the QLQ-C30 score, HBV DNA negative conversion rate and HBeAg negative conversion rate in the EVT group were obviously increased with significant differences. It may be due to the significant efficacy of Entecavir therapy. These are similar to the results reported by Shepherd et al. [28]. In addition, immune-mediated damage plays an important role in development of hepatitis B cirrhosis. Regulatory T cells can inhibit the differentiation, proliferation, activation and effector functions of many other types of immune cells. The roles of regulatory T cells in HBV infection range from inhibiting antiviral T-cell responses to protecting the liver. TNF-α is produced by Th1 cells. IL-10 is produced by Th2 and can inhibit the expression of proinflammatory cytokines such as TNF-α. The imbal-

ance of cytokine production could affect the outcome of hepatitis B cirrhosis. In this study, IL-10 was evaluated for the expression of inhibitory cytokine. TNF-α was evaluated for the expression of Th1 cytokines. In terms of hepatic fibrosis and inflammation, Entecavir treatment has a better advantage with lower levels of serum PC III, IV-C, LN and HA and TNF-α and higher level of serum IL-10. It is because Entecavir is directly able to reduce the HBV-DNA load in liver, which helps to relive the inflammatory reaction in liver, and subsequently decrease the degree of liver fibrosis induced by virus. It is similar with the results reported by Wu et al. [29].

In conclusion, Entecavir is more effective than Adefovir dipivoxil in antiviral treatment for patients with hepatitis B cirrhosis, with better therapeutic effect, higher HBV-DNA negative conversion rate and HBeAg negative conversion rate, with significant improvement in life quality and reactions of hepatic fibrosis and inflammation. The results of this research provide experimental basis for clinical treatment of hepatitis B cirrhosis. However, there were some limitations about this trial with a small sample, being a single-center study, no classification comparison, lacking of long-term follow-up results, and no reports of the related mechanism. In the future, a larger sample size and multicenter controlled long-term follow-up study is needed for further confirmation.

Disclosure of conflict of interest

None.

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