The efficacy and safety of entecavir in patients with advanced schistosomiasis co-infected with hepatitis B virus

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**SUMMARY**

**Objective:** To evaluate the efficacy and safety of entecavir (ETV) in patients with advanced schistosomiasis and hepatitis B virus (HBV) co-infection.

**Methods:** Sixty-seven patients with advanced schistosomiasis and HBV co-infection were enrolled in this study. The patients were randomly divided into the ETV treatment group (n = 35) and the control group (n = 32). The patients in the control group adopted routine supportive therapy for 52 weeks, and those in the ETV treatment group received ETV at a dose of 0.5 mg once daily on the basis of routine supportive therapy for 52 weeks. Hepatic fibrosis markers (hyaluronic acid, type III procollagen, type IV collagen, laminin, and fibronectin), Ishak fibrosis score, alanine transaminase (ALT), HBV DNA, and Child–Pugh score were compared between the two groups. The intention to treat (ITT) population was used for the analysis. The measurement data and count data were analyzed by t-test and Chi-square test, respectively.

**Results:** After 52 weeks of treatment, the hepatic fibrosis markers (hyaluronic acid, type III procollagen, type IV collagen, laminin, and fibronectin) were significantly improved in the ETV treatment group compared to the control group (all \(p < 0.05\)). A \(\geq 1\)-point improvement in the Ishak fibrosis score was found in 25.7% (9/35) of the ETV group, and the mean change from the baseline in the Ishak fibrosis score was a 0.3-point reduction. The control group showed disease progression in the Ishak fibrosis score. More patients in the ETV group than in the control group had undetectable serum HBV DNA levels (82.9% vs. 3.1%, \(p < 0.05\)) and ALT normalization (68.6% vs. 18.3%, \(p < 0.05\)). The ETV treatment group demonstrated an improvement in Child–Pugh score at week 52 (\(-3.7\) vs. 0.3, \(p < 0.05\)). In addition, no obvious adverse reactions were observed during ETV treatment.

**Conclusion:** ETV is safe and effective in patients with advanced schistosomiasis and HBV co-infection.

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1. Introduction

Schistosomiasis, caused by infection with trematode blood flukes of the genus *Schistosoma*, is one of the world’s most important helminth infections in terms of the global burden of human morbidity and mortality.\(^1,2\) Advanced schistosomiasis japonica can be regarded as an extreme form of chronic Asian schistosomiasis. In China, advanced schistosomiasis japonica is a chronic disabling condition associated with portal hypertension, splenomegaly, ascites, and gastro-esophageal variceal bleeding. These cases are registered and managed independently from patients with general chronic schistosomiasis,\(^3,4\) and the chronic *Schistosoma* infection leads to portal hypertension in these cases, with the resultant characteristic noncirrhotic ‘pipestem fibrosis’ and *Schistosoma* ova within granulomas in portal vein radicles in portal tracts.\(^5\) The prevalence of HBV co-infection in those with advanced schistosomiasis japonica is greater than the general population.\(^6,7\) Liver damage will be more serious, as it can present as schistosomiasis hepatic fibrosis combined with HBV mixed-type hepatic fibrosis and even hepatocirrhosis.\(^8,9\) In the past, the emphasis of treatment has been on Schistosoma de-worming and conventional supplements, such as albumin, hepatoprotective and diuretic treatment, and correcting water electrolyte disorders, but the efficacy is far from satisfactory.\(^10,11\) Hence the need for an effective treatment is urgent. The efficacy and safety of entecavir (ETV) has been shown in chronic hepatitis B (CHB) and HBV-related decompensated cirrhosis patients.\(^12,13\) The aim of this research was to examine the efficacy and safety of ETV for schistosomiasis japonica in patients co-infected with HBV.
2. Materials and methods

2.1. Case selection

From January 2009 to March 2011, 67 outpatients and inpatients with a diagnosis of advanced schistosomiasis japonica and HBV co-infection at the Fifth People’s Hospital of Wuxi, the Third People’s Hospital of Kunshan, and the Jiangsu Institute for Prevention and Treatment of Parasitic Diseases were selected. All patients had HBV DNA >1000 copies/ml; 18 were HBV e-antigen (HBeAg)-positive, 50 had HBV DNA, and 17 had giant spleen. Patients with the following concomitant conditions were excluded: those co-infected with HIV, hepatitis A, C, D, and E, and those with alcoholic liver, autoimmune diseases, cholestasis, malignant tumors, serious heart diseases, and diabetes; pregnant and lactating women were also excluded. All patients were informed of the long-term use of medication and the possible adverse effect of virus drug resistance and changes in the disease. Written informed consent was obtained from each subject before treatment.

2.2. Group allocation and treatment

Sixty-seven patients with advanced schistosomiasis japonica and HBV co-infection were randomly assigned to the ETV treatment group or the control group. The two groups were similar in terms of age, sex, ratio of ascites/giant spleen, hepatic fibrosis markers, Ishak fibrosis score, levels of alanine transaminase (ALT) and HBV DNA, ratio of patients with positive e-antigen, and Child–Pugh score before treatment, and there were no statistically significant differences. Demographic data and clinical features of the study patients at baseline are shown in Table 1. Thirty-two patients in the control group adopted routine supportive therapy (including Schistosoma deworming, diet regulation, hepatoprotective, diuretic, albumin, anti-infection, and symptomatic treatment) and 35 patients in the ETV treatment group received ETV (Baraclude, Sino-America Shanghai Squibb Pharmaceutical Company) 0.5 mg once a day in addition to routine supportive treatment. Both groups were treated for 52 weeks.

2.3. Study assessment

Laboratory assessments at baseline and at weeks 12, 24, and 52 included serum hepatic fibrosis markers (hyaluronic acid, type III procollagen, type IV collagen, laminin, and fibronectin), liver function, HBV markers, and HBV DNA. A liver biopsy was performed at baseline and again after 52 weeks, for all patients. Therapeutic effects and adverse reactions were observed during the 52 weeks. Fibrosis markers were tested with a BL-9600 Micropore Plate Chemiluminescent Immunity Analyzer. HBV DNA was tested with a Light Cycle Gene Fluorescent Quantitative Analyzer (Swiss Roche). HBV DNA reagent kits were bought from Shenzhen Pittsburgh based Engineering Co., Ltd, and had a sensitivity of 1000 copies/ml. HBV markers were determined with a 1235 Time-Resolved Fluorescent Immunity Analyzer (Finland, Perkin Elmer Life Science Company). Reagents were provided by New Wave of Suzhou Bio-technology Co., Ltd. Liver function was tested with a Hitachi 7600 Auto Bio-chemical Analyzer (Hitachi High-Tech Company) and its corollary reagents. All liver biopsy samples were evaluated by a single, central histopathologist. Fibrosis was assessed with the Ishak modification of the histology activity index (HAI) scoring system, as follows: score 0: no fibrosis; score 1: fibrous expansion of some portal areas, with or without short fibrous septa; score 2: fibrous expansion of most portal areas, with or without short fibrous septa; score 3: fibrous expansion of most portal areas with occasional portal to portal bridging; score 4: fibrous expansion of portal areas with marked bridging (portal to portal as well as portal to central); score 5: marked bridging (portal to portal and/or portal to central) with occasional nodules (incomplete cirrhosis); score 6: cirrhosis, probable or definite.14,15

2.4. Statistical analysis

Analysis was by intention to treat (ITT) method. Measurement data were expressed as means ± standard deviations (SD). Differences in measurement data were examined by t-test and analysis of variance; the numeration data were analyzed by Chi-square test. The statistical analysis was performed using the Statistical Program for Social Sciences (SPSS 16.0 for Windows; SPSS Inc., Chicago, IL, USA); p < 0.05 was considered statistically significant.

3. Results

3.1. Changes in hepatic fibrosis markers before and after treatment

Baseline hepatic fibrosis markers (hyaluronic acid, type III procollagen, type IV collagen, laminin, and fibronectin) were similar in the two groups (Table 1). Compared with the control group, those who underwent ETV therapy showed a statistically significant improvement in fibrosis markers after 52 weeks of treatment (all p < 0.05) (Table 2).

3.2. Results of the Ishak fibrosis score

All biopsy samples with at least two portal areas were evaluated with the understanding that small biopsy samples tend to score lower for fibrosis. Baseline biopsy samples had a mean length of 15.1 mm (97% >10 mm), and week 52 biopsy samples had a mean length of 15.6 mm (98% >10 mm).

After 52 weeks of treatment with ETV, 25.7% (9/35) of patients showed an improvement in Ishak fibrosis score (≥1-point decrease), and the mean change from the baseline in the Ishak fibrosis score was 0.3-point reduction. In contrast, a ≥1-point progression in the Ishak fibrosis score was found in 53.1% (17/32) of patients in the control group, and the mean change from the baseline in the Ishak fibrosis score was a 0.5-point increase. The differences between the control group and the ETV group were statistically significant (all p < 0.05) (Table 2, Figure 1).
Table 2
Hepatic fibrosis markers, Ishak fibrosis score, Child–Pugh score, and biochemical, virological, and serological responses at week 52 of treatment

<table>
<thead>
<tr>
<th>Markers of hepatic fibrosis mean (SD)</th>
<th>Control group</th>
<th>ETV group</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyaluronic acid (ng/ml)</td>
<td>365.7 (64.6)</td>
<td>131.6 (40.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Type IV collagen (ng/ml)</td>
<td>279.1 (42.6)</td>
<td>151.1 (36.4)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Type III procollagen (ng/ml)</td>
<td>269.3 (45.6)</td>
<td>112.7 (26.3)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Laminin (ng/ml)</td>
<td>252.2 (76.9)</td>
<td>109.8 (50.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fibronectin (ng/ml)</td>
<td>423.5 (69.3)</td>
<td>220.1 (68.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Improvement in the Ishak fibrosis score (≥1-point decrease), n (%)</td>
<td>0/32 (0)</td>
<td>9/35 (25.7)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Development in the Ishak fibrosis score (≥1-point increase)</td>
<td>17/32 (53.1)</td>
<td>0/35 (0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean change from the baseline in the Ishak fibrosis score</td>
<td>+0.5</td>
<td>–0.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ALT (U/l), mean (SD)</td>
<td>126.3 (45.6)</td>
<td>67.8 (25.2)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>ALT level ≤1 × upper limit of normal, n (%)</td>
<td>6/32 (18.3)</td>
<td>24/35 (68.6)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HBV DNA (log copies/ml), mean (SD)</td>
<td>5.27 (2.63)</td>
<td>3.45 (1.86)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>HBV DNA level &lt;1000 copies/ml, n (%)</td>
<td>1/32 (3.1)</td>
<td>29/35 (82.9)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>e antigen seroconversion n/N (%)</td>
<td>0/8 (0)</td>
<td>2/10 (20.0)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Mean change from baseline in the Child–Pugh score</td>
<td>+0.3</td>
<td>–3.7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; DNA, deoxyribonucleic acid; ETV, entecavir; HBV, hepatitis B virus; SD, standard deviation.

3.3. Results of biochemical, virological, and serological responses, and Child–Pugh score of the two groups at week 52 of treatment

After 52 weeks of treatment, the ETV group showed improvement in levels of ALT and HBV DNA, and the mean change from baseline in the Child–Pugh score at week 52 was −3.7 for the ETV group and −0.3 for the control group. The differences between the control group and the ETV group were statistically significant (all p < 0.05) (Table 2).

Table 2 shows that 82.9% of patients in the ETV group achieved an undetectable HBV DNA level and that 68.6% achieved ALT normalization after 52 weeks of treatment; compared with control group, the ETV group showed a statistically significant ALT normalization rate and undetectable HBV DNA rate (<1000 copies/ml) (both p < 0.05). The seroconversion rate of e-antigen positive patients was similar in the two groups (p > 0.05).

3.4. Adverse effects

Three patients in the control group developed progressive liver function damage and severe hepatitis at 24, 26, and 42 weeks, respectively. After using ETV and plasma exchange treatment, two cases improved and were discharged and one died. No other serious adverse effects occurred during ETV treatment.

4. Discussion

Patients with advanced schistosomiasis japonica who are co-infected with HBV are quite common in China. According to reports, the hepatitis B surface antigen (HBsAg) positive rate in patients with advanced schistosomiasis japonica may be as high as 16–64%,7,16 which is significantly higher than that of the general population (7.18%).17,18 Routine conventional treatment (including schistosomicides, diet regulation, hepatoprotective, diuretic, albumin, anti-infection, and symptomatic treatment) is given to most patients with advanced schistosomiasis japonica who are co-infected with HBV,19 with few reports about nucleotide analogs for these patients. Some data indicate that for patients with advanced schistosomiasis who are co-infected with HBV, complications increase, disease progression is affected, and mortality is increased.16,20 In this study, liver tissue pathology results showed that liver fibrosis in most patients was Ishak fibrosis score 4 or above, and in some cases even active cirrhosis.21 Hence, we believe that once patients with advanced schistosomiasis are co-infected with HBV, the liver damage will become more serious on the basis of the original liver fibrosis, and that liver disease will progressively increase until cirrhosis. Doctors must be aware that patients with advanced schistosomiasis can often be co-infected with HBV. Early detection of HBV serological markers is necessary for early diagnosis in these patients.20 Patients should be considered for nucleos(t)ide analog treatment when they have positive HBV DNA (≥1000 copies/ml) to relieve the liver fibrosis and inflammatory necrosis and to delay or reduce liver decompensation, cirrhosis, and its complications.17,22–24

The efficacy and safety of ETV in CHB and cirrhosis patients is known.12,23 Furthermore, the cumulative probability of genotypic resistance to ETV was found to be only 1.2% in nucleos(t)ide-naive patients over 5 years of treatment.25–27 This study showed that ETV is also effective and safe for advanced schistosomiasis patients co-infected with HBV. Results showed that patients in the ETV group achieved hepatic fibrosis marker amelioration, and 25.7% (9/35) of patients showed an improvement in the Ishak fibrosis score (≥1-point decrease); the mean change from the baseline in the Ishak fibrosis score was a 0.3-point reduction after 52 weeks of treatment with ETV. With regard to the improvement in serum hepatic fibrosis markers, the decrease was found to be relatively profound; the Ishak fibrosis score did not decrease quite so much. This is due to the fact that serum fibrosis markers can be influenced by the grade of inflammation and some liver function indices, such as serum levels of ALT; an obvious improvement in Ishak fibrosis score may require longer-term treatment with ETV,26,28–30 which is consistent with other reports in the literature.

Data showed that 82.9% of patients in the ETV group achieved an undetectable HBV DNA level and 68.6% of patients achieved ALT normalization, and the mean change from baseline in Child–Pugh score at week 52 was −3.7. There was no serious adverse reaction in the course of treatment. For this reason, we consider that ETV is
safe and effective in the treatment of patients with advanced schistosomiasis japonica co-infected with HBV. Antiviral treatment is the basis of anti-fibrosis treatment for these patients. Because liver fibrosis or cirrhosis occurred in these patients, long-term ETV medication is recommended to avoid HBV DNA rebound or deteriorations in condition after medication is stopped.17,22–24

Because the number of cases in the present study was relatively small and the period of observation was short, further studies are required to determine its long-term effects and safety.

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Conflict of interest: No conflict of interest to declare.

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