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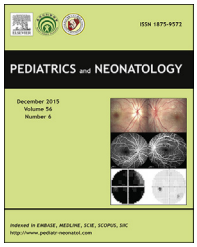

ORIGINAL ARTICLE

Entecavir Treatment in Children and Adolescents with Chronic Hepatitis B Virus Infection

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Key Words
chronic hepatitis B;
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Background: The aim of this study was to investigate the treatment response of entecavir (ETV) in children and adolescents with chronic hepatitis B (CHB) who acquired infection perinatally or during early childhood.
Methods: A total of nine treatment-naïve patients [median aged 12.2 years (range: 2.6–18.0); five girls and four boys], with hepatitis B e antigen (HBeAg) seropositive > 6 months, alanine aminotransferase (ALT) > 2 times of upper limit of normal value (30 IU/L), were enrolled for ETV therapy. They received ETV therapy with a dose of 0.015 mg/kg/d, with a maximal dose of 0.5 mg daily for at least 52 weeks. Another 27 untreated CHB patients matched for age, sex, ALT levels, and HBeAg status were recruited as the control group. A complete response at 48–52 weeks was defined as follows: (1) normalization of ALT; (2) undetectable hepatitis B virus DNA; and (3) HBeAg/anti-HBe seroconversion. All 36 patients were retrospectively reviewed for their biochemical, serological, and virologic responses.
Results: ETV-treated patients achieved rapid ALT normalization (all before 8 months of treatment) compared with the control group ($p < 0.001$) and they had a greater chance of achieving undetectable HBV DNA levels at Week 52 after treatment (55.6% vs. 11.1%, $p = 0.013$). The cumulative incidence rates of HBeAg seroconversion were similarly high in both groups (ETV group 44% at 1 year 78% at 2 years; control group 37% at 1 year 63% at 2 years, respectively). The ETV group also had a trend of better complete response than the control group (22.2% vs. 0%, $p = 0.057$). None of the ETV-treated patients reported significant adverse effects.

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Conclusion: Entecavir for pediatric CHB treatment is safe and shows clinical benefits in short-term biochemical and virologic responses. Further studies to determine long-term remission and drug resistance are required.

1. Introduction

Chronic hepatitis B virus (HBV) infection remains a health burden in both children and adults, especially in countries where HBV infection is highly endemic. Although universal HBV immunization has been well established for over 28 years in Taiwan, HBV infection still is not eradicated completely in vaccinated birth cohorts.[1–3] In spite of complete immunization with HBV vaccines and hepatitis B immunoglobulin, around 10% of infants acquired HBV infection perinatally through hepatitis B e antigen (HBeAg)-positive HBV carrier mothers.[2–4] Infection acquired at a young age and prolonged inflammation over decades predispose the children to the hazard of chronic liver injury, liver cirrhosis, and hepatocellular carcinoma (HCC) over their lifetimes.[5–7] For those who have been infected, treatment for children or young adults remains a great issue. In addition, strategies such as who may benefit from the intervention, what is the most appropriate timing for treatment, and the choice of antiviral agents are still unsolved.[8–10]

Although many kinds of effective and safe anti-HBV therapies are available in adults, few drugs are licensed to be used in the limited age range of the pediatric group. Currently, conventional interferon-alpha (IFN-α) can be used in children older than 1 year of age, lamivudine (LAM) in children older than 3 years of age, adefovir and tenofovir starting at 12 years of age, and entecavir (ETV) for children more than 2 years of age.[10–12]

Treatment for children with chronic hepatitis B (CHB) was initiated with IFN-α and LAM historically. In our previous experience of IFN-α, there was no significant difference in the rate of HBeAg seroconversion and HBV DNA suppression to $< 10^5$ copies/mL between IFN-α treated and untreated control patients at 1 year and at 6 years after stopping treatment.[13] IFN-α also has several adverse effects such as flu-like symptoms, neutropenia, and behavioral disorders. Our previous study of LAM showed no difference in the rate of HBeAg seroconversion (38% vs. 34%) and reduction in HBV DNA to less than 10^2 copies/mL (17% vs. 10%) at 1 year, as compared with untreated control patients.[14] Tyrosine-methionine-aspartate-aspartate mutants developed in 34% of this LAM-treated group, which was consistent with another study showing that LAM was associated with a high rate of drug resistance under long-term use.[14] Adefovir therapy showed no difference between treated patients and placebo control in children aged 2 years to < 12 years, with a lower risk of antiviral drug resistance than LAM.[15] ETV is superior to LAM in adult patients in terms of HBV viral suppression and much less HBV resistance strain development. These observations prompted us to consider ETV as the primary treatment choice of our CHB children from 2008 onwards.

2. Methods

2.1. Patients

We performed a retrospective, matched case-control study (1:3 ratio) consisting of ETV-treated and treatment-naïve CHB patients. We recruited pediatric CHB patients who started to receive ETV therapy in the Department of Pediatrics, National Taiwan University Hospital consecutively between January 2008 and July 2014. These children or adolescents with CHB had received long-term follow up in our outpatient clinics regularly since they were identified to be HBsAg-positive at initial screening. Most of them were identified to have acquired HBV infection perinatally or during early childhood. Patients were eligible for inclusion if they were younger than 19 years at the initiation of treatment and met the following criteria: (1) both HBsAg and HBeAg seropositive for > 6 months; and (2) elevation of alanine aminotransferase (ALT) levels > 2 times of upper limit of normal value (ULN; 30 IU/L) for at least two measurements over more than 6 months.[16]

Patients were excluded if they had concomitant infection with hepatitis C virus, hepatitis D virus, human immunodeficiency virus, decompensated liver disease or other severe systemic disease, or if they had positive serum anti-HBe at enrollment. In addition, patients could not have received IFN therapy or other antiviral agents before. A liver biopsy performed within 12 months before treatment was recommended but was not absolutely indicated.

In CHB children with elevated ALT serum levels (>2 ULN) for longer than 6 months, clinicians carefully explained the advantages and disadvantages of the current antiviral drugs available in the pediatric group to the parents and children, including the route of administration, adverse effects, and resistance rate. After deliberation, they finally gave consent to use ETV as their anti-HBV therapy with off-label use. In total, nine patients who had received ETV therapy fulfilled the study criteria and were enrolled in our ETV treatment group. The expenses of antiviral treatment were paid by health insurance coverage.

For comparison, three control participants were selected for each patient. Control participants consisted of treatment-naïve CHB patients who underwent regular, long-term follow-up at our department. Each control group patient who was matched for sex, age, HBeAg status, and ALT level with his/her corresponding treated patient (Table 1).

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