

Case Report

Seroconversion of Hepatitis B Envelope Antigen (HBeAg) by Entecavir in a Child with Chronic Hepatitis B

Mohammed Y. Hasosah, Heba S. Ghandourah, Ashraf F. Alsahafi,
Ghassan A. Sukkar, Kevan Jacobson¹

ABSTRACT

Department of Pediatric Gastroenterology, King Saud Bin Abdulaziz University for Health Sciences/National Guard Health Affairs, Jeddah, Saudi Arabia, ¹Pediatric Gastroenterology, British Columbia Children's Hospital, University of British Columbia, Vancouver, BC, Canada

Address for correspondence:

Dr. Mohammed Y. Hasosah,
King Saud Bin Abdulaziz
University for Health Sciences/
National Guard Health Affairs,
Department of Pediatric
Gastroenterology, King Abdul-
Aziz Medical City, National
Guard Hospital, Jeddah,
PO Box: 8202, Jeddah - 21482,
Saudi Arabia.
E-mail: hasosah2007@yahoo.com

Hepatitis B virus (HBV) infection is a worldwide health problem. Consensus guidelines for the treatment of chronic HBV in children have not been established, and indications for antiviral therapy in adults with chronic HBV infection may not be applicable to children. The medications that are Food and Drug Administration approved for the treatment of children with HBV include interferon (IFN)-alpha and lamivudine. Nondetectable serum HBV deoxyribonucleic acid, Hepatitis B envelope antigen (HBeAg) loss, and HBeAg seroconversion following 1 year duration of entecavir treatment. A review of the literature of entecavir treatment of chronic hepatitis B in children is also provided.

Key Words: Entecavir, hepatitis B virus, hepatitis B envelope antigen

Received: 26.09.2011, Accepted: 31.10.2011

How to cite this article: Hasosah MY, Ghandourah HS, Alsahafi AF, Sukkar GA, Jacobson K. Seroconversion of hepatitis B envelope antigen (HBeAg) by entecavir in a child with chronic hepatitis B. Saudi J Gastroenterol 2012;18:217-20.

Hepatitis B virus (HBV) infection is a worldwide health problem, which can cause acute hepatitis, acute liver failure, chronic hepatitis, liver cirrhosis, and liver cancer.^[1] The annual rate of progression to cirrhosis in patients with chronic HBV is 0.4–14.2% and for death is 4–10%.^[2] The established risk for progression of liver disease among patients with ongoing viral replication highlights the necessity to optimize available antiviral-based therapeutic strategies for infected individuals.

The treatment of chronic HBV should be considered in children 2–17 years of age who are Hepatitis-B surface antigen (HBsAg) seropositive for more than 6 months with persistent

elevation of alanine transaminase (ALT) levels $>2\times$ the Upper Limit of Normal (ULN) and evidence of active viral replication (positive hepatitis B envelope antigen (HBeAg), HBV deoxyribonucleic acid (DNA) levels $>10^5$ copies/mL or 20,000 IU/mL in their serum) for more than 3 months.^[3]

Medications approved by the Food and Drug Administration (FDA) for treatments of children with chronic HBV infection include interferon (IFN)-alpha, lamivudine, and more recently adefovir.

Entecavir (Baraclude[®]), a carbocyclic analog inhibits HBV replication at 3 different stages: The priming of HBV DNA polymerase, reverse transcription, and synthesis of HBV-DNA.^[4] It is more potent than lamivudine in suppressing wild-type HBV, but is less effective in adults with lamivudine resistance. Based on studies in adults entecavir has been approved by the FDA.^[4]

CASE REPORT

A 10-year-old Saudi boy presented with a history of chronic

Access this article online	
Quick Response Code: 	Website: www.saudijgastro.com
	DOI: 10.4103/1319-3767.96465

HBV since August 2005. The perinatal history revealed that his mother had chronic HBV and was not on treatment. He was delivered vaginally at term following uneventful pregnancy. His birth weight was 3.1 kg. He received both HBV vaccine and immunoglobulin at birth. There was no history of fever, change in appetite, weight loss, or change in activity. In addition, the child had no history of blood transfusion or tattoo marks. His medical history was otherwise noncontributory. The patient had normal developmental milestones and was not taking any medications. The family history revealed that his grandfather had hepatocellular carcinoma due to chronic HBV.

At age 6 years (July 2007), lamivudine 4 mg/kg/day was started orally twice a day. A pretreatment HBV DNA level was more than 100,000,000 IU/mL and his ALT was 119 U/L (normal range: 5–55 U/L). The patient was HBsAg positive, anti-HBV core antibody positive, HBs antibody negative, HBeAg positive, and HBe antibody negative. Because of a persistent elevation in ALT more than two times the normal, with no improvement in HBV DNA load and no seroconversion to HBe antibody, lamivudine was stopped after 6 months. Tyrosine–methionine–aspartate–aspartate (YMDD) mutation was not done.

The patient was referred to our center at the age of 8 years (January 2009) for further management. On physical examination, he had no palmar erythema or jaundice. There were no skin rashes, hepatosplenomegaly, lymphadenopathy, or ascites. The physical systemic examination was otherwise unremarkable. The laboratory findings revealed a normal hemoglobin, white blood cell and platelet count. The electrolytes, coagulation study, and lactate dehydrogenase level were normal. The liver function tests are summarized in Table 1. Viral hepatitis A, viral hepatitis C, cytomegalovirus, and Epstein–Barr virus were excluded serologically. Serum immunoglobulin IgG, serum antismooth antibodies and anti-liver-kidney antibodies were absent.

An ultrasound of the liver showed an enlarged liver with no evidence of cirrhosis. Percutaneous liver biopsy demonstrated evidence of mild chronic inflammatory infiltrate in the portal tracts with presence of mild interface hepatitis and single cell necrosis. Mild portal fibrosis was noted and no excess of iron or malignancy were evident. Immunohistochemistry demonstrated positive HBs Antigen. The liver biopsy showed grade 2, stage 1. The serum genotype of HBV was D.

The patient's father refused other options of treatment, including combination of interferon-alpha and lamivudine. He agreed with written consent for entecavir treatment based on adult studies. Entecavir was started orally at a dose of 0.5 mg (0.015 mg/kg) given once daily. The laboratory results before and after treatments are summarized in

Table 1. During his treatment course, liver tests, coagulation profiles, serum hepatitis B markers, and serum HBV DNA were monitored at 4, 8, 12, 24, 48 weeks intervals while he was on entecavir therapy at 0.5 mg/daily. The laboratory results and hepatitis B markers were monitored at 72- and 96-week intervals while he was not on treatment. He had undetectable serum HBV DNA levels and seroconversion of HBeAg at 12 weeks. He completed a 1 year course of entecavir. At 6 and 12 months post-treatment he maintained undetectable serum HBV DNA levels and seroconversion of HBeAg. The patient's father refused to repeat the liver biopsy. The patient was monitored for any side effects of entecavir. No symptoms or biochemical abnormalities were noted. The child's growth was normal. At present, he remains asymptomatic and is still being monitored in the pediatric gastroenterology clinic on a monthly basis for undetectable serum HBV DNA and HBeAg seroconversion.

DISCUSSION

HBV infection is considered chronic when it persists for longer than 6 months. Risk of chronic HBV infection is inversely related to age, with chronic infection developing in about 90% of infected infants, 30% of children younger than 5 years, and less than 5% in all other persons.^[1]

The optimal goal of antiviral therapy for chronic HBV infection is to eradicate HBV. However, due to the limited effect of available therapies on HBV eradication, the goal of current antiviral therapy is to reduce viral replication, minimize liver injury and related consequences in children and reduce infectivity.^[5]

Consensus guidelines for the treatment of chronic HBV in children have not been established, and indications for antiviral therapy in adults with chronic HBV infection may not be applicable to children.^[5] The treatment of the childhood chronic HBV should be considered in children 2–17 years of age who are HBsAg seropositive for more than 6 months with persistent elevation of ALT levels $> \times 2$ ULN and evidence of active viral replication (positive HBeAg, HBV DNA levels $> 10^5$ copies/mL or 20,000 IU/mL in their serum) for more than 3 months.^[3]

The medications that are Food and Drug Administration (FDA) approved for the treatment of children with HBV include IFN-alpha, lamivudine, and most recently adefovir.

Lamivudine is an oral nucleoside analogue. The most significant limitation of lamivudine is the development of viral resistance with prolonged use. HBV may acquire resistance to lamivudine due to a specific HBV mutation (YMDD mutation) in the polymerase gene.^[6,7] Unfortunately, investigation for this YMDD mutation was not done in our patient.

Table 1: The laboratory tests

	Normal range	Pre-treatment	Post treatment 4 weeks	Post treatment 8 weeks	Post treatment 12 weeks	Post treatment 24 weeks	Post treatment 48 weeks	Off treatment 72 weeks	Off treatment 96 weeks
WBC	6-16 × 10 ⁹ /L	9.2	8.4	8.1	7.7	4.5	5.9	ND	5.4
Hb	12-15.3 gm/dL	11.3	13.8	13.2	13.3	13.0	11.9	ND	13.8
Platelet	150-450 × 10 ⁹ /L	212	205	285	478	395	326	ND	371
Urea	1.1-8.0 mmol/L	4.4	5.0	ND	7.5	3.2	4.9	ND	4.8
Creatinine	18-35 umol/L	21	29	ND	31	17	25	ND	23
INR	0.8-1.2	1.2	1.1	1.0	1.1	1.2	1.0	ND	1.2
ALT	5-55 U/L	106	34	31	51	52	30	ND	29
AST	5-34 U/L	82	25	24	12	33	19	ND	24
GGT	12-64 U/L	18	24	29	30	49	16	ND	18
ALK	30-220 U/L	107	284	214	149	144	137	ND	168
Bilirubin	<20.5 umol/L	11	18	12	16	9	19	ND	14
Albumin	38-54 g/L	39	39	42	41	37	38	ND	40
HBs Ag	-ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
HBs Ab	0-15	0	0	0	0	0	0	0	0
HBe Ag	-ve	+ve	+ve	+ve	+ve	+ve	-ve	-ve	-ve
HBe Ab	+ve	-ve	-ve	-ve	-ve	-ve	+ve	+ve	+ve
HBc Ab	-ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve	+ve
HBc IgM	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve	-ve
Serum HBV DNA	<14 IU/mL	>100,000,000	3459	121	<11	<10	0	0	0

WBC: White blood counts, Hb: Hemoglobin, INR: International normalized ratio, ALT: Alanine transaminase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyltransferase, ALK: Alkaline phosphatase, HBsAg: Hepatitis B surface antigen, HBsAb: Hepatitis B surface antibody, HBeAg: Hepatitis B envelope antigen, HBeAb: Hepatitis B envelope antibody, HBcAb: Hepatitis B core antibody, HBV DNA: Hepatitis B virus deoxyribonucleic acid, ND: Not done, -ve: Negative, +ve: Positive

Entecavir is more potent than lamivudine in suppressing wild-type HBV, but it is less effective in adults with lamivudine resistance.^[4] Viral resistance to entecavir is rare.^[4]

We decided to treat our patient with entecavir based on the following reasons: Older age, positive HBsAg and HBeAg, elevated HBV DNA, the degree of necroinflammatory activity and fibrosis in the liver biopsy, the immunological activity as reflected in his ALT elevation, the patient's treatment history of lamivudine failure, absence of coexisting other liver disease or chronic illnesses, and the father's refusal to commence other options of treatment, including combination of (IFN)-alpha and lamivudine.

The recommended oral daily dose of entecavir in patients aged 16 years or older with creatinine clearance of 50 mL/min is 0.5 mg for patients naive to nucleoside therapy and 1 mg for lamivudine-resistant patients. As with the other oral antiviral agents for hepatitis B, the dosage should be adjusted downwards for patients who have impaired renal function.

We choose the dose of entecavir at 0.5 mg (0.015 mg/kg/day) as it is close to the adult dose and is also based on dosing used in a clinical trial that is underway to evaluate entecavir in pediatric patients with chronic HBV infection (<http://clinicaltrials.gov/show/NCT00423891>).

Our observation in the child [Table 1] indicates that normalization of ALT occurred at 4 weeks, a decrease in HBV DNA load was seen at 8 weeks, and undetectable HBV DNA at 12 weeks. HBeAg loss and HBeAg seroconversion occurred at 48 weeks; however, HBsAg was not eliminated in our patient.

The data of Dienstag *et al.*,^[8] taken together with the observation in our patient suggest that normalization of ALT, loss of HBeAg (seroconversion), and a decrease in serum HBV DNA level is indicative of the effectiveness of entecavir treatment.

The data of Chang *et al.*,^[9] taken together with the observation in our patient suggests that the optimal duration of entecavir treatment is around 48 weeks. In the registration entecavir trial, the durability of HBeAg seroconversion was approximately 70% among HBeAg-positive patients who had achieved HBeAg seroconversion and who stopped entecavir therapy at 48 weeks. Additionally, the data of Gish *et al.*,^[10] taken together with the observation in our patient with genotype D suggests that patients infected with HBV genotype A or D, are significantly more likely to lose HBsAg after 96 weeks of entecavir treatment. Our patient remained HBsAg positive after 48 weeks of entecavir treatment, which raises

the question whether he would have lost HBsAg had the therapy been continued for 96 weeks. HBsAg lost is not regarded as a marker for HBV treatment because it may take several years or decades to disappear.

Bortolotti *et al.*^[11] reported chronically HBV-infected children, particularly boys, have a high risk of progressing to cirrhosis and hepatocellular carcinoma, the likelihood of developing these complications being correlated to the length of time to achieve anti-HBe seroconversion. Our patient who is a male achieved anti-HBe seroconversion thus reducing his risk of progressing to cirrhosis and hepatocellular carcinoma.

Entecavir was well tolerated in our patient and no major side effects were noted including myopathy, nephrotoxicity, and severe lactic acidosis.^[9,12]

The data of Pawłowska *et al.*^[13] taken together with the observation of our patient suggests that 24 weeks of treatment with entecavir results in suppression of HBV DNA in a substantial proportion of children with prior ineffective therapy. However, the study of Pawłowska *et al.* had no cases of HBeAg seroconversion in any of the cases treated.^[13] Our patient had undetectable HBV DNA after 12 weeks and HBeAg seroconversion after 48 weeks of therapy, suggesting that longer treatment durations may be required in children, similar to adults.

CONCLUSION

We believe that entecavir treatment can have a significant impact on health care through its ability to speed up anti-HBe seroconversion, thus reducing the spread of infection and the development of serious complications associated with chronic HBV. Larger clinical trials are recommended to compare both short- and long-term efficacy and safety of entecavir in children.

REFERENCES

1. Lok AS, McMohan BJ. Chronic hepatitis B. *Hepatology* 2007;45:507-39.
2. Alberti A, Brunetto MR, Colombo M, Craxi A. Recent progress and new trends in the treatment of hepatitis B. *J Med Virol* 2002;67:458-62.
3. Shah U, Kelly D, Chang MH, Fujisawa T, Heller S, González-Peralta RP, *et al.* Management of chronic hepatitis B in children. *J Pediatr Gastroenterol Nutr* 2009;48:399-404.
4. Sherman M, Yurdaydin C, Sollano J, Silva M, Liaw YF, Cianciara J, *et al.* Entecavir for treatment of lamivudine-refractory HBeAg-positive chronic hepatitis B. *Gastroenterology* 2006;130:2039-49.
5. ACT-HBV Asian pacific steering committee members. Chronic hepatitis B: Treatment alert. *Liver Int* 2006;26:s47-58
6. Farrell G. Hepatitis B e antigen seroconversion: Effects of lamivudine alone or in combination with interferon alpha. *J Med Virol* 2000;61:374-9.
7. Ling R, Mutimer D, Ahmed M, Boxall EH, Elias E, Dusheiko GM, *et al.* Selection of mutations in the hepatitis B virus polymerase during therapy of transplant recipients with lamivudine. *Hepatology* 1996;24:711-3.
8. Dienstag JL. Hepatitis B virus infection. *N Engl J Med* 2008;359:1486-500.
9. Chang TT, Gish RG, de Man R, Gadano A, Sollano J, Chao YC, *et al.* A comparison of entecavir and lamivudine for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2006;354:1001-10.
10. Gish RG, Chang TT, Lai CL, de Man R, Gadano A, Poordad F, *et al.* Loss of HBsAg antigen during treatment with entecavir or lamivudine in nucleoside-naïve HBeAg-positive patients with chronic hepatitis B. *J Viral Hepat* 2010;17:16-22.
11. Bortolotti F, Guido M, Bartolacci S, Cadrobbi P, Crivellaro C, Noventa F, *et al.* Chronic hepatitis B in children after e antigen seroclearance: Final report of a 29-year longitudinal study. *Hepatology* 2006;43:556-62.
12. Lange CM, Bojunga J, Hofmann WP, Wunder K, Mihm U, Zeuzem S, *et al.* Severe lactic acidosis during treatment of chronic hepatitis B with entecavir in patients with impaired liver function. *Hepatology* 2009;50:2001-6.
13. Pawłowska M, Halota W, Smukalska E, Woźniakowska-Gęśicka T, Kupż J. HBV DNA suppression during entecavir treatment in previously treated children with chronic hepatitis B. *Eur J Clin Microbiol Infect Dis* 2012;31:571-4.

Source of Support: Nil, **Conflict of Interest:** None declared.