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# Response of Treatment of Hepatitis B in Children-A Case Series from India

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**Abstract**

Chronic Hepatitis B virus (HBV) infection is a major cause of liver disease leading to cirrhosis and hepatocellular carcinoma. Children are more likely to develop chronic HBV infection. Treatment with Interferon alfa (IFN-α), lamivudine (3TC) or adefovir are recommended in children with chronic active HBV with replicating virus. We present a series of 7 patients treated with combination IFN-α (5-10 million units/m² subcutaneously thrice a week)+3TC (4 mg/kg/day, not exceeding 100 mg/day) for 6 months and additional 3TC for 6 months alone). Of the 7 patients, one patient had complete response and viral load remained suppressed even after 2 years of therapy and remaining 6 patients had partial response (viral load became undetectable, but 'e' antigen remained positive). Thus we concluded that the antiviral treatment in children while effective remains partial as the reappearance of HBV DNA at variable time after stopping therapy can still occur.

**Keywords:** Hepatocellular carcinoma; Hepatitis B; Desferoxamine; Echocardiography

## Introduction

Chronic Hepatitis B Virus (HBV) infection is a major cause of liver disease throughout the world and can lead to acute liver failure, acute hepatitis, chronic hepatitis, liver cirrhosis and hepatocellular carcinoma [1]. The risk of developing chronic Hepatitis B infection ranges from 90% in neonates to <5% in adults [2]. HBV is more prevalent in Asia, Africa, Southern Europe and Latin America with hepatitis B surface antigen (HBsAg) positive ratio ranging from 2% to 20% [3]. Universal infant immunization with Hepatitis B vaccine has decreased rates of HBV infection, although transmission continues to occur via vertical (mother-to-child) and horizontal (Sexual, parenteral and household) routes [4]. Mother-to-infant transmission accounts for approximately half of the chronic HBV infectious [3]. Children are more likely to develop chronic HBV infection as they demonstrate greater immuno-tolerance to the virus, and response to therapy in children remains disappointing [1]. Three phases of chronic Hepatitis B have been identified: the immune-tolerant phase, the immune-active phase and the inactive hepatitis B phase. These phases of infection are characterized by variations in viral replication, hepatic inflammation, spontaneous clearance and response to antiviral therapy [3]. Three therapeutic agents for chronic HBV infection have been approved in the USA, including standard interferon (IFN)-alpha, lamivudine (3TC) and adefovir [1]. The goal of treatment is to reduce viral replication, minimize liver injury and to reduce infectivity [3]. At the present time, lamivudine and a combination of interferon and lamivudine seem to be the best options for HBV infection treatment in the pediatric population, even though they induce the presence of drug resistant mutations [2].

We present a series of 7 children with chronic HBV infection who were treated with combination IFN+3TC therapy and their response to them. Partial response was defined as normalization of SGPT and undetectable HBV viral load. Complete response was defined as normalization of SGPT, undetectable HBV viral load and seroconversion of 'e' antigen. Non-responders were defined as having persistently high HBV viral load and abnormal SGPT. Sustained response was defined as absence of HBsAg and presence of Hepatitis B surface antibody (anti-HBs) [5].

## Case Studies

### Case 1

An 8 years old boy presented with jaundice for 3½ months and abdominal distension for 6 months. He had not received any blood products and there was no jaundice in family members. On examination, he weighed 15 kg, length was 110 cm. He had pallor, splenohepatomegaly with ascitis. Other systems were normal. Investigations are depicted in (Table 1). He was treated with Interferon and Lamivudine as depicted in Table 1 following which Hepatitis B viral load became undetectable in 6 months and 'e' Antigen became negative though he had not yet developed 'e' Antibody. He is on regular follow-up.

### Case 2

A 6½ years old boy suffering from thalassemia on regular blood transfusion since 3 years of age was detected have Hepatitis B. He did not have jaundice. His HIV ELISA and Hepatitis C Antibody were negative. On examination, weight was 15 kg, height was 106 cm. He had hepatosplenomegaly. Other systems were normal. Investigations and treatment are depicted in (Table 1). Prior to treatment, he was 'e' Antigen negative and 'e' Antibody positive. At end of therapy, his viral load was 95 copies/ml. Even after 2 years after stopping therapy, his viral load is 1730 copies/ml and liver function tests are normal.

### Case 3

An 11 years old boy suffering from thalassemia on regular blood transfusion since 10 months of age was detected to have Hepatitis B at 6 years of age, but was not on any treatment. His HIV ELISA and

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| | Case 1 | | Case 2 | | Case 3 | Case 4 | | Case 5 | | Case 6 | | Case 7 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age (yrs) | 8 | | 6½ | | 11 | 14 | | 17 | | 9 | | 8 |
| Gender | Male | | Male | | Male | Male | | Male | | Female | | Male |
| Blood transfusion | No | | Yes (for thalassemia) | | Yes (for thalassemia) | Yes | | Yes | | No | | No |
| Clinical presentation | Jaundice+Ascitis | | Asymptomatic | | Jaundice | Asymptomatic | | Asymptomatic | | Asymptomatic | | Hematuria |
| Portal hypertension | Yes | | No | | Yes | No | | No | | No | | No |
| Oesophago-gastroscopy | Small oesophageal varices | | Not done | | Not done | Not done | | Not done | | Not done | | Not done |
| USG Abdomen | Hepatomegaly with coarse echotexture & splenomegaly | | Hepatosplenomegaly | | Hepatosplenomegaly with ascitis | Normal | | Normal | | Mesenteric adenopathy | | Normal |
| | Pre-treatment | Post-treatment (after 6 months) | Pre-treatment | Post-treatment (after 6 months) | Pre-treatment | Pre-treatment | Post-treatment (after 6 months) with adefovir | Pre-treatment | Post-treatment (after 6 months) | Pre-treatment | Post-treatment (after 6 months with interferon) | Pre-treatment |
| Bilirubin (mg/dl) | 0.6 | 0.9 | 0.6 | 1 | 2.3 | 0.6 | 1 | 0.4 | 0.6 | 0.6 | | 0.5 |
| SGOT (IU/L) | 138 | 52 | 107 | 51 | 1260 | 120 | 62 | 17 | 10 | 54 | | 48 |
| SGPT (IU/L) | 54 | 37 | 134 | 33 | 606 | 102 | 65 | 35 | 14 | 69 | | 23 |
| Total protein (gm/dl) | 7 | 8.2 | 6.3 | 6 | 6.5 | 6.3 | 8 | 6.9 | 6.7 | 6.4 | | 6.8 |
| Albumin (gm/dl) | 4.2 | 3.5 | 3.4 | 4 | 2.6 | 3.4 | 4 | 3.8 | 3.7 | 3.6 | | 3.8 |
| PT (sec) | 16.1 | - | 14.6 | - | 13.9 | 10.9 | - | - | - | - | - | - |
| PTT (sec) | 29.8 | - | 30.5 | - | >2 min | 40.5 | - | - | - | - | - | - |
| HBsAg | +ve | +ve | +ve | +ve | +ve | +ve | +ve | +ve | +ve | +ve | +ve | +ve |
| HBeAg | +ve | -ve | -ve | -ve | +ve | +ve | +ve | +ve | +ve | +ve | +ve | +ve |
| HBeAb | - | -ve | +ve | +ve | - | -ve | -ve | -ve | -ve | -ve | -ve | -ve |
| Hepatitis B viral load (copies/ml) | 19409400 (pre-treatment) | Undetectable | 10940800 | 95 | #### | 2.12E+08 | ## | 1.01E+09 | undetectable | 10677800 | undetectable | 1239651 |
| Interferon | 5 mU/m² for 6 months | | 10 mU/m² for 4 months 5 mU/m² for 2 months | | 3 mU/m² for 8 months | Treated in past at 9 years of age | | Treated at 15 years for 10 months | | 5 mU/m² for 6 months | | 5 mU/m² for 8 months |
| Lamivudine | 1 year | | 1 year | | 1 year | Received for 5 year from 9 year of age | | Received at 15 years for 10 months | | 1 year | | 1 year |
| Adverse effects | None | | Granulocytopenia after 4 months of Interferon | | - | - | | - | | Nil | | Nil |
| Liver Biopsy | Not done | | Hemosiderosis, No cirrhosis, HAI=6 | | Hemosiderosis early bridging necrosis with inflammation | Chronic hepatitis | | Periportal inflammation with periportal fibrosis, HAI=2 | | HAI-4 | | HAI- 2 |
| Adefovir | No | | No | | No | 6 months | | No | | Currently on treatment | | No |
| Associated disease | - | | - | | HIV at 13½ years | - | | - | | TB | | - |
| Tenofovir | No | | No | | Yes as part of ART at 14 years of age | No | | No | | No | | No |
| Response to therapy | Partial response | | Complete response | | Died due to sepsis at 15 years | Partial response | | Partial response | | Partial response | | Partial response |

Note: +ve=positive; -ve=negative; ART=antiretroviral therapy.

**Table 1:** Profile of all patients with Hepatitis B.

Hepatitis C antibody were negative. He did not have jaundice. On examination, weight was 20 kg. He was dark, had icterus, pallor with large hepatosplenomegaly. Other systems were normal. Investigations and treatment are depicted in Table 1. He also had high serum ferritin of 13,000/ml and echocardiography showed mild systolic and diastolic dysfunction for which he was started on Desferoxamine. He also had increased blood transfusion requirement with hypersplenism and pancytopenia for which he underwent splenectomy prior to start of interferon therapy. At end of 6 months of Interferon, his viral load was 367 copies/ml but he was still 'e' Antigen positive. At 13 years of age, he developed proteinuria for which he was given enalapril. At 13½ years of age, he was detected to have HIV and his Hepatitis B viral load increased to 5,57,560 copies/ml with elevated liver enzymes for which he was started on Tenofovir, Lamivudine, Abacavir and Efavirenz. At 14 years of age, his Hepatitis B viral load decreased to 367 copies/ml though he continued to be 'e' Antigen positive. At 14½ years of age, his CD4 count was 972 (32.4%) and Hepatitis B viral load was 5,68,080 copies/ml. At 15 years of age, he developed septicemia and died.

## Case 4

A 14 years old boy was detected to be Hepatitis B infected at 6 years of age on screening. He had Acute lymphoblastic leukemia at 4 years of age and received chemotherapy for 2 years. He also received blood transfusion at 5 years of age. He had no jaundice. At 9 years of age, he was given Interferon for 4 months and Lamivudine was continued till now. There were no Hepatitis B viral load, 'e' Antigen or liver biopsy done at that time. On examination, his height was 150 cms, weight was 34 kg. Systemic examination was normal. His investigations and treatment presently at 14 years of age given are depicted in Table 1. Even after 6 months of Adefovir, he continued to be 'e' Antigen positive, 'e'

Antibody negative and viral load decreased to 1,84,150 copies/ml. He continues to be asymptomatic and adefovir has been continued.

### Case 5

A 17 years old male was referred for management of Hepatitis B. He was diagnosed to have Non-Hodgkin's lymphoma at 4 years of age and had received chemotherapy and repeated blood transfusions. At 15 years of age, his hepatitis B viral load was 4,55,94,0592 copies/ml and 'e' Antigen was positive for which he had received interferon and lamivudine for 10 months following which viral load became undetectable. However within 5 months of stopping the treatment, his viral load again increased to 1,00,60,00,000 copies/ml and 'e' Antigen was still positive. He had no jaundice. On examination, height was 168 cms, weight was 35 kg. Systemic examination was normal. Current investigations and treatment are depicted in Table 1. In view of normal liver function tests and liver biopsy showing HAI Stage 2, patient was not started on any treatment and was advised regular monitoring of liver function tests and viral load.

### Case 6

A 9 years old girl was detected to be Hepatitis B infected on screening as mother was diagnosed to have Hepatitis B. Child had fever and weakness for past 2 months. There was no history of blood transfusion or jaundice. On examination, weight was 18 kg, height was 123 cms. Other systems were normal. For fever for 2 months, her Chest X-Ray showed primary complex, ultrasound abdomen showed mesenteric lymphadenopathy and Mantoux test was positive (15 × 15 mm). She was started on antituberculous therapy (ATT) which she received for 9 months. In view of liver dysfunction and high Hepatitis B viral load, she was treated with Interferon and Lamivudine as depicted in Table 1 after six months of initiation of ATT. Subsequently her viral load became undetectable though here Antigen remained positive. She was alright for a year when again viral load increased to 14,300,000 copies/ml and she was started on Adefovir for the same. Currently she is asymptomatic and on regular treatment.

### Case 7

An 8 years old boy presented for management of Hepatitis B. He was diagnosed to have acute glomerulonephritis 5 years ago at which time he was detected to be HBsAg positive. He had no jaundice, blood transfusion and was currently asymptomatic. Mother had jaundice 4 years ago and had received blood transfusion 15 years ago. Father had jaundice 3 years ago. On examination, weight was 20 kg and height was 129 cm. Rest of examination was normal. Investigations showed persistent microscopic hematuria. His C3 and ASLO were normal. Renal function tests were also normal. Kidney biopsy was done that showed thin glomerular basement membrane with mild mesangial matrix thickening and increased cellularity. In view of 'e' Antigen positive and high viral load, patient was started on Interferon and Lamivudine as depicted in (Table 1). His viral load decreased to 621 copies/ml but he remained 'e' Antigen positive following treatment.

## Discussion

Treatment of chronic Hepatitis B infection in children consists of IFN, IFN+3TC and adefovir [1]. IFN-alpha has Hepatitis B 'e' Antigen (HBeAg) seroconversion rate of approximately 30% & HBsAg seroconversion rate of 10%. Benefits are primarily observed in children with SGPT over two-times the upper limit of normal. Lamivudine's response rates are similar with 23-31% HBeAg seroconversion but lower HBsAg seroconversion (2-3%). However it has a high rate of drug resistance. Adefovir has lesser response rates with 16%. HBeAg seroconversion and <1% HBsAg seroconversion. However, it has low rates of resistance and good safety profile [1]. In our series, none of the patients had HBsAg seroconversion and only patient had HBeAg seroconversion One patient was already Hepatitis B 'e' antibody positive prior to treatment but showed sustained viral suppression even after 2 years after stopping therapy.

IFN+3TC combination therapy has been tried in Turkey with IFN in dose of 5 mU/m$^2$ subcutaneously thrice a week for 6 months and Lamivudine 4 mg/kg/day orally (maximum 100 mgl day) and continued alone for additional 6 months) and it was found that 54.2% were non-responders, 20.8% were partial responders and complete response was seen in 25% [5]. In our series, one patient with already HBeAg and 'e' Antibody had complete and persistent response whereas 5 children had partial response with rise in Hepatitis B viral load within 5 months to 2½ years of stopping therapy. One child had no response to therapy. Two of our patients are currently on adefovir on which their liver function tests have normalized but one patient still continues to have high HBV viral load. Adefovir is known to have poorer virologic response than lamivudine [1].

Thus treatment of chronic Hepatitis B in childhood still remains partially successful. Therapy is currently recommended for patients with evidence of chronic active Hepatitis B disease (high liver enzymes, positive HBV DNA findings, HBeAg) [6]. As per American Association for the Study of Liver Diseases (AASLD), for HBeAg positive patients with chronic HBV treatment is advised when HBV DNA level is ≥ 100,000 copies/ml and when serum SGPT is elevated for 3-6 months. For the HBeAg negative chronic HBV patients, treatment is administered when HBV DNA is >10,000 copies/ml and serum SGPT is elevated for 3-6 months [7]. In all our patients, HBV viral load were >100,000 copies/ml and SGPT was elevated suggesting a state of chronic active HBV.

However, certain attributes have been associated with poor response. High levels of aminotransferases, low viral load and infection with wild type are good prognostic factors. Asian patients and patients with precore mutant virus [Mutations of various nucleotides such as the 1896 (precore/core region) processing the production of the HBeAg (HBeAg negative strain) tend to have poor response to IFN-α treatment [6]. Among the several genotypes of HBV (A through H) genotype A or B have better response as compared to genotype C or D [6]. However in India, genotype D (HBV/D) is the most widespread genotype [8]. We were unable to do genotype testing in our patients due to unaffordability.

Also adverse effects of drugs-flu like syndrome, myelosuppression, nausea, diarrhea, fatigue with IFN, emergence of viral variants especially with patients on lamivudine due to mutation of the viral polymerase gene (YMDD variant) are other major complications of the disease [6]. In our case series, one patient developed myelosuppression with IFN and required dose reduction. None of the patients have been tested for YMDD mutation due to cost factor. Thus, it appears that immunotolerant Hepatitis B in children should be a wait and watch option since current therapies are only 30% effective at best and long-term impact of therapy in childhood on rates of cirrhosis and hepatocellular carcinoma remains unknown [1]. However, patients who had seroconversion of HBeAg and in whom HBV viral load is

undetectable have slower rate of disease progression, prolonged survival without complications, reduced rate of hepatocellular carcinoma and clinical and biochemical improvement after decompensation [6].

With newer drugs now being used for treatment of Hepatitis B in adults such as terbuvidine, entecavir and tenofovir and trials of tenofovir with emtricitabine & clevudine as combination therapy [6] treatment recommendations may modify in near future with better outcomes.

Till then, universal vaccination with Hepatitis B vaccine in infants will help to decrease prevalence of Hepatitis B virus infection. In Taiwan Seroprevalence declined from 10% in 1984 (before vaccination programs) to less than 1% in 1994 after implementation of vaccination programs [8].

## Conclusion

Combination IFN+3TC therapy for chronic active Hepatitis B infection in Indian children leads to partial response (undetectable HBV viral load) but fails to cause seroconversion of HBeAg. Antiviral treatment in children while effective remains partial as the reappearance of HBV DNA at variable time after stopping therapy can still occur.

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