Lamivudine Treatment of Chronic Viral Hepatitis B Infection in Lithuanian Children

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Introduction. Chronic hepatitis B virus (HBV) infection is a rare but serious children's disease. Age at infection in children is the most important determinant for chronicity: the younger the age at infection, the higher the probability of chronicity. The chronicity can be as high as 90% in infants born to hepatitis Be antigen (HBeAg)-positive mothers.

Therapeutic options for chronic hepatitis B include different drugs. Interferon-α (IFN-α) was the first drug created to treat patients with this infection. Therapy with this drug is cumbersome to deliver, is uncomfortable to receive, and has undesirable side effects. Children with chronic HBV infection are treated according to recommendations of European Society of Paediatric Gastroenterology, Hepatology and Nutrition (1).

Another option for treatment of HBV infection is lamivudine. Unfortunately there are no recommendations for treatment of HBV infection in children.

Materials and Methods. We analysed data on 14 children (age 4–14 years) treated with lamivudine in Vilnius University Children's Hospital in 2000–2003. Most of the patients were infected during leukaemia treatment.

The patients were divided into two groups according to the alanine aminotransferase (ALT) level at the beginning of the treatment. There were 8 patients in group 1 who had elevated ALT and 6 patients in group 2 who had normal ALT at the beginning of the treatment.

Children were treated with oral lamivudine (*Zeffix*®) (3 mg per kilogram of body weight; maximum, 100 mg) once daily for 12–24 months. We evaluated virologic response (defined by the absence of serum HBeAg and appearence of anti-HBe), ALT value, examination of liver-biopsy specimens and safety and tolerance of lamivudine.

Results. Lamivudine was well tolerated in both groups. After 12 months of treatment, in group 1 normalization of ALT occurred in 5 patients, in 2 children the ALT level decreased and in one didn't change. Seroconversion from hepatitis B e antigen to hepatitis B e antibody occurred in one patient from group 1 and in two from group 2. In other two patients from group 2 who had no seroconversion, the liver morphology was better after 18 months of treatment with lamivudine.

Conclusions. Lamivudine therapy was well tolerated. After 12 months of treatment, normalization of ALT occured in 5 out of 8 patients, in 2 children the ALT level decreased and in one didn't change. Seroconversion occurred in only 3 out of 14 patients (21.4%).

Key words: children, chronic hepatitis B virus, treatment, lamivudine (*Zeffix*®)

INTRODUCTION

Chronic viral hepatitis can be found both in symptomatic and asymptomatic patients. Patients with chronic viral hepatitis usually show a mild elevation of ALT (2–3 times above normal level), whose increase hardly correlates with liver inflammation (2, 3).

The hepatitis B virus is a small, noncytopathogenic, hepatotropic, encapsulated DNA virus which belongs to *hepadnaviruses*. The core is formed in the nucleus and the surface particles in the cytoplasm. The core contains a DNA polymerase. The DNA structure is double-stranded and circular with a single-strand-

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ed gap of 600–2100 nucleotides. The DNA polymerase reaction appears to repair the gap. The core contains a core antigen (HBcAg), and another antigen called 'e' (HBeAg) is a protein subunit of the core.

The surface of the hepatitis B virus is made of 's' antigen (HBsAg) particles.

The Hepatitis B virus has enzymes: reverse transcriptase and DNA polymerase, whose mutations in the pre-core zone are named YMMD mutations. Viruses with YMMD mutations don't have HBeAg and are resistant to lamivudine (4). About 2–3% of children with HBV have YMMD mutations (5).

Approximately 10% of patients contracting hepatitis B as adults and 90–98% of those infected as neonates will not clear HBsAg from the serum within 6 months. Such patients become carriers and this is likely to persist. Reversion to a negative HBsAg is rare, but may occur in old age. Males are six times more likely to become carriers than females (6).

AIM OF THE STUDY

To determine the efficacy of lamivudine in children with HBV infection.

MATERIALS AND METHODS

Fourteen children (7 girls, 7 boys) with HBV infection were treated with lamivudine in Vilnius University Children's Hospital in 2000–2003. The age of children was from 4 years to 14 years. Most of the patients had been infected during treatment of oncohematological diseases.

Children were divided into two groups according to ALT level before treatment. There were 8 children in the first group with elevated ALT level and 6 patients in the second group with normal ALT level before treatment. Children received lamivudine (*Zeffix*®) at a dose of 3 mg per kilogram of body weight (maximal dose, 100 mg) for 12–24 months. We examined virological response (HBeAg, anti-HBe), ALT level, liver morphology and lamivudine tolerance.

Twelve patients were treated only with lamivudine. Two children prior to lamivudine treatment 4 months were unsuccessfully treated with interferon alfa (*Realdirone*®) 3 MU t.i.w., however, on getting no response to the drug the treatment was continued with lamivudine.

RESULTS

In the first group of patients after 12 months of treatment with lamivudine, ALT activity became normal in 5 out of 8 children (62.5%), in two it declined (25%) and in one didn't change. Seroconversion from HBeAg to anti-HBe occurred only in one patient (No. 8, A.O.) (12.5%) (Fig. 1). We didn't perform liver biopsy in this group. Lamivudine treatment is continued in 7 patients.

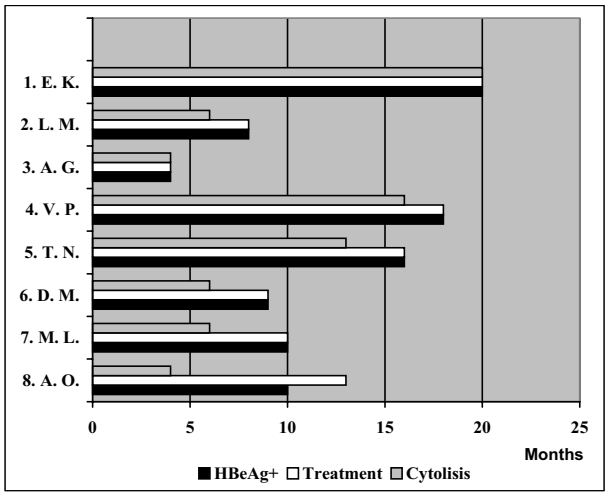

Fig. 1. Duration of HBeAg, cytolisis and treatment with lamivudine in group 1

In the second group, seroconversion from HBeAg to anti-HBe occurred in two patients (No. 5, D. R. and No. 6, A. B.) (33.3%) during a 12-months treatment period (Fig. 2). Four patients didn't respond with seroconversion. For two of them we perfomed liver biopsy after 18 months of treatment. Liver morphology improved in both (Table 1).

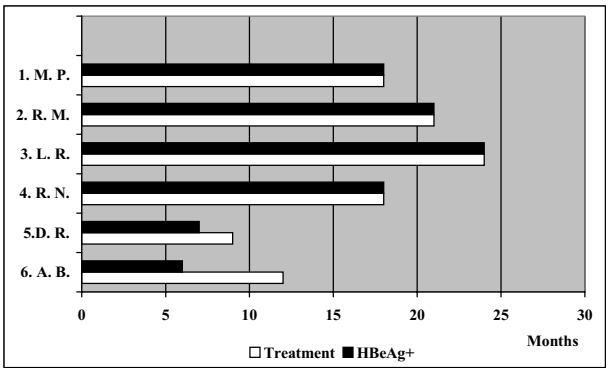

Fig. 2. Duration of HBeAg and treatment with lamivudine in group 2

Table 1. **Liver histology in the group 2 (according to Ishak)**

Nr.	Patients initials	Before treatment		After treatment	
		HAI*	Degree of fibrosis	HAI	Degree of fibrosis
1.	L. R.	3	2	1	1
2.	R. N.	4	2	2	1

* HAI – hepatitis activity index

Children from both groups tolerated lamivudine well.

DISCUSSION

The aim of HBV infection treatment is to suppress the proliferation of the virus and afterwards to eradicate it. The treatment is effective if :

1. HBeAg and HBV DNA (HBV-DNA < 105 copy/ml) disappears from the blood for 6–12 months, and one finds anti-HBe.
2. ALT becomes normal.
3. Liver necrosis and inflammation improves (3, 7).

Different drugs are used for the treatment of HBV (3):

1. Interferon α or β, pegylated interferon.
2. Nucleoside analogues: lamivudine, adefovir, famciclovir, ganciclovir, fialuridin, lobucavir, etc.
3. HBV vaccines.

Most of children are treated according to ESPGHAN recommendation (1, 8). Unfortunatelly, it covers only treatment with interferon, which has many side effects.

Lamivudine has been shown to be effective in terms of HBV–DNA suppression, ALT normalization and improvement in histology in both HBeAg-positive and HBeAg-negative/HBV-DNA-positive cases (precore mutant) (4). There are few data on the use of this drug in children. In young patients with chronic hepatitis B, 52 weeks of treatment with lamivudine were associated with a significantly higher rate of virologic response than placebo (23% *versus* 13%, P = 0.04) (5).

We treated only 14 patients – 8 in group 1 with elevated ALT level and 6 patients in the second group with normal ALT level before treatment. Seroconversion from hepatitis B e antigen to hepatitis B e antibody occurred in 3 of 14 patients (21.4%): in one patient from group 1 and in two from group 2. These data are similar in agreement with the data from the international pediatric lamivudine investigator group (5). Lamivudine treatment positively influenced 7 of 8 patients (normalized or decreased ALT level) in group 1 and 4 of 6 in group 2 (two patients had seroconversion and in two liver morphology improved after 18 months treatment with lamivudine). Overall, 11 of 14 (78.6%) patients with HBV had a benefit of lamivudine treatment.

Lamivudine was well tolerated in both groups. During treatment we didn't find any deterioration of the liver function, implying that YMMD mutants didn't occur.

CONCLUSIONS

1. After 12 months of treatment with lamivudine (*Zeffix*®) seroconversion from hepatitis B e antigen to hepatitis B e antibody occurred in 3 of 14 patients (21.4%).
2. After 12 months of treatment normalization of ALT occurred in 5 of 8 (62.5%) patients, in 2 children the ALT level decreased and in one didn't change.
3. Lamivudine therapy was well tolerated.

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VAIKŲ, SERGANČIU LĖTINIU VIRUSINIU HEPATITU B, GYDYMAS LAMIVUDINU

S a n t r a u k a

Lėtinis virusinis hepatitas B (VHB) yra reta, tačiau grėsminga vaikų amžiaus liga. Skirtingai nuo suaugusiųjų, užsikrėtus virusiniu hepatitu B vaikystėje, net 90% atvejų išsivysto lėtinis VHB.

Lėtinis VHB gydomas įvairiais medikamentais. Pirmiausia buvo pradėtas naudoti interferonas, tačiau jis nėra labai efektyvus ir dažnai sukelia įvairius pašalinius simptomus. Pastaraisiais metais vis plačiau naudojamas palyginti naujas medikamentas – lamivudinas. VHB sergantys vaikai gydomi remiantis Europos vaikų gastroenetrologijos, hepatologijos ir mitybos draugijos (ESPGHAN) rekomendacijomis (4), kurios skirtos gydymui interferonu (IFN), nes kol kas nėra didelio patyrimo gydant kitais medikamentais ar jų deriniais.

Mes apibendrinome 14 (4–14 metų) vaikų gydytų lamivudinu, duomenis. Ligoniai gydyti Respublikinėje Vilniaus universitetinėje vaikų ligoninėje 2000–2003 m. Dau-

guma jų infekavosi VHB sirgdami onkologinėmis kraujo ligomis.

Gydymo efektyvumui įvertinti ligoniai suskirstyti į dvi grupes pagal kepenų fermento ALT kiekį gydymo pradžioje. Pirmoje ligonių grupėje buvo 8 ligoniai, kuriems gydymo pradžioje buvo padidėjęs ALT. Antroje grupėje buvo 6 ligoniai, kurių ALT buvo normalus. Vaikai gydyti lamivudinu (*Zeffix*®) po 3 mg/kg/p (ne daugiau 100 mg/p) kasdien 12–24 mėnesių. Tirtas virusologinis atsakas (HBeAg, anti-HBe), kepenų biocheminis aktyvumas (ALT kiekis), kepenų morfologinis vaizdas ir lamivudino toleravimas.

Rezultatai. Metus pasigydžius lamivudinu penkiems pirmos grupės vaikams ALT aktyvumas normalizavosi, dviem sumažėjo, o vienam nepakito. Serokonversija iš HBeAg į anti-HBe įvyko vienam ligoniui. Antroje grupėje serokonversija iš HBeAg į anti-HBe nustatyta dviem vaikams, o dviem vaikams, kuriems jos nebuvo, pagerėjo kepenų morfologinis vaizdas. Abiejų grupių ligoniai lamivudiną toleravo gerai.

Išvados. VHB sergantys vaikai lamivudiną toleravo gerai. Po metų gydymo daugeliui ligonių normalizavosi ar sumažėjo ALT ir tik vienam ALT nepakito. Tačiau serokonversija iš HBeAg į anti-HBe nustatyta tik vienam pirmos grupės ligoniui ir dviem antros grupės ligoniams, t. y. 3 iš 14 (21,4%) abiejų grupių ligonių

Raktažodžiai: vaikai, lėtinis virusinis hepatitas B, gydymas, lamivudinas (*Zeffix*®)