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RAPID COMMUNICATION

Lamivudine therapy for children with chronic hepatitis B

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Abstract

AIM: To assess the effectiveness and side-effects of lamivudine therapy for children with chronic hepatitis B (CHB) who fail to respond to or have contraindications to interferon-α (IFN-α) therapy.

METHODS: Fifty-nine children with CHB were treated with 100 mg lamivudine tablets given orally once daily for 12 mo. Alanine aminotransferase (ALT) activity was evaluated monthly during the therapy and every 3 months after its discontinuation. HBe antigen, anti-HBe antibodies, HBV DNA level in serum were evaluated at baseline and every six months during and after the lamivudine therapy. Sustained viral response (SVR) to lamivudine therapy was defined as permanent (not shorter than 6 mo after the end of the therapy), namely ALT activity normalization, seroconversion of HBeAg to anti-HBe antibodies, and undetectable viral HBV-DNA in serum (lower than 200 copies per mL). The analysis of the side-effects of the lamivudine treatment was based upon interviews with the patients and their parents using a questionnaire concerning subjective and objective symptoms, clinical examinations, and laboratory tests performed during clinical visits monthly during the therapy, and every 3 mo after the therapy.

RESULTS: ALT normalisation occurred in 47 (79.7%) patients between the first and 11th mo of treatment (mean 4.4 ± 2.95 mo, median 4.0 mo), and in 18 (30.5%) of them after 2 mo of the therapy. There was no correlation between the time of ALT normalization and the children's age, the age of HBV infection, the duration of HBV infection, inflammation activity score (grading), staging, ALT activity before treatment, serum HBV DNA level, and lamivudnie dose per kg of body weight. HBeAg/anti HBe seroconversion was achieved in 27.1% of cases. The higher rate of seroconversion was connected with lower serum HBV DNA level and longer duration of HBV infection. There was no connection between HBeAg/anti HBeAb seroconversion and the children's age, age of HBV infection, grading, staging, ALT activity before treatment, and lamivudnie dose per kg of body weight. No complaints or clinical symptoms were observed during lamivudine therapy. Impairment of renal function or myelotoxic effect was noted in none of the patients.

CONCLUSION: One year lamivudine therapy for children with chronic hepatitis B is effective and well tolerated. Seroconversion of HBeAg/HBeAb and SVR are connected with lower pre-treatment serum HBV DNA level.

Key words: Chronic hepatitis B; Children; Lamivudine

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INTRODUCTION

Hepatitis B virus (HBV) infection is still an important problem due to its high incidence and may lead to chronic hepatitis[1]. Up to 90% of infected children develop chronic hepatitis[2]. Chronic hepatitis B greatly increases the risk of liver cirrhosis or hepatocellular carcinoma[3]. Spontaneous seroconversion of HBeAg/HBeAb during the course of chronic hepatitis B is observed only in less than 10% of children, and total recovery with the elimination of all virus antigens and the presence of anti-HBs occurs in approximately 2% of cases[4]. In recent years lamivudine treatment for chronic hepatitis B has been recommended for patients who fail to respond to IFN-α therapy or have contraindications for this therapy[5]. However clinical data concerning nucleotide analogue treatment for CHB children are lacking.

The aim of the present study was to analyze prospectively the results, tolerance, and side-effects of lamivudine therapy for children with chronic hepatitis B who fail to respond to or have contraindications for IFN-α treatment.

Table 1 Characteristics of the patients

	n (%)	Mean	Median
Sex			
Boys	48 (81.4)		
Girls	11 (18.6)		
Age (yr)	6-18	10.5±3.24	10
Age of HBV infection (yr)	1-14	3.7±3.09	3
Duration of HBV infection (yr)	1-16	6.8±3.09	6
Completed previous IFN-α treatment			
Yes	51 (86.4)		
No	8 (13.6)		
ALT activity before treatment (IU/L)	20-664	101±96.3	76
Inflammation activity score			
Grade 1	24 (40.7)		
Grade 2	33 (55.9)		
Grade 3	2 (3.4)		
Grade 4	0		
Staging			
Stage 0	7 (11.9)		
Stage 1	37 (62.7)		
Stage 2	12 (20.3)		
Stage 3	2 (3.4)		
Stage 4	1 (1.7)		
Serum HBV DNA level (copies/mL)	200-200 000	135 632±81 018	200 000
Lamivudnie dose (mg per kg of body weight)	1.3-4.1	3.0±0.85	2.9

MATERIALS AND METHODS

Fifty-nine children, 48 boys and 11 girls, aged 6 - 18.0 years were included in the study. The age of HBV infection varied from 1 to 14 years and the known duration of infection was 1-16 years (Table 1). The precise route of infection was not determined. Most of the children had a history of multiple hospital admissions. None of these children suffered from onco-hematological disorders. Fifty-three children were previously treated with recombinant (3 million units) IFN-α given subcutaneously, three times a week for 20 wk, recommended by the Polish Working Liver Group[6]. Fifty-one of them completed the therapy, in 2 cases the therapy was discontinued at the 8th and 12th wk due to repeated seizures. Interferon therapy was completed 1 - 7.5 years before the present study (mean 4.0 ± 1.8 years, median 4.0 years). Six patients (10.2%) were not previously treated because of relative contraindications for IFN-α therapy, including high grade fibrosis on liver biopsy in 3 cases and epilepsy in 1 case.

The inclusion criteria for lamivudine treatment were increased aminotransferase activities in serum noted at least three times during the last six months before therapy, the presence of HBsAg and HBeAg in the blood, measurable (above 200 genome copies/mL) HBV-DNA in serum for at least six months prior to the study, negative HCV-RNA and anti-HCV antibodies in serum, and evidence of inflammation on liver biopsy performed within 24 mo before the study.

Patients with coexisting clinically significant illness or other types of liver disease, or having received antiviral agents, immunomodulatory drugs within the previous 6 mo were excluded from the study. The teenage pregnant girls were excluded and advised not to get pregnant during and after 6 mo after the lamivudine therapy.

ALT activity as well as total and direct bilirubin, alkaline phosphatase (ALP) and gammaglutamyl-transpeptidase (GGT) activity in serum were measured before treatment, monthly during and every 3 mo after the therapy by routine laboratory method. Serological markers of HBV infection were analyzed before and every six months during and after the therapy by immunoenzymatical methods: HBeAg, anti-HBe and anti-HBs by Roche's diagnostics tests while HBsAg by Micro Elisa tests. HBV-DNA serum concentration was measured in all patients before and every six months during and after the lamivudine therapy by quantitative PCR method using the Roche Cobas Amplicor HBV Monitor Assay (Roche Diagnostics, Pleasanton, USA). Activity of inflammation (grading) and fibrosis (staging) of liver biopsy was classified according to Scheuer's scale modified by International Working Party in 1995[7].

All patients were treated with 100 mg lamivudine tablets given orally once daily for 12 mo (Zeffix, GlaxoSmithKline Pharmaceuticals, SA). A single dose of lamivudine varied from 1.3 mg/kg to 4.1 mg/kg (Table 1)

The analysis of the side-effects of the lamivudine treatment was based upon interviews with the patients and their parents using a questionnaire concerning subjective and objective symptoms, clinical examinations, and laboratory tests (level of hemoglobin, blood cell count, urea and creatinine level) performed monthly during and every 3 mo after the therapy. The duration of clinical observation was at least 6 mo after the therapy in all cases.

Sustained viral response (SVR) to lamivudine therapy was defined as permanent (not shorter than 6 mo after the end of the therapy): ALT activity normalization, seroconversion of HBeAg to anti-HBe antibodies, and undetectable viral HBV-DNA in serum (lower than 200 copies per mL).

In patients with ALT elevation during the lamivudine therapy mutations in the YMDD (tyrosine, methionine, aspartate, and asparate) motif of the reverse-transcriptase domain in the HBV polymerase gene were assessed by polymerase chain reaction and restriction-fragment-length polymorphism assay. Analysis of HBV genotype was performed only in these patients because of economical reasons.

The results of the study were statistically analyzed using Statistica 5.77 (StatSoft, Inc., Tulsa, OK, USA). The differences in frequency were analyzed using χ^2 test with Yate's correction if necessary. The differences between groups were achieved using U Mann-Whitney's test. $P < 0.05$ was considered statistically significant.

Children over 12 years of age and their parents or legal guardians provided their written informed consent. The study was approved by the Ethics Committee of the Medical University of Gdańsk.

Table 2 Statistical analysis of factors predicting response to lamivudine treatment

Factors that may predict response	ALT normalisation	HBe/anti-HBe seroconversion	Sustained viral response
Sex	$\chi^2_{(Y)}$=0.37, P=0.54	$\chi^2_{(Y)}$=0.13, P=0.72	$\chi^2_{(Y)}$=0.01, P=0.76
Previous IFN-α treatment	$\chi^2_{(Y)}$=0.70, P=0.76.	$\chi^2_{(Y)}$=3.29, P=0.07	$\chi^2_{(Y)}$=4.42, P=0.04
Children's age	Z=0.10, P=0.92	Z=1.83, P=0.07	Z=2.28, P=0.02
Age of HBV infection	Z=0.70, P=0.49	Z=-1.49, P=0.14	Z=-1.40, P=0.15
Duration of HBV infection	Z=0.13, P=0.89	Z=2.99, P=0.002	Z=3.33, P<0.001
Inflammation activity score (grading)	Z=0.23, P=0.82	Z=1.56, P=0.12	Z=1.76, P=0.08
Staging	Z=0.88, P=0.38	Z=1.46, P=0.14	Z=1.69, P=0.09
ALT activity before treatment	Z=-0.48, P=0.63	Z=1.49, P=0.14	Z=1.23, P=0.23
Serum HBV DNA level	Z=-0.80, P=0.07	Z=-3.29, P=0.001	Z=-3.22, P=0.001
Lamivudnie dose per kg of body weight	Z=-0.46, P=0.64	Z=-1.75, P=0.08	Z=-1.59, P=0.11

RESULTS

ALT activity before the lamivudine therapy varied from 20 to 664 IU/L (Table 1). The ALT level was lower than 100 U/L in 42 (71.2%) patients and higher than 100 U/L in 17 (28.8%) patients. All 59 children who completed the 12-mo therapy had normal serum, total and direct bilirubin, and ALP. GGT level in serum was slightly elevated only in 3 (5.1%) patients.

Inflammation activity in liver biopsy specimens was found at either low or medium levels in 96.6% of patients: grade 1 in 24 and grade 2 in 33 children. Only in 2 patients grade 3 inflammation activity was observed (Table 1). No liver fibrosis was found in 7 patients. Fibrosis of stages 1-4 was found in 37, 12, 2, and 1 patient, respectively (Table 1).

Before lamivudine treatment HBV-DNA serum level ranged between 200-200 000 copies/mL. HBV-DNA level was over 200 000 copies/mL in 33 children (55.9%), 10 000-200 000 copies/mL in 16 (27.1%) children, and below 10 000 copies/mL in 10 (16.9%) children (Table 1).

ALT normalization was achieved in 47 (79.7%) patients at the end of therapy. It occurred mostly between the first and the 11th mo of treatment (mean 4.4 ± 2.95 mo, median 4.0 mo). ALT normalization was observed in 37 of 48 boys and 10 of 11 girls, in 43 of 53 children previously treated and 4 of 6 not treated with IFN-α. There was no connection between the rate of ALT normalization and the children's age, age of HBV infection, duration of HBV infection, inflammation activity score (grading), staging, ALT activity before treatment, serum HBV DNA level, and lamivudnie dose per kg of body weight. Statistical results are shown in Table 2.

HBeAg/anti-HBeAb seroconversion was achieved in 16 cases (27.1%) at the end of therapy. It occurred mostly after 12 mo of treatment. This seroconversion was observed in 13 of 48 boys and 3 of 11 girls, in 12 of 53 children previously treated and 4 of 6 not treated with IFN-α. The higher rate of seroconversion was connected with longer duration of HBV infection (median 9 *vs* 5 years) and lower serum HBV DNA level (median 50 000 *vs* 200 000 copies/mL). There was no connection between HBeAg/anti-HBeAb seroconversion and the children's age, age of HBV infection, inflammation activity score (grading), staging, ALT activity before treatment, and lamivudnie dose per kg of body weight. Statistical results are shown in Table 2. HBsAg/anti-HBsAb seroconversion was observed six months after the end of the therapy only in one child (1.7%). In 14 patients (23.7%) with ALT normalization and HBeAg/anti-HBeAb seroconversion, sustained viral response (SVR) was achieved at the end of therapy. In these cases HBV DNA level in serum was lower than 200 copies/mL. In two patients with ALT normalization and HBeAg/anti-HBe seroconversion, the serum HBV DNA level remained high (14 400 and 145 000 copies/mL). SVR was observed in 11 of 48 boys and 3 of 11 girls, and more frequently achieved in children previously treated with IFN-α. The rate of SVR was connected with older children's age (median 12 *vs* 9 years), longer duration of HBV infection (median 9 *vs* 5 years), and lower serum HBV DNA level (median 50 000 *vs* 200 000 copies/mL). There was no connection between SVR and the age of HBV infection, inflammation activity score (grading), staging, ALT activity before treatment, and lamivudnie dose per kg of body weight. Statistical results are also shown in Table 2.

No complaints or clinical symptoms were observed during the lamivudine therapy. Slight and transient increase of ALT activity was observed in 4 children (6.8%) between the 3rd and the 12th mo of treatment. No association with hyperbilirubinemia or other signs of hepatic decompensation was found in all cases. Mutations in the YMDD were detected in 2 of 4 patients with ALT elevation during the lamivudine therapy.

Lamivudine did not show myelotoxic effect in treated children. There were no significant differences between erythrocyte or leukocyte peripheral blood count, platelet count, and hemoglobin level during or after the therapy.

Impairment of renal function was observed in none of the patients.

DISCUSSION

This study presented an analysis of the outcome, tolerance and side-effects of lamivudine therapy for children with chronic hepatitis B, who failed to respond to or had contraindications for IFN-α treatment. Up till now IFN-α is the therapy of first choice for children with chronic hepatitis B in Poland. However the treatment with IFN-α is uncomfortable (especially in children) and has many different side effects[8].

Lamivudine is the first oral antiviral therapy for chronic hepatitis B. Positive results of this treatment in adult patients have made lamivudine therapy possible in children with chronic hepatitis B[9-11].

The results of international research conducted in children with chronic hepatitis B have proved that a 52-wk course of lamivudine therapy results in the significantly higher rate of viral response. Furthermore, SVR with HBs Ag/HBsAb seroconversion and ALT normalization has also been observed[12]. There are also some other data confirming positive biochemical and viral response in children with chronic hepatitis B treated with lamivudine[13,14].

This study demonstrated that 100 mg lamivudine treatment for 12 mo resulted in a 23.7% sustained virologic response. Special stress must be put on the fact that 86% of patients did not respond to IFN-α therapy.

Lamivudine therapy is mainly used for children with chronic hepatitis who fail to respond to IFN-α[11-15].

Other nucleoside analogues (like adefovir) used in the treatment of adult patients with chronic hepatitis, are not widely accessible for pediatric patients[16,17]. Data on the results of combined IFN-α and lamivudine therapy vary[18-21], seem no more effective than monotherapy with either IFN-α or lamivudine.

Lamivudine has been proved to be more effective than IFN-α for chronic hepatitis HBeAg-minus[22,23]. Most trials on the effectiveness of lamivudine therapy in both adults and children with chronic hepatitis B showed that ALT normalization is significantly more frequent even though it is often not associated with the viral response[10-16].

In the present group of children, ALT normalization within the first 11 mo of therapy was observed in almost 80% of patients and in 30% of children in the first 2 mo. No connection was noted between the time of ALT normalization and clinical data, biochemical tests, histopathological changes in the liver tissue, viral load, or lamivudine dose per kg body weight. Jonas *et al*[12] showed that the median time of ALT normalization was 24 wk.

In our group of patients, HBeAg/HBeAb seroconversion was observed in 27.1% of children and after 12 mo of treatment in most cases. Only in one patient, HBsAg/HBsAb seroconversion took place 6 mo after the lamivudine therapy. The low rate of positive response to lamivudine therapy expressed by HBsAg/HBsAb seroconversion is consistent with other reports[12,13,15]. SVR was noted in 23.7% of patients. ALT normalization and HBeAg/HBeAb seroconversion were still accompanied with high viral load. The results of lamivudine therapy are similar to other reports[12,24]. Some authors investigating lamivudine therapy effectiveness demonstrated a higher viral response rate of 36-44%[13,14]. However, Kocak *et al*[11] observed HBeAg/HBeAb seroconversion only in 5% of cases while viral load significantly decreased in 90% of cases[11].

In the analyzed group of patients the positive response to the lamivudine treatment was connected with the older age of patients and lower serum DNA level before therapy. The similar connection between SVR and the pretreatment viral load has also been observed by other authors[12,13]. On the contrary to the published data[9,25], no connection between SVR and pretreatment ALT activity or grading was noted in our study.

Special attention must be paid to the histopathological improvement within the liver tissue and in ALT activity in patients with no viral response after lamivudine therapy[9].

Liver biopsy after lamivudine therapy was performed only in a few patients. No consent of patients and their parents for invasive diagnostic procedure was available at that time. Control liver biopsy has not been performed by other researchers[11].

Due to the limited number of data on representative groups of patients, establishing the optimal dose especially for children under the age of 12 years appears still problematic. It appears that increase in daily dose or in frequency of lamivudine administration does not improve the results[12,13,15,26]. The recommended dose of lamivudine results in the same serum concentration of the drug in children as in adults receiving 100 mg per 24 h[26]. The experiences with treatment of chronic hepatitis B in adult patients suggest that this dose of lamivudine seems to be satisfactory.

In our group of patients, 100 mg lamivudine tablets were administered, and the dose per kilogram of body weight varied from 1.3 to 4.1 mg/kg per d, mean 3.0 mg/kg per d. Lamivudine in suspension is not widely available. The average dose of lamivudine in our group is comparable with that recommended by other authors[12,13,15,26].

Based upon interviews with the patients and their parents using a questionnaire concerning subjective and objective symptoms, clinical examinations, and monthly laboratory tests during and every 3 mo after the therapy, no particular side-effects were observed in our group of children.

Lebensztejn *et al*[27] reported a case of a child with chronic hepatitis B treated with lamivudine who developed thrombocytopenia and found that withdrawal of lamivudine could normalize platelets count, while reintroduction of the drug results in relapse of thrombocytopenia.

Slight and transient increase of ALT activity during lamivudine therapy (between the 3rd and the 12th mo) was noted in 4 children of our group of patients. YMDD mutation was detected in 2 of them. Termination of lamivudine therapy after 12 mo did not result in any increase of ALT activity or any other symptoms of liver impairment in the follow-up. Some authors have reported the risk of liver dysfunction and even acute liver failure after cessation of lamivudine therapy especially in patients with advanced liver fibrosis or cirrhosis[9]. Advanced fibrosis (stages 3 and 4) could be detected only in 5.1% of children with chronic hepatitis B, which may be the reason for no complications in our group of patients.

Because of economical reasons, only patients with ALT increase were evaluated for YMDD mutation and thus no conclusions about the incidence of YMDD mutation in children with chronic hepatitis B treated with lamivudine can be established. Thus, it can not be ruled out that mutation in the YMDD motif is responsible for the development of resistance to lamivudine in non-responders.

Duration of lamivudine therapy increases not only the rate of positive viral response, but also the risk of YMDD mutations[9], which appears to rise up to 60% in patients treated with lamivudine for more than 4 years[16,24,28]. How-

ever, besides the high percentage of viral mutants, lamivudine is still capable of inducing HBeAg/HBeAb seroconversion and improving histopathological changes within liver tissue in the treated patients[29,30].

In conclusion, one year lamivudine therapy for children with chronic hepatitis B is effective and well tolerated. Seroconversion of HBeAg/HBeAb and SVR are connected with lower pre-treatment serum HBV DNA level.

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