Efficacy of combined interferon alpha and long-term lamivudine therapy in children with chronic hepatitis B

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The aim of this study was to evaluate the efficacy of interferon alpha (IFN-α) and long-term lamivudine therapy in children with chronic hepatitis B and to determine the optimal duration of lamivudine therapy. Thirty-eight HBeAg-positive children simultaneously received IFN-α2a 5 MU/m² to 10 MU/m² for six months and lamivudine (4 mg/kg/day). Lamivudine was administered until anti-HBe seroconversion and was continued for six months in responders. During the five-year study period, we evaluated the efficacy of treatment, occurrence of YMDD mutants and adverse effects. During the study period, alanine aminotransferase (ALT) normalization, clearance of hepatitis B virus (HBV) DNA, HBeAg/anti-HBeAb, HBsAg/anti-HBsAb seroconversion, and histological response were noted in 27 (71.1%), 14 (36.8%), 13 (34.2%), 2 (5.2%) and 10 (47.9%) patients, respectively. Complete response was determined in 34.2% (13/38), and in 69.2% of these responders, response was achieved within 18 months. Breakthrough and YMDD mutant rates were 65.8% and 55.2%, respectively. Breakthrough time was a median 24 months and was associated with low baseline ALT level ($p<0.01$). In conclusion, although lamivudine was used for a longer period, the response rate was not higher than in previous reports. We suggest that 18 months' duration of lamivudine treatment is sufficient for combination therapy.

Key words: interferon, lamivudine, chronic hepatitis B, children.

Medications that are approved by the Food and Drug Administration for the treatment of children with chronic hepatitis B (CHB) infection include interferon alpha (IFN-α), lamivudine and most recently adefovir[1]. Rates of hepatitis Be antigen (HBeAg) loss with IFN are 15-37%[2,3]. The efficacy of lamivudine is found to be similar to IFN with rates of anti-HBe seroconversion ranging from 18-23%[1,4,5]. Because these drugs have different mechanisms of action, it has been claimed that combination treatment of lamivudine and IFN-α have an additional effect against hepatitis B virus (HBV) and would lead to a higher response rate than monotherapy[6]. Many studies have emphasized the safety, tolerability and efficacy of IFN-α and lamivudine combination therapy, but there is no consensus on the optimal duration and the mode of administration[1,7,8]. Although studies in adults have shown that HBe seroconversion increases with duration of lamivudine therapy, the main problem with long-term use of lamivudine is the emergence of YMDD mutants[9-13].

To date, few trials exist investigating IFN and lamivudine combination therapy in children. The virologic response rate is 37% to 57%[14-22]. Lamivudine was administered for a defined time in these trials. The optimal length of time to achieve virologic response with lamivudine has not been defined. To the best of our knowledge, there is no experience with IFN and long-term lamivudine combination therapy in children with CHB. The aim of this prospective study was to evaluate the efficacy of IFN-α and long-term lamivudine combination therapy in children with CHB and to determine the optimal duration of lamivudine therapy in combination therapy.

Material and Methods

The patients were all positive for hepatitis B surface antigen (HBsAg) and HBeAg in serum for at least six months and HBV DNA level >5 pg/ml. Serum alanine aminotransferase (ALT) level was at least 1.5 times the upper limit of normal range (37 U/L) but <500 IU/L, and Knodell hepatitis activity index (HAI) was ≥4 in all patients. Exclusion criteria included patients younger than two years, the presence of hepatitis delta, hepatitis C or human immunodeficiency virus (HIV) antibodies, any other immunosuppressive treatment history, platelet count of <150 000/mm^3, leukocyte count of <3000/mm^3, hemoglobin of <10 g/dl, or presence of underlying problems such as any other central nervous system diseases, psychiatric disorders, kidney insufficiency, hepatic decompensation, or any other causes of chronic liver disease.

Patients randomly received 5 (n=19) to 10 (n=19) megaunits/m^2 IFN-α2a three times per week for six months and lamivudine (4 mg/kg/day, maximum 100 mg) until anti-HBe seroconversion had been achieved. Responders were maintained on lamivudine for an additional six months after seroconversion.

Patients were evaluated monthly while on IFN therapy and every six months thereafter. At each visit, in addition to physical examination, complete blood count, amylase, ALT and serological markers including HBsAg, anti-HBs, HBeAg, anti-HBe, and HBV DNA levels were evaluated. Presence of lamivudine-resistant mutants was assessed in patients with breakthrough. Liver biopsies were performed in 31 and 22 patients at baseline and at the end of therapy, respectively, when approval was obtained. We followed for loss of detectable HBV DNA, ALT normalization, loss of HBeAg and anti-HBe seroconversion as well as for development of lamivudine-resistant mutants. Safety was assessed using clinical and laboratory evaluations at the follow-up visits.

Complete response was defined as loss of HBeAg with anti-HBe seroconversion, normalization of ALT and clearance of serum HBV DNA. Relapse was defined as reappearance of HBV DNA and/or HBeAg after successful complete response had been achieved.

Histological response was defined as decrease in Knodell score by at least 2 points and worsening as increase by at least 2 points at the end of therapy. If the difference was between +1 and -1 points, it was defined as unchanged.

Breakthrough was defined as reappearance of HBV DNA while on therapy after response had been gained. *Virological resistance* was defined by the occurrence of lamivudine-induced HBV mutants, also known as YMDD mutants.

This study was approved by the local ethical committee. Sufficient information about the disease and the treatment procedure was given to parents, and informed consent was obtained before applying the protocol.

HBsAg, HBeAg, anti-HBe and anti-HBs were detected using commercially available immunoassays (ELISA) (Abbott Laboratories, Chicago, IL). ALT was measured by conventional methods (reference value 10-31 U/L). HBV DNA was tested by commercial liquid-hybridization assay (Digene, MD), with the lower limit of detection of 5 pg/ml. YMDD variant was assessed by polymerase chain reaction as previously described[23,24]. HAI was scored according to the Knodell method[25]. The overall Knodell score is the sum of scores for periportal ± bridging necrosis (0-10), intralobular degeneration and focal necrosis (0-4), portal inflammation (0-4), and fibrosis (0-4).

Statistical analysis was done using the SPSS 11 program. Statistical significance was assessed using Wilcoxon, Mann-Whitney U, paired samples T test, and chi-squared method. A p value of <0.05 was considered to be statistically significant. Results were expressed as mean±SD or median (range).

Results

Thirty-eight children (29 naive, 18 female) were enrolled between August 1999 and February 2005. The mean age was 8.9±4.1 years (range: 2-15 years). At the start of combination therapy, all children had elevated ALT (median ALT 2 x upper limit of normal (ULN), range: 1.5-12 ULN). Baseline HBV DNA was >2000 pg/ml in 81.6%, 200-2000 pg/ml in 13.2% and <200 pg/ml in 5.2%. Baseline mean HAI score was 6.6±2.2 (range: 4-12). None of the liver biopsy samples showed cirrhosis.

Lamivudine was administered for periods varying from 12 months to 60 months (median:

31 months). Evaluation of biochemical and virological characteristics during the five years of therapy is presented in Table I.

Biochemical and Virological Changes During Therapy

Median ALT levels during the therapy are shown in Table I. Following IFN and long-term lamivudine therapy, ALT normalization, clearance of serum HBV DNA and HBeAg/anti-HBeAb seroconversion were noted in 27 (71.1%), 14 (36.8%) and 13 (34.2%) patients, respectively. HBsAg/anti-HBsAb seroconversion was observed in 2 patients (5.2%) at the 12th and 18th months.

The patterns of HBV DNA levels through the study are shown in Table I. HBV DNA changes during the study period reflected the emergence of YMDD viral mutants. HBV DNA loss was obtained in all children except for 3 (92.1%) patients at the 3rd month of therapy. HBV DNA clearance was achieved in all patients at the 6th month of therapy. However, HBV DNA titer was re-elevated in 3 of 36 patients (8.3%) at the 12th month of therapy. At the 18th month of therapy, detectable HBV DNA level was observed in 6 of 36 (16.6%) patients. Detectable HBV DNA was observed in 19 of 32 (59.3%), 12 of 17 (70.5%), 11 of 17 (64.7%), 5 of 10 (50%), 3 of 7 (42.8%), 2 of 4 (50%), and 2 of 2 (100%) children at the 24th, 30th, 36th, 42nd, 48th, 54th, and 60th months, respectively. During therapy, the percent of patients with detectable HBV DNA level is shown in Figure 1.

Complete response was achieved in 13 patients (34.2%) during the study period. Response time was a median 12 months (6-42 months), and in 9 of the 13 responders (69.2%), complete response occurred within 18 months (Table I). Complete response was not different between patients treated with high-dose and standard-dose IFN. Baseline ALT levels were significantly higher in responders ($p<0.01$) (Table II). Except for one, all maintained normal ALT, undetectable HBV DNA and positive anti-HBeAg 12 months after lamivudine withdrawal.

There was no significant difference in the baseline and after therapy HAI scores (6, range: 3-12; 5: range 1-12, respectively) (p=n.s.). Twenty-one patients had paired liver biopsies

Table I. Follow-Up Biochemical and Virological Data of Patients During the Study Period

	Start of treatment	6 mo	12 mo	18 mo	24 mo	30 mo	36 mo	42 mo	48 mo	54 mo	60 mo
No. patients still on treatment	38	38	36	36	32	17	17	10	7	4	2
ALT IU/L, median (range)	60 (45-456)	35 (15-255)	25 (13-106)	25 (11-85)	26 (13-179)	29 (14-78)	30.5 (10-255)	34 (16-46)	26 (11-79)	33.5 (11-73)	65 (57-74)
HBV DNA pg/ml, median (range)	2000 (108-7725)	5 (5-5)	5 (5-7858)	5 (5-1971)	134 (5-4000)	379 (5-1681)	247 (5-13000)	340 (5-3824)	230 (5-880)	80 (5-680)	119 (100-139)
No. patients with HBe/Anti-HBe seroconversion	-	2	5	2	1	-	2	-	1	-	-
Time and number of emergence of breakthrough	-	-	3	3	13	4	1	-	1	-	-
Time and number of emergence of YMDD mutation	-	-	2	3	11	4	-	-	1	-	-

mo: Months.

Table II. Baseline and End of Therapy Features of Responders and Nonresponders

	Responders (n=13)	Nonresponders (n=25)	p
Median period of lamivudine therapy (month) Range	24 12- 50	34 24-60	
Mean age (year) ±SD	8.6±4.1	9.1±4.2	n.s.
Male sex (%)	53.4	52	n.s.
Naive (%)	76.9	76	n.s.
Baseline ALT (U/L), median Range	141 45-456	50 48-127	<0.001
Baseline HBV DNA pg/ml, median Range	2000 192-5692	2000 108-7725	n.s.
Baseline mean HAI score (Knodell) ±SD	6.6±2.5	6.3±2.1	n.s.

HAI: Hepatitis activity index.

at baseline and after therapy. Histological response was observed in 10 cases (47.9%), worsening in 5 cases (23.8%) and unchanged status in 6 cases (28.5%).

Viral Resistance and Breakthrough

Breakthrough occurred in 25 patients (65.7%) during the study period. Breakthrough time was a median 24 months (range: 12-48 months). Complete response occurred in one patient (7.6%) with breakthrough and YMDD mutations at the 36th month of therapy. Baseline ALT was significantly lower in children with breakthrough ($p<0.01$); sex, age, baseline HBV DNA and HAI score were not different (p=n.s.) (Table III). Although ALT elevation was observed in 44% of patients with breakthrough, hepatic decompensation did not occur. Virological resistance (YMDD mutation) rate was 55.2% (21/38). The time and number of emergence of breakthrough and YMDD mutation are shown in Table I.

Adverse Events

All patients tolerated the treatment well. Some patients displayed typical minor side effects, such as flu-like syndrome and gastrointestinal symptoms due to IFN. One patient who was clinically stable showed amylase elevation during lamivudine therapy and levels returned to normal. No any other adverse effect was observed.

Discussion

In our study, complete response rate was 34.2%, whereas the breakthrough rate is 65.8% in children with CHB infection who were treated with IFN- and long-term lamivudine. Data concerning combination treatment in children in which different combination regimens were tried are few[14-22]. Except for one study (18), lamivudine was given for 6 to 12 months[14-17,19-22]. Data in adults show that HBe seroconversion continues to increase with prolonged therapy and suggest that further

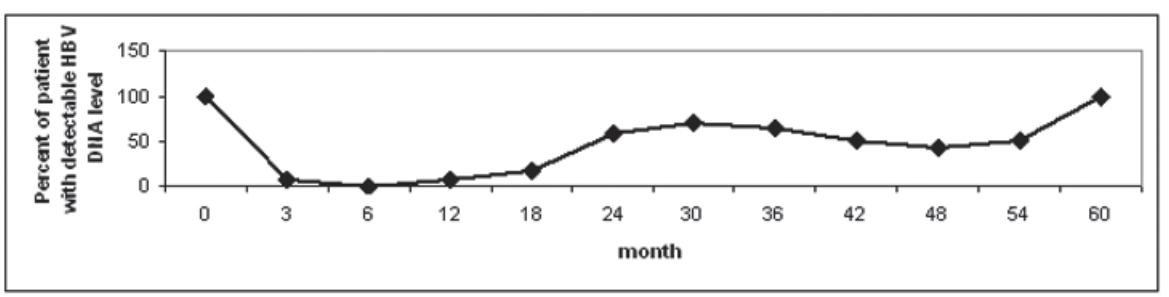

Fig. 1. During therapy, percent of patients with detectable HBV DNA level.

Table III. Features of Children With and Without Breakthrough

	Children with breakthrough (n=25)	Children without breakthough (n=13)	p
Mean age (years) ±SD	9.1±4.1	8.6± 4.1	n.s.
Male sex (%)	56	46.1	n.s.
Baseline ALT level median U/L (range)	50 (48-127)	141 (45-456)	<0.01
Baseline HBV DNA level, median pg/ml (range)	2000 (192-7725)	2000 (108-5692)	n.s.
Baseline mean HAI score (Knodell) ±SD	6.3±2.1	6.6±2.5	n.s.

increase will be seen with longer therapy [10,11,26]. An additional reason suggesting continuation of lamivudine is the histological improvement shown with prolonged treatment even in the absence of HBe seroconversion[27,28]. In previous reports about combination therapy in children, duration of lamivudine therapy was reported to be between 6 to 24 months, anti-HBe seroconversion rates were between 17% and 60.6% and HBV DNA clearance rates were between 70% and 100%[14-21]. In our study, although lamivudine was administered for a longer period, the anti-HBe seroconversion rate was 34.2%, which is similar to previous reports; however, the HBV DNA clearance was 36.8%, which is lower.

A relationship between baseline ALT, HAI score and HBV DNA level and response to therapy has been demonstrated, in both IFN and lamivudine monotherapy and in combination therapy[14,17,29]. In our study group, except for five patients, all patients had HBV DNA levels higher than 1000 pg/ml. In this study, complete response rate appeared to be greater in patients who had higher baseline ALT level. This phenomenon is closely related to the immunological status of infected patients. Patients with elevated ALT levels are less tolerant to HBV infection and have a higher chance of response to therapy.

Some recent studies have suggested that the different genotypes are correlated with the clinical features of HBV infection and response to antiviral therapy[30,31]. Genotype D was reported to be associated with a poor response to antiviral therapy[32-34]. Although genotype analysis was not performed in this study, less favorable response to therapy could be correlated with genotype D, which is the predominant genotype in Turkey[35-37].

Poor seroconversion rates were reported after 18 months of treatment in children with lamivudine monotherapy[38,39], but this has also been contradicted by other reports[40,41]. In recent studies, long-term treatment with lamivudine monotherapy led to significant improvement in the seroconversion rates of HBeAg and HBsAg[40,41]. In our study, complete response was 34.2%, and in 69.2% of our children with complete response, this was achieved within 18 months of combination therapy. We observed further complete response with prolonged lamivudine treatment; however, the incidence of YMMD mutations increased over time and resulted in lower response rates. Our results suggest that lamivudine therapy for 18 months duration seems sufficient for the additive effect of combination therapy.

The major drawback of lamivudine treatment is the selection of resistant mutants[42-45]. In our study, while incidence of YMDD mutant was 5.2% at the 12th month, it gradually increased to 55.2% at the end of therapy. It is known that viral breakthrough is usually associated with ALT elevation[44]. In our study, ALT elevation after viral breakthrough was observed in 44% of patients.

Only a few studies have analyzed the effect of IFN and lamivudine combination therapy on the histopathology in children with CHB[39,46]. Our results are in agreement with these results.

Interferon and prolonged lamivudine combination therapy was well tolerated. Adverse effects seemed to be related to the IFN therapy.

A potential limitation of this study is that during the five-year study period, the number of participants gradually decreased, mostly because of lack of efficacy of treatment or noncompliance of patients.

In our study, although lamivudine was used for a longer period, the response rate was not higher than in previous reports. In addition, IFN and long-term lamivudine treatment is associated with an increased rate of drug resistance. In conclusion, we suggest that 18 months duration of lamivudine treatment is sufficient for combination therapy.

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