

# Treatment results of chronic hepatitis B in children: a retrospective study

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**SUMMARY:** Selimoğlu MA, Ertekin V, Karabiber H, Turgut A, Gürsan N. Treatment results of chronic hepatitis B in children: a retrospective study. Turk J Pediatr 2010; 52: 360-366.

In this retrospective study, we aimed to share our experience with different treatment modalities for chronic hepatitis B in a series of children.

The study included 126 children (mean: 9.5±3.8 years). Normalization of alanine aminotransferase (ALT), loss of hepatitis B virus (HBV)-DNA and hepatitis B e antigen (HBeAg), and development of antibody to HBeAg (anti-HBe) altogether at the end of the treatment was considered as end of therapy response (ETR). Seroconversion ongoing one year after the cessation of therapy was considered as sustained response.

Of the total children, 90 (71.4%) were treated, whereas the remaining were just followed-up. High-dose interferon (IFN)- $\alpha$  (10 MU/m<sup>2</sup>) alone, standard-dose IFN- $\alpha$  (6 MU/m<sup>2</sup>) plus lamivudine (4 mg/kg/d), high-dose IFN- $\alpha$  plus lamivudine, or lamivudine alone was used, IFN- $\alpha$  thrice weekly for six months, and lamivudine daily for one year. Of children who had completed their treatment, 34 (37.8%) achieved ETR. Sustained response rate was 36.7%. Response rates were different in the different treatment groups (p: 0.01). The highest response rate was observed in those who received standard-dose IFN- $\alpha$  plus lamivudine treatment (61.5%). Of children without treatment, one (2.8%) had anti-HBe seroconversion.

Standard-dose IFN- $\alpha$  plus lamivudine treatment was found superior to the other treatment modalities. Predictors of ETR were similar to those found in previous studies.

**Key words:** chronic hepatitis B, treatment, children.

Chronic hepatitis B (CHB) infection is still a significant health problem worldwide, especially in countries where the routine vaccination program does not cover hepatitis B. Acquisition of infection during infancy or childhood causes many of the chronic infections that are responsible for the morbidity associated with this disease<sup>1</sup>. Because the current treatment protocols for childhood CHB are not able to clear the virus permanently, different treatment modalities are being tested. Appropriate patient selection is critical so that children who are most likely to benefit from therapy are identified<sup>1</sup>. The degree of the success of treatment varies with the regimen of drugs

used, the dose, the duration, and whether they are used in combination or alone<sup>2</sup>. Moreover, the most beneficial treatment modality should be preferred because the duration of the treatment is long, side effects are common and the cost is high.

In this retrospective study, we aimed to share our experience about various treatment modalities for CHB in 126 children.

## Material and Methods

One hundred and twenty-six children who had been treated for CHB or had been followed in two pediatric gastroenterology, hepatology, and

nutrition units of two different medical faculties in a 10-year period were included in the study. Patients whose records were complete and those who had presented for their routine visits were selected. Serological markers of hepatitis B virus (HBV), including hepatitis B surface antigen (HBsAg), hepatitis B e antigen (HBeAg), antibody to hepatitis B surface antigen (anti-HBs), antibody to hepatitis B e antigen (anti-HBe), hepatitis B DNA (HBV-DNA), and initial serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were recorded. Hepatic activity index (HAI) and portal inflammation and portal fibrosis scores, evaluated according to the Knodell scoring system, were noted, if biopsy had been performed. The mode of treatment, the duration of treatment and the times of seroconversion of HBe to anti-HBe and appearance of anti-HBs were assessed. Normalization of ALT, loss of HBV-DNA and HBeAg and development of antibody to HBeAg altogether was considered as complete response, and if the treatment was complete, it was considered as the end of therapy response (ETR). Seroconversion ongoing one year after the cessation of therapy was considered as sustained response.

initial AST, ALT and HBV-DNA levels of the children were  $68.7 \pm 68.1$  U/L (20-565),  $91.2 \pm 133.9$  U/L (10-1172), and  $2620.8 \pm 3755.6$  pg/ml (0.45-30000), respectively. Biopsy was performed in 96 (76.2%) of the children. Biopsy was not performed in those who had persistently normal transaminase values. Mean HAI and portal inflammation and portal fibrosis scores were  $5.8 \pm 2.6$  (0-14),  $1.8 \pm 1.0$  (0-4), and  $1.1 \pm 1.0$  (0-5), respectively.

Mean age, serum AST, ALT, HBV-DNA levels, HAI, and portal fibrosis scores were not different with respect to gender; however, mean portal inflammation score was higher in girls compared to boys ( $2.1 \pm 0.9$  vs.  $1.5 \pm 1.1$ ,  $p: 0.019$ ).

Ninety (71.4%) of the children had been treated, whereas the remaining 36 (28.6%) were just followed.

When mean age, serum AST, ALT, HBV-DNA levels, HAI, and portal inflammation and portal fibrosis scores of the children with or without treatment were compared, it was found that mean serum AST and ALT levels of those who had been selected as candidates for therapy were higher but the mean age was younger (Table I).

**Table I.** Mean Age, Serum AST, ALT, HBV-DNA Levels, HAI, Portal Inflammation and Portal Fibrosis Scores of the Children Followed or Treated for CHB

	Follow-up group N=36	Treatment group N=90	p value
HBV-DNA (pg/ml)	2069.2 ± 3263.7	2841.4 ± 3930.5	0.079
AST (U/L)	44.0 ± 23.6	78.6 ± 77.1	<0001
ALT (U/L)	52.8 ± 57.3	106.6 ± 151.8	0.002
HAI	4.8 ± 2.3	6.0 ± 2.6	0.1
Portal inflammation score	1.3 ± 1.1	1.8 ± 1.0	0.11
Portal fibrosis score	0.6 ± 0.5	1.2 ± 1.1	0.094
Age (yrs)	10.6 ± 3.8	9.1 ± 3.7	0.02

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. CHB: Chronic hepatitis B. HAI: Hepatic activity index.

Mean ± standard deviation (SD), Mann-Whitney U test, chi-square test, and one-way ANOVA test were used for statistical analysis.

## Results

Age range and mean age of the included children were 2-17 years and  $9.5 \pm 3.8$  years, respectively. Of the total children, 79 (62.7%) were male and 47 (37.3%) were female. Mean

Figure 1 shows the treatment modalities. High-dose and standard-dose interferon (IFN)- $\alpha$  and lamivudine treatments refer to 10 MU/m<sup>2</sup>, 6 MU/m<sup>2</sup> thrice weekly for six months, and 4 mg/kg/d for one year, respectively. IFN- $\alpha$  had been ceased and at least one year of lamivudine had been completed. In those with anti-HBe seroconversion, lamivudine was continued at least six additional months. Mean duration of lamivudine treatment was

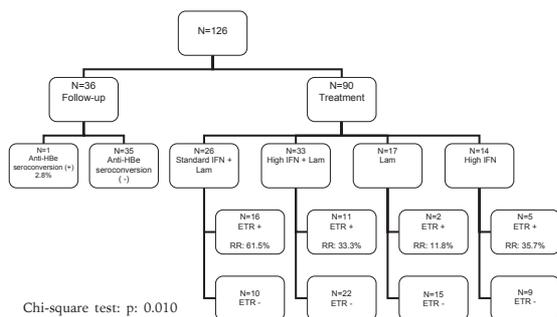


Figure 1. Treatment modalities of children and the results of the treatment.

17.3±7.7 months. When serum AST, ALT, HBV-DNA levels, HAI, and portal inflammation and portal fibrosis scores were evaluated, if they had affected the decision of the physician regarding the treatment mode, it was found that mean HAI, portal inflammation score and HBV-DNA levels were different between the different treatment groups (p: 0.041, p: 0.009 and p: 0.038, respectively) (Table II). When the same parameters were evaluated if they were different between patients who had received lamivudine or not, it was found that higher HBV-DNA levels and lower portal inflammation score had favored lamivudine treatment (p: 0.001 and p: 0.033, respectively) (Table III). The conclusion about HBV-DNA level was consistent when the presence of IFN-α was evaluated (p: 0.007) (Table III).

Thirty-four (37.8%) children had had ETR, while the other 56 (62.2%) had not. Three children (3.3%) had developed anti-HBs. At least one year had passed after the anti-HBe seroconversion in all patients; sustained

response rate was 36.7% (recurrence in one patient).

Response rate of children with respect to the therapy mode is shown in Figure 1. Anti-HBe seroconversion was observed from the 3<sup>rd</sup> to 81<sup>st</sup> month of the treatment (mean: 15.9±15.6 months). Response rates were different in the different treatment groups (p: 0.01). The highest response rate was observed in those who received standard-dose IFN-α plus lamivudine treatment (61.5%).

Mean age, serum AST, ALT, HBV-DNA levels, HAI, and portal inflammation and portal fibrosis scores of the children with or without ETR independent of the therapy model are shown in Table IV. Mean AST, ALT and portal inflammation score were found higher in those with ETR compared to others (p: 0.013, p: 0.024 and p: 0.004, respectively).

Two of three patients who had developed anti-HBs had been given high-dose IFN-α alone and the remaining had been given standard-dose IFN-α plus lamivudine treatment. Mean values of some parameters with or without anti-HBs seroconversion are shown in Table V. When these mentioned parameters were compared between those groups, it was found that mean HAI and portal inflammation scores gradually increased from the non-responsive group to the anti-HBs-positive group (p<0.001 and p: 0.001) (Table V).

Breakthrough was reported in 9 (11.8%; 9/76) of the children receiving lamivudine, either as monotherapy or combination therapy. Breakthrough had developed between the 6<sup>th</sup>-18<sup>th</sup> months of the treatment (mean: 9.0±4.24 months)

Table II. Mean Serum AST, ALT, HBV-DNA Levels, HAI, Portal Inflammation and Portal Fibrosis Scores in Children According to the Different Treatment Models

	HBV-DNA (pg/ml)	AST (U/L)	ALT (U/L)	HAI	Portal inflammation	Portal fibrosis
High-dose IFN-α (n=14)	972.3 ± 1782.9	96.2 ± 86.1	134.0 ± 139.9	7.4 ± 3.4	2.5 ± 1.0	1.4 ± 0.8
High-dose IFN-α + lamivudine (n=33)	2145.2 ± 1872.5	81.7 ± 93.7	99.9 ± 113.1	5.3 ± 2.1	1.5 ± 0.9	1.1 ± 0.8
Standard-dose IFN-α + lamivudine (n=26)	4251.9 ± 5829.8	75.0 ± 57.1	126.8 ± 221.2	6.6 ± 2.7	2.1 ± 1.0	1.3 ± 1.0
Lamivudine (n=17)	3574.6 ± 3921.0	63.7 ± 62.4	66.0 ± 84.2	5.5 ± 2.2	1.5 ± 1.0	1.1 ± 1.6
p value	0.038	0.071	0.135	0.041	0.009	0.449

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. CHB: Chronic hepatitis B. HAI: Hepatic activity index. IFN: Interferon.

**Table III.** Mean Serum AST, ALT, HBV-DNA Levels, HAI, Portal Inflammation and Portal Fibrosis Scores According to the Presence of IFN- $\alpha$  or Lamivudine in the Treatment

	Treatment including lamivudine	Treatment not including lamivudine	P value	Treatment including IFN- $\alpha$	Treatment not including IFN- $\alpha$	P value
HBV-DNA (pg/ml)	3185.7 $\pm$ 4124.2	972.3 $\pm$ 1782.9	0.001	1795.8 $\pm$ 1905.6	3884 $\pm$ 5118.5	0.007
AST (U/L)	75.3 $\pm$ 75.6	96.2 $\pm$ 86.1	0.559	86.0 $\pm$ 90.8	70.5 $\pm$ 58.8	0.385
ALT (U/L)	101.5 $\pm$ 154.3	134.0 $\pm$ 139.9	0.204	110.1 $\pm$ 121.7	102.8 $\pm$ 181.0	0.080
HAI	5.8 $\pm$ 2.4	7.4 $\pm$ 3.4	0.130	5.9 $\pm$ 2.7	6.2 $\pm$ 2.6	0.615
Portal inflammation score	1.7 $\pm$ 1.0	2.5 $\pm$ 1.0	0.033	1.8 $\pm$ 1.0	1.9 $\pm$ 1.0	0.702
Portal fibrosis score	1.2 $\pm$ 1.1	1.4 $\pm$ 0.8	0.347	1.2 $\pm$ 0.8	1.2 $\pm$ 1.3	0.528
Age (yrs)	8.9 $\pm$ 3.7	9.8 $\pm$ 4.0	0.431	9.3 $\pm$ 3.5	8.8 $\pm$ 4.0	0.463

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. CHB: Chronic hepatitis B. HAI: Hepatic activity index. IFN: Interferon.

The mean duration of the follow-up of all 126 patients was 42.1 $\pm$ 27.6 months (6-180 months). The mean durations in the patients who had received treatment or not were 50.4 $\pm$ 27.0 months and 22.9 $\pm$ 17.8 months, respectively. Of the children who had not received any treatment, one (2.8%) had developed anti-HBe seroconversion in the 48<sup>th</sup> month of the follow-up. She was an 11-year-old girl with elevated AST and ALT levels and relatively high HAI and portal inflammation score (118 U/L, 342 U/L, 8, and 3, respectively).

### Discussion

This retrospective study performed on 126 children with CHB helped us to evaluate the laboratory and histological features of our patients, and to self-criticize both our treatment decisions and mode of treatment.

The opinion regarding the need for performing a liver biopsy before and after therapy is debatable<sup>2</sup>. While it would be optimal to perform a liver biopsy at baseline, practically speaking, in children with increased transaminase levels and positive serology, the decision regarding drug therapy is unlikely to be affected by the result<sup>2</sup>. On the contrary, when the transaminases are normal and treatment is being planned in the so-called immunotolerant group, information obtained from the biopsy may be helpful<sup>2</sup>. In fact, we had performed liver biopsy in all children who were candidates for treatment. It was reported that males have a high risk of progressing to cirrhosis and hepatocellular carcinoma<sup>3-5</sup>. However, our results revealed that mean portal fibrosis score was not different between females and males, while mean portal inflammation score was higher in girls compared to boys. We

**Table IV.** Mean Age, Serum AST, ALT, HBV-DNA Levels, HAI, Portal Inflammation and Portal Fibrosis Scores of the Children with ETR

	Children with ETR	Children without ETR	p value
HBV-DNA (pg/ml)	2805.5 $\pm$ 5262.6	2863.1 $\pm$ 2894.9	0.194
AST (U/L)	94.6 $\pm$ 97.9	68.9 $\pm$ 60.2	0.013
ALT (U/L)	121.5 $\pm$ 124.1	97.5 $\pm$ 166.8	0.024
HAI	6.9 $\pm$ 3.1	5.5 $\pm$ 2.1	0.081
Portal inflammation score	2.3 $\pm$ 1.0	1.6 $\pm$ 0.9	0.004
Portal fibrosis score	1.3 $\pm$ 0.9	1.1 $\pm$ 1.1	0.088
Age (yrs)	8.6 $\pm$ 3.9	9.3 $\pm$ 3.6	0.483

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. CHB: Chronic hepatitis B. ETR: End of therapy response. HAI: Hepatic activity index. IFN: Interferon.

evaluated whether histological parameters as well as initial transaminases and HBV-DNA levels had any influence on the decision of the physician regarding the treatment mode. The only difference was found in portal inflammation score, with the highest score in the high-dose IFN- $\alpha$  treatment group (Table II). According to our data, higher HBV-DNA levels and lower portal inflammation score (immuno-tolerant group) favored lamivudine treatment whereas lower values of HBV-DNA favored IFN- $\alpha$  treatment (Table III).

The limitation of this study is the lack of a standard-dose IFN- $\alpha$  monotherapy group. The reason why standard dose IFN- $\alpha$  was not used in the last 10 years might be due to the fact that we knew the response rates of our pediatric CHB population who received standard-dose IFN- $\alpha$  treatment<sup>6</sup>. In the mentioned study, we found ETR and sustained response rates as 50% and 43%, respectively<sup>6</sup>. In two of the patients (6.7%), anti-HBs seroconversion was detected<sup>6</sup>.

Spontaneous HBeAg loss in chronically infected children occurs at an annual rate of 10%-16%, while spontaneous loss of HBsAg is as low as 0.6% per year, with the children achieving earlier seroconversion being those with biochemical

in those with histologically active disease, high transaminase activity and low HBV-DNA levels<sup>5</sup>. The only child with spontaneous seroconversion had had the above-mentioned features; likewise, children with treatment-induced seroconversion had had higher AST, ALT and portal inflammation scores (Table IV). Those with anti-HBs seroconversion had higher HAI and portal inflammation scores compared to those with only anti-HBe seroconversion. HBV-DNA was lower though not statistically significant (59.7 pg/ml vs 2186.8 pg/ml). That means that the lower the HBV-DNA and the higher the HAI and portal inflammation scores, the higher the probability of HBsAg clearance (Table V).

Current European guidelines advise non-treatment for immuno-tolerant children with normal transaminase levels, high HBV-DNA and mild changes on liver biopsy, because the published results in these children do not justify the cost and the particularly demanding nature of IFN treatment, which requires repeated injections<sup>5</sup>.

When we assessed our treatment decisions retrospectively, we saw that we had principally obeyed those guidelines, as the mean transaminase levels were lower in the follow-

**Table V.** Mean Age, Serum AST, ALT, HBV-DNA Levels, HAI, Portal Inflammation and Portal Fibrosis Scores of the Children with ETR with or without anti-HBs Seroconversion and without ETR

	Children with anti-HBs	Children with ETR without anti-HBs	Children without ETR	p value
HBV-DNA (pg/ml)	59.7 $\pm$ 29.3	2186.8 $\pm$ 2261.3	3293.4 $\pm$ 4528.9	0.218
AST (U/L)	113.3 $\pm$ 119.4	96.0 $\pm$ 102.4	68.6 $\pm$ 58.7	0.224
ALT (U/L)	151.7 $\pm$ 161.3	123.4 $\pm$ 128.4	96.3 $\pm$ 162.6	0.649
HAI	11.7 $\pm$ 2.1	6.4 $\pm$ 2.9	5.6 $\pm$ 2.1	<0.001
Portal inflammation score	3.3 $\pm$ 0.6	2.2 $\pm$ 1.0	1.6 $\pm$ 1.0	0.001
Portal fibrosis score	1.7 $\pm$ 1.2	1.3 $\pm$ 0.9	1.1 $\pm$ 1.1	0.487
Age (yrs)	8.0 $\pm$ 6.1	8.7 $\pm$ 4.0	9.3 $\pm$ 3.6	0.737

ALT: Alanine aminotransferase. AST: Aspartate aminotransferase. CHB: Chronic hepatitis B. ETR: End of therapy response. HAI: Hepatic activity index. IFN: Interferon.

and/or histological evidence of active disease<sup>5</sup>. Of our 36 children who had been followed for a mean duration of 22.9 $\pm$ 17.8 months (1-79 months), one (2.8%) had spontaneous anti-HBe seroconversion, and none had anti-HBs seroconversion. Probability of both spontaneous and treatment-induced seroconversion is higher

up group compared to others. HAI and portal inflammation scores were also lower though not statistically. The statistical insignificance may be due to the fact that some of the patients under follow-up were in fact suitable for treatment but were waiting for a more suitable period for treatment (summer vacation, etc.).

Interferon- $\alpha$  has been used in children with chronic HBV for about three decades. Response rates in children vary between 3-58% compared with 8-17% in untreated controls<sup>1</sup>. Although not routinely recommended, response rates with high-dose IFN- $\alpha$  are not unpromising<sup>7</sup>. In a series of Turkish children, sustained response rate was reported as 33% and 60% with standard- and high-dose IFN- $\alpha$ , respectively<sup>7</sup>. In our series, ETR was achieved in 35.7% of children receiving high-dose IFN- $\alpha$ .

It is known that lamivudine, a nucleoside analogue, has been introduced as a new hope for the treatment of CHB. Combination of lamivudine and IFN- $\alpha$  was offered as a rational therapeutic approach; however, it was demonstrated that adding lamivudine to IFN- $\alpha$  monotherapy did not increase the ETR rate of children in both standard-<sup>8-10</sup> and high-dose regimens<sup>11</sup>. The ETR rate of children who had received standard-dose IFN- $\alpha$  and lamivudine combination therapy was 61.5%, and was higher than the results of previous studies<sup>8,10</sup>.

As mentioned before, it seemed that lamivudine treatment was preferred in children with higher HBV-DNA and lower ALT and portal inflammation scores (Table III). In that group, so-called immuno-tolerant, in which lamivudine monotherapy had been chosen, ETR was achieved in 11.8%. Artan et al.<sup>12</sup> previously reported that none of their 17 immuno-tolerant patients had anti-HBe seroconversion with the use of lamivudine. However, D'Antiga et al.<sup>13</sup> recently reported that a combination of lamivudine and IFN- $\alpha$  can be used to successfully increase the rate of anti-HBe seroconversion to 22% and anti-HBs positivity to 17%.

Breakthrough was detected in 11.8% of children on either lamivudine monotherapy or combination therapy with IFN- $\alpha$ . Mutations in a specific region of HBV DNA polymerase (YMDD) develop in approximately 20-25% of patients during the first year of therapy, and the rate increases to 70% by five years of treatment<sup>14</sup>. YMDD mutations were reported in 0% to 60% of treated children<sup>13,15,16</sup>. In a Turkish pediatric series on lamivudine and IFN- $\alpha$  therapy, this rate was reported as 17.9%<sup>17</sup>.

In conclusion, although the treatment of CHB in children is complex and therapeutic approaches vary, those with high transaminases should be considered for treatment with either IFN- $\alpha$  and/or nucleoside analogues<sup>2</sup>. It seems that IFN- $\alpha$  is still the most effective treatment for chronic HBV infection in children, though optimal treatment should be individualized, based on clinical and histological features, ability to take medications and contraindications<sup>1</sup>. Hopefully new agents and treatment protocols will enhance response rates in childhood CHB.

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