"Interferon alfa-2b therapy in children with chronic hepatitis B."

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ABSTRACT

Twenty nine children (mean age 8.3 years, 18 boys, 11 girls) who had biopsy proved chronic hepatitis B virus infection (HBV) with active viral replication were given a 16 week course of interferon alfa-2b treatment (9 million units (MU)/m2, thrice weekly). Fourteen children (48%) showed persistent loss of HBV-DNA 8 months after the end of treatment; 11 (38%) lost hepatitis B e antigen (HBeAg), and two (7%) hepatitis B surface antigen (HBsAg). Alanine aminotransferase activities returned to normal in 12 children. Those who responded had significantly higher initial transaminase activities than those who did not ($p < 0.01$) but similar serum HBV-DNA. Results were compared with the natural evolution of the disease in a group of 25 children (mean age 8.3 years) with identical initial mean serum HBV-DNA values, followed up during the same period. Two of these (8%) lost HBeAg and one (4%) HBsAg. The 23 remaining control subjects had no decrease in serum HBV-DNA or in transaminase activities compared with values 1 year earlier. It is concluded that treatment with interferon alfa-2b in children may lead to inhibition of HBV replication similar to that described in adults, and may thus shorten disease evolution. Further studies are necessary to establish the best protocols and to identify those patients who are the most likely to respond to treatment.

CITE THIS VERSION

Sokal, Etienne ; Wirth, S ; Goyens, P ; Depreterre, A ; Cornu, C.. *Interferon alfa-2b therapy in children with chronic hepatitis B.*. In: *Gut*, Vol. 34, no. 2 Suppl, p. S87-90 (1993) http://hdl.handle.net/2078.1/12073 -- DOI : 10.1136/gut.34.2_Suppl.S87

Interferon alfa-2b therapy in children with chronic hepatitis B

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Abstract

Twenty nine children (mean age 8·3 years, 18 boys, 11 girls) who had biopsy proved chronic hepatitis B virus infection (HBV) with active viral replication were given a 16 week course of interferon alfa-2b treatment (9 million units (MU)/m², thrice weekly). Fourteen children (48%) showed persistent loss of HBV-DNA 8 months after the end of treatment; 11 (38%) lost hepatitis B e antigen (HBeAg), and two (7%) hepatitis B surface antigen (HBsAg). Alanine aminotransferase activities returned to normal in 12 children. Those who responded had significantly higher initial transaminase activities than those who did not ($p<0·01$) but similar serum HBV-DNA. Results were compared with the natural evolution of the disease in a group of 25 children (mean age 8·3 years) with identical initial mean serum HBV-DNA values, followed up during the same period. Two of these (8%) lost HBeAg and one (4%) HBsAg. The 23 remaining control subjects had no decrease in serum HBV-DNA or in transaminase activities compared with values 1 year earlier. It is concluded that treatment with interferon alfa-2b in children may lead to inhibition of HBV replication similar to that described in adults, and may thus shorten disease evolution. Further studies are necessary to establish the best protocols and to identify those patients who are the most likely to respond to treatment.

(*Gut* 1993; **supplement:** S87–S90)

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Alpha interferon is being considered more frequently in the treatment of children with chronic hepatitis B virus (HBV) infection. This is probably because of recent short and long term successes obtained with this drug in adults.[1–4] Despite the fact that disease severity is often mild in children, at least during the first decade, treatment to shorten disease duration and to prevent disease activation in adolescence and the long term possibility of cirrhosis and hepatocellular carcinoma is justified. Contagion and isolation of infected children are additional reasons for treatment. Experience of interferon in children with chronic HBV hepatitis is limited, but there are some data on drug tolerance and response to treatment.[5 6]

We present the results of an open study investigating the tolerance of patients to recombinant interferon alfa-2b (Schering-Plough) and its efficacy in inhibiting viral replication and promoting loss of hepatitis B e antigen (HBeAg) in 29 children with chronic HBV infection. Data are compared with those of a similar group of 25 children followed up during the same period. This study was performed as a pilot study for an international multicentre randomised trial which started in September 1992.

Patients and methods

This multicentre pilot study was conducted according to a protocol accepted by the local ethical committees of each centre. Informed consent was obtained from the parents of the children. Twenty nine children who had had chronic HBV infection and active viral replication (HBeAg+) for at least 6 months were included. A further 25 HBV positive children who were not being treated were followed simultaneously to study natural evolution and seroconversion rate. The age, ethnic origin, and biological and histological parameters of the patients are shown in Table I. The disease had been discovered incidentally or by family screening in all 54 patients. In three children who had been adopted, the diagnosis was established after the 'mother' developed acute HBV infection. The mode of transmission was unknown in 33, from mother to child in 13, horizontal intrafamilial in 5, and after blood transfusion in 3 patients. Any associated viral, toxic, metabolic, or autoimmune causes of chronic HBV were excluded before enrolment in the study. Exclusion criteria included cirrhosis, renal insufficiency, recent immunomodulatory treatment, pregnancy, antibody to HIV or hepatitis delta virus, or any associated severe illness.

Liver biopsies were performed percutaneously, using the Menghini technique (Hepafix 1·4 mm needle, Braun, Melsungen, Germany). Patients in the treatment group received interferon alfa-2b (Schering-Plough, Belgium and Germany) subcutaneously, three times a week for 17 weeks. The dosage was increased

TABLE I *Patient characteristics in the treated and control groups*

	Treated	*Controls*	*Statistical significance*
Mean (range) age (Y)	8·3 (0·75–17)	8·7 (1·5–17)	NS
Male:female	18/11	16/9	NS
White/non-white	14/15	16/11	NS
Chronic active hepatitis (%)	22 (76)	14 (56)	NS
Chronic persistent hepatitis (%)	7 (24)	11 (44)	NS
Mean (SD) ALT (IU/l)	112·5 (89)	51·5 (28)	$p<0·01$
Mean (SD) serum DNA (pg/ml)	136·8 (172·4)	136·9 (109·3)	NS

NS=non-significant difference (χ^2/Student's *t* test); ALT=alanine aminotransferase.

progressively during the first week from 3 to 9 million units (MU)/m^2 body surface area. The dosage of 9 MU/m^2 was maintained for 16 weeks unless side effects occurred. These were recorded, with special attention to fever, epistaxis, flu like syndrome, myalgia, and hair loss. Paracetamol was given for fever or flu like syndrome, when necessary, at a dosage of 10 mg/kg at the time of injection.

Blood chemistry and cell counts were performed twice in the first week, once weekly for 3 weeks, once a month until 1 month after the end of treatment, and then every 3 months up to 1 year. Virological serum markers and HBV-DNA were determined at least twice before inclusion, every month until 1 month after the completion of treatment, and every 3 months thereafter. In control patients, liver enzyme and serum virology investigations were performed every 3 months and HBV-DNA every 6 months. No liver biopsy was carried out after treatment as there were no obvious advantages to the patients. Family screening and vaccination were offered to all relatives. Statistical analysis was performed using Student's t test and the χ^2 test. Differences were considered to be statistically significant where the p value was <0·05.

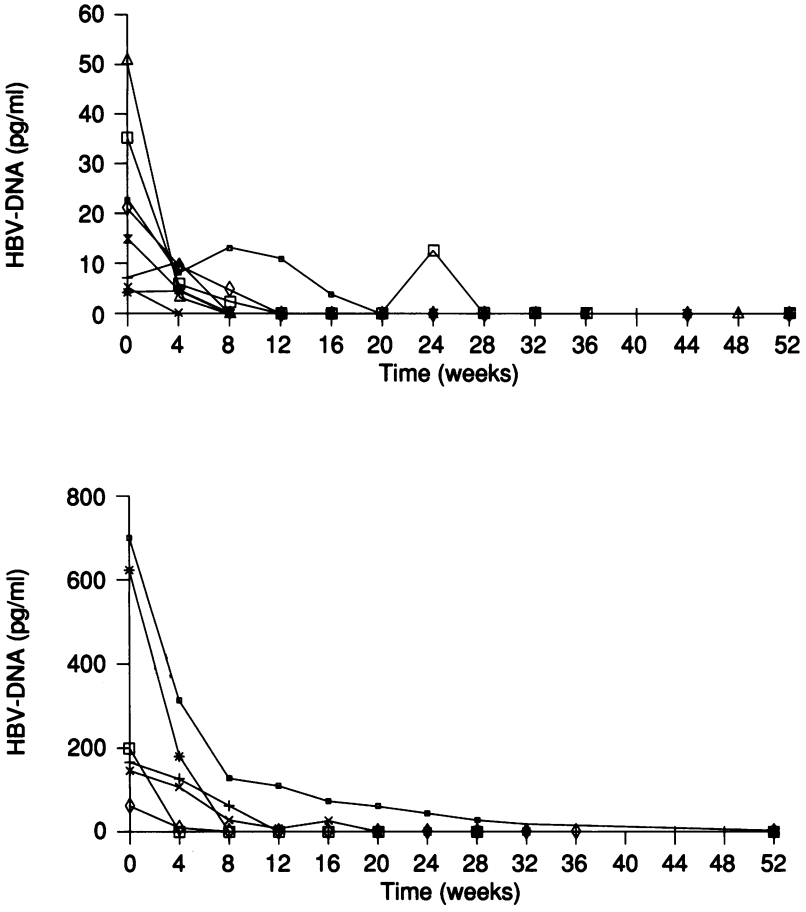

Figure 1 Serum hepatitis B virus (HBV)-DNA evolution in patients responding to interferon treatment. (Above) Eight patients with initial HBV-DNA titre ≤50 pg/ml. (Below) Six patients with initial HBV-DNA titre >50 pg/ml..

TABLE II *Mean (SD) serum DNA and alanine aminotransferases (ALT) in the controls (one year interval) and in treated patients (before and six to eight months after completion of therapy)*

	Controls (n=29)	*Responders (n=14)**	*Non-responders (n=15)*
Before:			
DNA (pg/ml)	137 (109)	147 (228)	130 (108)
ALT (IU/l)	51·5 (28·0)	146·9 (102)	77·7 (61·4)
Follow up:			
DNA (pg/ml)	114 (69·3)	0	138 (110)
ALT (IU/l)	59·4 (53·1)	29·7 (20·9)	73·7 (42·2)

*Responders: persistent loss of HBV-DNA.

Results

Although patients were clinically asymptomatic at the time of inclusion, the knowledge that they were HBV positive caused intense stress and disturbance of family life. Furthermore, several families faced important social problems as a result of the infection, and experienced fear among friends and relatives.

Fever was common after injections in the interferon treated group but this side effect was well tolerated when injections were given at night and was easily controlled with paracetamol in all but three patients. For these, the dose had to be decreased by 2/3, 2/3, and 1/2 dose, respectively. Two adolescent girls complained of considerable hair loss, which occurred from week 13 and 15 respectively up to 4 weeks after the end of treatment. One patient had several episodes of epistaxis.

A low neutrophil count (between 600 and 800 cells/ml) was observed in three patients but did not necessitate dosage reduction, except in one patient who also had a high fever. In all other patients, the neutrophil count remained higher than 1000 neutrophils/ml. No patient was lost from the study and compliance with treatment was excellent.

Evaluation of treatment efficacy was made 6 to 8 months after the end of therapy (that is, at weeks 44 to 52 after beginning treatment). Fourteen (48%) of the 29 treated patients showed persistent loss of HBV-DNA, 13 during treatment and one in the following weeks. Twelve of these had chronic active HBV hepatitis before treatment compared with 10 of 15 who did not respond (p<0·01). The changes in serum DNA for these patients are shown in Fig 1 (A) (low initial DNA) and (B) (high initial DNA). Eleven (38%) subsequently lost HBeAg at 1 year, nine (31%) developed anti-HBe antibodies, and two (7%) lost hepatitis B surface antigen (HBsAg) with anti-HBs antibody formation. Mean transaminase activities and DNA values before and after treatment are given in Table II.

Patients who responded had significantly higher transaminase activities before treatment than those who did not (p=0·05). After treatment, a significant decrease in alanine aminotransferases was seen in responders compared with baseline values (p<0·01); levels returned to normal in 12 of 14 responders. Full social rehabilitation of the patients was an important result of treatment. Gender did not affect the response rate, as evidenced by this group which included seven boys and seven girls. Nine of 15 white children compared with five of 14 non-whites responded to treatment showing no statistical difference between the response rates in these subgroups.

In seven patients (24%) the response was transient: they showed an appreciable decrease

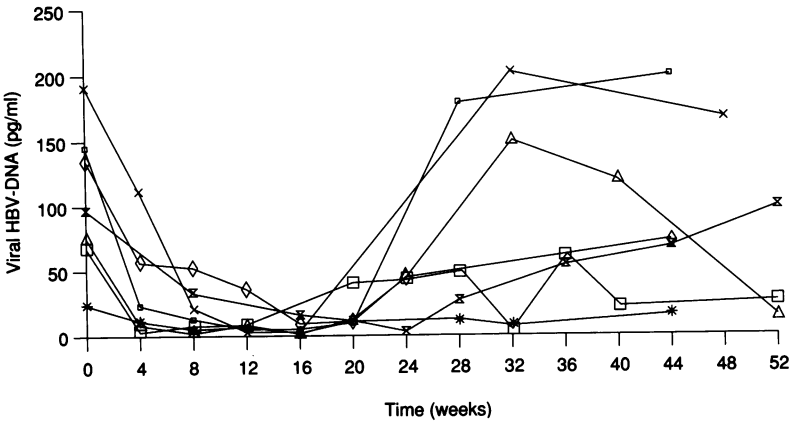

Figure 2 Serum hepatitis B virus (HBV)-DNA evolution in transient responders: sustained inhibition of viral replication is observed during therapy, but relapse occurs soon after the end of treatment.

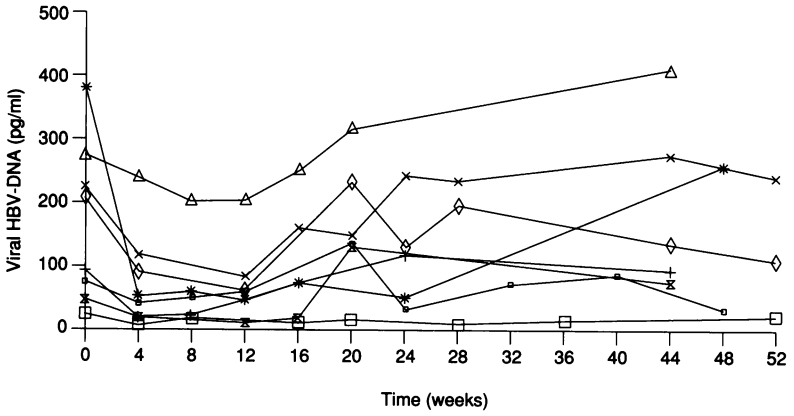

Figure 3 Serum hepatitis B virus (HBV)-DNA evolution in non-responders: despite some initial decrease in HBV-DNA, this effect remains limited and without continuous decrease during treatment.

in HBV-DNA, which reached undetectable values in two at the end of treatment (Fig 2). This inhibition of viral replication was not sustained after the end of therapy, however, and no HBeAg-anti-HBe seroconversion had occurred in this group six to eight months afterwards.

Eight patients (28%) showed no sustained reduction of serum HBV-DNA during treatment (Fig 3). Their mean initial transaminase value was not significantly lower than in the transient response group (alanine aminotransferase 86 (120) IU/l *v* 112 (77) IU/l). All those in the groups that did not respond were still HBeAg positive at one year follow up. In the total group of 15 patients who did not respond to therapy, liver enzymes and DNA were not improved when compared with values before treatment (Table II).

Three pairs of siblings were included in the study and showed similar responses during treatment. Both siblings of the first family developed HBeAg-anti-HBe seroconversion, those in the second family had a transient response, and no response was seen in the third family.

Serum transaminase activities and DNA evolution in the control group are shown in Table II. Two patients (8%) lost serum HBV-DNA and HBeAg and one developed HBsAg-anti-HBe seroconversion at the one year follow up. All others remained HBeAg-positive without a significant decrease in serum HBV-DNA or transaminase activities six months or one year after follow up.

Discussion

This prospective study was conducted to evaluate the potential benefit of interferon treatment in children with chronic HBV and active viral replication. The persistent loss of HBV-DNA and HBeAg in 48% and 38% respectively of patients, is comparable with previous reports in adults and children,[1-5 7] and it may be expected that a high percentage of these patients will later develop HBsAg-anti-HBs seroconversion.[3] In our treated patients, responders had higher mean initial transaminases activities than the non-responders, a factor known to reflect response to treatment in adults.[1 2] There were no differences in mean serum HBV-DNA values between responders and non-responders, and two responders had a very high initial DNA (Fig 1A and 1B); all other patients had a serum DNA value below 200 pg/ml. The lack of difference in mean serum HBV-DNA values between responders and non-responders contrasts with findings in adults[1 2] but agrees with a recent study in Spanish children.[6] Similarly, we did not find differences in response according to gender or ethnic origin.

In the control group, only two children (8%) lost HBV-DNA and HBeAg after one year of follow up, a natural seroconversion rate comparable with previous reports in children.[6-8] None of the remaining control patients showed any change in serum HBV-DNA values, HBeAg status, or transaminase activities during the study. The lower initial transaminase values in the control group compared with the treatment group may have reduced the chances of natural seroconversion in these controls.[7 8]

The benefits of successful treatment include interruption of disease evolution and prevention of more aggressive disease (including cirrhosis) in later childhood. In patients in whom liver transplantation is necessary, there is a high risk of graft reinfection.[9 10] In addition, we may hope to decrease the risk of hepatocarcinoma,[11-13] although this remains to be proved in large and long term prospective trials. Finally, loss of contagion[14 15] helps the children to return to a normal social life. Social isolation of these children is, unfortunately, frequent once friends or relatives know the diagnosis and can lead to important psychological and even socioeconomic stress for the child and family.

In the subgroup that responded transiently, the continuous fall in HBV-DNA values during treatment (Fig 2) suggests that patients may benefit from continuing this until complete loss of HBV-DNA occurs. Earlier studies have shown that the duration of treatment influences the response to interferon in children with chronic HBV infection.[6 16 17] In the group of children who do not show a sustained loss of HBV-DNA during treatment,

therapy could perhaps be stopped earlier—when no further decrease, or even relapse, is observed. Finally, corticosteroid treatment beforehand may improve the response to alpha interferon in patients with low initial transaminases activities.[1 4]

We conclude that recombinant interferon alfa-2b seems to be as effective in children as in adults in promoting both inhibition of viral replication and of HBeAg-anti-HBe seroconversion in chronic HBV infection. It can thereby interrupt disease evolution, prevent unfavourable progression and eliminate contagion, and the psychological and social problems caused by the disease. Optimal treatment regimens must be found, and patients must be selected on the basis of those most likely to respond, to avoid unnecessary treatment in about half of these children.

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