Interferon : a meta-analysis of published studies in pediatric chronic hepatitis B

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Abstract

Perinatally infected Asian children respond poorly to interferon (IFN) therapy. In contrast, IFN therapy seems to be more effective in Caucasian children who presumably acquired HBV infection later in life. We reviewed seven controlled studies of IFN treatment in children with chronic hepatitis B living in western countries (216 treated, and 200 untreated children). Before treatment all patients were HBeAg and HBV-DNA +ve, with a biopsy proven chronic hepatitis B. Ages ranged 1 to 16 years (mean age 7 years). Most patients were Caucasian. Protocols which have been adopted may schematically be divided into protocols which have used high doses of IFN (7.5 to 10 MU/sqm/TIW), and protocols which have used low doses of IFN (3 to 6 MU/ sqm/TIW), with a short (3 to 6 months) or a long duration of treatment (12 months). The percentage of treated patients who, at the end of treatment, lost HBV-DNA (that in most studies corresponded also to HBeAg serum conversion) averages 20 to 58% (mean 35.5%) that is much higher than that observed in controls (range 8-17% ; mean 11.4%). A better trend is probably observed only in patients who received the treatment for a longer period of time. At the end of treatment, low percentages of patients lost BsAg (range 0-4% ; mean 1.1%) : again higher doses tend to be more effective than lower doses. In some studies IFN has been shown to significantly accelerate the termination of viral replication.

Data on longer term outcome of IFN treatment in Caucasian children are scarce and confirm results obtained at short and at medium-term FU either in horizontally either in perinatally infected children. Results from few randomized controlled trials of interferon therapy with prednisone priming in Chinese and Caucasian children were comparable to results obtained without prednisone. In one study steroid priming did not potentiate the effect of IFN, however it existed a tendency of prednisone to improve HBeAg clearance in patients with normal aspartate aminotransferase, and alanine aminotransferase activity lesser than 100 u/l. In most studies, factors positively influencing response rates of IFN treatment are represented by severe inflammation in the basal liver biopsy, high basal levels of serum transaminase, low basal levels of serum HBV-DNA. Vertical trasmission may be considered a factor adversely affecting the response to IFN treatment both in Chinese and Caucasian population.

In general in most controlled studies, the majority of responders have shown a significant reduction in hepatic inflammation and transaminase normalization. Children have a low risk of developing severe IFN-induced side effects. Adverse reactions and worsening of health-related quality of life were tolerable and did not seem to be a limiting factor for IFN therapy in young candidates. (Acta gastroenterol. belg., **1998**, 61, **219-223**).

Key words : interferon, chronic hepatitis B, children.

Introduction

Chronic hepatitis B (CHB) is a frequent complication when the infection is acquired in childhood. It may soon progress to cirrhosis (1,2), liver failure and hepatocellular carcinoma (3). Delta superinfection may accelerate the clinical course of the disease in adults and in children (4,5). Pending acceptance of universal vaccination (6,7), infection with hepatitis B virus at all ages remains a public health problem of worldwide importance which still causes several thousands of deaths per year. Ideally, the treatment should therefore be instituted as early as possible.

Targets of a treatment in patients affected by CHB should aim to :

- stop or decrease viral replication as judged by clearance of HBeAg and loss of viral HBV DNA, which are sometimes heralded by a peak of cytolysis ;
- obtain the clearance of HBsAg, although it is a much rarer event ;
- normalize hepatic histopatology, in particular to decrease hepatic inflammation (and fibrosis) ;
- normalize liver function tests (that most often just means to normalize serum levels of slightly elevated basal transaminase).

The long term target is, obviously, to avoid progression of the liver disease, to improve the quality of life with an advantageous cost/benefit ratio of the treatment.

Nowadays αInterferon (IFN) is the only drug against HBV that has been extensively studied in adults (8) and, more recently, in pediatric patients as well. Nonetheless, its use is still controversial and recommendations are still cautious, since

- dose and duration are not yet standard ;
- the drug is ineffective in about half the patients treated ;
- there are a certain number of side effects ;
- studies dealing with cost/long term benefits ratios are still scarce.

Analysis and discussion of published IFN studies in pediatric CHB

It is well extablished that perinatally infected Asian children respond very poorly to IFN therapy (Table I) : low reponse rate is probably related to the development of immune tolerance as shown by the presence of an inactive liver disease with normal transaminase levels and high HBV-DNA serum concentrations (9-10).

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Table I. — **Interferon schedules and HBeAg/HBV-DNA clearance in controlled trials of treatment in children affected by chronic hepatitis B**

Authors	*Cases (n)*	*Therapy*	*HBeAg and/or HBV-DNA % clearance*		
			End therapy	+ 6-9 *mos*	+ 12 or > *mos*
Lai *et al.* (9)	12	IFN (2,5 MU →)10 MU/sqm TIW × 3.5 mos	17	—	17
(Chinese patients)	12	controls	17	—	17
Lai *et al.* (10)	31	PDN × 6 weeks + IFN 5 MU/sqm TIW × 4 mos	—	13	—
(Chinese patients)	29	IFN 5 MU/sqm TIW × 4 mos	—	3	—
	30	controls	—	0	—
Ruiz-Moreno *et al.*	12	IFN 10 MU/sqm TIW × 6 mos	58	58	—
(11)	12	IFN 5 MU/sqm TIW × 6 mos	42	42	—
	12	controls	17	17	—
Utili *et al.* (12)	10	IFN 3 MU/sqm TIW × 12 mos	20	30	—
	10	controls	10	10	—
Sokal *et al.* (13)	29	IFN 9 MU/sqm TIW × 4 mos	—	48	48
(50% non white pts)	25	controls	—	NR	8
Barbera *et al.* (14)	21	IFN 7.5 MU/sqm TIW × 6 mos	—	—	30
	19	IFN 3 MU/sqm TIW × 6 mos	—	—	21
	39	controls	—	—	13.5
Vajro *et al.* (15)	9	PDN × 6 weeks + IFN 10 MU/sqm TIW × 12 mos	44	—	55
	13	IFN 10 MU/sqm TIW × 12 mos	50	—	58
	9	controls	11	—	33
Gregorio *et al.* (16)	34	PDN × 4 weeks + IFN 5 MU/sqm TIW × 3 mos	39	44	38
(11% non white pts)	30	IFN 3 MU/sqm TIW × 3 mos	41	33	40
	31	controls	13	10	16
Sokal *et al.* (17)	70	IFN 6 MU/sqm TIW × 6 mos	—	26	—
(—% non white pts)	74	controls	—	11	—

IFN = interferon ; PDN = prednisone ; TIW = three times a week ; NR = not reported.

In contrast, IFN therapy seems to be more effective in Caucasian children who presumably acquired HBV infection later in life. Table I shows seven (11-17) controlled studies of IFN treatment in children with CHB living in western countries. Before treatment all patients were HBeAg and HBV-DNA +ve, with a biopsy proven CHB. Ages ranged 1 to 16 years (mean age 7 years). Most patients were Caucasian. Total number of IFN alone treated patients was 216 ; controls were 200. Protocols which have been adopted may schematically be divided into 2 groups :

— protocols which have used high doses of IFN (ranging from 7.5 to 10 MU/sqm/TIW), and
— protocols which have used low doses of IFN (ranging from 3 to 6 MU/sqm/TIW).

Some of these studies have had a short duration of treatment (3 to 6 months) and some have had a long duration of treatment (12 months).

The study of Ruiz-Moreno *et al.* (11) and that of Barbera *et al.* (14) compared high and low doses of the drug in the same protocol.

As shown in table I, the percentage of treated patients who at the end of treatment presented HBeAg serum conversion (that in most studies corresponded also to lost HBV-DNA) averages 20 to 58% (mean 35.5%), that is much higher than that observed in controls (range 8-17% ; mean 11.4%). A better trend is probably observed only in patients who received the treatment for a longer period of time.

At the end of treatment, low percentages of patients lost HBsAg (range 0-4 % ; mean 1.1%) ; again higher doses tend to be more effective than lower doses.

In some studies IFN has been shown to significantly accelerate the termination of viral replication. Figure 1 represents a graphical example of the timing and of the percentage of HBeAg clearance of IFN treated children as opposed to controls observed in one study (15). The statistically significant difference during the year of treatment tends to disappear thereafter during short — and medium-term follow-up (FU). Similary to this study, also other authors have shown the same trend of poor influence of IFN upon response rates of HBeAg clearance and/or HBV DNA loss in the post-treatment FU. Infact in the study of Barbera *et al.* (14), one and half year after the end of treatment percentages of HBV DNA loss in patients increased only from 24% to 30% whereas controls went from 3% to 13.5%. In the sudy of the Gregorio *et al.* (16) percentages of HBV-DNA loss in patients increased only from 30 to 37% whereas controls went from 13% to 26%.

Data on longer term outcome of IFN treatment in Caucasian children with CHB are scarce and seem to confirm results obtained at short and at medium-term FU either in horizontally (18) either in perinatally (19) infected children.

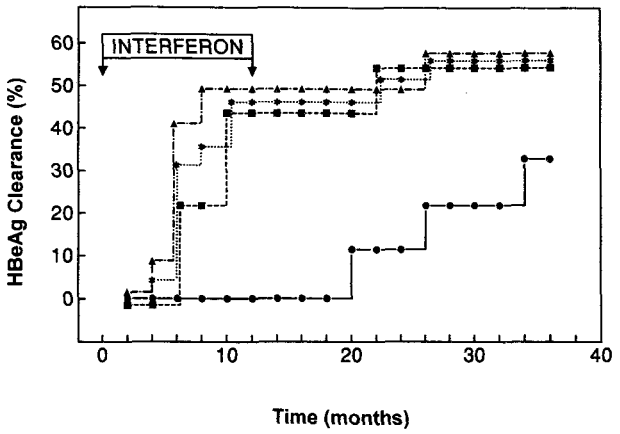

Fig. 1. — HBeAg clearance in patients treated with IFN only (▲), IFN after prednisone priming (■), or no dugs (●). The group of all 21 treated patients is indicated by the line with asterisks (*). No statistically significant differences is found between the outcome of patients who were or were not pretreated with prednisone. Differences between the treated patients and the controls were p = 0.05, 0.120, and 0.050, respectively for patients treated with IFN, prednisone + IFN, and pooled treated patients. Note the the dramatic acceleration of HBeAg clearance in treated patients. 47% and 61% treated patients lost HBeAg during the first year of treatment and within the two years of post treatment follow-up, respectively, as opposed to 11% ($p < 0.05$) and 33% (p = NS) observed in controls. HBeAg clearance was obtained at a mean time of 10.2 months in treated patients as opposed to 23.0 months in controls ($p < 0.01$). The average annual rate of HBeAg clearance in treated patients is twice that of spontaneous seroconverters (21% vs 11%). After 2 years the improvement in serologic data in treated patients occurred significantly earlier (12 months, on average) than in controls (p = 0.026) (From Vajro *et al.*, modified (15)).

Prednisone alone does not benefit children with chronic hepatitis B (20), although this drug affects some *in vitro* abnormalities of the immunoregulatory system implicated in this disease (21). On the other hand, a short course of corticosteroids given immediately before IFN treatment may enhance its antiviral efficacy. In theory, the withdrawal of prednisone should induce an acute exacerbation of the underlying hepatitis, thus making the patient more susceptible to IFN treatment. However, prospective studies in adults have failed to show clear benefits of pre-treatment with prednisone over and above treatment with interferon alone except, perhaps, in cases with low ALT values at entry (22-24). Results from randomized controlled trials of alpha-interferon therapy with prednisone priming in Chinese (10) and Caucasian (15-16, 25) children were comparable to results obtained without prednisone. In one study (15) biochemical and serological response rates, and timing of these responses were comparable in patients pretreated or not with prednisone also after stratification by low and high basal levels of amino-transferases. The study of Gregorio *et al.* (16) who compared Caucasian patients who had or had not been pretreated with prednisone found that steroid priming does not potentiate the effect of IFN although it does exist a tendency of prednisone to improve HBeAg clearance in patients with normal aspartate aminotransferase, and alanine aminotransferase activity lesser than 100 u/l. The study of Sira *et al.* (19) conducted in a group of heterogeneous ethnic origin found a significant effect of prednisone on late seroconversion and transaminitis.

In most studies, factors positively influencing response rates of IFN treatment are represented by :

— severe inflammation in the basal liver biopsy ;
— high basal levels of serum transaminase ;
— low basal levels of serum HBV-DNA.

Vertical trasmission has been postulated to predict a poor response in Chinese children (9-10), but it has been scarcely studied in the above mentioned trials in Caucasian children with CHB. Indeed, Bruguera *et al.* (26) in an uncontrolled study with IFN in European children, 6 months after the end of therapy found that 50% of his patients lost HBV-DNA. When type of trasmision was taken into consideration, it became evident that none of patients who acquired HBV infection through maternal trasmission, lost HBV DNA as opposed to 72% of patients who had been horizontally infected. Therefore vertical trasmission may be considered a factor adversely affecting the response to IFN treatment both in Chinese and in Caucasian population. Factors which seem to be not influent on response are represented by :

— prednisone priming, probably except for patients with low basal transaminase activity ;
— levamisole co-treatment (27) ;
— presence of pre-core HBV mutants (28).

Table II. — **Schedules of IFN treatment in controlled studies in Caucasian children affected by chronic hepatitis B**

IFN higher doses (7.5-10MU/sqm/TIW)		*IFN lower doses (3-6MU/sqm/TIW)*	
Short treatment	Long treatment	Short treatment	Long treatment
6 mos Ruiz Moreno (11) 4 mos Sokal (13) 6 mos Barbera (14)	12 mos Vajro (15)	3 mos Gregorio (16) 6 mos Barbera (14) 6 mos Ruiz Moreno (11) 6 mos Sokal (17)	12 mos Utili (12)

IFN = interferon ; PDN = prednisone ; TIW = three times a week.

In general in most controlled studies, the majority of responders have shown a significant reduction in hepatic inflammation and transaminase normalization.

Side effects of IFN treatment have been extensively studied only in one most recent paper from Italy (29), and it is concluded that children have a low risk of developing severe IFN-induced side effects. Adverse reactions and worsening of health-related quality of life were tolerable and did not seem to be a limiting factor for IFN therapy in young candidates. Very few studies have been dedicated to the aspect of cost/benefit analysis of IFN treatment. In their recent study, Louis Jaques and Olson (30), suggest that IFN therapy is cost effective and that cost-effectiveness in toddlers is more advantageous than in older patients. However further studies are necessary, expecially if one takes into consideration the above mentioned long-term results of HBV DNA loss in treated and untreated patients.

Conclusion

In conclusion, controlled IFN studies in Caucasian children with CHB have shown that either high or low doses IFN treatments for either a long or a short period of time :

- generally reduce viral replication in less than or equal to about 50% cases, i.e. a percentage significantly higher than in controls, followed by an improvement of biochemical and histological parameters ;
- have a poor effect on HBsAg clearance ;
- get no obvious further benefits after prednisone priming ;
- improve biochemical and histological picture of responders ;
- may accelerate the termination of viral replication during treatment.

Further studies are necessary to evaluate benefits in response rates during the post treatment medium and long term follow up. Infact, in the large studies by Bortolotti *et al.* (31,32) the medium-term spontaneous HBeAg seroconversion at the third year of follow-up during the natural course of the disease was remarkable and very close to that observed in controls of most IFN studies (i.e. between 33% and 51%). As a consequence, it is therefore possible that — as suggested by Bruguera *et al.* (26) — some children enrolled in IFN trials may have a post-treatment spontaneous interruption of viral replication. Indeed, up to two-thirds (31,32) and even 100% (33) of untreated Caucasian children with HBeAg and HBV-DNA-positive chronic hepatitis terminate active viral replication before reaching adulthood. In several studies IFN administration has probably played a pivotal role in clearance of serum HBV-DNA and HBeAg, particularly, if not exclusively, during the first months of treatment. Serologic changes related to HBeAg and HBV-DNA appeared, on average, remarkably earlier in treated patients than in controls, which indicates that IFN treatment not only affects the percentages of the response rate, but accelerates the natural course of the disease and results in earlier termination of active viral replication.

Predictive factors should be included among the criteria used to select candidates for treatment, and among those used to decide the timing of discontinuation of treatment once it has been started. Stringent patient selection and optimization of schedules of length of treatment will improve the ratio therapeutic benefit to side effects and cost, which includes evaluation and monitoring of the patient in addition to the cost of the drug itself. Indeed, the advantages of treatment over the natural course of the disease are not yet fully evident, especially in terms of avoidance of long-term complications and improvement in survival. The reduction of the length of the viral replication induced by IFN in children, in addition to the advantage of the mere reduction of the infectivity of the children with respect to their community, may help to avoid some of the complications of CHB. In fact, the degree of integration of HBV-DNA into the host cellular genome increases with time and is correlated with the development of hepatocellular carcinoma (34). Several questions, however, remain open : therapeutic options for the (still large proportion of) non responders, and ethics of not treating patients because of the need for controlled studies or because of the existence of predictors of poor therapeutical response. Since most Caucasian children will spontaneouly clear HBeAg before adulthood and become adult healthy HBsAg carriers a next step will be to determine predictive factors of (early or late) progression to "severe" liver disease. Treatment restricted to "only" this category of patients might be more rewarding than either universal treatment or treatment targetted to patients with predictive factors of an accelerated response.

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