

TREATMENT OF CHRONIC HEPATITIS B IN CHILDREN

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ABSTRACT

- ◆ Chronic hepatitis B virus infection acquired perinatally or during the first years of life is usually associated with mild liver disease throughout childhood and adolescence, but clinical observations suggest that progression to severe disease may occur in adult life in a yet unknown proportion of cases.
- ◆ Thus the rationale of treating children with chronic hepatitis B would rather be the prevention of future complications than the urgency of improving liver disease.
- ◆ Interferon (IFN) alfa is the single drug approved by regulatory agencies for the treatment of chronic hepatitis B in childhood. The data of randomized controlled studies indicate that IFN increases significantly the rate of spontaneous HBeAg clearance (30% versus 12%) and HBsAg clearance. The limits of IFN treatment are: poor effect in children with low-normal ALT, numerous side effects, parenteral administration and costs.
- ◆ Lamivudine monotherapy has been compared to placebo in a large controlled randomized study. After one year of daily oral assumption 23% of children had cleared HBeAg, but 19% had developed resistant HBV mutants. Further follow-up is needed to allow conclusions on lamivudine monotherapy which, at present, could be indicated only for children with persistently high ALT levels who did not respond or cannot be treated with IFN.
- ◆ Trials with the combination of lamivudine and IFN are under way and preliminary results seem to be encouraging.

Reasons for Treating and Endpoints of Therapy

Chronic hepatitis B is now a preventable disease thanks to the efficacy of HBV vaccine. In highly endemic areas vaccination campaigns, primarily addressed to infants and adolescents, have drastically reduced the prevalence of infection in these age groups¹. On a worldwide basis, however, the reservoir of infection is maintained by children born in areas without adequate vaccination policies, by children infected prior to vaccination campaigns and by the small percentage of cases who acquire infection despite HBV prophylaxis. Thus a consistent pool of chronically infected children still needs management and care.

The clinical management of chronic hepatitis B is best approached from an understanding of the natural history of the disease. In adult patients chronic hepatitis B is known to carry a significant lifetime risk of cirrhosis and hepatocellular carcinoma². These "hard outcomes" have strongly encouraged therapeutic investigation.

In children and adolescents two major patterns of chronic HBV infection have been recognized: 1) infection acquired at birth is usually asymptomatic and characterized by a prolonged immunotolerance phase: 85% of babies infected prior to vaccination in Taiwan were still HBeAg positive by the age of 15 years³. In the same area, prospective studies in adult patients, probably infected at birth, described a prolonged immunoclearance phase, lasting up to the age of 40^{4,5}. This phase was characterized by repeated bouts of ALT exacerbation worsening the prognosis of liver disease. 2) the second pattern is typical of intermediate endemicity areas, where infection is preferably acquired horizontally during the first months or years of life. The tolerance phase is shorter or does not exist, and long-term studies in different countries (Italy and Spain, Alaska) have recently shown that approximately 70 to 85% of such children will spontaneously become

inactive HBV carriers before adulthood.⁶⁻⁸ This latter condition is stable over the years, but many patients retain low levels of viremia, as detected by the polymerase chain reaction⁹. This finding is consistent with the possibility of late reactivation of virus replication or with persistence of low grade liver damage, which could be exacerbated by cofactors such as alcohol and drugs, operating in adult life.

Severe hepatitis, cirrhosis and hepatocellular carcinoma, as well as selection of HBV mutants leading to anti-HBe positive hepatitis have been reported in most series, but can be considered infrequent patterns of pediatric HBV infection among both vertically and horizontally infected children 10-12.

Taken together these data indicate that chronic hepatitis B is essentially a mild disease throughout childhood and adolescence, but complications can be expected in adult life, especially among perinatally infected subjects. As a consequence, the rationale for treating children with chronic hepatitis B would be the prevention of late complications rather than the urgency of improving liver disease. Thus far, the goal of treatment has been to induce or speed the transition from a phase of active virus replication to the inactive carrier state, eventually followed by eradication of infection. The short-term endpoints of treatment have been: HBV DNA clearance (by hybridization techniques), HBeAg loss and subsequent anti-HBe seroconversion, normalization of ALT, improved liver histology, and eventual clearance of HBsAg. At issue is whether a successful treatment may positively influence the outcome of infection in adult life. Interesting results come from long-term controlled studies in adults with chronic HBeAg positive hepatitis treated with IFN. Over a follow-up period lasting up to 7-11 years the risk of developing HCC or end-stage liver disease was lower in treated than in untreated patients 13-15. Given the limited efficacy of the drugs available today, and the mild disease encountered in most pediatric patients, the urgency of treating children with chronic hepatitis B has been questioned 16,17. Rather than discouraging treatment, however, the limits of current therapeutic resources should prompt a revision of the past experience, taking advantage of what we have learned from IFN and lamivudine trials to improve the quality of forthcoming studies.

IFN: The Lesson of Clinical Trials

The first therapeutic trials with this immunomodulant-antiviral drug were started in the late Eighties. Since then, a number of extended papers has been published, regarding different aspects of IFN treatment in children: efficacy in clinical trials, tolerability and side effects, predictors of response and candidacy to treatment, retreatment of non-responders and associations with other drugs; cost-benefit of treatment.

Efficacy. IFN alfa is efficient in accelerating HBeAg clearance and it significantly increases the rate of HBsAg clearance.

Although many children with chronic hepatitis B have been treated - 1122 cases reported by 18 European groups in 1999 18 and 1688 recorded in Poland between 1990-97 19 - the evaluation of efficacy relies on few therapeutic trials fulfilling more stringent experimental criteria. We revised 9 studies 20-28 which were full published controlled and randomized, and performed a meta-analysis with regard to treatment efficacy. HBeAg clearance at the end of follow-up was considered the major endpoint of treatment. Table 1 shows number of cases, treatment schedule, duration of treatment and of follow-up in each of the trials. Two studies involved exclusively Chinese children^{20,21}, the remaining series were almost entirely composed of Caucasian patients, while the study by Sokal et al.²⁸ included also black and oriental children. Age ranging between 1.5 and 17 years, and positive HBeAg and HBV DNA were inclusion criteria in all studies. Increased ALT and liver histology were not entry criteria for Chinese children. Post-treatment liver biopsy was not available. The heterogeneity of the sample and the methodological limits clearly introduce several biases in the evaluation of these studies. Overall 465 children either receiving IFN alone (238) or placebo or no treatment (227) were included. Table 2 shows the rate of HBeAg clearance at the end of post-treatment follow-up: the difference between treated and untreated patients (30% vs 12%) was statistically significant. At the same time HBsAg clearance was recorded in 12 of 238 treated children, but in one of 227 untreated or placebo-treated children.

Patients who respond to treatment clearing HBV DNA and HBeAg by the end of post-treatment follow-up are likely to seroconvert to anti-HBe and to normalize ALT during the subsequent months, and to persist in this

status thereafter. The medium-term prognosis of infection and disease in children with chronic hepatitis B treated with IFN has been investigated in a series of 107 children belonging to two controlled studies, and compared to that of 59 related controls 2829. After 5 years the proportion of treated children with sustained HBeAg clearance was similar in responders and non responders and did not differ from that of untreated controls. These data suggest that, at least in European children, IFN simply accelerates the spontaneous HBeAg clearance. HBsAg loss, however, was significantly more frequent in treated children who were early responders; thus treatment favors the eradication of infection in this subgroup of patients.

Predictors of response. Epidemiological, clinical, serological and histological criteria supporting the decision to treat or not to treat a child with chronic hepatitis B are highly desirable. The results provided by clinical trials are rather heterogeneous probably in relation to the small sample size, the different rate of perinatal infection, and the different duration of follow-up. High ALT levels were significantly associated with response to treatment in 3 of 5 controlled randomized trials 24-26 and, on the other hand response to IFN was poor in Chinese children with normal transaminases 20, 21. HBV DNA levels lower than 1.000 pg/ml or lower than 175 pg/ml, respectively, were recognized as significant predictors in 2 studies 25-27. Female gender was the single parameter of statistically significant value obtained in the largest study by Sokal et al. 28 Ruiz-Moreno et al. 30 pooled the results of 3 randomized trials including 50 children treated in their unit, and found that response to IFN was significantly correlated with high ALT levels, low HBV DNA levels, and a higher score for histological activity.

No definite data have emerged to indicate that high doses of IFN (10MU/m²) are better than standard doses (5MU/m²) or that better results can be obtained prolonging treatment. Recently Comanor et al. 31 proposed a statistical model, based on the paper by Sokal et al. 28 to evaluate the chances of response to IFN or of spontaneous anti-HBe seroconversion and found that female gender, dose of IFN and low HBV DNA levels were predictors of response to treatment, while high ALT levels predicted spontaneous seroconversion.

Other therapeutic experiences with IFN. The efficacy of IFN treatment preceded by a short course of corticosteroids, in an attempt to increase ALT levels after withdrawal, has been evaluated in controlled and uncontrolled studies 21,24,27,32,33. All but one of the authors failed to demonstrate any advantage with this schedule.

IFN beta and gamma, and the association of IFN with levamisole have been experimented without evidence of additional benefit 34-36. Also retreatment of non responders with IFN proved to be inefficient in a controlled study 37.

Side effects. Side effects are frequent in children with chronic hepatitis B during IFN treatment, but fortunately they are rarely severe enough to require withdrawal of treatment 38. The most frequent are fever and flu-like syndrome which appear in more than 80% of cases during the first weeks after starting treatment. Neutropenia is the most frequent cause of dose reduction. Vegnente et al. 39 and Gottrand et al. 40 investigated the influence of IFN on the nutritional status of children with chronic viral hepatitis and found that weight loss was the rule during therapy. Few months after cessation of IFN, however, weight normalized. Comanor et al. 41 showed that children's growth was temporarily disrupted during IFN treatment, although children with chronic hepatitis B could have a compromised growth even in the absence of treatment.

Cost-benefit analysis of IFN treatment.

IFN treatment is expensive. In 1997 Jacques and Olson 42 calculated the cost per year of life saved by alpha interferon therapy for three cohorts of patients with chronic hepatitis B treated at 2, 12 and 25 years, and concluded that IFN is cost-effective especially in young children because of the low dose required and the long life expectancy. However, the risk of severe complications was calculated applying the annual rates observed in adults, and this could be misleading since the long-term outcome of HBV infection acquired early in life is only partially known.

IFN: How to Use It.

In spite of its limits (a minority of patients are responders, side effects are frequent, treatment is expensive), IFN alfa is currently the only drug approved by regulatory agencies for the treatment of children with chronic

hepatitis B. A consensus advice based on experience of European pediatricians and hepatologists published in 1999 18 indicated that candidates to treatment should be children aged 2 years or more, HBeAg positive, HBV DNA positive at “intermediate-low levels”, and with abnormal ALT. Children with normal ALT should not be treated. A decisional cut-off value for ALT has not been established, however values of twice the normal or lower would suggest the delay of treatment. Children with normal or low ALT levels should enter a regular follow-up and should be considered for treatment after significant increase of cytotoxicity (not leading to spontaneous seroconversion within 12 months). A liver biopsy is desirable before treatment to support the clinical diagnosis and evaluate the stage of the disease. The recommended regimen of IFN α is 5 or 6 MU/m² thrice weekly given subcutaneously for 6 months. Clinical and biochemical monitoring should be performed two weeks after starting treatment and then monthly up to six months after stopping treatment. Virologic parameters should be checked at the end of treatment and at the end of follow-up. Neutropenia is the most frequent cause of dose reduction, but rarely requires therapy withdrawal. ALT increase during treatment is common, especially prior to HBeAg clearance, but IFN withdrawal is indicated only in the presence of a sharp flare. Side effects are generally well controlled.

Lamivudine: A Recent Experience

Lamivudine is a nucleoside analogue that inhibits HBV DNA replication by termination of the nascent proviral DNA chain. It is administered orally and is very well tolerated. In 4 controlled trials in adults, a one-year course of lamivudine at a daily dose of 100 mg induced HBeAg loss in 17% to 33% as compared to 11% in controls 43-46. Extension of treatment up to 5 years increased the response rate 47,48. There are, however, two major limitations in the use of this potent antiviral drug:

- ◆ lamivudine cannot clear stable pre-existing cccDNA, thus recurrence of virus replication after therapy withdrawal is frequent, unless sustained anti-HBe seroconversion has been achieved. The reappearance of HBV DNA in serum may be accompanied by an ALT flare 49.
- ◆ Long term treatment can induce viral resistance through the selection of mutants in the YMDD motif of the HBV polymerase 50. The consequence is usually the reappearance of virus replication and of increased ALT despite continuation of therapy.

Lamivudine has been recently used in children with HBeAg positive chronic hepatitis B in small pilot studies and in a large international randomized and controlled study 51: 191 children received lamivudine at the dose of 3mg/kg daily, according to a previous dose finding study 52, and 97 received placebo for 12 months. At this time HBeAg loss (complete virological response) was observed in 23% of treated children and in 13% of controls, with rates of 34% and 16%, respectively, in children with baseline ALT levels greater or lower than twice the normal. YMDD variant HBV was detected in 19% of treated patients at week 52. A follow-on study of these children is under way. Treatment has been safe and well tolerated.

Combination therapy with lamivudine and IFN has been recently investigated with interesting, but not univocal, results⁵³. Preliminary data in children seem promising⁵⁴.

Lamivudine: Current Use

The information on the efficacy, treatment duration and adverse events of lamivudine in children with chronic hepatitis B is too limited to allow conclusions. The percentage of responders after one year of treatment seems to be similar or even lower than the average value reported with a 6-month course of IFN. Akin to IFN, lamivudine monotherapy is effective especially in patient with high ALT levels. At present, then, it seems reasonable to limit the use of lamivudine monotherapy to those few cases with high ALT and severe histological lesions, who did not respond, or cannot be treated with IFN. Therapy withdrawal and selection of YMDD mutants require careful clinical and biochemical monitoring of the patients.

Conclusions

Only α IFN has been approved for the treatment of children with chronic hepatitis B. A 6-month course of IFN at a dose of 5-6 MU/m² thrice weekly is efficient in children with high ALT values and low viremia levels.

Lamivudine monotherapy is well tolerated, but its efficacy is also limited to children with high ALT levels, and the development of resistant HBV mutants has to be weighed cautiously. There are currently no drugs to treat children with normal ALT and high viremia levels who are expected to maintain long-lasting virus replication. Studies investigating different regimens of combination of lamivudine and IFN are under way in adults and children. Other nucleoside analogues are currently investigated in adult patients.

Table 1. Regimens of treatment and follow-up in 9 controlled randomized trials of alfa interferon in children with chronic hepatitis B

Author	Cases (n)	Schedule	Duration of Therapy	Duration of Follow-up*
Lai 20	12 12	IFN (2.5 MU -) 10MU/m2 TIW Placebo	12 weeks	15 mo
Lai21	31 29 30	PDN x 6 weeks+IFN 5MU/m2 TIW IFN 5MU/m2 TIW placebo	16 weeks 16 weeks	18 mo
Ruiz- Moreno 22	12 12	IFN 10MU/m2 TIW Untreated	3 mo	15 mo
Ruiz- Moreno 23	12 12 12	IFN 10MU/m2 TIW IFN 5MU/m2 TIW Untreated	6 mo 6 mo	9 mo
Utili 24	10 10	IFN 3MU/m2 TIW Untreated	12 mo	6 mo
Barbera 25	21 19 39	IFN 7.5 MU/m2 TIW IFN 3 MU/m2 TIW Untreated	6 mo 6 mo	12 mo
Vajro 26	9 13 9	PDN x 6 weeks+IFN 10MU/m2 TIW IFN 10MU/m2 TIW Untreated	12 mo 12 mo	12 mo**
Gregorio 27	34 30 31	PDN per 4 weeks+IFN 5MU/m2 TIW Placebo + IFN 5MU/m2 TIW untreated	12 weeks 12 weeks	18 mo
Sokal 28	70 74	IFN 6MU/m2 TIW untreated	24 weeks	24 weeks

* the duration is the same for all arms of each study

** follow up results analysed at 12 mo and at 24 mo.

Table 2: Proportion of treated and untreated patients who clear HBeAg at the end of follow-up in the 9 controlled randomized IFN trials. Odds ratio (OR) calculated by Peto's meta-analysis (Yusuf S, et al. Prog. Cardiovasc Dis 1985 ;27 :335-71).

Author	Treated Children	Untreated Children	OR (95% CI)	P value
Lai 20	1/12	1/12	1.0 (0.0-17.0)	.47
Lai 21	1/29	0/30	7.6 (0.1-99.9)	.49
Ruiz-Moreno 22	4/12	3/12	1.4 (0.2-8.2)	1.00
Ruiz-Moreno 23	11/24	2/12	3.4 (0.8-14.1)	.14
Utili 24	2/10	1/10	2.1 (0.1-23.0)	1.00

Barbera 25	10/39	5/37	2.1 (0.6-6.5)	.18
Vajro 26	7/12	2/9	4.1 (0.74-22.4)	.10
Gregorio 27	12/30	5/31	3.2 (1.1-9.7)	.04
Sokal 28	23/70	8/74	3.6 (1.6-8.1)	.001
Pooled	71/238	27/227	2.9 (1.8- 4.6)	.0001

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