

# A controlled trial of high dose interferon, alone and after prednisone withdrawal, in the treatment of chronic hepatitis B: long term follow up

V Perez, J Findor, H Tanno, J Sordá

## Abstract

This study was designed to evaluate the safety and effectiveness of high dose interferon, with or without prednisone pretreatment, in patients with chronic hepatitis B. Patients were randomised to two treatment groups: group I (n=26) received six weeks of prednisone followed by a two week, drug free period, and then 10 million units (MU) of interferon alfa-2b three times weekly subcutaneously for 16 weeks; group II (n=24) were used as controls for 24 weeks and then treated with interferon. Loss of hepatitis B e antigen (HBeAg) and hepatitis B virus (HBV)-DNA, with a return to normal alanine aminotransferase (ALT) activity, was seen in 16 of 26 group I patients (61.5%), in one group II patient (4.2%) during the control phase, and in 13 of 23 group II patients (56.5%) after interferon. Three of 26 (11.5%) in group I and one of 23 (4.3%) in group II eliminated the surface antigen (HBsAg). There were no statistically significant differences in response between groups I and II. Liver biopsies carried out in 20 patients showed that responders had a noticeable reduction in inflammation and disappearance of core antigen in liver tissue, changes not seen in non-responders. On long term follow up (four years), nine out of 28 responders (32.1%) eliminated HBsAg, and four initial non-responders had a late seroconversion.

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Despite numerous clinical trials, the optimal dose and duration of interferon treatment in chronic hepatitis B has not yet been determined. Several factors are known to influence the response to interferon, such as age, sex, race, duration of disease, alanine aminotransferase (ALT) activity and hepatitis B virus (HBV)-DNA values, HBV variants, and the immunological status of the patient. Low doses of interferon (for example 1.5 million units (MU) thrice weekly) or short courses of treatment (for example one month) have not been effective<sup>1</sup>; doses of 50 MU have been tried but have not been well tolerated.<sup>2</sup>

A large multicentre and multinational study has shown that interferon 10 MU three times weekly for three to six months has a greater efficacy than lower doses.<sup>3</sup> Our randomised,

controlled trial was designed to evaluate the efficacy and safety of high doses of interferon.

## Methods

The study included 53 patients with documented hepatitis B e antigen (HBeAg) and HBV-DNA positivity for at least six months, who had serum ALT activities at least 1.5 times the upper normal limit. Their liver biopsy specimens before treatment were compatible with chronic hepatitis; patients with other causes of liver disease were excluded.

Patients were randomised to two groups (ALT and HBV-DNA were not matched in the two groups). Patients in group I received decreasing doses of prednisone (60, 40, 20 mg daily) every two weeks, followed by two weeks' rest. Interferon alfa-2b (INTRON A, Schering-Plough Corporation) 10 MU three times weekly was then administered subcutaneously for 16 consecutive weeks. Patients in group II were followed without treatment for 24 weeks (control period) and then interferon alfa-2b was given in the same dose and for the same duration as in group I. Both groups were followed for 24 weeks. Efficacy was determined by HBeAg and hepatitis B surface antigen (HBsAg) seroconversion, a return to negative of HBV-DNA, ALT normalisation, and histological activity as measured by the Knodell index score. Safety was determined by assessing the number and type of adverse reactions, reduction of doses, and rates of withdrawal.

## Results

### VIROLOGY AND BIOCHEMISTRY

Interferon (10 MU three times weekly) produced a sustained inhibition of HBV replication in more than half the patients. The results are summarised in Table I. In group I, 16 of 26 patients (61.5%) had lost HBeAg and HBV-DNA and their ALT had returned to normal at the end of interferon treatment. Only one patient in group II seroconverted during the control period, but 13 of 23 (56.5%) eliminated HBeAg and HBV-DNA after treatment with interferon. Three patients (11.5%) in group I and one patient (4.2%) in group II also lost HBsAg after treatment.

Hospital de Clínicas,  
Buenos Aires Medical  
School,  
Buenos Aires,  
Argentina  
V Perez  
J Findor  
J Sordá

Clínica de Hígado and  
Rosario Medical  
School,  
Rosario, Argentina  
H Tanno

Correspondence to:  
Dr V Perez,  
Hospital de Clínicas,  
Buenos Aires Medical  
School,  
Buenos Aires, Argentina.

TABLE I *Virological and biochemical results in groups I and II at the end of treatment*

Patients	No	HBeAg (-)	HBV-DNA (-)	HBsAg (-)	Anti-HBe (+)	ALT WNL
Group I	26	16 (61.5%)	16 (61.5%)	3 (11.5%)	14 (53.8%)	16 (61.5%)
Group II (control period)	24	1 (4.2%)	1 (4.2%)	0	0	1 (4.2%)
Group II interferon	24	13 (56.5%)*	13 (56.5%)	1 (4.2%)	11 (45.8%)	13 (56.5%)

\*Of 23 patients (one patient seroconverted spontaneously in the control phase).

#### HISTOLOGY

Twenty patients underwent a second liver biopsy at the end of treatment. There was a marked reduction of inflammation in seroconverted patients while fibrosis remained unchanged (Table II). Hepatitis B core antigen (HBcAg) in liver cells disappeared in all but one of the responding patients. In contrast, inflammation remained the same in non-seroconverted patients, and in all but one case HBcAg remained positive. Fibrosis was unchanged before and after treatment in both groups.

#### EVOLUTION OF ALT AS PREDICTOR OF RESPONSE

Patients in group I who seroconverted started with higher ALT values compared with those who did not (Table III); when prednisone was given, the decrease was marked, and after withdrawal the peak was very high. In contrast, patients who did not seroconvert started with a lower ALT activity, and the reduction in ALT during prednisone treatment and the rebound after withdrawal were modest.

#### RESULTS IN PRETREATED PATIENTS

Eight of the patients included in this study (six from group I and two from group II) were non-responders to a previous course of treatment. Five of these seroconverted in the present trial, four from group I. Four of the seroconversions occurred late, at months 12, 12, 14, and 20, respectively.

#### SIDE EFFECTS

Side effects experienced during the first few weeks of the study included fever, myalgia,

herpes infection, and diarrhoea. Leukopenia, chronic asthenia, loss of appetite, depression, hair loss, impotence, and paraesthesia developed later in the course of treatment.

In general, treatment was well tolerated. Side effects were mild or transient and did not necessitate a reduction in dose in most patients. Nevertheless, in four patients (two from group I and two from group II) the dose of interferon was reduced to 5 MU three times weekly because of severe side effects. The lower dose was well tolerated in these patients. One further patient stopped treatment at week 10 because of intolerable side effects, and another withdrew at week 12 as a result of severe tachyarrhythmia. One patient also retired voluntarily in the first week of treatment.

#### LONG TERM FOLLOW UP

Viral markers in 49 patients were assessed four years after finishing the study. The results are summarised in Table IV. After four years, 33 (67.3%) of these 49 patients had eliminated HBeAg and HBV-DNA, and nine out of 48 (18.8%) had eliminated HBsAg. Almost one third (32.1%) of responders had eliminated HBsAg. Only one patient (a responder) died during the four year follow up, and this was a result of oesophageal carcinoma.

#### Discussion

Previous experience has shown that the treatment of chronic hepatitis B with interferon produces a sustained response in 30–60% of patients.<sup>1–5</sup> Several factors seem to influence response, such as dose, age of infection, race, sex, degree of liver lesion, baseline ALT and HBV-DNA values, immunological status, sexual habits, appearance of HBV with mutation in the pre-core region, and association with other viral infections such as HIV, hepatitis delta virus (HDV), and hepatitis C virus (HCV).

In this study, a sustained inhibition of HBV replication was seen in 61.5% of patients in group I and in 56.5% of patients in group II. Since these results are at the upper end of the spectrum as regards good responses, an explanation for these favourable effects should be found. Firstly, a dose of 10 MU interferon three times weekly was given for 16 weeks. This dose of 30 MU a week has been shown previously to produce the best response, given either as 10 MU three times weekly or 5 MU daily.<sup>6</sup> Secondly, our patients were white, and most were middle aged. It has been shown that

TABLE II *Results of liver biopsies before and after treatment*

	Seroconverted (n=11)			Non-seroconverted (n=9)		
	Inflammation	Fibrosis	Nuclear HBcAg +ve	Inflammation	Fibrosis	Nuclear HBcAg +ve
First biopsy	8.2	2	11/11	7	2.7	9/9
	p<0.01	NS		NS	NS	
Second biopsy	3.2	2.3	1/11	3.3	3.3	8/9

Probability determined by Student's *t* test.

TABLE III *Evolution of alanine aminotransferase activity (ALT) during the prednisone phase\**

	ALT values (IU/l)	
	Responders 10/17	Non-responders 7/17
Pretreatment	200	100
ALT fall during prednisone treatment	-140	-20
ALT peak after prednisone withdrawal	+200	-20

\*n=17, subgroup of group I (patients in the trial conducted by Perez).

TABLE IV *Long term follow up of viral markers: four years after treatment withdrawal*

Elimination of HBeAg and HBV-DNA:	
At the end of treatment	29/49 (59.2%)
After 4 years	33/49 (67.3%)
Elimination of HBsAg:	
At the end of treatment	4/49 (8.2%)
After 4 years	9/48 (18.8%)
Elimination of HBsAg in responders:	
At the end of treatment	4/29 (13.8%)
After 4 years	9/28 (32.1%)

white patients respond better than Asian patients, probably because most of the patients from southeast Asia acquire the disease at birth or early childhood when immunotolerance perpetuates the viral infection.<sup>7</sup> In addition, there was a predominance of chronic active hepatitis (39 out of 53) *v* chronic persistent hepatitis (six out of 53) and cirrhosis (eight out of 53) in our patient population. Patients with chronic active hepatitis are more likely to respond than those with chronic persistent hepatitis, as there is little immunological response in the latter. The inclusion of many cirrhotic patients in a previous trial yielded poor results, since high doses of interferon are not tolerated well by patients with impaired liver function.<sup>8</sup> A small proportion of the patient population was homosexual (seven out of 46). This may have had a favourable effect on the response rate, as homosexuals are known to be bad responders,<sup>9</sup> especially those who are immunocompromised.<sup>10</sup> It is known, however, that women respond better than men,<sup>11</sup> and there was a predominance of men in this study.

There is a consensus that baseline ALT values are good predictors of response.<sup>1 6 11</sup> In both groups, the mean baseline ALT was greater than 100 IU/l. Baseline ALT values in responders were higher than those in non-responders (200 *v* 100). During prednisone treatment, the reduction in ALT was greater (-140) in responders than in non-responders. These changes in ALT are an expression of the differences in immunocompetence and, in our study, changes were one of the best predictors of response. There were no significant differences between the response rates of patients in groups I and II; that is, in patients given prednisone followed by interferon or interferon alone. This is in contrast to other studies which have shown better results in patients with previous prednisone treatment when baseline ALT values were less than 100 IU/l.<sup>12 13</sup>

Analysis of the liver biopsy specimens before and after treatment showed a noticeable reduction in the necroinflammatory component (Knodell score) in seroconverted patients. In most, chronic active hepatitis changed to chronic persistent hepatitis, and HBcAg disappeared in all but one case. Fibrosis was unchanged before and after treatment in both groups. The biopsy specimen after treatment showed no significant changes in nonresponders, and core antigen remained positive in all but one case. There was very good correlation between elimination of HBcAg and the return to normal of ALT. No patients were HBeAg-negative and HBV-DNA-positive, in contrast with the high frequency of pre-core mutants reported from the Mediterranean countries.<sup>14 15</sup>

Eight patients included in our study were non-responders in a trial that had been performed more than one year previously; five of these seroconverted in the present trial. Four of the seroconversions occurred late, after at least 12 months of follow up. While it is not known whether this late seroconversion was

spontaneous or induced by interferon, it does encourage us to give non-responders more than one chance to respond to treatment. Other investigators have also reported delayed seroconversion.<sup>16</sup>

Four years after finishing the trial, a study of viral markers showed that nine out of 28 (32.1%) seroconverted patients had eliminated HBsAg. Other studies have shown similar results in up to 61% of cases after seven years of follow up.<sup>17 18</sup> In most patients, the elimination of HBsAg was accompanied by HBV-DNA negativisation, as shown by polymerase chain reaction (PCR).

Previously, repeat liver biopsy has shown a noticeable regression of histological lesions, even in the cirrhotic stage.<sup>19</sup> In our study, a small proportion of patients remained HBV-DNA-positive by PCR and showed evidence of mild liver disease on liver biopsy specimen. There were no recurrences of liver disease during the trial, although at the third year of follow up one patient developed jaundice, an increase in transaminases, reappearance of HBeAg and HBV-DNA, with negative HCV and HDV tests. The recurrence lasted around three months, then the patient developed a spontaneous seroconversion with a return to normal ALT and bilirubin. Previous studies have shown that reactivation occurs in a small proportion of patients and can vary in intensity from mild liver disease to fulminant hepatitis.<sup>20</sup>

### Summary and conclusions

Interferon alfa-2b, 10 MU three times weekly for 16 weeks induced a sustained inhibition of HBV replication in 56.5–61.5% of cases. In this study, there was no difference in the rate of seroconversion between patients treated with prednisone followed by interferon alfa-2b and those treated with interferon alfa-2b alone. Seroconversion was associated with clearance of HBV-DNA and histological improvement; HBsAg disappeared in 4.2–11.54 of cases. Five of eight patients who had been non-responders to an earlier course of interferon, seroconverted in the present trial. Responders had characteristically higher ALT activities than non-responders before treatment. Under prednisone treatment, significant reductions in ALT activities were followed by a noticeable peak on withdrawal. The changes seen in non-responders were modest. The doses of interferon were, in general, well tolerated.

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