Results of long term interferon treatment in non A non B/C chronic active hepatitis

J M Métreau and the French Group for the study of NANB/C chronic hepatitis treatment

Abstract

One hundred and eleven patients with non-A, non-B/type C (NANB/C) chronic active hepatitis were randomly assigned to two groups to receive recombinant interferon alfa-2b treatment as follows: 3 million units (MU) interferon three times weekly for six months or 3 MU interferon three times weekly for the first six months, 2 MU for the next three months, and 1 MU for the last three months. At the end of treatment, the number who had responded completely was similar in both groups (47.2% in the six months group *v* 41.4% in the 12 months group). Cirrhosis was found to be the only predictive factor for response; a complete response was observed in 50.6% of patients without cirrhosis *v* 33.3% of those with cirrhosis ($p=0.04$). After one year of treatment, the rate of relapse was lower in patients who had received longer treatment (33%) than in those who had received six months of interferon (60%). The difference between the groups was not statistically significant and the trend favouring longer treatment for sustained response requires further confirmation.

(Gut 1993; supplement: S112-S113)

Several recent studies of patients with chronic non-A, non-B/type C (NANB/C) hepatitis have shown that six months' treatment with alpha interferon produced a return to normal serum aminotransferase activity in about 50%.¹⁻⁴ Unfortunately, the relapse rate at the end of treatment varied from 50-90%.¹⁻² Thus, the optimal dose and duration of interferon treatment in NANB/C chronic active hepatitis is still not clearly defined.

This French multicentre study aimed to compare the efficacy of 12 months of interferon treatment with six months of treatment to determine whether longer periods of treatment can (a) increase the response rates; and (b) reduce the frequency of relapse.

Patients and methods

The study included 120 patients from 12 different centres, randomly assigned to two groups. Patients fulfilled all of the following criteria: history of parenteral exposure (transfusions in about 80% of cases); serum alanine aminotransferase (ALT) value greater than 1.5 times the upper limit of normal for at least one year; absence of serum hepatitis B surface antigen (HBsAg), hepatitis B virus (HBV)-DNA and human immunodeficiency virus (HIV); absence of any other cause of chronic liver disease or severe hepatic failure, or both; histologically proved chronic active hepatitis (Knodel score ≥ 6). After randomisation and before day 0, nine patients were excluded because they did not fulfil all inclusion criteria. Thus, only 111 patients were studied.

Group I (53 patients) received six months' treatment with recombinant interferon alfa-2b (INTRON A, Schering-Plough) 3 million units (MU) subcutaneously three times a week. Group II (58 patients) received 12 months' therapy with interferon 3 MU three times weekly for the first six months, 2 MU for the next three months, and 1 MU for the last three months.

Serum ALT determinations were performed every month during follow up to 18 months – that is until 12 months after the end of treatment in group I and six months in group II. A liver biopsy was performed in all the patients before treatment and at the end of follow up. This paper reports only the results observed for serum ALT, as the histological study is still under investigation.

A complete response to interferon alfa-2b was defined as a return to normal of serum ALT values at the end of treatment, partial response as a more than 50% decrease in ALT compared with day 0 without a return to normal, and no response as a serum ALT that remained high (more than 50% of the value at day 0) at the end of treatment. In complete responders, relapse was defined as a return to abnormal serum ALT values within six months of the end of treatment.

Results

The baseline characteristics of patients are summarised in Table I. The two groups were similar with regard to age, sex, anti-hepatitis C virus (HCV) antibodies, initial ALT value, Knodel score, and cirrhosis.

During the study, interferon treatment was withdrawn because of side effects in four patients (two in group I for thrombocytopenia and hyperthyroidism, and two in group II for diarrhoea and acute cholecystitis leading to an operative death). These four patients, as well

Service d'Hépatologie
et de
Gastroentérologie,
Hôpital Henri Mondor,
94010 Créteil, France
J M Métreau

Correspondence to:
Dr J M Métreau,
Service d'Hépatologie et de
Gastroentérologie,
Hôpital Henri Mondor,
94010 Créteil, France.

TABLE I Baseline characteristics of the 111 patients with non A, non B/C chronic active hepatitis

	Group I (n=53)	Group II (n=58)	Difference between groups
Age (y) (mean (SD))	48.8 (15.8)	47.4 (14.0)	NS
Sex ratio (M/F)	33/20	35/23	NS
Anti-HCV positive (%)	82.2	84.5	NS
Alanine aminotransferase at day 0 ($\times$ ULN) (mean (SD))	5.1 (4.5)	4.4 (2.7)	NS
Knodel score at day 0 (mean (SD))	10.2 (3.2)	9.7 (2.4)	NS
Cirrhosis at day 0	15 (28.3%)	21 (36.2%)	NS

ULN=upper limit of normal

TABLE II Results at the end of interferon alfa-2b treatment (six months for group I, 12 months for group II)

Response	Group I (n=53)	Group II (n=58)	Difference between groups
Complete*	25 (47.2%)	24 (41.4%)	NS
Partial†	8 (15.1%)	8 (13.8%)	NS
None	20 (37.7%)	26 (44.8%)	NS

*Normal alanine aminotransferase (ALT) at the end of treatment.

†More than 50% decrease in ALT compared with day 0, without normalisation at the end of treatment.

TABLE III Relapse rates in complete responders, six months after the end of treatment

	Group I at 12 months (n=25)	Group II at 18 months (n=24)	
Number of relapses	15 (60%)	8 (33%)	p=0.06 (NS)

as four other patients who were lost during the follow up, were included in the efficacy analysis and were considered as non-responders.

The overall results at the end of interferon treatment are shown in Table II. As can be seen, there was no statistically significant difference in the response to interferon treatment between the two groups. Complete response was achieved in 47.2% of patients in group I and 41.4% in group II.

Age, sex, initial serum ALT value, initial Knodell score, presence of anti-HCV antibodies, and cirrhosis were studied as possible predictive factors for a complete response to interferon treatment. These factors were tested in both groups after six months of treatment, a point in the trial where all patients had received the same dose of interferon (3 MU three times weekly). Cirrhosis was found to be the only significantly predictive factor for response: complete response to treatment was more frequent in patients without cirrhosis (38 of 75, 50.6%), than in those with cirrhosis (12 of 36, 33.3%) ($p=0.04$). Age (more or less than 40 years), sex, initial serum ALT values, Knodell score, and presence of anti-HCV antibodies were of no prognostic value.

A comparison of relapse rates in the two groups six months after the end of treatment is shown in Table III. In group I, 15 of the 25 complete responders (60.0%) relapsed compared with eight of the 24 complete responders (33.3%) in group II. Although there was a tendency for patients treated for one year to relapse less frequently than those treated for six months, the difference did not reach statistical significance ($p=0.06$).

At the end of follow up – that is 18 months after beginning interferon therapy – serum ALT values remained normal in seven of the 53 patients in group I (13.2%) and in 16 of the 58 patients in group II (27.6%). As with the rate of relapse, there was a tendency favouring the longer treatment, but this trend did not achieve statistical significance ($p=0.07$).

Discussion

In this multicentre study, the 12 month treatment regimen seemed to offer no therapeutic advantage over the six month regimen in terms of response rate. The number

of complete responders in group II (41.4%) was not greater than the number in group I (47.2%). This rate of complete response at six and 12 months is similar to previous reports for six months of treatment.¹⁻⁴ In addition, in a previous uncontrolled study, the number of complete responders after one year of treatment was 58%.⁵ The results from this study, carried out on a small number of patients ($n=30$), are not very different to those observed in our trial. Thus, it is probable that the rate of complete response is similar after six and 12 months' treatment.

Factors predictive of response to treatment are still poorly documented in NANB/C chronic infection. Conflicting reports have been published. For example, one author found that ALT activity at day 0 was a good prognostic index,² whereas others found that age, cirrhosis, or sex were the best indicators.⁴ Marcellin *et al* found no prognostic index.³ In our study, the only predictive factor for response was cirrhosis; the rate of complete response was significantly higher in patients without rather than with cirrhosis (50.6% *v* 33.3%).

As in previous reports,¹⁻⁵ relapse six months after the end of treatment occurred in about half of the patients. No significant difference in the rate of relapse was found between the two groups, but there was a tendency for fewer patients to relapse after longer rather than shorter treatment. Thus, as already suggested,⁷ a longer duration of treatment with interferon alfa-2b may not improve the complete response rate at the end of treatment, but could increase the number of patients with a sustained response – that is with normal transaminase values six months or more after the end of treatment. Additional trials are required to describe further the influence of longer term interferon treatment on the rate of relapse.

The author acknowledges the members of the French group for the study of NANB/C chronic hepatitis treatment: Y Calmus, R Poupon (Hôpital Saint Antoine, Paris), H Jouanolle (Hôpital Pontchaillou, Rennes), J P Miguet (Hôpital J Minjoz, Besançon), C Bréchet (Hôpital Laënnec, Paris), J L Payen, P Calès (Hôpital de Purpan, Toulouse), A Tran (Hôpital de l'Archet, Nice), M Beaugrand (Hôpital de la Tronche, Grenoble), M Doffoël (Hôtel Dieu, Strasbourg), E A Pariente (Hôpital la Source, Orléans), C Lemonnier (Schering-Plough, Levallois-Perret).

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