Treatment of chronic hepatitis C with recombinant interferon alfa-2b for nine months

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Abstract

This randomised, controlled trial was designed to assess the response to a nine month course of interferon (IFN) alfa-2b, starting with a higher than usual dose. Forty eight patients received IFN 5 million units (MU) three times a week for eight weeks followed by 3 MU three times weekly for seven months; 25 patients in the control group received no treatment. The overall response to treatment was 68.7%, an improvement over other studies, but the high rate of relapse (85% in patients who responded) suggested that a nine month treatment period was insufficient in most cases. Histological improvement was seen in more than 80% of responders to interferon, including a reduction in inflammatory activity, necrosis, and fibrosis.

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Alpha interferon has been shown to be effective in about 50-75% of patients with chronic hepatitis C (HCV). Most studies have used a dosage of 3 million units (MU) three times a week for six months. We have conducted a large, randomised controlled trial to assess the response to a nine month course of interferon alfa-2b (INTRON A) starting with higher doses (induction phase).

Patients and methods

Seventy five adult patients who were positive for antibodies to HCV (anti-HCV) on ELISA and RIBA-2 were randomised 2:1 to receive interferon or no treatment. Two were withdrawn in the first two months because of

vertigo and flu like syndrome. Liver biopsies were performed within three months before interferon and within one month after treatment. Pretreatment patient characteristics are shown in Table I.

Forty eight patients (33 men and 15 women) were given interferon alfa-2b subcutaneously at a dose of 5 MU three times weekly for eight weeks followed by 3 MU three times weekly for seven months. The other 25 patients (15 men and 10 women) received no treatment (control group).

Responses to treatment were defined as follows:

Complete response: return to normal of serum alanine aminotransferase (ALT) activities nine months after the start of treatment.

Partial response: decrease in ALT to less than 50% of baseline values.

No response: no change in ALT or decrease to more than 50% of baseline values.

Responses were also evaluated at eight weeks and at six months.

Results

The overall response among interferon-treated patients was 68.7% (33 of 48), including 21 (43.7%) with a complete and 12 (25%) with a partial response (Table II). In only one (4%) of the 25 control patients did serum ALT activities return to normal for two consecutive months. Among the treated patients, mean baseline ALT activities were significantly higher in the partial response than in the complete response group ($p=0.0011$, Student's t test). Mean serum ALT values according to response group are shown in Figure 1.

The decrease from a 5 MU to a 3 MU dose of interferon was followed by a twofold increase in ALT values over the next three months in 11 patients (four complete response, five partial response, and two no response). Comparing ALT values at the end of treatment with 5 MU and at the end of interferon

TABLE I Patient characteristics before treatment (*) with interferon (IFN) alfa-2b

	IFN group (n=48)	Control group (n=25)
Sex (M/F)	33/15	15/10
Mean (SD) age (y)	41.5 (13.8)	46.3 (16.6)
Age range (years)	18-65	24-65
Chronic active hepatitis	31 (64.5%)	15 (60%)
Active cirrhosis	17 (35.4%)	10 (40%)
Acute hepatitis	19 (39.6%)	8 (32%)
Risk factors:		
Blood transfusion	19 (39.6%)	9 (36.0%)
Intravenous drug abuse	7 (14.6%)	5 (20.0%)
Professional exposure	5 (10.4%)	1 (4.0%)
Tattoos	1 (2.1%)	0
Major surgery	10 (20.8%)	7 (28.0%)
Sporadic (unknown)	6 (12.5%)	3 (12.0%)
Presumed duration of infection:	(n=32)	(n=15)
≤5 years	18 (56.3%)	7 (46.7%)
>5 years	14 (43.8%)	8 (53.3%)

* No significant differences were found between the two groups (using Student's t test for quantitative variables (for example, age) and χ^2 test for proportions).

TABLE II Evolution of serum alanine aminotransferase values in interferon (IFN) treated and control patients. (Values mean(SD), (range) (IU/l))*

Response	Baseline	2 months	9 months	After IFN
Complete n=21 (43.8%)	165 (59) (69-509)	25 (10) (12-49)	26 (7) (16-40)	173 (116) (16-472)
Partial n=12 (25.0%)	316 (144) (107-569)	75 (60) (16-243)	68 (23) (42-109)	227 (203) (46-714)
No response n=15 (31.2%)	211 (189) (67-722)	140 (118) (12-474)	158 (107)† (59-366)	168 (122)† (19-506)
Control group n=25	215 (118) (83-531)	194 (87) (36-398)	223 (102) (47-564)	202 (93) (78-597)

* Normal range of serum ALT is 10-40 IU/l.

† Seven patients completed the nine months of treatment.

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Figure 1 Mean serum alanine aminotransferase (ALT) values in the three response groups. CR=complete; PR=partial; NR=no response; ULN=upper limit of normal.

treatment, four patients had changed from complete to partial response and two from complete to no response. When ALT values at months six and nine were compared, five patients had changed from a partial to complete response, and four from no to partial response.

Liver biopsy specimens were available for 39 patients at the end of treatment. Nine treated patients with chronic active hepatitis (seven complete and two partial response) evolved to four with chronic persistent hepatitis, two with chronic lobular hepatitis, and three with minimal changes. A decrease in the Knodell's

hepatitis activity index score was found in 86% of complete and 83% of partial response patients. Changes in the Knodell's index scores for global and lobular inflammation, necrosis and fibrosis fell significantly (sign test) from values before treatment in both complete and partial response patients.

The mean (SD) follow up period was 8.1 (4.1) months (range seven to 20). A rebound in ALT was found in 28 of 33 (85%) responder patients. Patients who relapsed received a second course of interferon for 12 months (1.5 to 3.0 MU three times weekly, depending on

Figure 2 Change in Knodell's hepatitis activity index score in complete and partial responders to interferon alfa-2b.

the response achieved during the first three months) and achieved similar responses to those obtained during the first course.

Conclusions

The overall response to interferon treatment was 68.7% (43.8% complete response). Induction with interferon at a dose of 5 MU three times weekly for eight weeks followed by 3 MU three times weekly for nine months improved the response rate compared with other studies using 3 MU three times weekly for six months. The high relapse rates suggest,

however, that the nine month treatment period is insufficient in most cases and should be prolonged to 12 months or more. Patients who relapse should be treated with a second course of interferon.

The decrease from 5 MU to 3 MU resulted in an increase in serum ALT activities. Nevertheless, responses at the end of the ninth month were better than those at the end of the sixth month.

Histological improvement was found in more than 80% of responding patients. Interferon alfa-2b reduced not only inflammatory activity and necrosis but also fibrosis.