Interferon alfa for chronic hepatitis C in haemophiliacs

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Abstract

Chronic hepatitis C virus (HCV) associated liver disease is an important cause of morbidity and mortality in haemophilia. Recombinant interferon alfa-2b was used in a randomised controlled liver biopsy trial to treat haemophiliacs with chronic HCV. All 18 patients entered had antibodies to HCV. During the first year of the study, 10 patients were randomised on the basis of histology to receive interferon alfa-2b, 3 million units subcutaneously, thrice weekly and eight to receive no treatment (control group). After 12 months, all patients had a second liver biopsy and the control group patients were offered interferon at the same dosage but for only six months. The alanine aminotransferase (ALT) activity had returned to normal in four of 10 patients treated for one year and five of six patients treated for six months, compared with none of the eight patients in the control group ($p < 0.01$). Although the histological scores of the two groups

were similar at entry into the study, after one year the biopsy specimens in the treated group showed significant improvement compared with controls ($p < 0.01$). It is concluded that interferon alfa-2b is effective in returning ALT values to normal and improving liver histology in at least 50% of patients treated.

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Most patients with haemophilia treated with non-virally inactivated clotting factor concentrate for the first time develop non-A, non-B (NANB) hepatitis.¹ Although the acute event is trivial, at least 50% develop chronic hepatitis and up to 20% have cirrhosis.² Chronic liver disease in haemophilia is associated with hepatitis C virus (HCV) and can be progressive, contributing to significant morbidity and mortality.^{3,4}

After encouraging reports of the treatment of NANB hepatitis with interferon in patients without haemophilia,⁵ we studied the effect of this agent in haemophiliacs, a group specifically excluded from most trials.

Patients and methods

A summary of the trial design is shown in Figure 1. Haemophiliacs with abnormal transaminase activities for at least six months were randomised on the basis of liver histology to receive interferon alfa-2b (INTRON A) or no treatment for one year. To reduce the incidence of side effects, patients were given interferon 1 million units (MU) thrice weekly for one month, 2 MU thrice weekly for the second month, and 3 MU thrice weekly for the last 10 months. At the end of this period all patients, including the controls, underwent a second liver biopsy and the control group were offered interferon 3 MU thrice weekly without dose alteration for six months.

A complete response was defined as a return to normal alanine aminotransferase (ALT) activities by the end of treatment and sustained for at least one month. A partial response was defined as reduction in the ALT value greater than 50% of the mean value before treatment to a level less than 1.5 the upper limit of normal.

Liver biopsies were scored by the scheme devised by Knodell⁶ (Knodell Scheme) as well as a local scheme (Sheffield Scheme)⁷ designed before the study and based on histological features representing disease activity.

Figure 1 Schematic outline of the trial.

TABLE I Baseline characteristics of patients entered into the study

Feature	Interferon group no (%)	No treatment group no (%)
Number	10	8
Mean age (y)	38.2	38.2
Haemophilia A	9 (90%)	6 (75%)
Haemophilia B	1 (10%)	2 (25%)
HIV antibody positive	3 (30%)	1 (13%)
Hepatitis C virus antibody positive	10 (100%)	8 (100%)
Chronic persistent hepatitis	4 (40%)	3 (37%)
Chronic active hepatitis	5 (50%)	4 (50%)
Cirrhosis	1 (10%)	1 (13%)

TABLE II Biochemical response to interferon

	Complete	Partial	No response
Treatment group (n=16)			
6 Months of interferon	4	1	1
12 Months of interferon	3	1	6
Total treated	7	2	7
Non-treatment group (n=8)	0	0	8

Results

PATIENT CHARACTERISTICS

Eighteen patients, 15 with haemophilia A and three with haemophilia B, entered the study. All had received non-virally inactivated factor VIII/IX concentrate in the past and had had abnormal liver enzyme values for many years. Four patients with asymptomatic HIV infection were included in the trial. None of the patients were hepatitis B surface antigen

(HBsAg) positive but 14 had evidence of previous exposure to hepatitis B. All 18 patients had antibodies to HCV by second generation ELISA assay with RIBA-2 confirmation. Sixteen patients tested for HCV-RNA using the polymerase chain reaction (PCR) were all positive before starting interferon. The liver biopsy undertaken at entry to the study showed chronic persistent hepatitis in seven, chronic active hepatitis in nine, and cirrhosis in two. The baseline characteristics of the two groups are shown in Table I.

SERUM AMINOTRANSFERASE ACTIVITIES AFTER TREATMENT

Nine of 16 patients treated with interferon alfa-2b achieved a complete or partial remission compared with none of the eight patients in the control group ($p < 0.01$) (Table II). Complete remission was achieved in three of 10 patients treated for one year compared with four of six treated for six months. Mean ALT values in the treated and control groups are shown in Figure 2.

FOLLOW UP AFTER STOPPING INTERFERON

Of the nine responding patients, four relapsed within one month and a fifth patient relapsed within three months. Four patients continue to have normal liver enzymes; three of these were treated with interferon for one year, and one for six months. The patients with no relapse treated for one year have been observed for 34, 33, and 27 months, while the patient treated for six months was observed for two months.

LIVER HISTOLOGY

There was no statistical difference between the scores of the initial biopsy specimens of the two groups. The histological activity score of the second specimen was significantly less in the interferon group however, compared with the untreated group ($p < 0.01$) (Fig 3). Similar results were obtained with both the Sheffield and Knodell schemes.

SIDE EFFECTS

Subcutaneous interferon was well tolerated and was not associated with bleeding problems at the injection site. Side effects observed while patients were receiving interferon included flu like symptoms in 10 patients, lethargy in three, alopecia in three, and migraine type headaches, mouth ulcers, and thrombocytopenia in single patients.

Discussion

In this study of interferon treatment in chronic hepatitis C in haemophiliacs we have shown a significant improvement in liver histology and a return to normal liver enzyme activities in more than 50% of the patients treated. Similar results have been reported by Davis *et al*⁸ and Di Bisceglie *et al*⁹ who treated

Figure 2 Alanine aminotransferase (ALT) activities in (above) patients randomised to receive interferon for one year; and (below) in the six patients randomised to the non-treatment group but who received interferon for six months after their second liver biopsy.

Figure 3 Histological activity scores at the start and after one year using the Sheffield Scheme for analysis. ●---● HIV antibody positive, ○—○ HIV antibody negative.

non-haemophilic, hepatitis C patients with interferon. We believed that a separate trial in haemophiliacs was indicated as these patients have been exposed to repeated and much heavier viral loads over a long period of time.

Most haemophiliacs treated with non-virally inactivated concentrates develop non-A, non-B hepatitis, and have been shown to have anti-HCV.³ Although, in theory, these antibodies could represent past infection, most patients have abnormal liver transaminase activities and are HCV positive by polymerase chain reaction, indicating active infection.¹⁰ We have shown that as many as 29% of HCV positive haemophiliacs have cirrhosis,¹¹ and mortality data indicate that end stage liver disease is an important cause of death in this group.¹²

Our finding that interferon alfa-2b given subcutaneously thrice weekly improves the liver histology and normalises the liver transaminase values in at least 50% of the patients treated, offers, for the first time, the opportunity to attempt to alter the natural history of chronic HCV in haemophiliacs.

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