

A Randomized Controlled Trial of Recombinant Interferon- α in Chronic Hepatitis C in Hemophiliacs

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Chronic liver disease associated with hepatitis C virus (HCV) is an important cause of morbidity and mortality in hemophilia. We have used recombinant interferon α -2b (IFN α -2b) in a randomized controlled liver biopsy trial to treat hemophiliacs with chronic hepatitis. Eighteen patients entered the study, 16 of whom were subsequently shown to have antibodies to the HCV. All underwent liver biopsy at entry and were randomized to either treatment with self-administered IFN α -2b, 3 million units subcutaneously thrice weekly ($n = 10$) or no treatment (control group) ($n = 8$). Nine subjects had chronic active hepatitis, seven had chronic persistent hepatitis, and two had cirrhosis. Twelve months after entry into the study 17 patients underwent a second liver biopsy. All biopsies were coded, assessed, and scored according to the histologic severity of the liver disease. Ten patients were administered IFN for 1 year, and in four patients normalization of alanine aminotransferase (ALT) occurred compared with none in the untreated group. After the second liver

biopsy, six of the eight initial no-treatment patients were treated with interferon 3 million units thrice weekly for 6 months, and normalization of ALT was seen in five patients. Biochemical relapse within 4 months of stopping IFN occurred in one of four patients treated for 1 year and in four of five patients treated for 6 months. IFN treatment was well tolerated. Although the histologic scores of the two groups were similar at entry into the study, after 12 months the biopsy appearances in the treated group were significantly improved compared with the controls ($P < .01$). Histologic improvement was noted in the three interferon-treated human immunodeficiency virus antibody-positive patients and also in other patients who had no biochemical response. We conclude that low-dose recombinant IFN α is effective in normalizing transaminases and improving the histologic appearances in at least 50% of hemophiliacs with chronic hepatitis C.

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OVER 90% of hemophiliacs receiving non-heat-treated factor VIII/IX concentrate for the first time develop non-A, non-B hepatitis (NANBH).¹ Although the acute event is often trivial, at least 50% develop chronic hepatitis and possibly as many as 20% may develop cirrhosis.^{2,3} We have shown previously that chronic liver disease is progressive² and may contribute to significant morbidity and mortality in hemophilia.⁴ Most chronic hepatitis in hemophilia is associated with hepatitis C virus (HCV)⁵ with hepatitis B virus (HBV) and delta agent responsible in a minority of patients.^{6,7}

Until recently there was no effective therapy for chronic NANBH, with both acyclovir and corticosteroids having been shown to be ineffective.^{8,9}

Preliminary reports have shown a beneficial effect of interferon α (IFN α) on serum aminotransferases and liver histology in both posttransfusion and community acquired "sporadic" NANBH^{10,11}; this has recently been confirmed by two large randomized trials.^{12,13} Because these studies excluded patients with hemophilia as well as human immunodeficiency virus (HIV)-positive subjects, we conducted a randomized, controlled study of IFN α in hemophiliacs with NANBH.

PATIENTS AND METHODS

Trial Design

The criteria for inclusion into the study were hemophilia, elevation of alanine and/or aspartate aminotransferase for more than 6 months or a previous liver biopsy showing chronic liver disease, and a liver biopsy on entry into the trial consistent with NANBH.⁵ Exclusion criteria were the presence of factor VIII (FVIII) or factor IX (FIX) inhibitors, clinically significant cardiomyopathy, previous exposure to IFN or other lymphokines, the presence of life-threatening disease, or significantly impaired renal or bone marrow function.

Ethical approval was obtained from the local ethical committee. Written informed consent was obtained from all patients entering the study.

After a liver biopsy all patients were stratified into three histologic groups: chronic persistent hepatitis (CPH), chronic active hepatitis (CAH), and cirrhosis. Patients in each group were randomized to receive either self-administered subcutaneous IFN α -2b (Intron A; Schering-Plough, Bury St Edmunds, UK) or no treatment for 1 year. Randomization was stratified according to the histologic classification. After 12 months in the trial a second liver biopsy was performed in 17 of 18 patients.

In an attempt to reduce IFN-associated side effects, patients received thrice weekly 1 million units for 1 month, 2 million units for the second month, and 3 million units for the subsequent 10 months. After the second biopsy, six of eight patients in the initial no-treatment group were administered IFN at 3 million units three times weekly without dose escalation for 6 months. Further biopsies were not performed on these patients.

Follow-up

Follow-up was performed at 2-week intervals for 12 weeks and monthly thereafter. This was the same for both IFN and control groups. At each visit patients had a full blood count with white blood cell differential and liver biochemical tests (aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, bilirubin, globulin, albumin) measured. At the end of 1 year the six control patients who were administered IFN were observed at 2-week intervals for 12 weeks and monthly thereafter. The rest were observed monthly for 1 year or until they relapsed as defined by increased enzymes on three occasions.

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Hepatitis C Serology

Stored samples taken before the commencement of IFN were tested using a radioimmunoassay for anti C-100 antibodies with the hepatitis C antibody test developed by the Chiron Corp (Emeryville, CA).¹⁴

Biopsy Procedure

Following baseline assessment, FVIII or FIX concentrates were administered 1 hour before the biopsy to increase the FVIII level to 1.00 U/mL (FIX to 0.80 U/mL). FVIII level was re-assayed 12 hours postbiopsy and patients were retreated to an FVIII level of 1.00 U/mL (FIX to 0.80 U/mL). At 24 hours postbiopsy levels of FVIII were increased to 1.00 U/mL (FIX to 0.80 U/mL) and at 48 hours to 0.50 U/mL for both FVIII and FIX.

Histologic Assessment

Stained sections of the liver biopsies were coded to conceal their identity with respect to patient origin, treatment group, and biopsy sequence. The liver histology was scored by one of us (JCEU) using two schemes.

Sheffield scheme. A disease activity score was derived by the summation of the unweighted scores, each on a scale of 0 to 3, of the following features: steatosis, apoptotic necrosis, piecemeal necrosis, sinusoidal infiltrates, and portal infiltrates. These features were selected before the study as being representative of disease activity in NANBH.

Knodell scheme. Biopsies were also scored by the scheme devised by Knodell et al¹⁵ for the assessment of chronic hepatitis.

Definition of Response

Complete response (CR) was defined as normalization of alanine aminotransferase (ALT) by the end of treatment sustained for at least 1 month. Partial response (PR) was defined as reduction in ALT by greater than 50% of mean pretreatment value to a level of less than 1.5 × the upper limit of normal. Temporary and nonsustained normalization of ALT during treatment was considered as failure.

Statistics

The Wilcoxon matched pairs test was used to compare biopsies at the start and end of the trial. The Mann-Whitney U test was used to compare differences between treatment and control groups. Fisher's exact test was used to compare the biochemical response in the two groups.

RESULTS

Patient Characteristics

Eighteen patients entered the study and 17 have been observed for at least 18 months. Fifteen patients had hemophilia A and three had hemophilia B (Table 1). All had received non-heat-treated FVIII/IX concentrate in the past and had abnormal liver biochemistry for many years. Four patients were HIV antibody-positive but none had HIV-related clinical features during the study. The liver biopsy on entry showed seven patients had CPH, nine had CAH, and two had cirrhosis.

None of the patients were hepatitis B surface antigen (HBsAg)-positive, but 14 of 18 had evidence of previous exposure to hepatitis B. Sixteen of 18 were positive for antibodies to HCV (anti C-100).

Table 1. Characteristics of Patients Entered in the Study

Feature	IFN Group n (%)	No-Treatment Group n (%)
Number (n)	10	8
Mean age (y) (mean ± SD)	38.2 ± 13.1	38.2 ± 5.4
Hemophilia A	9 (90)	6 (75)
Hemophilia B	1 (10)	2 (25)
HIV antibody-positive	3 (30)	1 (13)
HCV antibody-positive	3 (80)	8 (100)
CPH	4 (40)	3 (37)
CAH	5 (50)	4 (50)
Cirrhosis	1 (10)	1 (13)
Biochemistry (means ± SD)		
ALT U/L	123.6 ± 94.0	106.5 ± 45.2
AST U/L	66.5 ± 48.5	56.0 ± 31.6
GGT U/L	56.3 ± 34.6	70.9 ± 55.1
Alkaline phosphatase U/L	86.0 ± 48.5	68.5 ± 30.3
Bilirubin μmol/L	14.1 ± 5.9	14.0 ± 4.5
Albumin g/L	43.5 ± 3.3	46.0 ± 2.9
Globulin g/L	28.9 ± 4.0	31.6 ± 6.5
Histologic score (mean ± SD)		
Sheffield scheme	5.0 ± 2.6	5.3 ± 2.3
Knodell scheme	4.3 ± 3.2	5.8 ± 3.7

Normal ranges for biochemical variables: ALT 7 to 45 U/L, AST 7 to 40 U/L, GGT 6 to 45 U/L, alkaline phosphatase 35 to 105 U/L, bilirubin 1 to 20 μmol/L, albumin 35 to 53 g/L, globulin 16 to 33 g/L.

Abbreviations: AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase.

After the first liver biopsy 10 patients were randomized to receive IFN and eight to no treatment. The characteristics of these two groups were similar (Table 1).

Serum Aminotransferase Activity During Therapy

Nine of 16 patients treated with IFN achieved a CR or PR compared with zero of eight patients in the no-treatment group ($P < .01$) (Table 2). Normalization of liver enzymes occurred at a median of 4 months (range 0.5 to 10 months). CR was achieved in 3 of 10 patients treated for 1 year and in four of six patients treated for 6 months. Two patients, one treated for 12 and one for 6 months, were classified as partial responders. In one, ALT levels normalized with IFN and remained in the normal range throughout most of the 12 months of treatment, apart from a single elevation (62 U/L, normal range [NR] < 45 U/L) at 12 months. After discontinuation of IFN his ALT returned to

Table 2. Biochemical Response to IFN

	CR	PR	No Response
Treatment group			
6 mo IFN	4	1	1
12 mo IFN	3	1	6
Total treated	7	2	7
No-treatment group	0	0	8

normal and remained in the normal range for the subsequent 15 months of follow-up. The second PR patient treated for 6 months had a slightly increased ALT level at 6 months (49 U/L), but on stopping treatment the ALT decreased to normal and remained in the normal range for 18 weeks. Mean ALT values in the treated and untreated patients are presented in Fig 1.

Follow-up After Therapy

Four patients continue to have normal liver enzymes; three of these had been treated for 1 year with IFN and one for 6 months. The patients treated for 1 year have been observed for 20, 19, and 15 months, while the other patient still in CR has been treated for 6 months and only observed for 2 months. After withdrawal of treatment, rapid biochemical relapse occurred in some patients. Of the nine responding patients, four relapsed within 1 month of stopping IFN treatment and another patient relapsed at 3 months. Two patients with symptoms of chronic fatigue attributed to chronic NANBH before entering the trial improved dramatically as the liver biochemistry normalized with IFN. Their symptoms returned when they relapsed biochemically, and both were again retreated with IFN off trial. Once more their serum aminotransferases normalized and their symptoms improved at the same time.

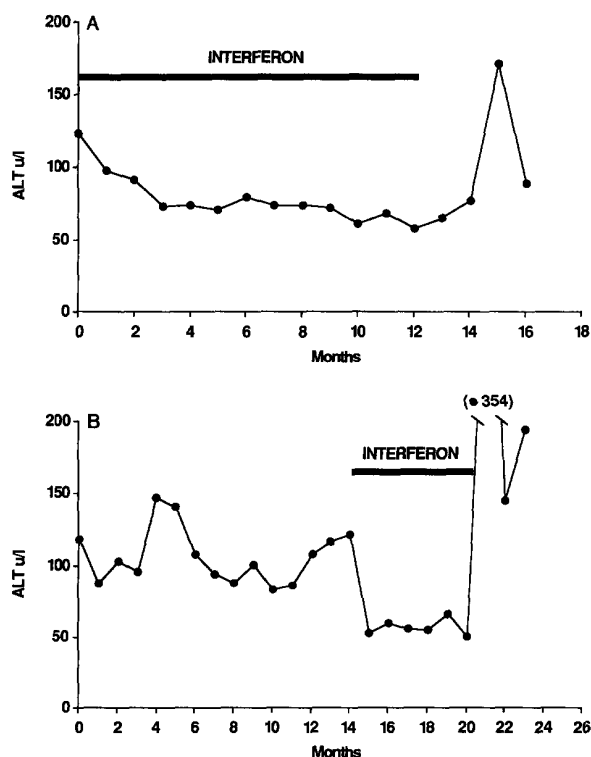


Fig 1. (A) ALT levels in the patients randomized to receive treatment with IFN for 1 year. (B) ALT levels in the six patients randomized to the no-treatment group but who received IFN for 6 months after their second liver biopsy.

Liver Histology

Seventeen pairs of liver biopsies were available for histologic assessment (nine from the treated group and eight from the nontreated group). One patient did not have a second biopsy because of thrombocytopenia (platelet count $67 \times 10^9/L$).

There was no statistically significant difference between the scores of the initial biopsies of the two groups (Table 1). However, the histologic activity score of the second biopsy was significantly less in the IFN group compared with the untreated group ($P < .01$, Fig 2). Similar findings were noted with both the Sheffield and Knodell schemes.

Using the Wilcoxon matched pairs test, no significant difference was detected between the first and second biopsies in either group of patients. (The lack of significant difference in the IFN group is due to the small number of biopsies involved and the magnitude of the deterioration in one of the patients.)

Histologic improvement after IFN treatment was also seen in patients who were HIV antibody-positive (two CPH, one CAH) as well as in individuals where the liver biochemistry was unchanged.

The liver histology deteriorated and aminotransferase levels increased in one patient receiving IFN. This patient was previously shown to have CAH and was entered in the study on the basis of this, despite the fact that the three baseline enzymes were normal; on IFN his ALT was increased but it was never higher than twice the upper limit of normal. Apart from mild alopecia this patient felt well throughout the trial.

Features Predictive of a Response to IFN

Table 3 shows the relationship of various biochemical, histologic, and serologic parameters to biochemical response to IFN. Patients were more likely to respond if they had CAH, a higher initial histologic score, and a higher baseline ALT, but the small numbers preclude statistical evaluation.

Side Effects

IFN was well tolerated and bleeding problems were not encountered at the injection sites. Ten of 16 patients treated with IFN experienced flu-like symptoms that were mild and limited to the start of treatment. They were ameliorated by the use of acetaminophen before IFN. Slow escalation of the IFN dose failed to prevent the development of flu-like symptoms. The dose of IFN was temporarily reduced in two patients because of fatigue in one and vomiting in the other. No patient had to discontinue therapy with IFN. Other side effects observed were lethargy in 3 of 16 patients (19%), alopecia in three, migrainous type headaches in one, mouth ulcers in one, and thrombocytopenia (platelet count $< 100 \times 10^9/L$) in one. The patient with thrombocytopenia (platelet count $67 \times 10^9/L$) at the end of 1 year of IFN had mild thrombocytopenia on entry into the trial (platelet count $115 \times 10^9/L$) and has remained thrombocytopenic more than a year after the completion of therapy.

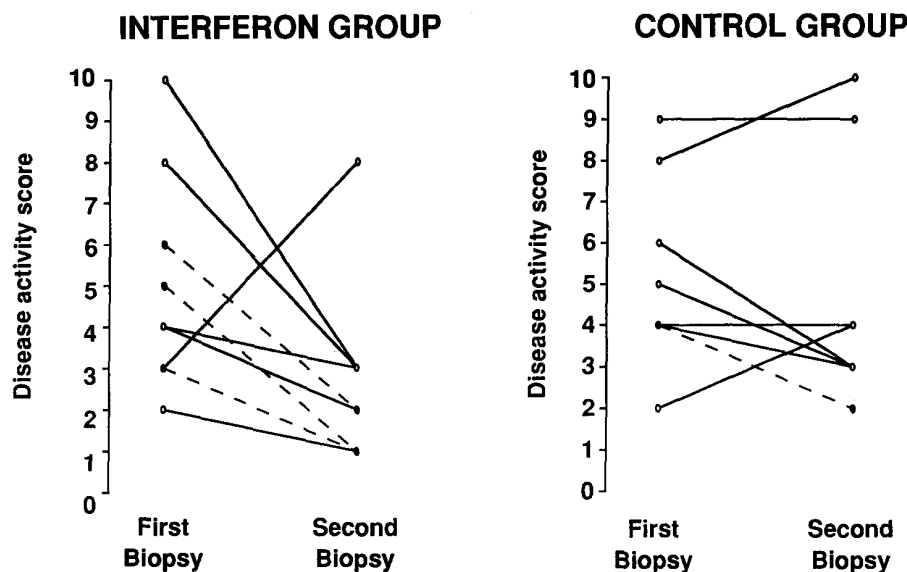


Fig 2. Histologic activity scores at the start and after 1 year using the Sheffield scheme for analysis. (---●---), HIV antibody positive; (—○—), HIV antibody negative.

One patient who received IFN for 6 months died suddenly 2 months after discontinuing treatment. At necropsy he was found to have dilated cardiomyopathy. He had no symptoms of heart failure at any time during or after treatment with IFN. Before commencing IFN his cardiovascular system was normal on physical examination. During the period of treatment with IFN it was discovered that this patient was abusing opiate analgesics parenterally.

DISCUSSION

In this study of hemophiliacs with chronic NANB liver disease, we have shown that treatment with IFN for 1 year resulted in a significant improvement in liver histology. Normalization or near-normalization of the liver enzymes was always accompanied by histologic improvement. In four patients histologic improvement was noted despite persistent and unresponsive enzyme abnormalities.

Similar observations have been reported by Davis et al¹² and Di Bisceglie et al¹³ in patients with chronic posttransfusion and sporadic hepatitis. However, in both of these studies, hemophiliacs and HIV antibody-positive individuals were excluded. A separate study in hemophilia was indicated because important differences exist between chronic HCV liver disease in hemophilia and that in "simple" posttransfusion hepatitis: many hemophiliacs have been exposed to repeated and much heavier viral loads, extending over longer periods, and there is evidence that some have also been exposed to different viral strains.¹⁶ Also, immunologic abnormalities that might influence the natural history of chronic liver disease have been reported in both HIV antibody-positive and -negative hemophiliacs.¹⁷

The overall biochemical response rate to IFN in our cohort of patients was 56%, which is similar to that of other reported trials in nonhemophiliacs.^{12,13}

There was a significant relapse rate after discontinuation of therapy, but there is a suggestion that this was less in patients treated for 12 rather than 6 months. Further larger studies are required to confirm this. If relapse occurred it usually did so within 1 month. We have observed sustained biochemical remission in patients for more than 15 months. Our experience suggests that for patients who do relapse, biochemical abnormalities can be controlled once again by the reintroduction of IFN.

Treatment with IFN for 1 year resulted in significant histologic improvement in the treatment group compared with that of the no-treatment group. Furthermore, improvement was noted in eight of nine treated patients (88%), which is a higher response rate than that suggested by liver enzyme changes. We used two schemes for the histologic assessment of the liver. The first (Sheffield scheme) was devised by JCEU before the study was started and is based on the histologic features that are likely to reflect disease activity of NANBH rather than on the architectural changes.

Table 3. Features Predictive of Biochemical Response to IFN

Parameter	Total Treated	Responders (CR + PR)	Nonresponders
	n	n	n
CPH	7	3	4
CAH	8	6	2
Cirrhosis	1	0	1
HIV antibody-positive	4	2	2
HIV antibody-negative	12	7	5
		Mean ± SD	Mean ± SD
ALT U/L at trial entry		135.7 ± 95.3	93.4 ± 43.2
AST U/L at trial entry		58.0 ± 39.0	54.9 ± 44.9
GGT U/L at trial entry		46.9 ± 33.9	78.7 ± 52.0
IgG g/L at trial entry		15.8 ± 3.5	15.2 ± 2.9
Histology of first biopsy			
Sheffield scheme		5.1 ± 2.6	4.0 ± 1.1
Knodell scheme		5.1 ± 3.2	3.0 ± 1.6

The second (Knodell scheme)¹⁵ was devised to score the severity of chronic hepatitis irrespective of etiology. The histologic improvement induced by IFN was almost exclusively confined to the hepatitic component of the liver biopsy, with both methods of analysis producing similar results and conclusions.

Histologic examination of the liver is the ideal method of assessing response to treatment, and for this reason a biopsy was essential to confirm that IFN produced similar responses in hemophiliacs to nonhemophilic individuals. It is questionable whether hemophiliacs should undergo liver biopsy routinely before receiving IFN therapy. There is an understandable reluctance to perform biopsies in hemophiliacs due to the relative cost and potential hazards, but in some cases there may be genuine doubt as to the cause of abnormal liver biochemistry. In our experience,⁵ 11 of 35 hemophiliacs with persistently abnormal liver enzymes showed no histologic features of NANBH, and in four of these there was no evidence of hepatitis, cirrhosis, or HCV infection. IFN therapy would have been inappropriate for such patients.

Improvement was noted in the liver histology of all three HIV antibody-positive patients treated with IFN, a potentially important observation because the prevalence of coexisting HCV and HIV infection in hemophiliacs is high.^{5,18} Martin et al¹⁹ have suggested that the progression of HCV chronic liver disease may be accelerated in the presence of HIV.

We are unable to offer an explanation for the biochemi-

cal and histologic deterioration that occurred in one patient treated with IFN. Similar deterioration in liver biochemistry has been reported in IFN α -treated patients with autoimmune chronic active hepatitis.²⁰

Treatment with IFN was well tolerated and it was not found necessary to discontinue the drug in any individual. The side effects, such as flu-like symptoms, were mild and usually confined to the early treatment period.

One patient died suddenly with dilated cardiomyopathy diagnosed at autopsy, 2 months after completing a 6-month course of IFN. Although dilated cardiomyopathy has been reported as a complication of IFN therapy, in all previous reports there was associated heart failure while the affected individual was receiving the drug.²¹⁻²³

We conclude that 3 million units recombinant IFN α -2b self-administered subcutaneously thrice weekly improves the liver histology of most hemophiliacs and normalizes the ALT levels in more than 50% of patients treated. Further trials are required to establish the ideal dose, frequency of administration, and length of treatment. It remains to be established whether these beneficial effects of IFN can influence the natural history of HCV-related chronic liver disease in hemophiliacs.

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