

Brief report

Sustained suppression of hepatitis C virus by interferon and ribavirin in hemophilic patients not responding to interferon monotherapy

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Thirty-nine hemophilic patients, negative for human immunodeficiency virus, with chronic hepatitis C who failed to respond to interferon (IFN) at 3 million units (MU) given subcutaneously thrice weekly for at least 3 months were retreated with 5 MU IFN for 6 months followed by 3 MU IFN in combination with daily oral doses of 1 or 1.2 g ribavirin. Thirty-four patients (87%) completed the

study. In 4 patients treatment was discontinued because of treatment-related symptoms; 1 patient dropped out. Dosage reduction was required in 10 patients (26%) because of ribavirin-related anemia or IFN-related side effects. By intention-to-treat analysis, 14 (37%) had a sustained virologic response with preference for those infected by genotypes other than type 1 (43% versus 12%) and with high

transaminases levels (168 U/L versus 116 U/L). Thus, IFN and ribavirin combination therapy led to a sustained suppression of hepatitis in one third of hemophilic patients resistant to conventional monotherapy. (*Blood*. 2002;99:1089-1091)

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Introduction

Chronic infection with hepatitis C virus (HCV) is the leading cause of liver-related morbidity and mortality in patients with hemophilia who have received multiple transfusions.^{1,2} It is not clear whether the cumulative lifetime risk of cirrhosis or hepatocellular carcinoma in these patients can be attenuated by treatment with interferon α (IFN- α). Hemophilic patients are frequently resistant to IFN therapy due to the long duration of HCV infection, high levels of viremia, and high prevalence of HCV genotype 1, which is an IFN-resistant virus strain.³⁻⁶ Controlled studies in nonhemophilic patients with chronic hepatitis C have demonstrated that higher rates (30%-40%) of sustained response are obtained with the administration of IFN in combination with the guanosine analogue ribavirin than with IFN monotherapy.^{7,8} Ribavirin is known to inhibit viral RNA polymerases *in vitro*,⁹ to increase the rate of virus mutations,^{10,11} to influence Th1/Th2 balance by causing a shift toward Th1 responses,¹² and to suppress HCV-specific interleukin-10 (IL-10) production.¹³ The fact that nonhemophilic patients resistant to IFN monotherapy could achieve more sustained responses with combined administration of IFN and ribavirin¹⁴ provided the rationale for retreating all hemophilic patients refractory to IFN monotherapy with combination therapy.

Between January and December 1998, we treated antihuman immunodeficiency virus (HIV)-negative adults (older than 18 years) with inherited bleeding disorders and chronic hepatitis C, not responding to or having a hepatitis relapse after treatment with 3 million units (MU) IFN given thrice weekly for a minimum of 3 months. Patients were included in the study after a 6-month washout period if they had abnormal serum aminotransferase (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) levels and detectable serum HCV-RNA by reverse transcription-polymerase chain reaction (RT-PCR) as previously described.³ Nineteen patients (49%) were previously treated in the context of the multicenter controlled trial of IFN- α 2b at the dose of 3 MU thrice weekly³ and the remaining 20 were patients with similar features who had received 3 MU of IFN- α 2a or IFN- α 2b outside the trial (Table 1).

Each patient received 5 MU recombinant IFN- α 2b (Intron A, Schering-Plough, Milan, Italy) by subcutaneous injections thrice weekly for 6 months followed by 3 MU thrice weekly for 6 additional months. An oral dose of 1000 to 1200 mg ribavirin (1200 mg if body weight was above 75 kg; Rebetol, Schering-Plough) was given daily for 12 months. Combination therapy was interrupted if a biochemical and virologic response was not achieved after the first 6 months or a permanent breakthrough occurred.

Pretreatment serum levels of HCV-RNA were quantitatively measured by a branched-DNA signal amplification assay (bDNA, Quantiplex, HCV-RNA 2.0 assay; Chiron, Emeryville, CA; sensitivity threshold of this assay is 0.2 mEq/mL¹⁵). HCV was typed by a hybridization assay (Inno-Lipa II, Innogenetics, Zwijndrecht, Belgium). Serum HCV-RNA was assessed by nested RT-PCR, using specific primers from the 5' noncoding region with a limit sensitivity of 50 copies/mL.¹⁶

Continuous variables were expressed as mean or median values and ranges. Categorical variables were expressed as frequency and percent values and compared by the Fisher exact test. The Wilcoxon rank sum test was used to analyze the distribution of quantitative variables of the relevant clinicopathologic parameters. The median values were compared by the median test for 2 samples. All comparisons were 2-tailed. Response to treatment was evaluated in accordance with the intention-to-treat analysis.

Study design

This multicenter open trial consisted of a treatment period of 12 months and a 6-month posttreatment follow-up period. The study was designed by the Hepatitis Study Group of the Association of Italian Hemophilia Centers, which includes all the hemophilia centers participating in the previous IFN treatment trial of naive patients.³ The study was carried out according to the international standard criteria for good clinical practice. Written informed consent was obtained from each patient.

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Table 1. Characteristics of the 39 patients at study entry

Patient characteristics	
Mean age, y (range)	40 (22-65)
Sex (M/F)	37/2
Hemophilia A (%)	30 (77)
Hemophilia B (%)	7 (18)
Other inherited bleeding disorders (%)	2 (5)
Disease duration, y (range)	24 (14-40)
Mean ALT, IU/mL (range)	135 (46-441)
Median HCV-RNA, MEq/mL (range)	4.3 (< 0.2-43.0)
HCV genotype (%)	
1a	21 (54)
1b	8 (20)
2b	2 (5)
3a	7 (18)
4	1 (3)
Outcome of previous IFN monotherapy (%)	
Nonresponse	24 (62)
Transient response	15 (38)

Univariate analysis was performed with each variable to assess any association with response to treatment.

Results and discussion

All but one patient who refused to continue therapy at month 2 completed the study. Twenty-seven patients (69%) became HCV-RNA negative during the first 6 months of therapy and were continued on combination therapy until month 12. One responder, however, discontinued treatment at month 6 because of the occurrence of side effects. Five (19%) patients experienced a hepatitis breakthrough 6 to 11 months after starting therapy. At the end of treatment, 18 (46%) patients had normal ALT values and no HCV-RNA. Hepatitis relapse occurred in 4 end-of-treatment responders during the posttreatment follow-up period. Overall, 14 patients (36%) had a sustained response.

In nonhemophilic patients with chronic hepatitis C, retreatment of transient responders to IFN monotherapy with IFN plus ribavirin was associated with a high rate (49%) of sustained virologic response.¹⁷ Relatively high rates (30%) of sustained virologic responses to retreatment with combination therapy of nonhemophilic patients who failed to respond to IFN monotherapy, including those infected by genotype 1, have been recently reported.^{13,18} In this study, we were surprised to see that retreatment with combination therapy led to a sustained virologic response not only in the 7 (47%) hemophilic patients who transiently responded to IFN monotherapy, but also in the 7 (29%) hemophilic patients who were primary nonresponders to IFN monotherapy. One possible explanation for these favorable results might be the use of relatively high doses of IFN, that is, 5 MU in the initial 6 months of therapy, which is known to overcome resistance of HCV infection to the first course of treatment with standard doses of 3 MU IFN.¹⁹ In both our study and that performed in the United States in nonhemophilic nonresponders,¹³ HCV genotype 1 was a strong

Table 2. Pretreatment characteristics of the patients who had a sustained response and those without sustained response to combination therapy

Patient characteristics	Sustained responses (n = 14)	Not sustained responses (n = 25)	P
Mean age, y (range)	39 (27-65)	40 (22-63)	NS
Mean ALT, IU/mL (range)	168 (56-441)	116 (46-234)	.028
Median HCV-RNA, MEq/mL (range)	2.5 (< 0.2-43.0)	4.9 (< 0.2-33.0)	NS
HCV			.047
HCV 1* (%)	8 (57)	22 (88)	
HCV 2 or 3 (%)	6 (43)	3 (12)	
Outcome of previous IFN monotherapy (%)			
Nonresponse	7 (50)	17 (68)	NS
Transient response	7 (50)	8 (32)	NS

NS indicates not significant.

*Includes 1 patient with genotype 4.

predictor of nonresponse to retreatment with combination therapy. These findings parallel previous data showing that genotype 1 is an independent predictor of resistance to combination therapy in both naive and relapsed patients. The serum ALT level became normal at month 1 (86%) in 12 sustained responders compared to 1 (25%) patient with a posttreatment relapse. At variance with previous studies^{20,21} we found that high pretreatment serum ALT levels predicted a therapeutic response (Table 2).

Treatment was generally well tolerated by most patients, but it had to be discontinued in 4 (10%) because of the occurrence of side effects such as fatigue, anorexia, and nausea. Reduction of IFN dosage was required in 4 patients (10%) because of onset of fatigue, thrombocytopenia, and hypothyroidism. Ribavirin reduction was required in 6 patients (16%) because of the occurrence of hemolytic anemia 1 to 3 months after treatment onset. In all patients, hemoglobin levels transiently decreased during treatment (median variation from baseline, 2.9 g/dL; range, 0.2-5.2 g/dL). The 10% dropout rate caused by unwanted effects compares favorably with the figures of treatment toxicity reported by the megatrials in nonhemophilic patients.^{7,8,17}

In conclusion, our finding that one third of nonresponders eventually achieved a sustained response with retreatment by combination therapy may have an important clinical impact, because chronic hepatitis C is a major cause of morbidity and mortality from liver disease in HIV-free hemophilic patients.^{1,22} The relevance of our findings lies also in the fact that hemophilic patients not responding to IFN monotherapy represent more than two thirds of all treated patients^{3,5,23} and that health-related quality of life, markedly impaired in patients with chronic hepatitis C, is expected to improve in those who respond to IFN treatment.^{24,25}

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Appendix

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