

A Comparison between Pegylated Interferon Alpha-2a and Standard Interferon in Combination with Ribavirin in Treating Patients with Bleeding Disorders and Chronic Hepatitis C

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ABSTRACT

Background

Patients with bleeding disorders are frequently infected with hepatitis C virus (HCV). There are few reports on the effect of standard interferon in these patients and no published report on pegylated interferon. The aim of this study was to compare pegylated interferon alpha-2a and standard interferon alpha with ribavirin in patients with bleeding disorders and chronic HCV infection.

Materials and Methods

Consecutive patients referring to a specialized clinic in Tehran were included in the study. The first 37 patients received pegylated interferon (PEGASYS, Hoffmann-La Roche Inc., Basel, Switzerland), 180 µg weekly and the next 38 patients received standard interferon, 3 million units 3 times a week. Both groups also received ribavirin 800 mg daily. Patients were treated for 48 weeks and were followed for 24 weeks. Liver biopsy was not performed due to the potential risks involved in patients with bleeding disorders.

Results

34 patients in each group completed the study. The intention-to-treat sustained viral response was 34% and 62% in the standard interferon and pegylated interferon group, respectively ($p=0.02$).

Conclusions

Pegylated interferon alpha-2a and ribavirin is almost twice as effective as standard interferon and ribavirin in treating HCV infection in patients with bleeding disorders and is an acceptable treatment option even when histologic data is not available.

Keywords: Inflammatory disorders, Liver descriptors, Hepatitis C, Hemophilia

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INTRODUCTION

Due to the nature of bleeding disorders, patients with these conditions frequently require factor replacement therapy. The most common practice is

using concentrated factors prepared from sera of multiple donors being injected parentally whenever the need arises.

Before the recognition of the hepatitis C virus (HCV) and before universal screening for HCV, these factor concentrates were frequently infected with the virus. It follows that patients with bleeding disorders, especially hemophiliacs, were frequently exposed to infected sera. HCV from various sources have been repeatedly injected parentally to these patients. It is thus not surprising that worldwide, a very high percentage of these patients show serologic markers of HCV infection. Rates as high as 80% have been reported.(1-3)

Another problem with patients with bleeding disorders is that liver biopsy involves a much higher risk.(4), It may require many days of hospitalization and expensive techniques such as the transjugular approach. Many physicians believe the risks outweigh the benefits, so it frequently happens that the treatment of HCV in these patients is carried out without histologic guidance.

This population is thus different from the general HCV infected patients in many ways. It could be assumed that the course of HCV and the way it responds to treatment may be different in these patients, too.

The introduction of pegylated interferon was a major advance in the treatment of hepatitis C. Two different pegylated interferons have been developed so far: pegylated interferon alfa-2b and pegylated interferon alfa-2a. They are longer-lasting alpha interferons developed through attachment of a large polyethylene glycol molecule to the interferon-alpha protein. This interferon can be administered once per week due to the prolonged absorption time and the elimination half-life of 40 hours (pegylated interferon alfa-2b) to 65 hours (pegylated interferon alfa-2a). Combination therapy with

pegylated interferon and ribavirin is now considered to be the standard therapy for chronic hepatitis C.(5), This combination has resulted in a sustained virologic response in more than 50% of treated patients in several landmark studies.(6-8)

There are few reports on the effect of standard interferon in patients with bleeding disorders and hemophiliacs(9-13) and no published report on the use of pegylated interferon. In this study, we have evaluated the safety and efficacy of pegylated interferon alpha-2a in combination with ribavirin in treating patients with bleeding disorders infected with HCV. We have also compared it to standard interferon and ribavirin given in the same population.

MATERIALS AND METHODS

Patients were selected from the central hemophilia clinic in Tehran. This center specifically provides service to patients with bleeding disorders. Although the vast majority of patients are different variations of hemophilia, patients with other bleeding disorders such as von Willebrand's disease and Glanzmann thrombasthenia are also served.

Patients with anti-HCV antibodies detected by third generation ELISA* (Abbott Laboratories, Chicago, USA) were tested for the presence of HCV RNA** by qualitative PCR.*** Patients with positive PCR were then evaluated for eligibility and inclusion in the study. Liver biopsy was not performed due to the potential risks involved.

Patients were excluded if they had concomitant HIV or hepatitis B infection. Patients with severe comorbid conditions such as renal failure, heart failure, severe psychological disease and malignancies as well as patients with cirrhosis were also excluded. Since histologic data was not available, cirrhosis was diagnosed by clinical criteria and surrogate markers such as platelet count or other evidence of portal hypertension. The exclusion criteria are given in Box 1.

Written consent was obtained from all patients and the spouses of married subjects. The consent of the spouse was necessary because of the

* Enzyme Linked Immunosorbent Assay

** Ribonucleic Acid

*** Polymerase Chain Reaction

Box 1. Exclusion criteria

Total bilirubin above 2 mg/dL
Presence of any degree of ascites or hepatic encephalopathy
Presence of other hepatic disease (hepatitis B, autoimmune hepatitis, alcoholic liver disease)
Uncontrolled thyroid disease
Debilitating disease (heart failure, renal failure, chronic pulmonary disease)
Concomitant HIV infection
Splenomegaly
Ultrasonographic evidence of portal hypertension
Platelet count less than 60,000 /mm ³
White blood cell count less than 4,000 /mm ³
Hemoglobin less than 10 g/dL
Uncontrolled epilepsy or psychological disease

teratogenicity of ribavirin and the required prevention of pregnancy; a subject which both spouses should agree upon. All women as well as spouses of men were tested for pregnancy at baseline, and were warned about the potential risks of the treatment for pregnancy. Patients not consenting to the study were excluded.

At the time of the study, pegylated interferon was not commercially available and HCV patients were treated using standard interferon. A limited amount of pegylated interferon became available to the central hemophilia clinic of Tehran. Due to ethical reasons, the patients were not randomized and the first 37 patients consenting to the study received pegylated interferon alpha-2a (PEGASYS, Hoffmann-La Roche Inc., Basel, Switzerland), 180 µg weekly and ribavirin 800 mg daily. The next 38 patients received standard interferon alpha, 3 million units 3 times a week and ribavirin 800 mg daily. All patients were treated for 48 weeks and were followed for 24 weeks after end of treatment.

Routine visits were scheduled every 4 weeks for evaluation of adverse events and probable dose adjustments. ALT* levels and complete blood

counts were monitored at every visit and other tests such as thyroid function tests were performed every 12 weeks. HCV RNA was measured qualitatively by PCR at weeks 24, 48, and 72 (24 weeks after end of treatment).

The dose of pegylated or standard interferon was decreased by 25% when platelet counts fell below 50,000/mm³ or neutrophil counts fell below 750 /mm³. The dose was also decreased if other troublesome adverse effects occurred.

Ribavirin was discontinued if hemoglobin levels dropped below 10 g/dL in the face of normal platelet and white blood cell counts.

In all cases of adverse events mandating dose reductions, patients were re-evaluated in 2 weeks. When the adverse event was controlled, returning to the previous dose was attempted only once.

“Early viral response” was defined as negative PCR on week 24, “end-of-treatment viral response” as negative PCR on week 48, and “sustained viral response” as negative PCR on week 72 (or 24 weeks after end of treatment). “Biochemical response” was defined as normalization of ALT levels.

HCV genotyping was done where possible. HCV RNA was isolated from serum as described by Norder *et al.*(14), The cDNA was amplified within the NS5B region using primers hep101 and hep120 as outer primers, and hep101 and hep105 for nesting.(15), In samples for which the NS5B region could not be amplified, the 5'-UTR region was amplified with primers univ1 and univ2 as outer primers, and with univ3 and univ4 for nesting.(16), The sequences obtained were aligned with sequences from GenBank. The genetic distances of the aligned sequences were calculated using the Kimura-two parameter model in DNA DIST in the Phylip program package version 3.52.

Quantitative PCR for HCV RNA was performed using RT-PCR amplification of 5'-URT with nested primers. The lower detection limit of this test was 50-100 copies/mm³.

The study protocol was approved by the ethics committee of Digestive Disease Research Center, Tehran University of Medical Sciences.

* Alanine aminotransferase

RESULTS

Of the 75 patients enrolled, 71 were men and 4 women. Patients included 2 cases of Glanzmann thrombasthenia and 3 cases of von Willebrand's disease. The other 70 patients were hemophiliacs. All patients were asymptomatic and were diagnosed through routine screening, thus the duration of infection is unknown. None of the patients were alcohol abusers. Among the pegylated interferon group, 10 had previously failed standard interferon therapy (one in combination with ribavirin). None of the standard interferon group had received previous treatment. The mean age of patients was 28.6 ± 9.5 yrs. Details are given in table 1.

Dropouts

Sixty-eight patients completed the study, 34 from each group.

One patient refused to continue treatment because of severe flu-like reactions after the first injection of pegylated interferon. She had previously failed 6 months of interferon monotherapy and did not believe she could be helped.

Table 1. Initial characteristics of HCV patients treated with pegylated interferon vs. standard interferon*

	Standard interferon group	Pegylated interferon group
Number	38	37
Sex (Men/Women)	36/2	35/2
Age (mean±SD, yrs)	28.3±10.2	28.8±8.9
ALT level (mean±SD, IU)	81.8±69.6	95.0±42.2
Platelet count (mean±SD, count/mm ³)	181000±64000	188000±75000
Number failing previous treatment	0	10
Genotype		
1	13	12
2	1	1
3	7	7
Not tested	17	17

*None of the differences between the two groups is statistically significant except for the number failing previous treatment.

Another patient died of a cerebrovascular accident on week 18 of treatment. This 48-year-old man was a case of von Willebrand's disease in the pegylated interferon group and had a normal platelet count on his latest visit two weeks earlier. The event was considered unrelated to treatment. This patient was considered a treatment failure.

Two pegylated interferon patients refused to continue treatment after PCR turned negative at week 24. One of these patients was subsequently lost to follow-up and was considered a treatment failure. The other patient had negative PCR 24 weeks after discontinuation of treatment, and was considered as treatment success.

Four patients, all from the standard interferon group, failed to complete follow-up after the end of treatment. Only one of these patients had a negative PCR at this time. All four patients were considered as failures.

Adverse events

Most frequent adverse events reported by the patients included easy fatigability in 19, mood changes in 18, hair loss in 16, musculoskeletal pain in 14, pruritus in 9, and hypothyroidism in 5.

No significant difference was observed between the two groups.

One patient withdrew due to severe flu-like reactions to the first dose of pegylated interferon. Except for this case, adverse effects leading to discontinuation of treatment were not observed in either group.

Adverse events leading to dose reductions are given in table 2. In all cases, full dose treatment was successfully resumed within 4-6 weeks.

Viral response

Negative PCR at week 24 (early viral response) was

Table 2. Reasons for dose reduction in patients being treated for hepatitis C*

Adverse event	Number	Dose reduction
Neutropenia	5 patients	Pegylated interferon
	2 patients	Standard interferon
Anemia	1 patient	Ribavirin
Anemia and neutropenia	1 patient	Pegylated interferon
	1 patient	Standard interferon
Thrombocytopenia	1 patient	Pegylated interferon
	4 patients	Standard interferon
Aggressive behavior	1 patient	Pegylated interferon
Elevated ALT	2 patients	Pegylated interferon
	1 patient	Standard interferon

*Neutropenia: absolute neutrophil count < 750/mm³, Thrombocytopenia: platelet count < 50,000/mm³, anemia: Hgb < 10 g/dL

observed in 48% of the standard interferon group and 91% of the pegylated interferon group (p<0.001). The end-treatment viral response was 62% in the standard interferon group and 91% in the pegylated interferon group (p<0.005) and sustained viral response (negative PCR at 24 weeks after end of treatment) was 38% and 68% (p<0.02), respectively. The intention-to-treat sustained viral response was 34% and 62% for the standard and pegylated interferon group, respectively (p=0.02). Where data was available, among the standard interferon group 36% (5/14) of cases with early viral response and 59% (13/22) of cases with end-treatment response achieved sustained viral response. In the pegylated interferon group 71% (22/31) of cases with early viral response and 74% (23/31) of cases with end-treatment response achieved sustained viral response. Pre-treatment AST and ALT levels and platelet counts were not predictive of viral response in any of the groups or in all patients as a whole.

Biochemical response

End-treatment biochemical response was observed in 75% of the standard interferon group

and 67% of the pegylated interferon group and sustained biochemical response was achieved in 60% of the standard interferon group and 74% of the pegylated interferon group. The differences between the two groups were not statistically significant.

Genotype

Genotype info was available for only 41 patients, 25 cases were genotype 1 and 16 non-1 (table 1). The genotypes were not significantly different between the two groups. Among patients with known genotype, the intention-to-treat sustained viral response in the standard and pegylated interferon group was 2/11 (15%) and 5/7 (42%) in genotype 1 and 4/8(50%) and 5/8 (63%) in non-1 genotypes. The number of patients with known genotype was too low to allow comparisons between response rates of different genotypes, although an obvious trend to better response is observed for non-1 genotypes.

Re-treatment group:

Ten patients had failed previous treatment, all in the pegylated interferon group. Six of these patients achieved sustained viral response (60%), 3 did not, and one withdrew from the study after her first injection. Notably the one patient who had previously failed 12 months of combination therapy with standard interferon and ribavirin did achieve sustained viral response.

DISCUSSION

The combination of pegylated interferon and ribavirin is currently well established as the most effective treatment for hepatitis C.(5), This combination, for the first time, has allowed sustained viral response rates above 50%.(6-8), Pegylated interferon has also significantly improved treatment success in difficult-to-treat patients, including cirrhotics, non-responders, and relapsers.(17), In the present study, we have shown the high efficacy of this combination in patients

with bleeding disorders as compared to standard interferon.

Hemophiliacs and other patients with bleeding disorders presumably have been repeatedly exposed intravenously to high concentrations of different strains of HCV starting early in life. For this reason, one might predict treatment success in these patients would be different than other patients. However, it seems that the natural history of hepatitis C and the potential for progressive disease in patients with hemophilia is similar to the non-hemophilic population.(18, 19)

A few studies have evaluated the use of interferon-alpha with or without ribavirin for the treatment of chronic hepatitis C in patients with hemophilia.(10), Monotherapy with interferon in this patient population has been found to be marginally effective.(11, 20, 21), Rumi *et al.* reported a sustained virologic response of 13% in their randomized study including 107 HIV-negative hemophiliacs with chronic hepatitis C either treated with interferon-alpha 2b or observed for a duration of 48 weeks.(22), The use of ribavirin, a nucleoside analogue, greatly enhanced the antiviral efficacy of interferon, and the combination became the standard of care by the end of the 1990s.(23, 24), Combination therapy with interferon and ribavirin in patients with hemophilia and chronic hepatitis C has led to sustained viral response in roughly one third of the patients.(13, 25-27), In our standard interferon group, we have obtained an intention-to-treat sustained viral response of 34% which agrees with similar reports in this population. But the response rate observed in our pegylated interferon group is 62% which is higher than many reports from non-hemophilic patients using the same treatment combination.(6, 7), Various factors can be responsible for this higher sustained viral response. One such factor is the genotype combination of our patients. The reported sustained viral responses of 50-60% in other studies all apply to populations with over 70% genotype 1, which is well known to be resistant to treatment. In our pegylated interferon group,

genotype 1 constituted 60% of cases in which genotyping was available, slightly less than other reports. Furthermore, our patients were all fairly young (mean age: 28 years); also known to be a predictive factor for treatment success.

Unfortunately genotype information was not available for many of our patients and we do not have viral load data. We used 800 mg/day of ribavirin for all cases which is less than the current recommendations for genotype 1 where 1000 or 1200 mg/day is recommended. The duration of treatment in our study was 48 wks for all patients regardless of genotype, whereas 6 months would be enough for genotype 3 patients. At the time of study, this was standard procedure of the hemophilia center. Another shortcoming of our study is the lack of randomization. But in spite of these short-comings, our data shows the advantage of pegylated interferon over standard interferon in patients with bleeding disorders. It is likely that we would have obtained better results if higher doses of ribavirin were used. It should be also pointed out that almost one third of the pegylated interferon group were re-treatment cases, difficult to treat, while all patients in the standard interferon group were treatment naïve.

We observed that biochemical response was similar in both groups, although there was a trend for the pegylated interferon group to have lower ALT levels at follow-up. This finding could indicate that it takes some time for the recurrent HCV to start damaging hepatocytes and increase ALT levels again.

An important point of our study is the lack of histologic data. Generally, it is believed that histologic data is helpful and should be sought when possible. But recently, with high response rates observed with new treatments, especially in non-1 genotypes, and the recognition that patients with mild histologic changes respond just as well, and even better, the question arises that how important liver biopsy may be. Many authorities no longer recommend liver biopsies in non-1 genotypes. In patients with bleeding disorders, such as hemophiliacs, the risks of liver biopsy is

too high, or is very expensive. Although, it is still possible to perform biopsies with hospitalization and factor replacement or using transjugular approach,(28, 29) many physicians caring for these patients chose not to routinely perform liver biopsies in this high-risk group. Our results now provide evidence that the option of treating patients with bleeding disorders, including hemophilic patients, with pegylated interferon and ribavirin without performing a liver biopsy may be justified with an over 60% success rate.

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