ORIGINAL ARTICLE

Peginterferon Alfa-2a and Ribavirin in Patients with Chronic Hepatitis C and Inherited Bleeding Disorders

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Abstract

BACKGROUND: Patients with inherited bleeding disorders who regularly receive clotting factors are frequently infected with hepatitis C virus (HCV). Liver biopsy in these patients is high-risk and not always performed. There is no report on pegylated interferon (PEG-IFN) and ribavirin in patients with bleeding disorders in whom no histologic data is available.

AIM: To assess the safety and efficacy of combined PEG-IFN alfa-2a and ribavirin in patients with inherited bleeding disorders and hepatitis C.

Methods: We studied 37 patients with inherited bleeding disorders and HCV infection. Patients where planned to receive pegylated interferon alfa 2a (PEG-IFN alfa-2a) 180micg weekly and ribavirin 800mg daily for 48 weeks. They were then followed for 24 weeks after the end of treatment.

RESULTS: Early virologic response at week 12 of treatment was achieved in 31/34 patients (91%) and end-of-treatment response was achieved in 30/31 patients (97%). Sustained virologic response was 26/32 (81%) and 26/35 (74%) on per-protocol and intention-to-treat analysis respectively. Dose reduction due to adverse effects was necessary in 11 patients.

CONCLUSION: The combination of PEG-IFN alpha 2a and ribavirin is safe and highly effective in patients with inherited bleeding disorders and HCV infection, even when histologic data is absent.

KEYWORDS: Hepatitis C Virus, Hemophilia, Pegylated interferon alfa-2a, Ribavirin

Introduction

Hepatitis C is a major world health problem. The global prevalence has been estimated to average 3%. It has been estimated that there are 170 million infected individuals in the world.[1] Individuals with inherited bleeding disorders and hepatitis C represent a unique population of patients who are mostly males, are generally infected at a young age, and are more likely to have been exposed repeatedly to hepatitis C from multiple donors

and with higher concentrations of virus.[2] Before the introduction of heat treatment of clotting factor concentrates in the mid to late 1980s, almost all people with hemophilia and other inherited disorders of coagulation who were exposed to clotting factor concentrates developed non-A, non-B hepatitis which was later identified as hepatitis C (HCV).[3,5] In countries with access to viral-inactivated concentrates there has been virtually no transmission of HCV since 1986.[6] However, it remains a problem in countries where single donor unsterilized concentrate (e.g., cryoprecipitate) is used.[7,8] The prevalence of hepatitis C in this group of patients has been reported to range between 70% and 95% in different parts of the world.[4,9] More than 60% of Iranian hemophilic patients are infected with HCV virus.[2a] Another concern in patients with bleeding disorders is the cost and risks associated with liver biopsy in these patients. Hemophilic patients are thus frequently treated without histologic data.The introduction of pegylated interferon (PEG-IFN) was a major advance in the treatment of hepatitis C. Two different PEG-IFNs have been developed so far: PEG-IFN alfa-2b and PEG-IFN alfa-2a. They are longer-lasting alpha interferons developed through attachment of a large polyethylene glycol (PEG) 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 (PEG-IFN alfa-2b) to 65 hours (PEG-IFN alfa-2a). Combination therapy with PEG-IFN and ribavirin is now considered to be the standard therapy for chronic hepatitis C.[10] This combination has resulted in a sustained virologic response (SVR) in more than 50% of treated patients in several landmark studies.[11,13] To date, no report has been published regarding the use of this combination in patients with inherited disorders of coagulation.

Patients and Methods

The design on our study was a quasi-experimental clinical trial with no control group. Patients were selected from the Central Hemophilia Clinic in Tehran. This center specifically provides services to patients with bleeding disorders. Although the majority of patients are different variations of hemophilia, patients with other bleeding disorders such as von Willebrand's disease and Glansman's thrombocythemia are also served. Thirty seven consecutive patients with chronic hepatitis C infection were enrolled. Patients were considered eligible for the study if they had a positive HCV RNA measured by PCR methods, and elevated alanine transaminase (ALT) levels to at least 1.5 times as much as the upper normal limit. Patients failing previous treatment with standard interferon with or without ribavirin were also included if over 3 months had elapsed from the end of previous treatment. 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 decompensated cirrhosis were also excluded (table 1). Liver biopsy was not performed due to the potential risks involved. Patients were planned to receive PEG-IFN alfa-2a (Pegasys,Hoffmann-La Roche Inc., Basel, Switzerland) 180µg weekly and ribavirin 800mg daily for 48 weeks. Patients were followed for 24 weeks after the 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 checked 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 (end of treatment), and 72 (24 weeks after end of treatment). Ribavirin was discontinued if hemoglobin levels dropped below 10 g/dL in the face of normal platelet and white blood cell counts. The dose of PEG-IFN was decreased by 25% when platelet counts fell below 50,000/mm3 or neutrophil counts fell below 750 /mm3. The dose of PEG-IFN was also decreased if other troublesome adverse effects occurred. 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 virologic response (EVR) was defined as negative HCV RNA on week 24, end-of-treatment virologic response (ETR) as negative HCV RNA on week 48, and sustained virologic response (SVR) as negative HCV RNA on week 72 (24 weeks after end of treatment). Biochemical response was defined as normalization of ALT levels. Patients were included in the analysis if they completed at least 3 months of treatment. Written consent was obtained from all patients and their spouses. All female patients as well as wives of male patients were tested for pregnancy at baseline, and were warned of the potential risks of the treatment for pregnancy. Patients not consenting to the study were excluded. 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. The lower detection limit of the PCR used in this study was 600 copies/ ml. The study protocol was approved by the ethics committee of Digestive Disease Research Center, Tehran University of Medical Sciences.

Results

Thirty-seven patients, 35 males and 2 females, were enrolled, of whom 2 cases were Glansman's thrombocythemia and 2 cases were von Willebrand's disease. The other 33 patients were hemophiliacs. Ten patients had previously failed standard interferon therapy (one in combination with ribavirin). The mean±SD age of patients was 30.1±8.6 yrs.

Dropouts: Two patients refused to continue treatment because of severe flu-like reactions after the first and second injections. Both patients had previously failed 6 months of interferon monotherapy and did not believe they could be helped. Since these patients did not complete the minimum

of 3 months required by the protocol, they were excluded form the analysis.

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

Two patients refused to continue treatment after HCV RNA 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 a negative HCV RNA at week 48, 24 weeks after discontinuation of treatment, and was considered as treatment success. No genotype data was available for this patient.

Thirty two patients completed the 48-week treatment. One other patient was lost during the subsequent 24-week follow-up. This patient was also considered a treatment failure.

Table 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
Platelet count less than 60,000/mm3
White blood cell count less than 4,000/mm3
Hemoglobin less than 10 mg/dL
Uncontrolled epilepsy or psychological disease

ADVERSE EVENTS: Most frequent adverse events reported by the patients included easy fatigability, hair loss and mood change in 11/35 each (31.4%), musculoskeletal pain in 10/35 (28.6%) and pruritus in 7/35 (20%). Dose reduction was necessary in 11 patients (table 2). One patient developed autoimmune hypothyroidism as evidenced by elevated TSH and anti-TPO antibodies in the 11th week of therapy. He was placed on thyroid replacement therapy.t

GENOTYPE: Genotype info was available for only 20 patients (table 3).

Table 2

Reasons for dose reduction in patients being treated for hepatitis C*

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

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

Table 3

Genotypes of 20 patients treated with PEG-IFN and ribavirin

Genotype	No (%)
1a	9 (45)
1b	3 (15)
2b	1 (5)
3a	6 (30)
3b	1 (5)

EVR: Early virologic response was observed in 31/34 (91%) and 31/35 (88.6%) per-protocol and intention-to-treat respectively. The non-responders were genotypes 1a, 1b, and 3b. One of the non-responders (genotype 1a) had poor compliance during the first 3 months of treatment. Another had 25% dose reduction of PEG-IFN due to neutropenia.

ETR: Thirty two patients completed 48 weeks of treatment. End-of-treatment PCR was available for 31. ETR was observed in 30/31 (97%) and 30/35 (85.8%) per-protocol and intention-to-treat respectively.

SVR: Thirty two patients completed the 24-week post-treatment follow-up. Sustained virologic response was achieved in 26/32 (81%) on a per-protocol basis. The intention to treat SVR was 26/35 (74%). Interestingly, one of the 3 patients who had not achieved EVR at week 24, did achieve SVR (genotype unknown). Among the 11 patients requiring dose reduction during treatment period, SVR was reached in all but two. These 2 patients were one patient who was lost in follow-up (genotype unknown) and one with genotype 3a.

Re-treatment Group: Eight patients had previously failed standard interferon therapy. Five of these patients achieved SVR (63%), 2 did not, and one was lost to follow-up. Notably, the only patient who had previously failed 12 months of combination therapy with standard interferon and ribavirin did achieve SVR.

Discussion

The combination of peginterferon alfa 2a and ribavirin is currently well established as the most effective treatment for hepatitis C.[10] This combination, for the first time, has allowed SVR rates above 50 percent.[11, 12] PEG-IFN has also significantly improved treatment success in difficult-to-treat patients, including cirrhotics, non-responders, and relapsers.[17] In the present study, we have clearly shown the high efficacy and safety of this combination in hemophilic patients.

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 not to be as high as in 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]

Several studies have evaluated the use of interferon-alfa with or without ribavirin for the treatment of chronic hepatitis C in patients with hemophilia.[20] Monotherapy with interferon in this patient population has been found to be marginally effective.[21, 23] Rumi et al reported a SVR of 13% in their

randomized study including 107 HIV-negative hemophiliacs with chronic hepatitis C either treated with interferon-alfa 2b or observed for a duration of 48 weeks.[24] 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.[25, 26] Combination therapy with interferon plus ribavirin in patients with hemophilia and chronic hepatitis C has led to SVR in roughly one third of the patients.[20, 27, 29] We have obtained a per-protocol SVR of 81% which is higher than that of many reports from non-hemophilic patients using the same treatment combination.[11, 12] Various factors can be responsible for this higher SVR. Probably the most important is the genotype of our patients. The reported SVRs 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 group, genotype 1 constituted a little less than 50% of cases in whom genotyping was available. On the other hand, non-1 genotypes are reported to have response rates of above 80% with only 24 weeks of treatment.[30] So, in our study population with over 50% non-1 genotypes, all being treated for 48 weeks, the numbers we have obtained may not be too unexpected. Furthermore, our patients were all fairly young (mean age: 30 years) also known to be a predictive factor for treatment success.

Another important point in 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 knowing 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 where the liver biopsy is too high risk, or is very expensive, it may not be routinely performed, either.

In our study, we have observed an SVR of 81% without performing liver biopsies. It may be concluded that with such high rates, performing liver biopsies may not be indicated.

We conclude that the combination of PEG-IFN and ribavirin in hemophilic patients is highly effective and the success rate is not much different from that observed in non-hemophilic patients. Treatment can be started without having histologic data

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