ORIGINAL ARTICLE

Efficacy and Safety of Pegylated Interferon Alfa-2a plus Ribavirin for Treatment of Chronic Hepatitis C and Cirrhosis in Iranian

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Abstract

BACKGROUND AND AIMS: Pegylation of Interferon (IFN) prolongs the medication half-life, which has resulted in introducing Pegylated Interferon (PEG-IFN) as the new modality for treatment of chronic hepatitis C. This clinical trial was conducted to assess the efficacy and safety of Peg-INF in combination with ribavirin in a number of Iranian patients with chronic hepatitis C or cirrhosis.

METHODS: Fifty two patients with HCV RNA in serum, persistently elevated aminotransferase levels, and chronic hepatitis (n=45) or cirrhosis (n=7) on liver biopsy were enrolled to this study. The patients received PEG-IFN (40 kD) 180 mcg per week plus ribavirin 10-15 mg/kg per day. Treatment lasted 48 weeks and was followed by a 24-week follow up period to assess sustained virologic response (SVR). The patients consisted of 46 males and 6 females with a mean age of 38.5 ± 10.9 years.

RESULTS: In an intention-to-treat analysis HCV RNA was undetectable in 43 patients (83.7%) at week 48 and SVR was achieved in 28 patients (53.8%). SVR was achieved in 62.9% of naive patients, 35.3% of the patients who had a past failed treatment with IFN-based therapy, 60.0% of patients with chronic hepatitis and 14.3% of cirrhotic patients. In two patients (3.8%) adverse event led to treatment discontinuation and in eight patients (15.3%) dose modification of medication was required.

CONCLUSION: This study showed that combination therapy with PEG-IFN plus ribavirin was associated with a promising SVR rate and acceptable tolerability in Iranian patients. This regimen may be effective for patients who failed prior IFN-based treatment.

KEYWORDS: Clinical trial, Chronic hepatitis C, Cirrhosis, Pegylated interferon, Ribavirin

Intruduction

The beneficial effects of Interferon (IFN) alfa in treatment of hepatitis C were first reported in 1986, and subsequently it was approved to use in hepatitis C in 1990. Further studies

revealed that addition of ribavirin to IFN based therapy improved response rate. Most recently, Pegylated Interferon (PEG-IFN) as a new generation of IFN has further improved response rates.

Pegylation is the process by which an inert molecule of polyethylene glycol is covalently attached to a protein, giving it a higher molecular weight and thus causing an effective increase in serum half-life.[1] Pegylation of IFN has prolonged the half-life from a few hours for standard IFN to several days for PEG-IFN, which resulted in prolongation of injection interval from 3 times a week for standard IFN to once a week for PEG-IFN [1, 2] Two formulations of PEG-IFN have been developed: PEG-IFN alfa-2b (12 kD) and PEG-IFN alfa-2a (40 kD).

The combination of PEG-IFN and ribavirin has recently been sanctioned by NIH Consensus Development Conference as the optimal treatment for the patients with chronic hepatitis C. [3] Iranian consensus on HCV treatment as a regional guideline also has recommended this regimen for difficult to treat patients. [4]

The prevalence of HCV infection in Iran is low among general population (less than one percent) but it seems to be increasing. [5] However, not only the overall data about treatment of hepatitis C in Iran as well as the Middle East are too rare but also no specific data about PEG-IFN therapy from the Middle East have been published as yet. This study aimed to assess the safety and efficacy of regimen of PEG-IFN alfa-2a in combination with ribavirin in a number of Iranian patients with chronic hepatitis C or cirrhosis.

Methods

Patients Selection: The patients older than 18 years with HCV RNA in serum on polymerase-chain-reaction (PCR) assay (Cobas Amplicor HCV Monitor, Roche Diagnostics, Branchburg, N.J.), persistently raised aminotransferase levels, and chronic hepatitis or cirrhosis on liver biopsy were enrolled to this study.

The exclusion criteria were : other known liver diseases, decompensated cirrhosis, autoimmune disease, an evidence of cancer on ultrasonography or a high serum alfa-fetoprotein concentration, co-infection with HBV or HIV, neutropenia (neutrophil count <1500 cells/mm3), thrombocytopenia (platelet count <90,000 cells/mm3), anemia (hemoglobin level <12 gr/dL for women and <13 gr/dL for men), creatinine concentration more than 1.5 times the upper limit of normal range, organ transplant, neoplastic disease, severe cardiac or chronic pulmonary disease, poorly controlled psychiatric disorder, seizure disorder, retinopathy, active drug or alcohole abuse, or unwillingness to use contraception.

Study design: This open-label, uncontrolled clinical trial was conducted between February 2002 and April 2004 at Tehran Hepatitis Center, Tehran, Iran. All patients provided written informed consent and the study was conducted according to the guidelines of the Declaration of Helsinki. Patients who met the criteria for entry were assigned to receive subcutaneous treatment with PEG-IFN alfa-2a (PEGASYS®, Hoffmann–La Roche, Switzerland) 180 micg once a week plus oral treatment with ribavirin 10-15 mg/kg per day for 48 weeks. Three patients who had contraindication for ribavirin because of thalassemia major received PEG-IFN mono-therapy. Patients were followed until week 72 to assess whether there was a sustained virologic response (SVR) to treatment.

Assessment and endpoints: The patients were initially assessed on weeks 2 and 4 and then every 4 weeks. Complete physical examination was performed and cell blood count and biochemistry laboratory exams were checked every visit session. HCV RNA, thyroid function tests, and urine analysis were checked every 12 weeks. Beta HCG was measured in sera for the females or males' wives before beginning the trial and at the 4th week. After that, the patients were ordered for home based urine pregnancy test every 4 weeks. The primary efficacy was the SVR, defined as undetectable HCV RNA in serum at the end of follow-up by a qualitative PCR assay with a sensitivity of 200 copies/mL (Cobas Amplicor HCV Monitor [version 2.0], Branchburg, N.J.).

Safety: Hematologic adverse events were recorded if: hemoglobin level decreased to less than 10 gr/dL, neutrophil count decreased to less than 750 cells/ mm^3, and platelet count decreased to less than 50,000 cells/mm^3. Other adverse events were recorded if led to dose modification of drugs, or if led to additional therapy. For significant adverse events, the dose of PEG-IFN was decreased to 90 micg per week, and/or the dose of ribavirin was lowered to 600-800 mg/day. On resolution of the event, doses could be restored to their original levels. If the event persisted, both drugs were discontinued. Patients were withdrawn from the study if they missed four consecutive weeks of treatment or if the investigators were concerned about safety.

Statistical Analysis: The major objective of the study was to define the rate of SVR. Patients who received at least one dose of study medication were included in the both safety and efficacy analysis, and intention-to-treat analysis was used for all measures of efficacy. Patients who missed the examination at the end of the follow-up period (week 72) were considered not to have a response at that point. The continuous variables of hematologic values in various sections of the trial course were compared by paired samples T-test.

Results

Fifty two patients who met the criteria were enrolled in the study. Out of them, 48 patients completed treatment and 43 patients completed follow up. All efficacy and safety analyses were based on all 52 patients, who received at least one dose of medication. The base line characteristics of the patients were summarized in table 1. The mean age was 38.5 ± 10.9 years ranged between 19 and 67 years. Because of the lack of facilities when the trial started, we could not determine the patients' HCV genotype at the base line. Patients were prematurely withdrawn during the treatment course for failure to return (2 cases) and adverse event (2 cases). Two out of three patients who were on PEG-IFN monotherapy because of thalassemia major were withdrawn during treatment course.

Table 1
Baseline characteristics of the patients

Characteristic	Number (%)
Male sex	46 (88.5)
Histologic diagnosis	
Chronic hepatitis	45 (86.5)
Cirrhosis	7 (13.5)
Past history of treatment	
Naive	35 (67.3)
Hx. of IFN mono-therapy	5 (9.6)
Hx. of IFN+ribavirin therapy	12 (23.1)
Mode of infection	
Intra-venous drug abuse	16 (30.8)
Transfusion	16 (30.8)
Job exposure	6 (11.5)
Others (cupping, tattooing, war injury, sexual exposure)	5 (9.6)
Unknown	9 (17.3)

Table 2
Virologic response at the end of treatment and follow-up

End point	Number (%)
End of treatment (week 48)	
Response	43 (82.7)
No response	5 (9.6)
Withdraw	4 (7.7)
End of follow up (week 72)	
SVR	28 (53.8)
Relapse	10 (19.2)
No response	5 (9.6)
Withdraw	9 (17.4)

Efficacy

At the end of the treatment (48 weeks), 43 patients (82.7%) had undetectable levels of HCV RNA. At the end of the follow up period on week 72, 28 patients (53.8%) had an SVR (table 2). All of 28 patients with SVR had a sustained biochemical response as well. Ten patients (19.2%) cleared virus on week 48 but relapsed by the end of follow up period. Among them HCV genotype was 1a or 1b in 8 patients, 3a in one patient and non-typeable in the last case. Five patients of responders at week 48 missed the examination at the end of the follow-up period and were added to withdrawn cases.

SVR was 62.9 percent in naive patients. In addition, 6 out of 17 patients who had a failed past treatment could achieve SVR (table 3). The majority of patients (71.4%) who were HCV RNA negative for the first time at week 12 and less than half of those (42.9%) who lost HCV RNA for the first time at week 24 achieved SVR. The patient who did not respond by treatment week 24 did not achieve SVR (table 3).

Table 3
Proportion of SVR by histology, past treatment history and early response

Variable	Number (%)
SVR by histologic diagnosis	
Chronic hepatitis	27/45 (60.0)
Cirrhosis	1/7 (14.3)
SVR by past history of treatment	
Naive	22/35 (62.9)
Hx. of IFN mono-therapy	2/5 (40.0)
Hx. of IFN + ribavirin therapy	4/12 (33.3)
SVR by the week of HCV eradication	
Week 12	25/35 (71.4)
Week 24	3/7 (42.9)
Week 48	0/1 (0)

Safety

A total number of 31 episodes of adverse events were recorded in 20 patients (38.5%), listed in table 4. Anemia, the most frequent adverse event, was reported in 7 patients, which in one case led to withdrawal. The mean of hemoglobin level at week 48 (12.4±1.6 gr/dL) was significantly lower than mean of pre-treatment hemoglobin level (15.2±1.5 gr/dL) (P=0.000). However, after the 24-week follow up this value returned to near pre-treatment level (15.2±1.1 gr/dL). Neutrophil count was another value that significantly decreased during treatment (3707±1574 cells/mm^3 at base line vs. 2045±1380 cells/mm^3, P=0.000) but returned to near base line value at week 72 (3539±1804 cells/mm^3).

The mean of platelet count was 211,765±67,305, 152,936±55,160, and 189,000±49,292 cells/mm^3 at base-line, week 48 and week 72, respectively. The difference was significant only between base-line and week 48 (P=0.000). A platelet count of less than 50,000 cells/mm^3 occurred in 3 patients, which led to dose modification of PEG-IFN. None of these patients with thrombocytopenia had a serious bleeding. In two patients therapy was discontinued because of severe adverse events. One of them attempted suicide due to major depression about 40 days after treatment initiation. The other one was a thalassemic patient in whom the treatment was discontinued at 28th week because of severe anemia as well as severe fatigue, myalgia, rigors and nightly fever.

One patient died of an accidental heroin overdose 2 months after completing 48 weeks of treatment. The patient had a history of intra-venous drug abuse, and the death was considered by the investigators to be unrelated to therapy.

Table 4
Incidence of discontinuation, dose modification and adverse events

	How many patients (%)	How many episodes (%)
Discontinuation	2 (3.8)	-
Dose modification	8 (15.3)	-
Adverse events		
Anemia	7 (13.5)	7
Neutropenia	1 (1.9)	1
Thrombocytopenia	3 (5.8)	4
Hyperthyroidism	1 (1.9)	1
Hypothyroidism	5 (9.6)	5
Depression	3 (5.8)	3
Skin rash	2 (3.8)	2
Severe flu-like Syn.	2 (3.8)	2
Mouth ulcer	1 (1.9)	1
Dyspnea	1 (1.9)	1
Nausea	1 (1.9)	1
Uric acid elevation	2 (3.8)	2
Gum bleeding	1 (1.9)	1

Discussion

The overall SVR rate of PEG-IFN plus ribavirin therapy by intention-to-treat analysis found in this study was 53.8%. The initial pilot studies evaluating efficacy of PEG-IFN plus ribavirin reported a response rate of 60-70 percent. [6, 7]Two phase III large clinical trials by Manns et al [8] and by Fried et al [9] showed an SVR of 54% for PEG-IFN 2b plus ribavirin and 56% for PEG-IFN 2a plus ribavirin, respectively. Approximately two-thirds of the patients in both studies had HCV genotype 1 infection. In addition, both of these randomized trials revealed a better response for PEG-IFN compared with standard IFN. Insufficient data of pre-treatment HCV genotype and viral level in the study population were two main shortcomings in our study. These are the well-known factors that strongly affect the response rate.[3] According to the previous studies, SVR was 42-46% in genotype 1 versus 76-82% in genotype 2 and 3 [8, 9] A most recent study that stratified patients based on genotype and initial viral level showed the highest SVR of 51% for genotype 1 and 73-78% for genotype 2 and 3. [10] This study indicated that treatment with PEG-INF plus ribavirin may be individualized by genotype. Patients with HCV genotype 1 require treatment for 48 weeks and a standard dose of ribavirin but those with HCV genotypes 2 or 3 seem to be adequately treated with a low dose of ribavirin for 24 weeks. Although we were not able to obtain genotype data in most of our patients, a recent study surveyed HCV genotype distribution in Iran reported that about 66% of patients were infected with genotype 1a or 1b subgroups. [11] This proportion indicated that the most of patients in Iran are probably categorized as difficult to treat patients.

Although the SVR rate found in our study is near to previous reports [8, 9], it should be considered that the study population in these trials was a homogenous population of naïve patients. If we seclude naive patients in our study, SVR will be 62.9%, which is a little higher than that of previous trials. [8, 9] Despite the higher response in our naïve patients compared to patients who had failed treatment with IFN-based therapy, SVR in prior non-responders or relapsers in our study was 6/17 (35.3%), which was a considerable rate. Two other studies which evaluated efficacy of re-treatment in such patients showed an SVR of 15-20 percent. [12, 13] The highest SVR was achieved in those who had relapsed following IFN plus ribavirin therapy. [12] In addition, in line with our study, SVR was significantly higher in patients previously treated with IFN mono-therapy versus combination therapy with ribavirin.[13]

Fried et al. showed that the patients who did not achieve early response, defined as at least a two-log decline in HCV RNA by week 12, had only a 3% chance of achieving SVR. [9] Therefore, some studies recommended that stopping therapy after 12 weeks in such patients should be considered. [9, 14] Since we defined the early response as a negative HCV RNA at week 12, we observed that 3/7 (43%) of patients who lost HCV RNA for the first time at week 24 achieved SVR. This proportion in the study by Manns et al is 32percent. [8] This important point illustrated that if the clinicians have to use qualitative PCR to evaluate virologic response, such as in the most parts of Iran, they are recommended to continue the treatment by week 24 even if HCV RNA remains positive at week 12.

In our study, 1/7 of patients (14.3%) with cirrhosis had an SVR, a rate much lower than findings from the other studies. [8, 10, 15] There have been no studies of combination therapy focused specifically on patients with cirrhosis. In a few studies, [8, 9] which information on cirrhotic patients was derived from subgroup analyses of enrolled patients with all stages of liver disease, the SVR was 43-44% in cirrhotic cases treated with PEG-IFN plus ribavirin. In the study by Hadziyanis S et al, cirrhotic patients could even achieve an SVR of over 70% when they had HCV genotype 2 and 3. [10] It should be mentioned that these studies combined the cases of bridging fibrosis with those with cirrhotic ones for analysis. Another trial that examined PEG-IFN monotherapy exclusively on patients with bridging fibrosis and cirrhosis reported a 30 % of SVR. [15] All of these SVR rates are much higher than what we found in our study although the number of our cirrhotic patients (7 cases) was not enough to get a realistic comprehensive ratio.

The patients in this study mostly tolerated the medications. A total number of 20 patients experienced at least one episode of adverse event and in most of them adverse event was not serious. In two patients (3.8%) adverse event led to treatment discontinuation and in eight patients (15.3%) dose modification was required. We noted that, compared with the other reports of the PEG-IFN plus ribavirin trials, our study had a lower number of dose modifications and fewer patients who discontinued therapy. Haemoglobin level, neutrophil and platelet count decreased after the initiation of treatment but rapidly returned to base-line values in follow up period. The studies that compared side effects between PEG-IFN and standard IFN did not find any significant difference between two groups with respect to side effects frequency and withdrawal. [8, 9] Fried et al reported that flu-like symptoms and depression were less common in patients receiving PEG-IFN compared with those who received standard IFN. [9]

A study that compared quality of life in patients who were treated with PEG-IFN or standard IFN showed that patients

receiving PEG-IFN experienced statistically better quality of life and less fatigue than those receiving standard IFN.[16] Another most recent study compared quality of life (QOL), work productivity, and medical resource utilization in patients who received either PEG-IFN mono-therapy or standard IFN plus ribaverin. [17] This study indicated that patients receiving PEG-IFN had improved work productivity, less activity impairment, decreased need for prescription drugs to treat adverse effects, and better adherence to therapy.

In summary, this study showed that combination therapy with PEG-IFN plus ribavirin was associated with a promising SVR rate and acceptable tolerability. Thus, the primary benefit of PEG-IFN plus ribavirin may be convenience of administration of a once-weekly injection compared with alternate-day injections, and the potential for better compliance. This regimen may be effective for patients who failed prior IFN-based treatment, particularly those who relapsed to prior combination therapy with standard IFN plus ribavirin or after standard IFN mono-therapy. If the clinician evaluates virologic response with a qualitative PCR, the treatment is recommended to be continued by week 24, even if HCV RNA is positive at week 12.

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