Original Article

Safety and Efficacy of Locally Manufactured Pegylated Interferon in Hepatitis C Patients

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Abstract:

Background: To evaluate the safety and effectiveness of locally produced pegylated interferon-α2a in treatment-naïve patients with chronic hepatitis C.

Methods: All treatment-naïve patients diagnosed with chronic hepatitis C who referred to two university based outpatient clinics in Tehran from December 2007 to May 2008 were enrolled. Exclusion criteria included the presence of a debilitating disease, decompensated cirrhosis, or refusal to participate in the study. Patients were treated with 180 μg pegylated interferon-α2a (Pegaferon) weekly and 800 – 1200 mg ribavirin daily for 24 or 48 weeks depending on genotype and weight. Viral and biochemical response and adverse drug reactions were recorded.

Results: A total of 108 patients were enrolled; 63 with genotype 1 and 45 with genotypes 2 and 3. The mean age of the patients was 39 years (range: 19 – 65). Ninety-seven patients completed the study and 76 achieved sustained viral response. The sustained viral response among patients completing the study was 67% for genotype 1 and 95% for genotypes 2 and 3. Adverse events were well tolerated and none led to discontinuation of treatment, however dose adjustment was necessitated in 16 patients. The most common adverse events were fatigue (73.5%), poor appetite (66.2%), and feverishness (57.4%). The mean hemoglobin drop was 2.9 g/dL.

Conclusions: Locally produced PEG-IFN in Iran is safe and effective in treatment-naïve chronic hepatitis C. ClinicalTrials.gov identifier: NCT01137383

Keywords: Hepatitis C, peginterferon alfa-2a, ribavirin

see the page 269

Introduction

Chronic hepatitis C (CHC) is a major cause of liver-related morbidity and mortality worldwide.[1,2] In Iran, the most common cause of chronic viral hepatitis is still hepatitis B with a prevalence of 2.6%[3] while the seroprevalence of hepatitis C virus is almost 0.5%,[4] much lower than many developed countries.[2] Following implementation of the newborn vaccination program in most counties, the prevalence of hepatitis B is decreasing whereas the prevalence of hepatitis C appears to be increasing,[4] emphasizing the need for an effective treatment. The treatment of CHC has always been a challenge. Currently, the best available treatment is the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV).[5–7] Unfortunately, even in the best hands, sustained viral response (SVR) is seen in a portion of subjects and in the case of genotype 1, which is more difficult to treat, barely exceeds 60%.[5–7] The treatment is often 48 weeks long and adverse drug reactions (ADR) are frequent, many leading to discontinuation of treatment. To add to this difficulty, PEG-IFN is quite expensive. Unfortunately, health insurance companies in Iran do not cover PEG-IFN, thus many patients cannot afford treatment.

Recently, an Iranian pharmaceutical company has produced a 40 KD PEG-IFN at a much lower cost

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under the trademark of Pegaferon (Pars No Tarkib, Tehran, Iran). If the safety and efficacy of this product are proven, its lower cost would allow for the treatment of a much wider range of patients.

We designed a study to evaluate the safety and effectiveness of Pegaferon in treatment-naïve patients with CHC.

Patients and Methods

Subjects

Consecutive patients who referred to two outpatient departments affiliated with Tehran University of Medical Sciences during a six month period from December 2007 to May 2008 were evaluated for enrollment. Patients aged between 15 and 65 years were included if the diagnosis of CHC was confirmed by at least two positive tests for HCV RNA, at least three months apart.

Patients underwent a full medical workup that included a liver biopsy which was scored according to Ishak et al.[8]

Exclusion criteria included previous treatment for CHC, co-infection with HIV or HBV, having major thalassemia or hemophilia, active drug abuse, under treatment for major depression or psychosis, having decompensated cirrhosis, serum creatinine >1.5 mg/dL, solid organ transplant, untreated thyroid disease, uncontrolled diabetes mellitus, uncontrolled autoimmune disease, and advanced cardiac or pulmonary diseases. Patients who planned to become pregnant during the next 1 – 1.5 years (depending on genotype), patients with inadequate contraception or those not consenting to the study were also excluded.

Treatment

Subjects were treated according to the standard of care in 2007. All patients received 180 μg of Pegaferon (Pars No Tarkib, Tehran, Iran) weekly combined with RBV. Patients with genotypes 2 or 3 received 800 mg RBV daily and were treated for 24 weeks. Patients with genotypes 1 or 4 were treated for 48 weeks and received 1000 mg RBV daily if they weighed less than 75 kg and 1200 mg if over 75 kg.

Follow-up

Subjects were visited at the end of weeks 1, 2, 4, and then every 4 weeks until the end of treatment. The patients were also visited 24 weeks after end of treatment. At each visit, patients were asked in detail about ADRs and complaints were registered carefully in special forms. Complete blood count and liver enzymes were also performed. Viral RNA counts were performed before treatment and on week 12 (Roche COBAS Amplicor HCV Monitor v2.0, Roche Diagnostics, Mannheim, Germany). Qualitative HCV RNA PCR (Roche COBAS Amplicor HCV 2.0, Roche Diagnostics, Mannheim, Germany) was performed at week 4, end of treatment and 24 weeks after treatment end for all subjects. For genotypes 1 and 4, an additional qualitative HCV RNA PCR was performed on week 24. Thyroid stimulating hormone (TSH) was requested before treatment, at week 12, and at the end of treatment. Anti-TPO was checked if TSH was abnormal at the initial work up and so forth. Pregnancy tests were performed every 24 weeks for female subjects and spouses of male subjects. Definitions of terms used for describing viral response and treatment failure are given in Table 1.

Dose adjustments and treatment discontinuation

The dose of RBV was decreased by 200 or 400 mg/day if hemoglobin levels dropped below 10 g/

Table 1. Terms and abbreviations commonly used in describing response to treatment

Rapid viral response	Undetectable viral RNA at week 4 of treatment
Early viral response (EVR)	≥2 log decrease in viral count at week 12
Partial EVR	EVR with detectable viral RNA
Complete EVR	EVR with undetectable viral RNA
Null response	Not achieving ≥2 log decrease in viral count at week 12
Breakthrough	Reappearance of viral RNA during treatment after viral RNA has become negative
End-of-treatment response (ETR)	Undetectable viral RNA at end of treatment
Sustained viral response	Undetectable viral RNA 24 weeks after end of treatment
Recurrence (relapse)	Reappearance of viral RNA within 24 weeks after end of treatment in a patient with ETR

Table 2. Initial characteristics of patients

Male/female ratio	92/16, (85% male)
Age (yr, mean±SD)	39±11.4 (range: 19–65)
Height (cm, mean±SD)	173±7 (range: 154–188)
Weight (kg, mean±SD)	72±12 (range: 43–120)
Body mass index (kg/m^2, mean±SD)	24±4 (range: 17–35)
Aspartate transaminase (IU/L, mean±SD)	63±72 (range: 13–640)
Alanine transaminase (IU/L, mean±SD)	87±84 (range: 10–683)
Hemoglobin (g/dL, mean±SD)	14.8±1.5 (range: 10.4–17.8)
White blood cell count (/mm^3, mean±SD)	6,900±1,900 (range: 3,000–12,400)
Neutrophil count (/mm^3, mean±SD)	3,800±1,400 (range: 1,300–10,400)
Platelet count (/mm^3, mean±SD)	204,000±51,000 (range: 89,000–335,000)
Genotype	
Genotype 1	63 (58%)
Genotype 1a	50 (46%)
Genotype 1b	13 (12%)
Genotype 2	2 (2%)
Genotype 3a	43 (40%)
Viral count (IU/mL, mean±SD)	2,090,000±3,560,000 (range: 541 – 18,600,000)
Low viral count [<800,000 IU/mL, No (%)]	59 (55%)
Liver histology (Ishak et al.)[8]	
Grade [n (%)]	5.7±1.9 (mean±SD)
Grade 0–8	87 (96%)
Grade 9–13	4 (4%)
Grade 14–18	0 (0%)
Stage (mean±SD)	1.8±1.4 (mean±SD)
Stage 0–2	66 (72%)
Stage 3–4	19 (21%)
Stage 5–6	6 (7%)

dL and discontinued if below 8 g/dL. The dose of Pegaferon was decreased by 25% or 50% if the neutrophil count decreased to below 1,000 or 750/mm^3, respectively. Treatment was discontinued if neutrophils decreased to less than 500/mm^3. The dose of Pegaferon was decreased by 50% if the platelet count dropped below 50,000/mm^3 and was discontinued if less than 25,000/mm^3. After normalization of laboratory tests, the original dose was reinstituted. Treatment was also discontinued if the levels of liver enzymes increased over three times their initial value at any point during treatment.

Extra safety measures

The first 4 doses of Pegaferon were given in the hospital under direct supervision of the researchers and patients were observed for 4 hours. A 24-hour telephone line was available for patients to call in case of emergencies.

Ethics

Use of Pegaferon in human subjects was authorized by the Iranian Ministry of Health and Medical Education after detailed studies on the product. The research protocol was approved by the Institutional Review Board and Ethics Committee of the Digestive Disease Research Center of Tehran University of Medical Sciences. Patients were fully informed that there was no published study available on Pegaferon, although other brands of 40 KD PEG-IFN have been routinely used. The study protocol was also explained in detail. Subjects were enrolled only if they signed the informed consent form. In the case of married patients, written consent was also obtained from the spouses.

Statistical methods

Patients receiving at least one Pegaferon injection and referring for at least one follow-up visit were included in the final analysis if their outcome was known. A worst-case analysis was also performed assuming all patients lost to follow-up were non responders. All analysis was performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 108 patients were enrolled. The initial patients' characteristics are given in Table 2. We did not find any cases with genotype 4. There was no significant difference in demographic data or baseline laboratory findings among the different genotypes. Low viral load (<800,000 IU/mL) was observed in 59 patients (55%). The most common risk factor was drug addiction (either intravenous or non-intravenous) followed by a history of surgical

or dental procedures (Table 3).

Of the 108 patients included, rapid viral response (RVR) was achieved in 68/103 (63%), early viral response (EVR) in 93/100 (93%), cEVR in 89/100 (89%), pEVR in 4/100 (4%), and SVR in 76/97 patients (78%, Figure 1). Eleven patients were lost to follow-up. Assuming all patients lost to follow-up were non-responders (worst-case scenario), the SVR rate would be 76/108 (70%). The viral responses for the different genotypes are given in Table 4.

Table 3. Frequency of risk factors observed in 108 patients with CHC

	%
Non-intravenous drug addiction	40
History of surgical procedure	37
Intravenous drug addiction	34
History of dental procedure	29
History of imprisonment	27
History of cupping	20
Extramarital sex	19
Tattooing	19
History of blood transfusion	10

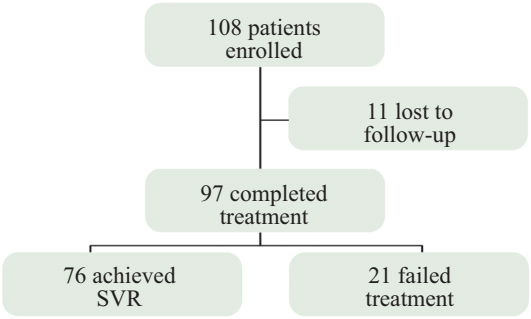

Figure 1. Patient flow

The most common ADR reported by patients was fatigue (73.5%) followed by loss of appetite (66.2%). Other common ADRs were feverishness (57.4%), musculoskeletal pain (55.9%), and hair loss (48.5%). Significant weight loss (≥10% of body weight) was observed in 29% of the patients.

The mean hemoglobin level dropped from 14.8 g/dL before treatment to 11.9 g/dL at the end of treatment. The mean platelet count dropped from 204,000/mm^3 to 170,000/mm^3 with a minimum of 152,000/mm^3 at week 36, and neutrophil count from 3800/mm^3 to 2300/mm^3, with a minimum of 1800/mm^3 at week 36. Seventy-five percent of the maximum decrease in hemoglobin level occurred over the first 12 weeks of treatment (12.2 mg/dL). In the case of platelet and neutrophil counts, 90% of the maximum decrease occurred during the first 4 weeks (mean 169,000/mm^3 and 2100/mm^3, respectively). Changes in hemoglobin levels, neutrophil counts and platelet counts are charted in Figure 2. Hypothyroidism occurring during treatment (TSH>5 IU/L) was observed in 9 patients (8%) which was managed accordingly.

ADRs leading to Pegaferon dose adjustment were seen in 8 patients (7%), all due to neutropenia. Two of these also had low platelet counts. In no patients did the neutrophil count fall below 500/mm^3 or the platelet count below 40,000/mm^3. In 12 patients (11%), all expressing genotype 1, the RBV dose was adjusted due to anemia. In 4 of these patients, the Pegaferon dose was also adjusted due to low neutrophil counts. No dose adjustments were necessary due to low platelet counts alone, increased liver enzyme levels, or other ADRs. No patients discon-

Table 4. Viral response of 108 patients with CHC treated by Pegaferon

	Genotype 1	Genotypes 2 and 3	Total
Number of patients	63 (58%)	45 (42%)	108
RVR	29/59 (49%)	39/44 (87%)	68/103 (63%)
EVR	53/59 (90%)	40/41 (98%)	93/100 (93%)
cEVR	52/59 (88%)	37/41 (90%)	89/100 (89%)
pEVR	1/59 (2%)	3/41 (7%)	4/100 (4%)
No EVR (null response)	6/59 (10%)	1/41 (2%)	7/100 (7%)
ETR (intention-to-treat)	46/63 (73%)	42/45 (93%)	88/108 (81%)
SVR			
Per-protocol	38/57 (67%)	38/40 (95%)	76/97 (78%)
Worst-case scenario	38/63 (60%)	38/45 (84%)	76/108 (70%)
Breakthrough	8/50 (16%)	1/40 (3%)	9/90 (11%)
Recurrence	5/46 (11%)	1/42 (2%)	6/88 (7%)
Lost to follow-up	6/63 (10%)	5/45 (11%)	11/108 (10%)

RVR=rapid viral response; EVR=early viral response; pEVR=partial EVR; cEVR=complete EVR

tinued treatment due to ADRs. Of the 16 patients requiring dose adjustments, 10 (63%) achieved SVR whereas in the 81 patients not requiring adjustment, SVR was observed in 66 (82%). This difference was not statistically significant even when separately calculated for each genotype.

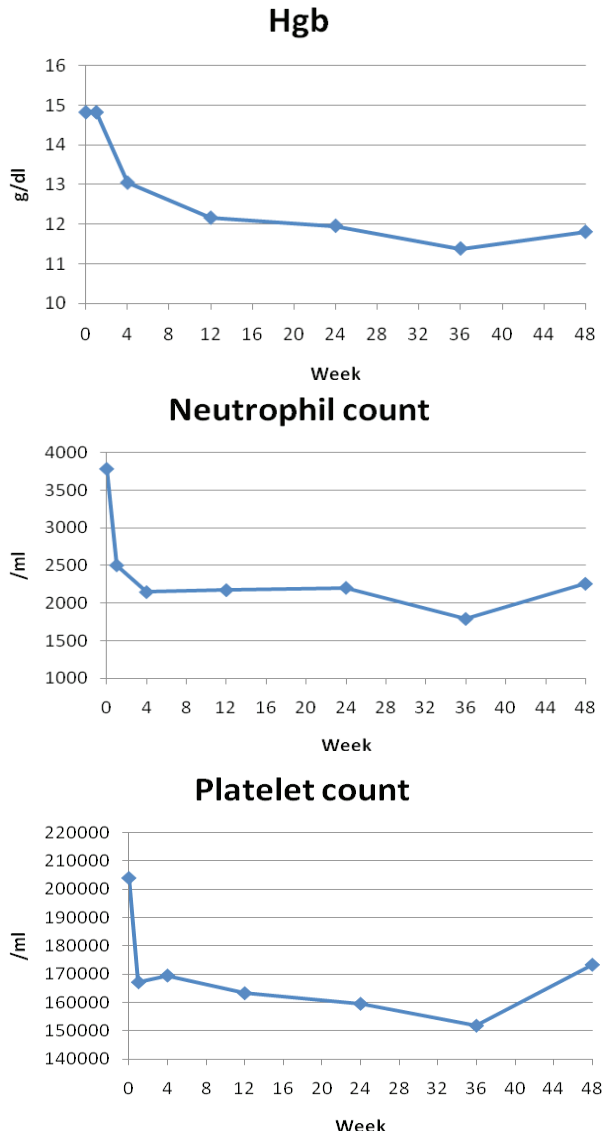

Figure 2. Changes in hemoglobin level, neutrophil count and platelet count during treatment of 108 cases of hepatitis C with pegylated interferon and ribavirin

Discussion

Hepatitis C is a major cause of chronic liver disease. The current seroprevalence of hepatitis C infection in the general population of Iran is estimated to be 0.5%.[4] The rate is much higher in certain subgroups such as drug addicts or subjects with hemophilia or thalassemia.[9–11] Unfortunately the burden of HCV is increasing and will soon become a major health problem, especially in high-risk groups. The standard of care for HCV is treatment with PEG-IFN and RBV. Suggested treatment is at least 24 weeks long and durations up to 72 weeks are being recommended in certain cases.[12,13] The currently available PEG-IFN formulations are very expensive, especially when not supported by health insurance companies. In this study we have implemented a newly introduced formulation of PEG-IFN (Pegaferon) for the treatment of CHC and have shown its safety and effectiveness. Assuming all our lost-to-follow-up patients were non responders (worst-case scenario), we observed an SVR rate of 60% in genotype 1 and 84% in genotypes 2 and 3 which is comparable to other studies reporting SVR rates of approximately 52% and 84% for genotypes 1 and non-1, respectively.[5] Among patients completing the study, our per-protocol SVR rates were even better at 67% and 95% for genotypes 1 and non-1, respectively. Many factors are known to influence SVR rates including viral load, age, sex, race, fibrosis, and body mass index.[14–16] We did not find any significant effect of these factors in our study but the numbers of our subjects were too small to allow a reliable statistical inference.

The adverse effects observed in our study were generally mild and tolerable. No patient discontinued treatment due to adverse effects. We observed that the major decrease in hemoglobin level occurred by week 12 of treatment and over 90% of the decreases in platelet and neutrophil counts occurred by week 4 (Figure 2). This indicates the importance of close monitoring of bone marrow function during early weeks of treatment. In many cases with advanced liver disease, the initial low platelet count discourages patients and physicians from starting treatment. As seen in Figure 2, 90% of the decrease in platelet count is discernible as early as week 1. Thus, observing an acceptable platelet count after the first week of treatment might be a good indicator that the platelet counts will stay high enough during the full treatment course, even when the pre-treatment counts are low.

Sixteen of our patients required adjustments in doses of Pegaferon and/or RBV. In 8 patients (7%),

the dose of Pegaferon was adjusted due to low neutrophil counts. Other reports for the rate of neutropenia requiring dose adjustment are in the range of 18 – 20%.[6,7] Anemia requiring dose adjustment was observed in 12 patients (11%). This number, too, was more favorable than previous reports of approximately 20%.[7] Our better numbers might be partially explained by the fact that in the second half of our study we used prophylactic granulocyte colony stimulating factor (G-CSF) or erythropoietin as soon as the neutrophil counts or hemoglobin levels fell below 1500/mm^3 or 11 g/dL, respectively.[17] The SVR rate for patients requiring dose adjustments (either Pegaferon or RBV) was much lower (63% vs. 82%) although this difference was not statistically significant. Three patients who received less than 80% of the total dose of both RBV and Pegaferon had viral breakthrough and did not achieve SVR. The other 13 patients did receive over 80% of their medications and the SVR rate in this group was 77%, very close to the SVR among patients not requiring dose adjustments (82%). This finding is in line with the belief that if over 80% of medications are taken, the SVR rate will not be significantly affected.[18,19]

Besides the troublesome and often severe adverse effects, patients have to deal with the expenses of treatment. Some patients may require frequent injections of erythropoietin or G-CSF which further adds to treatment cost. It is frequently observed that patients refuse treatment solely because of the cost. In the current study we have demonstrated the safety and efficacy of Pegaferon, the PEG-IFN locally produced in Iran, which will reduce the cost of treatment to less than half.

In conclusion, we expect that the introduction of this locally produced PEG-IFN (Pegaferon) will reduce the cost of treatment by more than 50% and make treatment available to many patients which otherwise would be unable to afford it.

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Arg-é Bam (Bam Citadel) before December 26, 2003 earthquake. This lofty, ancient city-citadel lies 190 kilometers South-East of Kerman in central Iran, dates back to two thousand years ago, and is listed by UNESCO as a World Site Heritage.
(***Source:*** Behzadi AS. Ard-e Bam. In: Shahbazi ASH, ed. *The Splendour of Iran.* Vol.2. London: Booth-Clibborn Editions; 2001: 74 – 75.)(See page 351)