Pegaferon in hepatitis C: Results of a Multicenter Study

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ABSTRACT

BACKGROUND

Chronic hepatitis C (CHC) is a major contributor to cirrhosis and hepatocellular carcinoma and major global public health problem that causes mortality in both developed and developing countries. For the past decade, treatment with pegylated interferon (peg interferon α) and ribavirin (RBV) has been associated with rates of sustained virologic response of $\leq 66\%$ among patients with hepatitis C virus (HCV) infection. In this study, we report the response rate of Iranian treatment-naïve CHC patients to Pegaferon, a locally developed pegylated interferon-α2a (PEG-IFNα2a).

METHODS

Patients diagnosed with CHC who referred to two university based outpatient clinics in Tehran from December 2007 to May 2011 were enrolled in a single-group, open-labeled experimental design. Eligible patients were above 15 years of age and had HCV infection with evidence of chronic hepatitis. Exclusion criteria included the presence of a debilitating disease, decompensated cirrhosis or refusal to participate in the study. Patients were treated with 180μg Pegaferon weekly in addition to 800-1200 mg daily, weight-based RBV for 24 or 48 weeks depending on genotype. Viral response and adverse effects were recorded.

RESULTS

A total of 216 patients were enrolled in the study of which 83.3% were male and 16.7% were female. In 93 (43.1%) patients, the HCV RNA viral load was $\geq 800,000$ IU/ml before starting treatment. "As-treated analysis" indicated that a total of 168 (77.8%) patients achieved sustained viral response (SVR, undetectable plasma HCV RNA 24 weeks after the last planned dose of study treatment).

CONCLUSION

This study, with a larger number of participants, confirms the results of a previous study by the authors that Pegaferon, a PEG-IFNα 2a locally produced in Iran, is effective in treatment-naïve CHC patients.

KEYWORDS

Hepatitis C virus; Pegylated interferon; Pegaferon; Ribavirin

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INTRODUCTION

Hepatitis C virus (HCV) infection affects 170 million people worldwide. There is ample evidence that this infection is a major contributor to cirrhosis and hepatocellular carcinoma (HCC),

and is one of the most common indications for liver transplantation.[1] CHC is a major global public health problem in both developed and developing countries.[2] In Iran, the prevalence of HCV infection is estimated to be around 0.16%- 0.5%.[3, 4] Although the prevalence of hepatitis B is decreasing, the prevalence of hepatitis C appears to be increasing in recent years.[4] These figures justify the enormous research efforts that have been undertaken since the HCV genome was first discovered in 1989.[5]

Understanding of the etiology and pathogenesis of HCV infection has improved considerably. This has led to the development of therapeutic strategies which have evolved significantly over the past decades. Initially, interferon (IFN)-α monotherapy was administered to HCV patients three times a week for 24 or 48 weeks, but outcomes were generally poor, with only 10-20% of patients achieving a sustained virological response [SVR; defined as undetectable (<50 IU/ml) HCV RNA 24 weeks post treatment].[6, 7]

However, approval for the use of ribavirin (RBV) in combination with IFN-α in 1998 and further advances with the advent in 2000 of pegylated IFN (PEG-IFN), brought about dramatic improvements that led to SVR rates of 30-40% and ≤ 66%, respectively.[8-14]

Two PEG-IFNs are currently available. PEG-IFNα 2a, a 40 KDa, branched PEG moiety attached to IFNα 2a by a stable amide bond (PEGASYS; Roche, Basel, Switzerland), that consists of six positional isomers and PEG-IFNα 2b (12 KDa; Peginteron; Schering- Plough Corporation, Kenilworth, NJ, USA).[14]

Recently, an Iranian pharmaceutical company has produced a 40 KD PEG-IFN at a much lower cost under the trademark of Pegaferon (Pars No Tarkib, Tehran, Iran).[15, 16] Here, we report the results of response to Pegaferon in treatment-naïve patients with CHC.

MATERIALS AND METHODS

Subjects

We enrolled sequential treatment naïve CHC patients who referred to two university based outpatient HCV clinics of Digestive Diseases Research Center (DDRC) Located at Shariati Hospital and Firoozgar Hospital, both affiliated with Tehran University of Medical Sciences from December 2007 to May 2011. Eligible patients were above 15 years of age and had HCV infection with evidence of chronic hepatitis, as evidenced by a liver biopsy performed not more than one year before study screening. Exclusion criteria included previous treatment for CHC, co-infection with HIV or HBV, active drug user, major thalassemia or hemophilia, under treatment for major depression or psychosis, presence of 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. We do not offer treatment to patients above 65 years of age unless requested by the patient.

Treatment

Patients with genotypes 2 or 3 received 800 mg RBV daily in two divided doses for 24 weeks. Patients with genotypes 1 or 4 received 1000 mg RBV daily if they weighed less than 75 kg and 1200 mg if over 75 kg for 48 weeks. All participants received 180 µg of Pegaferon weekly.

Efficacy assessments and end points

Plasma HCV RNA levels were measured with the COBAS TaqMan HCV RNA assay (Roche COBAS Amplicor HCV Monitor v 2.0, Roche Diagnostics, Mannheim, Germany). HCV

Table 1: Terms, abbreviations and definitions used for efficacy assessment.

Terms and abbreviations	Definitions
Rapid virologic response (RVR)	Undetectable viral RNA at week 4 of treatment
Early virologic response (EVR)	≥2 log decrease in viral count at week 12
Partial early virologic response (pEVR)	EVR with detectable viral RNA at week 12
Complete early virologic response (cEVR)	EVR with undetectable viral RNA at week 12
Null response (NR)	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 virologic response (SVR)	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

RNA levels were measured before treatment, at week 4, end of treatment and 24 weeks after end of treatment for all subjects. For genotypes 1 and 4, an additional qualitative HCV RNA PCR was performed on week 24. Definitions of terms used for describing viral response and treatment failure are given in Table 1.

Safety assessments

Hematologic, chemical and hormonal evaluations were performed at periodic durations along with ongoing efficacy assessments. Data on adverse events were collected at each treatment visit and at the safety follow-up assessment. Full physical examinations were performed at each visit and at the safety follow-up evaluation. Physical examinations were performed as needed for the assessment and treatment of symptoms during visits. Complete blood count (CBC) and liver function tests (LFT) were requested at each visit to assess possible adverse effects. 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 12 weeks for female subjects and spouses of male subjects.

Anemia was managed by parenteral injections of erythropoietin at doses of 2000-4000 IU/lit when hemoglobin levels were less than 10 g/dl and with reductions in dose of RBV in accordance with product labeling if there was no response to erythropoietin. Granulocyte colony stimulating factor (G-CSF) was used to correct white blood cell count when absolute neutrophil count (ANC) was less than 1000 cell/mm^3. For any abnormalities in TSH, patients were referred to an endocrinologist.

Ethics

The Institutional Review Board and Ethics Committee of the Digestive Disease Research Center of Tehran University of Medical Sciences approved the research protocol. Subjects were enrolled only if they signed the informed consent form. Use of Pegaferon in human subjects was authorized by the Iranian Ministry of Health and Medical Education after detailed studies on the product.

Statistical methods

Efficacy and safety analyses included data from all patients who participated in the study and received at least one dose of any study drug. An "as-treated analysis" was performed considering our previous experience of very low rate of drop out and high adherence. All analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 216 patients were enrolled in the study of which 83.3% were men and 16.7%

women. Of these, 93 (43.1%) had HCV RNA viral loads above 800,000 IU/ml before starting treatment. Patients' major baseline demographic and disease characteristics are presented in Table 2.

There was a low drop out rate (2%) and high rate of adherence (> 95%), therefore an "as-treated analysis" was performed. A total of 168/216 (77.8%) patients achieved SVR (undetectable plasma HCV RNA 24 weeks after the last planned dose of study treatment) implementing the standard of care treatment with Pegaferon and RBV. Also, a significantly greater proportion of patients with genotypes 2 or 3 (75%) who received Pegaferon plus RBV for 24 weeks compared to those with genotypes 1 or 4 (69%) who received Pegaferon plus RBV for 48 weeks met the criteria for SVR ($p < 0.051$; Table 2).

Table 2: Baseline characteristics of study patients.

Parameter	No.
Age [median(Range)]	40 (20-75)
Male/female	180/36 (83.3 male)
HCV subtype [no (%)]	
1	112 (51.8)
1a	91 (42.1)
1b	10 (4.6)
1a/1b	8 (3.7)
1(?)	3 (1.4)
3	96 (44.5)
3a	95 (44)
3(?)	1 (0.5)
2	3 (1.4)
4	--
Mixed genotype	5 (2.4)
HCV RNA $\geq$ 800,000 IU/ml [no. (%)]	93 (43.1%)

DISCUSSION

These results confirm earlier studies showing a significantly better rate of SVR among patients infected with HCV genotypes 2 or 3 as compared to genotypes 1 or 4.[8-14] In the current study, we have used a locally manufactured pegylated IFN, Pegaferon (Pars No Tarkib, Tehran, Iran) in combination with standard doses of RBV in treatment of patients with CHC. The effectiveness of this regimen has been previ-

ously shown in a study with a smaller number of patients.[15] However, the larger number of patients in this study confirms previous results, determining that use of this newly developed pegylated IFN is effective and safe for treatment naïve cases of CHC.

Moreover, in addition to 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 costs.[15]

Refusal of CHC therapy and follow up because of cost is a common phenomenon among patients with HCV infection, especially since most of these patients are ex-injectional drug users and from poor socioeconomic status. In the current study we have demonstrated the safety and efficacy of Pegaferon which will reduce the cost of treatment to less than half.

The high rate of SVR in this study confirms previous reports from the Asian race.[17-20] However, part of this high SVR might be related to a thorough preliminary work up and screening, educational programs for patients to increase their awareness, before starting treatment adherence to medications and a qualified clinical setting for management. Also, use of erythropoietin-stimulating agents and G-CSF decreased the rate of drop out and non-adherence, thus increasing patient satisfaction during treatment course.

In conclusion, it seems that the introduction of this new brand of locally produced PEG-IFN (Pegaferon), with proven acceptable efficacy will reduce treatment expenditure by more than 50%, making treatment affordable for many patients whose poor economic conditions are a major obstacle for proper management.

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CONFLICT OF INTEREST

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