ORIGINAL ARTICLE

The Efficacy and Side Effects of Therapy Peginterferon Alpha-2a (PEGASYS) Combined with Ribavirin in Chronic HepatitisC Patients: an open label Clinical Trial

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Abstract

BACKGROUND AND AIMS: Peginterferon alpha-2a is a known standard therapy for patients with chronic HCV infection. However efficacy and safety of this treatment is still unclear in regional settings. This study was designed to clarify efficacy and safety of peg-interferon based therapy in Iranian patients.

METHODS: 23 patients were treated with Peginterferon alpha-2a in combination with ribavirin for 48 weeks. The patients were observed for adverse effects and response to therapy during treatment and 24 weeks after the end of therapy.

RESULTS: Early virologic response, end of treatment response, and sustained virologic response rates were 86.9 % (20/23), 82.6 % (19/23), and 78.3 % (18/23) respectively. The most common adverse effects in descending order were flue-like symptoms (74%), mood changes (48%), and weight loss (43%).

CONCLUSION: Combination therapy with Peginterferon alpha-2a and ribavirin for 48 weeks is an effective treatment with minimal adverse effects.

KEY WORDS: Hepatitis C, Pegylated interferon-alfa-2a, Ribavirin, Therapy

Introduction

Chronic hepatitis C is the leading cause of chronic liver disease and liver transplantation, affecting 170 million persons worldwide.[1, 2] It is a condition leading to life-threatening complications such as cirrhosis and hepatocellular carcinoma; two situations that are difficult and costly to treat. Its prevalence in Iran varies from 0.12% in volunteer blood donors to

13 % in hemodialysis patients and up to 40 % in some high-risk groups such as intravenous drug users. Patients with major thalassemia and hemophilia are also at high risk for hepatitis C virus (HCV) infection due to history of receiving multiple blood product transfusions.[3, 4]
Although the annual incidence of hepatitis C decreased dramatically in the 1990s, the morbidity and mortality from hepatitis C are projected to continue to increase over the next 10–20 yrs because of the high prevalence of this disease and the development of progressive liver disease in some cases.[5, 8] Great emphasis has been placed on treatment of this potentially life-threatening illness. Therapy has steadily improved over the last decade. Previously it was found that 24-wk monotherapy with interferon alfa-2b led to viral eradication in 8% of cases, and 24–48 wk of interferon alfa-2b plus ribavirin led to viral eradication in 40 percent.[9,10] Previous studies demonstrated that sustained virological response (SVR) can now be achieved in over 50% of individuals treated with the combination of long-acting pegylated interferon and ribavirin.[11,13] This combination is considered to be the standard treatment for chronic hepatitis C at present time.[14] Although these newer agent is significantly more effective than earlier versions of standard interferon, the side-effects profile of interferon-based therapies has remained largely unchanged.[11,15,16] Response rate seems to be different among different ethnic groups.[17] Short-term outcomes of administration of this newly established standard regimen has not been studied in our region. We designed the present study to show efficacy and safety of this treatment in Iranian patients.

Patients and methods

In a two-year period (from 2002 to 2004), we enrolled consecutive patients with detectable anti-HCV antibody and HCV-RNA in the serum, who had elevated serum alanine aminotransferase (ALT). Written informed consent was taken from them. Patients with decompensated cirrhosis have not been entered in the study. For women of childbearing age, urine or blood pregnancy test has been taken within the 24-hour period prior to the first dose of study drug. All males and females receiving ribavirin had to use two forms of effective contraception during treatment and for 6 months after treatment ended. Women with ongoing pregnancy or breast feeding, and patients under any systemic anti-neoplastic or immunomodulatory treatment, with severe psychiatric disease or seizure disorder, autoimmune disease, thyroid malfunction, severe retinopathy, severe underlying disease, or evidence of drug abuse within one year of study entry were excluded. The mentioned excluding factors were investigated by comprehensive history taking and seeking in patients past medical records. In case of any suspicious finding, the patient was referred to specialist(s) to rule in/out the suspected disorder (such as major depression disorder, retinopathy, etc.). Liver biopsies were taken for all patients, except two of the three hemophiliacs, before beginning the therapy (biopsy was contraindicated in these two patients due to bleeding tendency but the other hemophilic patient did not have contraindication for biopsy and the procedure was performed for him). The specimens were studied by a certain pathologist and reported in modified HAI scoring system.[18] All patients were treated with Pegylated interferon alpha-2a (Pegasys, Roche) 180 micg subcutaneously weekly and ribavirin 800 mg daily (patients over 75 kg received 1200 mg daily dose). The treatment duration was 48 continuous weeks that was followed by a 24-week post-treatment follow up period. Since the intervention was found to be the standard effective treatment for the patients, including an observational group taking placebo or conventional interferon would be against the ethics of this study and there was no observation group in this study. Patients were examined , laboratory tests were requested on baseline visit and then 2, 4, 8, 16, 32, 40 and 48 weeks after beginning of therapy and then at 8th and 24th weeks after cessation of treatment. Subjects were questioned about any new experience that might be an adverse event caused by the present therapy. Complete blood count was performed at each visit to screen for anemia, neutropenia and thrombocytopenia. Thyroid function tests were also performed regularly to assess possible thyroid dysfunction. Investigation for serum HCV RNA was done by qualitative PCR method (RT-PCR nested) at Park clinic laboratory, Tehran-Iran, before beginning the treatment, 12 and 48 weeks after treatment and also 24 weeks after discontinuation of therapy to assess initial viral status of the patients, early virologic response (EVR), End Of Treatment response (EOT), and Sustained Virologic Response (SVR) respectively. The sensitivity of the test was 300 copies per ml.

Results

We enrolled 23 cases (20 males and 3 females) were included in this study, 3 of whom were known cases of hemophilia and 4 had a previous history of conventional interferon-alpha based therapy. Mean patients' age was 45.43 years (ranged 27-67 yrs). The mean stage for liver biopsy of patients was 3.26 (Min=1, Max=6, SD=1.40) and the mean for grade was 6.57 (Min=3, Max=10, SD=2.26). Biopsy results showed homogeneity of the study group. Patients were questioned for the risk factors that could possibly be associated with hepatitis C infection. Baseline characteristics of the studied patients are presented in table 1.

Table 1
Baseline charactristics of chronic HCV infected patients treated with combination of Pegylated interferon alpha-2a and ribavirin

Charecteristics		No (%)
Risk factors	IV drug use	8 (35)
	Hemophilia	3 (13)
	War injury	1 (4)
	Unknown	11 (47)
Positive Baseline PCR		23 (100)
Male gender		20 (87)
Previous IFN-based therapy		4 (17)
		Mean+/-SD [min-max]
Age		45.3+/-9.7[27-67]
Baseline Serum AST		62.3+/-33.5[36-201]
Baseline Serum ALT		74.2+/-32.8[49-185]
Baseline HAI Scores	Stage	3.26 +/-1.40[1-6]
	Grade	6.57 +/-2.26[3-10]

3 of 23 patients dropped out of study due to lack of cooperation to consecutive follow up visits. All 20 remaining patients had EVR and all except one showed EOT response at the 48th week of antiviral therapy. Virologic response sustained in all EOT responders except one hemophilic patient (1/19 = 5.2% relapsed). Two other hemophiliacs responded well. To calculate the total failure rate we considered the three dropped out patients as non-responders to our treatment strategy. 5 out of 23 studied cases (21.7 %) failed to achieve a sustained virologic response (SVR) and 18 patients had sustained virologic response (overall response rate was 78.3 %). In both cases of relapse the patient was male, had genotype 1b and over-mean baseline biopsy results. . One of them was a 50 y/o man without pervious history of antiviral therapy but with a baseline stage of 5/6 and grade of 4/18 in modified HAI scoring system. The other one was a hemophilic patient previously treated for chronic hepatitis C with conventional interferon-based therapy and had a baseline stage of 4/6 and grade of 9/18. Important side effects of therapy that led to dose reduction or temporarily stopping the therapy were observed in 3 patients. One female patient became thrombocytopenic with a platelet count of 42000 that led to temporary reduction of Peginterferon dose by 25%. The dose of Peginterferon was elevated to 180 micg/ week after resolution of thrombocytopenia. In another male patient, absolute neutrophil count decreased to 588 /mm3 (from baseline 3480/mm^3) that led to a temporary Peginterferon dose reduction until the count reached normal values. Another male patient became anemic with hemoglobin of 9.4 g/dl (baseline measurement =13.9 g/dl) in whom case ribavirin was discontinued and not administered until anemia was resolved. These three patients did not experience the mentioned adverse effects more than once during the therapy and all ended in SVR. One patient's wife became pregnant during the treatment period in spite of contraception and was instructed to abort the fetus. None of the patients experienced a side effect that could significantly affect the treatment plan. Other side effects that were more common are listed in table 2. Flu-like symptoms were the most frequently observed finding and fortunately were self-limiting and rarely existed more than a few weeks from the first administration of the study drug. This problem was helped a lot by limited use of acetaminophen or ibuprofen tablets just before injection of peginterferon. Mood changes were seen in 11 patients who were observed closely and helped by psychiatrist. Weight loss was also a common finding, ranging from mild to severe. Alopecia, pruritus and dry skin were also symptoms observed in a significant number of patients. 3 cases developed non-productive cough for whom pneumonia and interstitial pneumonitis were ruled out by appropriate work-up. Sleep disorder was observed in 6 patients and was controlled with medication. The 36 y/o male patient who became hypothyroid was treated with levothyroxin tablet daily and thyroid hormone levels became normal and remained normal after cessation of hormone therapy. One 42 y/o male patient presented with herpes simplex infection of lips followed by painful oral ulcers produced on tongue and buccal regions.

Table 2

adverse effects observed during treatment with pegylated interferon and ribavirin

Adverse Efectt	NTo. (%)
Flu-like symptoms	17 (74)
Mood change	11 (48)
Weight loss	10 (43)
Pruritus	7 (30)
Alopecia	7 (30)
Sleep disorder	6 (26)
Local pain (injection site)	4 (17)
Cough	3 (13)
Hypothyroidism	1 (4)
Oral ulceration	1 (4)

Discussion

The results from various clinical trials clearly demonstrate that Pegylated interferon alfa-2a provides a significant improvement over standard interferon alfa-2a therapy and confers even further benefit when administered with ribavirin. SVR is improved in patients with difficult-to-treat disease, such as patients infected with HCV genotype 1 and in patients with cirrhosis. Histological improvement is observed in patients with and without SVR. Viral RNA measurements during the first 12 weeks of treatment can be used to predict those patients who will and will not go on to achieve a sustained virological response. Peginterferon alfa-2a also contributed to significant improvements in quality of life both during and after treatment. Two recent multi center trials on the efficacy of peginterferon alfa-2a (180 micg/ Subcutaneous each week) revealed that SVR rate was 56 percent and 52 percent, respectively. For patients with genotypes 2 or 3 it raised to 76 percent and 80 percent in these studies, respectively.[11, 19] The results of our study were near to the response rate among patients with genotype 2 or 3 in previous studies. In this study we did not determine the HCV genotype among study cases. So, it is possible to suspect that most of our patients had easy to treat genotypes. Also, EVR was obtained in all 20 patients who remained in the study that is another positive feature to establish this idea. According to previous studies flu-like symptoms may develop in virtually all cases treated with Interferon. But fortunately these symptoms resolve or become less severe after the first month of therapy. Also, acetaminophen or ibuprofen taken at the time of injection may resolve these symptoms. [11,12,1 5] We observed similar results in our studied patients. Psychiatric disorders are reported to be another common side effect seen in treated cases (reported in approximately 50 % of patients). In our study similar result was obtained. Suicidal attempts have been reported in less than 1 percent of patients and no such result was found in our study.[20] Both relapsing patients had baseline liver biopsy results showing over-average scores. One of them had stage 5, which shows a pre-cirrhotic status and the other had a stage of 4 showing the preliminary higher histopathologic scores in patients who will not respond to the therapy. Other side effects were similar to those of previous studies.[16] It is concluded that the combination of peginterferon and ribavirin in chronic hepatitis C patients is highly effective with minimal adverse effects. Further studies in greater scales are recommended to determine epidemiology of HCV and also response to therapy in our region.

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REFERENCES

1- National Institutes of Health Consensus Development Conference Panel Statement: Management of hepatitis C. Hepatology 1997; 26:2–10S.
2- Alter MJ, Kruszon-Moran D, Nainan OV, et al. The prevalence of hepatitis C virus infection in the United States 1988 through 1994. N Engl J Med 1999; 341:556 –62.
3- Alavian SM, Gholami B, Massarat S. Hepatitis risk factors in Iranian volunteer blood donors: A case-control study. J Gastroenterol Hepatol 2002; 17:1092-1097.
4- Alavian SM, Einollahi B, Hajarizadeh B, Bakhtiari S, Nafar M, Ahrabi S. Prevalence of hepatitis C virus and related risk factors among Iranian hemodialysis patients. Nephrology 2003; 8,256-260.
5- Wong JB, McQuillan GM, McHutchison JG, Poynard T. Estimating future hepatitis C morbidity, mortality, and costs in the United States. Am J Pubic Health 2000; 90: 1562–9.
6- Armstrong GL, Alter MJ, McQuillan GM, Margolis HS. The past incidence of hepatitis C virus infection: Implications for the future burden of chronic liver disease in the United States. Hepatology 2000;31: 777–82.
7- Kim WR. The burden of hepatitis C in the United States. Hepatology 2002; 36:S30 –4.
8- El-Serag HB. Hepatocellular carcinoma and hepatitis C in the United States. Hepatology 2002; 36:S74 –83.
9- Poynard T, Marcellin P, Lee SS, et al. Randomized trial of interferon alpha2b plus ribavirin for 48 wk or for 24 wk versus interferon alpha2b plus placebo for 48 wk for treatment of chronic infection with hepatitis C. International Hepatitis Interventional Therapy Group. Lancet 1998; 352: 1426 –32.
10- McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Group. N Engl J Med 1998;339: 1485–92.
11- Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Goncales FS, Haussinger D, et al. Combination of peginterferon alfa-2a plus ribavirin in patients with chronic hepatitis C virus infection. N Engl J Med 2002; 347: 975-982.
12- Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: A randomized trial. Lancet 2001; 258: 958 –65.
13- Hadziyannis S, Cheinquer H, Morgan T, et al. Peginterferon alfa-2a (40kD) (PEGASYS) in combination with ribavirin (RBV): efficacy and safety results from a phase III, randomised, double-blind multi-centre study examining effect of duration of treatment and RBV dose. J Hepatol 2002; 36(Suppl 1): 3.
14- National Institutes of Health Consensus Development Conference Statement: Management of hepatitis o3-S20
15- Fried MW. Side effects of therapy for hepatitis C and their management. Hepatology 2002; 36: S237-S244.
16- Russo MW, Fried MW. Side effects of therapy for chronic hepatitis C. Gastroenterology 2003; 124:1711-1719.
17- Muir AJ, Bornstein JD, Killenberg PG. Peginterferon alpha-2b and ribavirin for the treatment of chronic hepatitis C in blacks and non-hispanic whites. N Engl J Med. 2004; 350: 2265-2271.
18- Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, Kiernan TW, Wollman J.Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology. 1981; 1(5):431-5.
19- Hadziyannis S, Sette H, Morgan T, et al. Peginterferon alfa-2b and ribavirin combination therapy in chronic hepatitis C:a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140:346.
20- Pariante CM, Orru MG, Baita A, et al. Treatment with interferon alpha in patients with chronic hepatitis and mood or anxiety disorders. Lancet 1999; 354:131