ORIGINAL ARTICLE

Combination Therapy of Interferon-alpha (PDferon B®) and Ribavirin for Chronic Hepatitis C

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Abstract

Introduction: The addition of ribavirin (RIBA) to the standard treatment with interferon (IFN) alpha led to an improvement in sustained virologic response (SVR) from less than 20% with IFN monotherapy to 40-45% in combination therapy. The aim of this study is to assess the therapeutic efficacy and safety of IFN alpha (PDferon B®) in combination with RIBA on Iranian patients with chronic hepatitis C (CHC).

Methods: 48 naive patients aged 18 years or more with CHC were enrolled and treated with 3 mega units (MU) IFN alpha-2b three times a week plus 800-1000 mg RIBA per day for 48 weeks. Follow-up after therapy was 6 months. The efficacy was evident at the end of treatment and at the end of follow-up in terms of sustained normalization of alanine aminotransferase and sustained serum HCV-RNA loss.

Results: The rate of sustained biochemical and virologic response were 68.3% and 78%, respectively. Virologic response was 80.9% and 86.4% at weeks 12 and 48 as well. Any patient didn't have serious complication.

Conclusion: Although we had no control group who used standard IFN, our preliminary finding showed acceptable and promising response rate of PDferon. On the other hand, it seems that adverse events with PDferon are as like as other standard IFNs. Fax: +98-21-8975730

Key words: Interferon, Ribavirin, Hepatitis C, Treatment

Introduction

Chronic hepatitis C infection is now recognized as an important health care problem [1]. Approximately 2-3% of the worlds population is infected with hepatitis C virus (HCV); HCV is one of the leading causes of liver failure and cancer and is the single most common indication for liver transplantation [2, 3]. In Iran the prevalence of HCV infection is about

0.12% in blood donors [4], but increasing. It seems that the prevalence of HCV infection is less than 1 percent in general population, but the infection is emerging mostly due to problem of intravenous drug use and needle sharing in the country. HCV infection is the most prevalent cause of chronic hepatitis and cirrhosis in hemophilic and thalassemic patients and cases with renal failure in Iran [5].

The addition of ribavirin (RIBA) to the standard treatment with IFN-a led to an improvement in sustained virologic response (SVR) from less than 20% with IFN monotherapy to 40-45% in combination therapy [6].

The aim of the present study is to assess the therapeutic efficacy and safety of IFN in combination with RIBA on Iranian patients with CHC.

Materials and Methods

This is a quasi-experimental study on patients with chronic hepatitis C referring to Tehran Hepatitis Center between May 2001 and May 2003. All patients received IFN a-2b (PDferon, Pooyesh Darou, Tehran, Iran) at a dose of 3 mega units (MU) given subcutaneously three times a week for 48 weeks with RIBA which was given orally twice or thrice a day to a total dose of 1000 mg (body weight ≥ 75 kg, 14 patients), 800 mg (body weight < 75 kg, 34 patients) per day.

Naive patients 18 years or older, with compensated chronic HCV infection (43 patients) or cirrhosis (5 patients) were eligible for the study. Eligible patients were positive for serum HCV-RNA by RT-PCR (reverse transcriptase polymerase chain reaction), liver biopsy sample had histopathological confirmation of chronic hepatitis and abnormal serum aminotransferase concentration for at least 6 months before start of protocol or normal enzymes while knodell score is exceeding or equal 4 and fibrosis stage is more than 2.

Entry hemoglobin values had to be at least 120 g/L for women and 130 g/L or more for men. Patients with evidence of decompensated liver disease, HIV-1 or hepatitis-B coinfection, previous organ transplantation, pre-existing psychiatric conditions, seizure disorders, cardiovascular disease, hemoglobinopathies, hemophilia, poorly controlled diabetes, or autoimmune-type disease were not included in the study. All patients were assessed for safety, tolerance, and efficacy at the end of weeks 12, 24, 36, 48 and week 24 after the end of treatment. Serum HCV-RNA was measured qualitatively (Amplicore II, Roche) before treatment and at weeks 12, 48 and week 24 after the end of treatment.

The estimated sample size of 48 patients was based on a type I error rate of a=0.05, with an assumption of treatment benefit being 50% of sustained response rate, the accuracy around this rate equal to 0.15% of standard deviation of this response, using the ratio estimation formula and loss rate equal to 10%.

A serum sample was taken and HBV, HCV, and HIV seromarkers were checked for every subject. For detection of HBV infection, HBV surface antigen (HBsAg) was determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (Hepanostika HBsAg Uni-Form II microelisa system, Organon Teknika, Holland). For HCV infection, anti-HCV antibody (anti-HCV Ab) was detected using a third-generation ELISA kit (ETI HCV K-3, DiaSorin, Spain). Complementary test was done with the recombinant immunoblot assay (RIBA-3 Chiron, New Jersey, USA) for positive results of anti-HCV Ab. Patients with both ELISA and RIBA positive reports were considered to be infected with HCV. The serum samples were tested for anti-HIV antibody using ELISA kits (Genscreen HIV, Bio Rad, France).

Statistical tests such as t and chi-square, correlation coefficients such as phi, odds ratio and repeated measurement method were used in analysis by SPSS version 11.5 software (SPSS Inc. Chicago, Illions, USA). Correlations with P value < .05 were considered statistically significant. Informed consent was obtained from each patient in writing and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Results

A. Patients characteristics: Five patients were lost to follow-up due to non hepatic problems in 2 persons, and not having the compliance of drugs in three. Characteristics of other 43 patients are mentioned in table 1.

B. Efficacy:

B.1. Virologic response: Serum HCV-RNA level became undetectable in 38 (80.9%) patients at week 12 (EVR: early virologic response). It was 38 (86.4%) at week 48 (ETR: end of treatment virologic response) and 32 (78%) after the end of 24 weeks follow-up (SVR: sustained virologic response). There was a significant correlation between EVR and ETR (P<0.001, r=0.823). In other words, all 36 patients with negative HCV RNA at 12th week (with EVR) had an ETR (negative HCV RNA at the end of treatment), as well. On the contrary, 2 patients from the 7 cases without EVR had an ETR and SVR as well. There was not any significant correlation between EVR and SVR. However, ETR can predict SVR significantly that is negative HCV RNA at the end of treatment causes 24-fold the probability of SVR [P=0.008, OR=24.8(2.28-269.63)]. EVR, ETR, and SVR were observed in 4, 4, and 3 cases of five cirrhotic patients.

B.2. Biochemical response: Biochemical response, during and after treatment is shown in table 2. Mean AST and ALT decreased during treatment, but had a slow rising at the end of follow-up in comparison with the end of treatment. This alteration was significant (P<0.001). Biochemical and virologic response were closely linked, that is 78.1% of patients with a sustained virologic response had also a sustained biochemical response (P=0.018).

C. Adverse events and dose reduction: White blood cell and hemoglobin had decreasing amount until 9th month and then increased till 6 months after the end of treatment (P<0.001). Platelet, neutrophil, PT and weight had a similar pattern, but it was not significant. Anemia (hemoglobin ≤ 10 g/dl) in 3 patients, dose reduction of RIBA in one non-cirrhotic patient and cease the treatment due to not having the compliance of drugs in three non-cirrhotic patients were

adverse effects of this regimen on these patients. After the beginning of the therapy, thrombocytopenia (platelet < 150000 per milliliter) was observed in 29.2% of the patients at the 12th week and reached to 45.2% at the 36th week. Then, it decreased till 17.9% at the 24 weeks after the end of treatment. These were 2.4%, 15.4%, and 3.1% regarding neutropenia (neutrophil < 1500 per milliliter), respectively.

Reticulocyte (P=0.012), total bilirubine (P=0.018) and lactate dehydrogenase (P=0.01) increased until 3rd month after the beginning of treatment. Then, they had a continuous decrease until 6 months after the end of treatment.

Hypothyroidism developed in three patients and required hormone replacement without need for IFN dose reduction. Other complications consists of depression in three cases, and upper limb purpura, vitiligo, and alopecia each one in 1 case. In fact, 40 patients (83.3%) had at least one not serious complication. Any patient didn't have serious complication. There was not any death.

Table 1
Baseline characteristics of the patients

Patients' details	No. (%)
Sex (% male)	41 (85.4%)
Age (years, mean (SE))	39.8 (1.7)
Body weight (kg, mean (SE))	74 (2)
Source	
Transfusion	30 (62.2%)
Intravenous drug abuse	5 (10.5%)
Hejamat [a]	5 (10.5%)
Extramarital sexual contact	3 (6.3%)
Sporadic, other or unknown	5 (10.5%)
Biochemistry	
AST [b] (U/I, mean (SE))	76 (5)
ALT [b] (U/I, mean (SE))	109 (10.4)
Histology [c]	
Grading (mean (SE))	5.9 (0.7)
Staging (mean (SE))	2.5 (0.3)
Cirrhosis (No.(%))	5 (11.1)

[a]: A procedure in Iranian traditional medicine done by making shallow cuts on the trunk (upper back) and producing a suction effect that results in drawing blood from cuts (less than 100 cc). It is usually done by a non-physician, using non-standard instruments (done for healing or cure purposes).
[b]: ALT: alanine aminotransferase; AST: aspartate aminotransferase
[c]: Classification according to modified knodell score

Table 2
Biochemical response in different visits

Liver enzyme \ Treatment week	12	24	36	48	End of follow up	Six months after the end of treatment	Sig.
AST*	38 (79.2%)	9 (18.8%)	8 (16.7%)	7 (14.3%)	6 (14.3%)	10 (22%)	<0.001
ALT*	44 (91.7%)	14 (29.2%)	9 (18.8%)	21.4 (10%)	11 (24.4%)	13 (31.7%)	<0.001

*: values are number and the percent of people with normal enzyme (AST≤45U/L, ALT≤40U/L)

Discussion

Although, the number of patients with cirrhosis was small (10.4% of patients in this study); but, it seems that this group will benefit from 48 weeks of treatment because these patients have extensive fibrosis, are mostly older than 40 years, and are often men [7].

AST and ALT had a continuous decrease until the 36th week and a slow rising until 24 weeks after the end of treatment; although, it didn't reach to its primary level. Likewise, WBC, hemoglobin, platelet and weight had a similar pattern. What happens during the first 36 weeks? Maybe the efficacy of this combination therapy is temporary. Fortunately, it seems that complications are not constant, too. In other words, there is a probable resistance to the efficacy and complications of this therapy after 36 weeks.

In our study 2 patients from the 7 cases without EVR had an ETR and SVR as well. Consequently, late clearance of HCV RNA from serum during combination therapy was also associated with a sustained response. This phenomenon is uncommon in patients who are treated with IFN alone, which suggests that stopping therapy at week 12 because of persistent viremia, as previously suggested [1] may not be appropriate in the case of therapy with IFN and RIBA.

This relatively high SVR should induce a parallel decrease in the rate of complications. However, this hypothesis must be confirmed by long-term follow-up of the sustained responders to establish the durability of the virologic response and reduction in the development of cirrhosis. Previous trials have already shown that sustained responders are less likely to develop fibrosis-stage cirrhosis [8].

Discontinuation of therapy was 10.4% for all hepatic

related and non-related causes that is, equal or less than other similar studies [9-10]. Likewise, no serious adverse effects were seen in this study which meta-analysis studies are in agreement as well [9-10].

The safety profile in these patients reflects the known side effects of each drug given as monotherapy and is consistent with that reported for patients in relapse [11]. SVR is usually between 40-45% in combination therapy [6]. In the present study SVR was 78%. Even though all patients were easy to treat, it is an acceptable response rate. The differences between the results of this study with others may be explained by different populations with respect to genotype, numbers of previous antiviral treatments, and condition of the immune system. Type, dose and duration of IFN appeared to be less important [12].

Iron in the liver has been associated with decreased responsiveness to alpha interferon therapy [13]. According to liver biopsy, only two patients had hemosiderosis in this study which can be an alternative cause of the acceptable sustained response. In conclusion, although we had no control group who used standard IFN, our preliminary finding showed acceptable and promising response rate of PDferon. On the other hand, it seems that adverse events with PDferon are as like as other standard IFNs, although for scientific judgment a control group is necessary. At present, combination therapy with IFN plus RIBA is an acceptable choice in treatment of patients with CHC. Long term follow-up will show the relation between SVR and histological improvement in responder patients.

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