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EFFICACY AND SAFETY OF COMBINATION THERAPY OF INTERFERON-ALPHA 2B PLUS RIBAVIRIN FOR CHRONIC HEPATITIS C

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ABSTRACT

Introduction: The aim of this study is to assess the therapeutic efficacy and safety of a particular brand of IFN alpha (PDferon B®) in combination with ribavirin (RIBA) on Iranian patients with chronic hepatitis C (CHC). The addition of 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.

Methods: 69 naive patients aged 18 years or older with CHC were enrolled and treated with 3 mega units (MU) IFN alpha-2b three times a week plus 800-1200 mg RIBA per day for 48 weeks and the patients were followed for 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 rates of sustained biochemical and virologic response were 63% and 61%, respectively. Virologic response was 83.1% and 86.4% at weeks 12 and 48 as well. No patients had serious complications.

Conclusion: Although we had no control group using standard IFN alone, our preliminary findings showed an acceptable and promising response rate to PDferon. On the other hand, it seems that adverse events with PDferon are as other standard IFNs.

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Keywords: 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 world's population is infected with hepatitis C virus (HCV). Although the annual incidence of acute hepatitis C is decreasing because of universal screening of blood products and safe needle programs, the prevalence of liver disease as a result of CHC is increasing because of more frequent detection and diagnosis of asymptomatic individuals as well as the development of clinical manifestations in other patients with CHC.[2] The most significant clinical sequel of CHC stems from the development of progressive liver fibrosis, which can lead to cirrhosis, liver failure, and hepatocellular carcinoma (HCC) in some patients. An estimated 5%–15% of chronically infected

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individuals might develop cirrhosis during a period of 20 years.[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 the general population, but the infection is emerging mostly due to the problem of intravenous drug use and needle sharing in the country. HCV infection is the most prevalent cause of chronic hepatitis and cirrhosis in hemophiliacs, thalassemic patients, and renal failure patients in Iran.[5]

The addition of ribavirin (RIBA) to the standard treatment with IFN-α 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 efficiency and safety of a particular brand of IFN in combination with RIBA on Iranian patients with CHC.

PATIENTS AND METHODS

This is a quasi-experimental design, according to single group time series, on patients with chronic hepatitis C referring to Tehran Hepatitis Center and Imam Khomeini Hospital between May 2001 and November 2003. All patients received IFN α-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 (Hoffman La-Roche LTd Basel, Switzerland) which was given orally twice or thrice a day to a total dose of 1000-1200 mg (body weight >75 kg, 28 patients), 800 mg (body weight <75 kg, 41 patients) per day.

Naive patients 18 years or older, with compensated chronic HCV infection (61 patients) or cirrhosis (8 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 serum aminotransferase concentration more than 1.2 times normal values for at least 6 months before start of the protocol or normal enzymes while Knodell score is exceeding or equals 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, preexisting 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, NJ, USA) before treatment and at weeks 12, 48 and week 24 after the end of treatment.

The estimated sample size of 69 patients was based on a type I error rate of $\alpha = 0.05$, with an assumption of the treatment benefit being 50% of sustained response rate, the accuracy around this rate equal to 0.125, 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 micro Elisa 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). At the time of study, the genotyping of the patients with HCV infection was not possible in Iran.

Statistical tests such as t and chi-square, correlation coefficients such as phi, kappa, and odds ratio; Wald forward logistic regression and repeated measurement method were used in analysis by SPSS version 11.5 software (SPSS Inc. Chicago, Illinois, 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. Patient characteristics

Characteristics of these 69 patients are mentioned in Table I. Ten patients (14.5%) were lost to follow-up due to nonhepatic problems in 2 persons (1 case due to cost of drugs and another case due to return to addiction), not having the compliance of drugs in 4 (high fever and fatigue in two cases and exaggeration of depression in another two cases) and unknown in other 4 patients.

B. Efficacy

B.1. Virologic response

Serum HCV-RNA level became undetectable in 49 (83.1%) patients at week 12 (EVR: early virologic response). It was 51 (86.4%) at week 48 (ETR: end of treatment virologic response) and 36 (61%) after the end of 24 weeks follow-up (SVR: sustained virologic response). There was a significant correlation between EVR and ETR ($p<0.001$, kappa= 0.87). In other words, all 49 pa-

Table I. Baseline characteristics of the patients.

	No. (%)
Patients' details	
Sex (% male)	58 (84.1%)
Age (years, mean (SE))	40.6 (1.42)
Body weight (kg, mean (SE))	73.1 (1.97)
Biochemistry	
AST[a] (U/I, mean (SE))	78.1 (4.91)
ALT[a] (U/I, mean (SE))	104 (7.93)
Histology[b]	
Grading (mean (SE))	5.76 (0.5)
Staging (mean (SE))	2.34 (0.24)
Cirrhosis (No. (%))	8.1 (0.68)

[a]ALT: alanine aminotransferase; AST: aspartate aminotransferase

[b]Classification according to modified Knodell score

tients with negative HCV RNA at the 12th week (with EVR) had an ETR (negative HCV RNA at the end of treatment), as well. On the contrary, 2 patients from the 9 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 increases the probability of SVR 12.5-fold [p= 0.027, OR=12.5; 95% confidence interval of OR: 1.34-116.8].

EVR, ETR, and SVR were observed in 6, 6, and 3 cases in 8 cirrhotic patients.

Intention to treat response was 54 (78.3%) for EVR, 52 (75.4%) for ETR and 36 (52.2%) for SVR.

B.2. Biochemical response

Biochemical response, during and after treatment is shown in Table II. 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 80.6% of patients with a sustained virologic response had also a sustained biochemical response (p<0.001, r=0.515).

C. Adverse events and dose reduction

White blood cell and hemoglobin had decreasing levels until the 12th month and then increased till 6 months after the end of treatment (p<0.001). Platelets had a similar pattern, but it was not significant. Anemia (hemoglobin <10 g/dL) in 7 patients, dose reduction of RIBA in 2 non-cirrhotic patients and cease of treatment due to improper drug compliance in 10 non-cirrhotic patients were adverse effects of this regimen on these patients.

Hypothyroidism developed in 4 patients and required hormone replacement without need for IFN dose reduction. Other complications consisted of depression in 5 cases, and upper limb purpura, vitiligo, and alopecia, each in one case. In fact, 47 patients (79.7%) had at least one non-serious complication. No patients had serious complications. There was not any death.

DISCUSSION

Although the number of patients with cirrhosis was small (11.6% of patients in this study), 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 during treatment and a slow rising until 24 weeks after the end of treatment; although it didn't reach its primary level. Likewise, WBC, hemoglobin, platelet and weight had a similar pattern. Maybe the efficacy of this combination therapy is temporary and it is dependent to usage of the therapy or it is a rebound response to withdrawal of combination therapy. Fortunately, it seems that complications are not constant. In our study 2 patients from the 9 cases without EVR had an ETR and SVR. Conse-

Table II. Biochemical response in different visits.

Treatment week / Liver enzyme	week 12	week 48 (End of follow up)	Six months after the end of treatment	Significance
AST*	50 (84.7%)	53 (89.8%)	39 (73.6%)	<0.001
ALT*	44 (74.6%)	47 (79.7%)	37 (62.7%)	<0.001

*Values are number and the percent of people with normal enzyme levels (AST<45 U/L, ALT<40 U/L).

quently, 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. Although these are only two cases, it may suggest 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.

The relatively high SVR observed in our study 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 14.5% for all hepatic related and non-related causes, and was equal to other similar studies.[9,10] Likewise, no serious adverse effects were seen in this study, and 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 61%. Even though all patients were easy to treat, it is an acceptable response rate. However, it can be due to the 48 weeks duration of the treatment in cases with genotypes 2 and 3 in this study in comparison with 24 weeks in similar studies. Further studies should consider the genotypes for determination of the period of the treatment.

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] There is not enough data about combination therapy for HCV in Iran.

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 findings showed an acceptable and promising response rate for PDferon. On the other hand, it seems that adverse events with PDferon are similar to 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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