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A MULTICENTER STUDY TO EVALUATE THE SAFETY AND EFFICACY OF HEBERON (INTERFERON ALFA-2b) IN COMBINATION WITH RIBAVIRIN FOR THE TREATMENT OF CHRONIC HEPATITIS C IN IRAN

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ABSTRACT

Background: Combination therapy with interferon and ribavirin is the most effective treatment for chronic hepatitis C today. The aim of this study was to evaluate the efficacy and safety of thrice-weekly Heberon (interferon alfa-2b) in combination with ribavirin as first-line treatment of chronic hepatitis C.

Methods: A total of 97 treatment-naive patients received Heberon three million units thrice-weekly subcutaneously in combination with ribavirin for 12 months. Serum HCV RNA levels were measured before and during therapy and 6 months after the end of therapy. End-of-treatment and sustained virological responses was defined as an undetectable HCV-RNA level at the end of treatment, and 6 months after treatment was completed (end of follow-up), respectively.

Results: In an intent-to-treat analysis, HCV-RNA was undetectable at the end of treatment in 49.5% of patients. At the end of follow-up, sustained virological response was 36.1%. Combination treatment was generally well tolerated. Six patients stopped therapy because of side effects: severe cytopenia (n=4), depression (n=1), and hyperthyroidism (n=1). Common side effects of therapy include: Flu-like syndrome (85.6%), generalized alopecia (41.2%), injection site inflammation (37.1%), mood changes (36%), anorexia (34%) and weight loss (32%).

Conclusion: Heberon as an IFN product in combination with ribavirin for treat-

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ment of patients with chronic hepatitis C is relatively safe, feasible, and potentially efficacious. It has comparable results in achieving end-of-treatment and sustained virological responses in chronic hepatitis C.
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INTRODUCTION

Hepatitis C virus (HCV) infects an estimated 170 million persons worldwide and thus represents a viral pandemic.[1,2] It is responsible for significant morbidity and mortality world-wide. It is the most common chronic blood-borne infection. Chronic infection with hepatitis C virus (HCV) is the leading cause of chronic liver disease and the most common indication for liver transplantation.[3,4] Cirrhosis will eventually develop in 10 to 30 percent of chronic infections.[5] Most studies have reported rates of conversion to chronic HCV infection of 70 to 84 percent.[6,7] The primary treatment options for HCV infection include IFN alfa-2b with ribavirin. The multicenter trial reported herein was conducted to test the safety and efficacy of Heberon as an IFN alfa-2b product in combination with ribavirin in treatment-naive patients with HCV.

PATIENTS AND METHODS

Selection of patients

Adult patients who were 18 years and older with verifiable hepatitis C infection who had not been previously treated with IFN were eligible to participate in this trial. Eligibility was based on meeting the following inclusion criteria: seropositive for anti-HCV antibodies (RIBA); detectable serum HCV-RNA on testing with polymerase chain reaction (PCR); an elevated serum alanine transaminase (ALT) more than 1.5 times the upper limit of normal for at least six months; and had undergone, within one year of entry, liver biopsy, the results of which were consistent with a diagnosis of chronic hepatitis. Women had to be surgically sterile or postmenopausal, and men were required to practice barrier contraception. In addition, potential participants had to provide informed consent and be able to comply with the requirements of the study, including at-home SC injection of IFN according to the schedule designated in the protocol. Exclusion criteria included previous treatment with IFN; infection with HIV or hepatitis B virus; any cause other than HCV for liver disease; decompensated liver disease, manifesting as ascites, bleeding esophageal varices, or encephalopathy; anemia (hemoglobin concentration less than 12 g/dL in women and less than 13 g/dL in men), leukopenia (defined as a leukocyte count of less than 3000 per cubic millimeter), thrombocytopenia (defined as a platelet count of less than 100,000 per cubic millimeter), decompensated renal disease (defined by a serum creatinine level of more than 1.5 mg per deciliter), a psychiatric disorder such as severe depression or history of suicidal ideation or suicide attempt, a history of seizures, cardiovascular disease, poorly controlled diabetes mellitus, a history of organ transplantation, ongoing abuse of intravenous drugs or alcohol, autoimmune diseases and/or inability to practice adequate contraception.

Study design

This prospective, open-label trial was conducted at eight centers in Iran. The study was approved by the institutional ethics committees at each center, and all patients provided written, informed consent. The patients were assigned to treatment with recombinant interferon alfa-2b (Heberon alfa R, Center for Genetic Engineering and Biotechnology, Havana, Cuba) given subcutaneously in a dose of three million units three times per week plus ribavirin administered orally twice daily at a total daily dose of 1000 mg for patients who weighed 75 kg or less and 1200 mg for those who weighed more than 75 kg for 12 months. Both drugs were started and stopped at the same time. The severity of adverse events was graded as mild, moderate, severe or life-threatening.[8] Therapy was discontinued in the case of life-threatening events. For severe adverse events other than anemia, the dose of interferon alfa-2b was reduced to 1.5 million units three times a week and the dose of ribavirin was reduced to 600 mg/day. The full dose could be resumed after the event or discontinued if the effect persisted. The dose of ribavirin was reduced to 600 mg/day in patients whose hemoglobin concentrations fell below 10 g/dL; ribavirin was discontinued if the hemoglobin concentration fell below 8.5 g/dL. Patients were evaluated as outpatients before therapy, at weeks two, four, and then every month during treatment and 6 months after the end of therapy. Anti-HCV was tested by RIBA. HCV RNA was tested in serum by reverse transcriptase-polymerase chain reaction (RT-PCR), using two sets of primers specific for the 5' untranslated region of the HCV genome and nested amplification. Liver biopsies were assessed using modified Histologic Activity Index (HAI). The inflammation score was obtained by combin-

ing the scores for the first three components of this index: portal, periportal, and lobular inflammation. The scores could range from 0 to 18, with higher scores indicating more severe abnormalities. The degree of fibrosis was graded as 0, no fibrosis; 1, portal fibrosis; 3, bridging fibrosis; or 4, cirrhosis.

Assessment of efficacy

Efficacy analyses were conducted on an intent-to-treat population (n = 97). The primary efficacy variables were assessments of HCV RNA. The primary endpoint was a sustained virological response (SVR), defined as the absence of serum HCV-RNA 6 months after treatment was completed. Secondary endpoint was end-of-treatment virological responses, defined as the absence of serum HCV-RNA at the end of treatment. All patients discontinued therapy at 12 months and assessments at that time provided the end-of-treatment response; the evaluation at 18 months determined SVR. Sustained and end-of-treatment virological responses were summarized using percentages with corresponding 95% confidence intervals. Virological responses were determined from the absolute laboratory results. HCV-RNA was quantitatively measured. The lower level of detection was 1000 HCV copies per milliliter of blood (600 IU/mL).

Assessment of safety

Safety assessments were obtained in all patients (n = 97) who received at least one dose of study medication. Treatment-related adverse events were graded as mild, moderate, severe or life-threatening.

Statistical analysis

The study was designed to have 86 patients per group in order to have a power of 80% to detect a difference of percentage points between the rates of sustained virological response (35% v. 55%) at a 5% level of significance (with two-sided tests). These assumptions were based on the available data by Reichard and colleagues.[9] Enrollment began in February 2002; in August 2002, 97 patients had been recruited and further recruitment was stopped. The trial was completed in February 2004. With the help of SPSS 10, descriptive statistics, Mann-Whitney test, independent test and repeated measurments the data were compared and analysed. The comparison was with values before the start of therapy. A P value of less than 0.05 was considered to indicate statistical significance. All P values were two-tailed.

RESULTS

Characteristics of patients

Ninety-seven patients fulfilled the inclusion criteria and were enrolled into the study at 8 centers and each received at least one dose of study medication. Seventeen patients did not complete the 12 months period of therapy. Of these patients, only six stopped treatment for severe side-effects; in the other 9 patients, the withdrawal was a result of missed follow-up. 82 patients completed therapy according to the protocol. Patients were 66 men and 31 women. The mean age was 35.1 years. The majority of patients in the study were diagnosed with mild to moderate histologic grade and stage. Table I describes the main baseline features of patients.

Table I. Baseline characteristics of patients. BMI, body mass index; ALT, alanine aminotransferase.

Characteristic	
No. of patients	97
Age (y), mean (range)	35.1 (18-67)
Sex (male/female)	66/31
BMI (kg/m2), mean±SD	22.1±4
ALT (IU/l), mean±SD	106.2±38.7
ALT above upper limit of normal, n(%)	
1.5-2	35 (36.1)
2-3	36 (37.1)
>3	26 (26.8)
Grade, mean±SD	5±2.3
Grade, n(%)	
Mild (< 6)	56 (57.7)
Moderate to severe (>6)	41 (42.3)
Stage, mean±SD	2.6±1.5
Stage, n(%)	
Mild (<2)	53 (54.6)
Moderate to severe (> 2)	44 (45.4)
Cirrhosis, n(%)	12 (12.4)

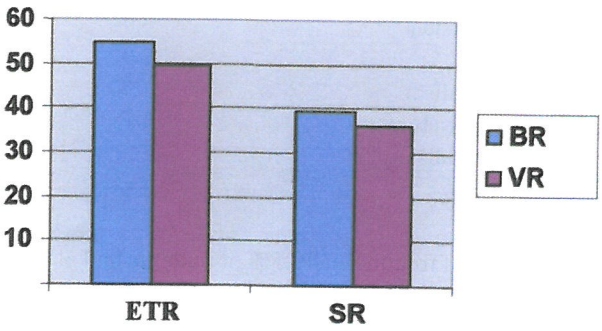

Fig. 1. Virological and biochemical response at end of treatment (ETR) and follow-up (SR). BR, biochemical response; VR, virological response.

Table II. End-of-treatment virologic response according to pretreatment variables.

Characteristic	With virologic response n= 48	Without virologic response n= 49	P value
Age (y), mean mean±SD	34.6±14	33.7±13	0.15
BMI (kg/m^2), mean±SD	21.8±3.9	22.7±4.3	0.09
Sex (male%)	68.2	65.2	0.42
ALT above upper limit of normal, n(%)			
<2.5	31 (64.6)	33 (67.3)	0.08
>2.5	17 (35.4)	16 (32.7)	
Grade, n(%)			
Mild (< 6)	29 (60.4)	28 (57.1)	0.22
Moderate to severe (>6)	19 (39.6)	21 (42.9)	
Stage, n(%)			
Mild (<2)	27 (56.2)	23 (46.9)	0.07
Moderate to severe (> 2)	21 (43.8)	26 (53.1)	

Table III. Rates of discontinuation of treatment, and adverse events.

Variable	Percent
Discontinuation of treatment due to adverse events	5.8
Adverse events	
Any adverse event	94.8
Flu-like syndrome	85.6
Generalized alopecia	41.2
Injection site inflammation	37.1
Mood changes	36
Anorexia	34
Weight loss	32
Fever	24.3
Thrombocytopenia	17.5
Headache	13.6
Leukopenia	10.7
Diarrhea	6.8
Nausea	5.8
Sleep disorder	4.9
Taste perversion	3.9
Rash	2.9
Hypothyroidism	1.9
Injection site abscess	1
Hyperthyroidism	1

Efficacy

At the end of treatment, 49.5% of patients had cleared HCV-RNA, and SVR was seen in 36.1% of patients. End of treatment and sustained biochemical response rates were 54.6% and 39.1%, respectively. Virologic relapse after therapy was 27.1 percent. Response rates are shown in Fig 1.

Undetectable levels of serum HCV RNA was associated with normalization of serum alanine aminotransferase values in all patients who had sustained virologic responses. Sustained virologic response was unrelated to age, sex, BMI, pretreatment serum ALT levels, grade or stage. The pretreatment variables related to end-of-treatment virologic responses are shown in Table II. Stepwise logistic-regression analyses revealed no association.

Safety

All patients (n = 97) were included in the safety population. Fifteen patients did not complete 12 months of therapy for discontinuation due to adverse events (six patients) or being lost to follow-up (nine patients). Nearly 95% of patients experienced at least one expected treatment-emergent adverse event that was characterized as related to study medications. Table III summarizes the IFN therapy adverse events that were reported during treatment. The most common adverse event across treatment were Flu-like syndrome (85.6%), generalized alopecia (41.2%), injection site inflammation (37.1%), mood changes (36%), anorexia (34%%) and weight loss (32%). The majority of events were mild to moderate (grades 1 and 2) and were expected based on the reported adverse effects of IFN. Typically they required no treatment, and were resolved without sequelae. Fewer than 10% of adverse events were listed as grade 3 or 4 events.

Therapy was well tolerated in all patients except the six who discontinued treatment due to serious adverse events; four severe cytopenia, one depression, and one hyperthyroidism. Seven of the 82 patients who completed treatment required dose modification. The incidence of discontinuation of treatment for any severe

event was 6.2% and was not different to previous reports of others.[10,11] The most frequent reasons for reductions in the dose of interferon were influenza-like symptoms and emotional disturbance. Reductions in the dose of ribavirin were necessary in 1.8%. The drug doses were reduced because of adverse events in 10.7 percent of patients.

Fifteen of the 97 patients experienced grade 3 leukopenia (12 lymphocytopenia, one granulocytopenia, two neutropenia) and three patients experienced grade 4 leukopenia (two lymphocytopenia, one neutropenia). Twelve of the 18 patients experienced only an isolated episode that resolved without treatment; in the other six cases, 2 had temporary discontinuation of therapy and 4 complete discontinuation of therapy.

DISCUSSION

HCV infection will continue to have a global impact on health in the foreseeable future. Sustained virologic response (SVR), is the standard measure of a favorable response to treatment. Recent reports suggest that sustained virologic responses are usually long-lasting (5 to 10 years) and are accompanied by progressive histologic improvement.

Combination therapy with interferon alfa and ribavirin has been shown to be the most effective treatment for chronic hepatitis C. Although IFN has direct antiviral actions, it also acts as an immunomodulator, influencing the activities of macrophages, cytotoxic T cells and NK cells,[11] which participate in the elimination of infected cells. Ribavirin, a synthetic guanosine analogue, has actions in vitro against a range of RNA and DNA viruses. When given alone to patients with chronic hepatitis C, ribavirin decreases serum aminotransferase concentrations but has no antiviral effect. Ribavirin has been postulated to inhibit viral-dependent RNA polymerase, the capping structure of viral messenger RNA, and inosine monophosphate dehydrogenase. Other immunomodulatory actions may also contribute to the drug's beneficial effects. Despite these potential actions, the exact mechanism responsible for the improved response that occurs when ribavirin is combined with interferon is unknown.

This study was designed to evaluate the feasibility, safety, and efficacy of Heberon as one IFN product in combination with ribavirin for treatment-naïve patients with hepatitis C. No control arm was included in this trial based on the requirements of the ethical committees; therefore, historical data from other trials are necessary to determine any potential benefit of the Heberon/ribavirin combination.

In this study, the thrice weekly application of three million units Heberon in combination with ribavirin was comparable to other interferon products in achieving end-of-treatment and sustained virological responses (SVR). However, the response rate in this study (36.1%) was similar to those observed in earlier large clinical trials (36–41%).[9,10] This observation of high SVR for standard combination therapy has been made in other, more recent trials and may be explained by better compliance with therapy and fewer patients discontinuing treatment.[9,12]

The majority of patients in this study were men, as inclusion criteria required women to be surgically sterile or menopausal, and men are usually associated with a lower rate of response to combination therapy than women are, which might further support the beneficial treatment effect of the Heberon/ribavirin combination.[13] In addition, it may be due to different numbers of patients with HCV genotype 1 infection, high baseline viral load and advanced fibrosis (not measured in this study) in comparision to those in previous trials.

IFN alfa-2b use is classically followed by a flu-like syndrome, fever, leukopenia and thrombocytopenia. Patients treated with ribavirin commonly experience anemia. Side effects of IFN-based combination therapy can be grouped broadly into influenza-like symptoms, neuropsychiatric symptoms, and hematologic abnormalities. In large treatment trials, adverse events prompted therapy discontinuation in 10 to 14% of patients and dose reductions in 32 to 42%. Depression can occur in up to one-third of patients on therapy,[14] and many practitioners are treating mild to moderate depression with selective serotonin reuptake inhibitors and other antidepressants. For patients developing significant therapy-related cytopenias, hematopoietic growth factors have become increasingly popular as a means to complete therapy and to prevent both IFN and ribavirin dose reductions. In a prospective, open-label study of HCV-infected patients developing ribavirin-related anemia, patients receiving weekly epoetin alfa had increased hemoglobin levels and maintained ribavirin dosing compared with those patients receiving dose reductions only.[15] The spectrum of side effects was similar to that reported in previous trials of monotherapy with interferon alfa-2b.[10,11]

Combination therapy was relatively safe, but modifications in the dose and discontinuation of treatment were required more often in patients who received interferon and ribavirin than in those who were treated with interferon alone. Reversible, hemolytic anemia due to ribavirin occurred, as has been previously reported when this drug was given alone. Patients who are treated with ribavirin should therefore be monitored closely (hemoglobin should be measured two and four weeks after

therapy is begun and then as clinically indicated). The symptoms related to treatment with interferon and ribavirin have been reported previously, and there were no synergistic effects. Generally, the combination of Heberon and ribavirin was safe and well tolerated. Most patients experienced expected adverse events and the majority were mild-to-moderate in severity.

The attachment of polyethylene glycol to interferon alfa (peginterferon alfa) extends the half-life and duration of therapeutic activity of interferon alfa. The recently introduced combination of peginterferon alfa-2b and ribavirin proved to be more efficient than the standard regimen of interferon alfa-2b given three times per week.[9] Combination therapy with peginterferon alfa-2a or 2b and ribavirin eliminates the virus in 54 to 56 percent of cases of chronic infection.[16,17]

The lack of a control arm in this study precludes definitive conclusions regarding the efficacy of Heberon in combination with ribavirin treatment. However, these data indicate that Heberon as an IFN product in combination with ribavirin for treatment of patients with chronic hepatitis C is safe, feasible, and potentially efficacious and deserves further investigation. Additional studies are ongoing in combination with peginterferon and ribavirin.

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