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THE EFFICACY AND SAFETY OF INTERFERON ALFA FOR THE TREATMENT OF CHRONIC HEPATITIS B INFECTED SUBJECTS IN IRAN

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ABSTRACT

This preliminary study was designed to evaluate the effects of Heberon Alfa for the treatment of chronic hepatitis B infected subjects in Iran. A single center, open label, single treatment prospective study of Interferon Alfa (Heberon Alfa), 5 million units every other day for a period of 4 months, was performed between 1996 to 1998. A total number of 30 patients with histologically documented chronic hepatitis and positive serum HBsAg were included in the study. Serum ALT of all patients was greater than 1.5 times normal before start of therapy. Effect of therapy on aminotransferase activity and HBsAg, HBeAg seroconversion was monitored and all the patients underwent a second liver biopsy at the end of the study period.

Mean age of patients was 35.5 ± 12 (17 to 60 years old) and 73% of patients were male. Most patients experienced adverse effects, but none warranted stopping the treatment. No serious or unexpected adverse event was reported during the study period. Thrombocytopenia was recorded in 2 patients. Liver biopsy showed a decrease in hepatic inflammation in 53.5% of patients, no change in 36.7% and increase in hepatic inflammation in 10% of patients after the treatment. Serum ALT returned to normal in 18 patients (60%), decreased in 7 patients (23.3%) and didn't change in 5 patients (16.7%). There was a strong correlation between serum ALT normalization and histological improvement. HBsAg became negative in 5 patients (16.6%). 10 patients had positive HBeAg prior to therapy, which became negative in 4 of them (40%) by the end of the study.

The current study confirms the result of other clinical trials and indicates that Heberon Alfa is a safe and effective drug for the treatment of chronic hepatitis B infected subjects with histologically documented chronic hepatitis.

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INTRODUCTION

Hepatitis B (HBV) is an immense health problem globally that affects 300 million individuals or 5 percent of the world's population and about one third eventually develop liver cirrhosis or hepatocellular carcinoma (HCC).[1] In Iran over 3% of the general population are HBsAg positive and HBV is the leading cause of liver cirrhosis and HCC.[2]

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Interferon (IFN) has antiviral, antiproliferative, and immunomodulatory effects and is the first treatment approved for chronic HBV infection in most countries.[3] It decreases the viral burden and ameliorates hepatic necroinflammation in one third of Caucasian patients with hepatitis B e Ag (HBeAg)-positive chronic hepatitis B (CHB).[4]

A subtype of CHB, predominantly harboring a mutant strain of HBV with a mutation at nucleotide 1896, leading to a failure of HBeAg synthesis, usually has a fluctuating course and poor outcome.[5-7] The end-of-treatment response to INF is similar in HbeAg negative and positive patients; however, relapses frequently occur during long-term follow up.[9-17] Because of a lack of HBeAg for monitoring, the evaluation of treatment responses is difficult in these patients and requires a detection of serum HBV DNA.[8] Although in hepatitis B, tests for HBV DNA are widely used, they are limited by a lack of standardization and variability in sensitivity[18-20] and since, till now, we do not have any quantitation HBV DNA facilities available in our country, this problem is more prominent for us and there is a lack of reliable studies for evaluation of INF efficacy in the treatment of chronic HBV infected subjects in Iran. Some studies indicated that there is variability in response rate to INF in different races (e.g. Asians respond poorly to interferon[21,22]) while some others do not confirm that.[23] The current study was designed to evaluate the histological, biochemical and serological efficacy and safety of INF Alfa for the treatment of chronic hepatitis B infected subjects in Iran.

MATERIAL AND METHODS

This was a single center, open label, single treatment, prospective clinical trial. From December 1996 to August 1998, HBV infected patients who had been visited in our General Hospital or its related hepatology clinics were enrolled in the study if they met the following criteria:

Inclusion criteria: (1) Positive HBsAg for more than 6 months, (2)Serum ALT more than 1.5 times upper limit of normal, (3)Percutaneous liver biopsy compatible with chronic hepatitis (grade >= 4 according to Modified HAI scoring system[24]) with or without cirrhosis, and (4) signed informed consent form.

Exclusion criteria: (1) Positive serum AntiHCV or HIV, (2)Autoimmune hepatitis scoring >= 10 (International autoimmune hepatitis scoring system[25]), (3)Any contraindication to interferon therapy (severe heart failure, convulsion, history of autoimmune disease, hypersensitivity to INF products, thrombocytopenia (PLT< 50,000/mL) and documented psychiatric problems), (4) Decompensated liver disease (5), Pregnancy or lactation, and (6) Renal disease or any other serious systemic disease.

Heberon-Alfa-R (Interferon-α-2b) which has been developed by the Center for Genetic Engineering and Biotechnology (CIGB), Havana / Heber Biotech company was administered as 5 million units, every other day, by subcutaneous route injected at the deltoid region. All injections were performed in the clinic under supervision of investigators. Heberon Alfa-R has half the price of other INF preparations (Roferon or Interon) available in the market. The treatment phase of the study was 4 months and all treated patients were seen at outpatient clinics and evaluated by blood testing every two weeks for the first month, then monthly during the period of IFN treatment. After IFN treatment, the patients were at least followed for 6 months. Liver biopsy was performed with the patients' consent upon entry into the study and at the end of 4 months of therapy. An experienced pathologist, blinded to the patients' clinical data, examined the specimens and recorded the histological activity index (HAI) and fibrosis using a modified HAI scoring system.[24] Among 60 patients who screened for this study, 11 patients did not fulfill the inclusion or exclusion criteria, 8 patients requested to use another INF preparation and 11 patients did not sign the consent for a second liver biopsy. Finally 30 patients with mean age of 35.5 ± 12 (range 17 to 60 years old) were included in the study. 73.3% of patients were male.

Statistical analysis

An intention to treat approach was used for statistical analysis of the data. Results are shown as mean ± standard deviation. The statistical analyses were performed using SPSS for windows (ver10).

RESULTS

Mean duration of follow up in our patients was 12.5 ± 4 months (range 10 to 18 months). The pretreatment clinical profiles are shown in Table I. Liver biopsy showed active cirrhosis in 6 patients before therapy, which in 3 of them we find the stigmata of CLD in physical examination.

This study is the first evaluation of the efficacy, side effects and the acceptability associated with the vaginal route of administration of contraceptive pills in Iran.

Biochemical response

As we mentioned above all the patients had abnormal serum ALT values before treatment (mean=116±60 SD). By the end of 4 months of treatment, serum ALT returned to normal in 18 patients (60%), decreased in 7(23.3%) and did not change in 5 patients (16.6%)

Histological response

Regarding inflammation (grading), by the end of

Table I: Pretreatment clinical characteristics of 30 patients.

Number of patients	30
Age (years)	35.5 ± 12 SD
Sex (male:female)	22:8
Risk factors (n (%))	
Transfusion history	5 (16.6%)
Surgery	3 (10%)
Tatooing	3 (10%)
Unknown (mostly vertical)	19 (63.4%)
Stigmata of CLD*(n(%))	3 (10%)
ALT(IU/L)	116 ± 60 SD
HbeAg	
Positive	10 (33.3%)
Negative	20 (66.6%)
HBV DNA#	
Positive	15 (50%)
Negative	0
Not performed	15 (50%)
Histological inflammation score (grade 0-18)	
Mild (<6)	2 (6%)
Moderate (7-10)	15 (50%)
Severe (11-18)	13 (43.3%)
Histological fibrosis score (grade 1-6)	
Mild (<3)	15 (50%)
Moderate (3,4)	9 (30%)
Severe (5,6) [progression to cirrhosis]	6 (20%)

*stigmata of chronic liver disease
#measured by qualitative PCR assay

therapy, in 5 patients (16%) liver histology changed to normal and in another 10 patients (33.3%) there was only scant inflammatory infiltration which was limited to the portal tracts (grade<4). On the other hand, liver histology showed nadir inflammation and fibrosis in 15 patients (50%) by the end of therapy. Overall there was a decrease in hepatic inflammation (more than 2 score) in 53.5% of patients, no change in 36.7% and increase in 10% of our patients. There was no change in frequency of cirrhosis by the end of 4 months of therapy.

Virological and serological response

As mentioned above, only 15 patients checked for qualitative HBV DNA before therapy and PCR was positive in all of them. By the end of 4 months of therapy PCR was checked for all patients. Viremia was undetectable in 10 patients (30%). From the 10 patients with a positive HBeAg prior to therapy, it changed to negative in 4 of them (40%) by the end of therapy. HBsAg seroconversion happened in 3 patients at the end of 4 months of treatment (10%) and at the end of the follow up period (mean=12.5± 4) in another 2 patients HBsAg seroconversion occurred. Overall 5 patients had HBsAg seroconversion (16.6%) and all 5 had a negative HBV DNA at the end of the treatment period (Table II).

Factors associated with response

To minimize the effect of uncertainty of qualitative PCR methods we considered the histological response as the end point and divided the patients in to two groups:

Group 1: Patients with decrease of more than 2 scores in histology [16 patients (53.3%)]

Group 2: Patients not fulfilling the above criteria [14 patients(46.6%)]

Multivariate analysis showed that there was no association between our patient's age, sex and pretreatment HBeAg status with histological response to INF, but lower baseline serum ALT and higher pretreatment fibrosis score were significantly associated with a poor histological response (Table III)

Prognosis and adverse effects

Of the INF-treated patients, no patients progressed to decompensated liver disease or HCC, or died of hepatic failure during the treatment and follow-up period. No serious or unexpected adverse event was noted during the study.

The most common side-effects of INF-α (Heberon Alfa R) are shown in Table IV. All adverse events were transient and tolerable and responded well to acetaminophen ± codeine administration. Flu syndrome includ-

Table II: Virological, biochemical and serological response to INF in 30 patients with chronic hepatitis B infection.

	At the end of therapy (4 months)	**At the end of follow up (12.5±4 months)**
Biochemical response (normal ALT)	18/30 (60%)	13/30 (43.3%)
Virological response (negative PCR)	10/30 (30%)	6/30 (20%)
Patients with negative HBsAg (%)	3/30 (10%)	5/30 (16.6%)
HBeAg seroconversion (%)	4/10 (40%)	4/10 (40%)

Table III: Factors associated with response after 4 months of INF therapy.

	Histological responders N=16	P value
Age		
<35	10/19 (52.6%)	Non-
>35	6/11 (54.5%)	significant
Sex		
M	12/2(54.5%)	Non -
F	4/8 (50%)	significant
Baseline ALT		
<120	8/21 (38%)	0.03
>120	8/9 (88.8%)	
Baseline HAI(0-18)		
<10	11/17 (64.7%)	0.09
>10	5/13 (38.4%)	
Baseline Fibrosis(0-6)		
<4	16/24 (66.6%)	0.000
>4	0/6 (0%)	
HBeAg prior to therapy		
Positive	11/20(55%)	Non-
Negative	5/10(50%)	significant

Table IV. Common adverse events in 30 patients receiving INF α (Heberon).

Adverse event	Frequency (%) N=30
Flu syndrome	100%
Hair loss	50%
Mood change++	33.3%
Insomnia	23.3%
Local pain at injection site	23.3%
Gastrointestinal side effects*	16.5%
Thrombocytopenia#	6.6%

*including: nausea, anorexia, vomiting, weight loss
++including excitability (70%) or depression(30%)
#Platelet count < 150 x 10^9 /L

ing fever, chills, myalgia and headache were the most common adverse events and were reported in all patients but only in 2 patients a transiently decreasing dose or duration of INF was necessary. Thrombocytopenia was noted in 2 patients, which responded well to transient increase in duration of INF.

DISCUSSION

In this study, a high histological and biochemical response to INF was achieved, irrespective of the low dose of INF that we used. The end treatment biochemical and histological response in our patients was significantly correlated together. Although clearance of HBV DNA is an important goal of treatment for patients infected with HBV virus, in our study virological clearance of the virus at the end of the treatment was low, or better to say, not correlating significantly with end treatment biochemical and histological response and also seems to be slightly lower than western countries.[26-28] This might be because we were using a more sensitive qualitative PCR assay to detect HBV DNA in our country as compared to hybridization methods, which is being used in most of the western studies.

By considering those patients with both biochemical and virological response as having a complete response we can see that in the follow up period four of the complete responders relapsed (Table II). This might be due to ultimately residual virus within the hepatocyte.[29] In this study we did not find any significant difference between end treatment response of HBeAg negative and positive patients, a finding that has been confirmed by both western and Asian investigators.[9-17, 30] The small sample size of HBeAg negative subjects (precore mutant) of this study did not let us obtain a reliable result about the long term response of this group of patients.

Finding an HBsAg seroconversion rate of 16.6% in a mean follow up period of 12.6 months is a promising result and is in contradiction with Asian studies which has not shown a delayed clearance of HBsAg[31] but mostly resembles western studies.[26-28]

In this study we did not have any breakthrough during therapy, a finding that is not uncommon in Lamivudine therapy.[32-34] This implies that INF might contribute to the decreasing rate of resistant strain of HBV infection. No serious or unexpected adverse events were noted during this study and all patients fulfilled the 4 month period of the study.

In conclusion, INF alfa 2-b (Heberon alfa R) with the above dose and duration is a safe and inexpensive drug which effectively normalized ALT values, improved liver histology and suppressed viral replication in many patients with CHB infection in Iran. This drug has some beneficial effects in HBsAg seroconversion, lower rate of relapse and not creating a resistant mutant in com-

parison to the widely used oral nucleoside (Lamivudine) and we recommend its use in native patients with CHB infection in Iran.

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