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RAPID COMMUNICATION

Efficacy of low dose peginterferon alpha-2b with ribavirin on chronic hepatitis C

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Abstract

AIM: To assess the efficacy of peginterferon alpha 2b at doses of 50 μg weekly and 80 μg weekly (based on body weight) plus ribavirin in HCV genotype 2 and genotype 3 chronic hepatitis C patients.

METHODS: During the study period of Jan 2002 to Dec 2003, all patients diagnosed as chronic hepatitis C or HCV related compensated cirrhosis were treated with peginterferon alpha 2b 50 μg S/C weekly (body weight < 60 kg) or 80 μg S/C weekly (body weight > 60 kg) plus ribavirin 800 mg/d for 24 wk.

RESULTS: Overall 28 patients, 14 patients in each group (based on body weight) were treated during the period. Out of 28 patients, 75% were genotype 3, 18% were genotype 2 and 7% were genotype 1. The mean dose of peginterferon alpha 2b was 0.91 μg/kg in group 1 and 1.23 μg/kg in group 2 respectively. The end of treatment and sustained virologic response rates were 82% and 78% respectively. Serious adverse effects were seen in 3.5% patients.

CONCLUSION: Low dose peginterferon alpha 2b in combination with ribavirin for 24 wk is effective in HCV genotype 2 and 3 chronic hepatitis C patients.

Key words: Chronic hepatitis C; Peginterferon alpha 2b; Ribavirin

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INTRODUCTION

The hepatitis C virus is a major cause of liver diseases affecting 170 million people worldwide[1]. In India, the estimated prevalence of hepatitis C virus infection is 1.8%. Genotypes 2 and 3 are predominant in Indian population[2].

Therapy for chronic hepatitis C has greatly improved over the last decade and is still evolving[3-8]. The introduction of pegylated form of interferons and addition of ribavirin have further improved the efficacy of therapy in chronic hepatitis C. Higher sustained virological response (SVR) rates in patients with chronic hepatitis C have been reported with pegylated form of interferons compared with standard interferons both as monotherapy as well as in combination with ribavirin[9-13].

Peginterferon alpha-2b is recommended at a dose of 1.5 μg/kg body weight in combination with ribavirin for treatment of chronic hepatitis C. An earlier study has reported similar efficacy of peginterferon alpha-2b at doses of 1 μg/kg and 1.5 μg/kg body weight in treatment of chronic hepatitis C as monotherapy[9]. Recent studies have shown that 82%-90% SVR could be achieved in HCV genotype 2 and 3 patients using peginterferon and ribavirin combination[13,14].

Interferon-based regimens are associated with significant side effects and costs. The cost of therapy in developing countries is a major limiting factor in initiating treatment. There is limited data on efficacy of low dose peginterferon alpha 2b plus ribavirin on chronic hepatitis C. It would be worthwhile to study whether the dose of peginterferon alpha-2b could be lowered from 1.5 μg/kg body weight to 1 μg/kg body weight in combination with standard dose of ribavirin without compromising the efficacy of therapy in HCV genotype 2 and 3 chronic hepatitis C patients.

Therefore, we conducted a non-randomized pilot study to assess the efficacy of peginterferon alpha-2b, at doses of 50 μg and 80 μg (based on body weight) plus ribavirin at standard dose in HCV genotype 2 and 3 related chronic hepatitis and compensated cirrhotic patients.

MATERIALS AND METHODS

Subjects

All patients with chronic liver disease attending our hospital from Jan 2002 to Dec 2003 were evaluated for HCV infection. After detailed history and clinical examination, patients underwent routine hematological investigations, liver function test, abdominal ultrasound

and upper GI endoscopy. All patients were tested for the presence of anti-HCV antibodies with Abbott diagnostic test kit according to the manufacturer's instructions. Those patients who tested positive for anti-HCV were further investigated for HCV RNA. HCV RNA was tested by RT-PCR (SDS) using 30 base pair long dual labeled oligonucleotide TaqMan probe (Rotorgene from Corbett research Australia). HCV genotype was tested by molecular based linear array system using COBAS AMPLICOR.

All patients diagnosed with chronic hepatitis C and compensated cirrhosis were eligible for study. Patients meeting with the following criteria were excluded: Presence of decompensated cirrhosis, hepatitis B coinfection, HIV co-infection, renal failure, concomitant malignancy, co-morbid serious cardiac and respiratory diseases, neuropsychiatric disorders, pregnancy, lactating mothers and alcohol abuse.

Table 1 Demographic, clinical, biochemical and molecular profiles of patients (mean ± SD, *n* = 28)

Demographic profile	
M/F	25:3
Age (yr)	47.5 ± 13.2
Body weight (kg)	60.6 ± 9.18
Clinical profile	
Chronic hepatitis C (*n*)	15
Compensated cirrhosis (*n*)	13
ALT (> 40 IU/L)	18
ALT (< 40 IU/L)	10
Molecular profile	
Genotype 3 (*n*)	21
Genotype 2 (*n*)	5
Genotype 1 (*n*)	2
Follow-up (mo)	18.1 ± 6.7

Study protocol

All eligible patients who gave informed consent were included in the study. Patients were treated with either 50 μg or 80 μg subcutaneous (s/c) weekly dose of pegylated interferon alpha 2b based on body weight plus 800 mg daily dose of ribavirin. Those patients who weighed less than 60 kg were administered a dose of 50 μg per week of pegylated interferon alpha 2b while those weighing more than 60 kg received 80 μg S/C per week. All patients were evaluated as outpatients weekly for 4 wk, then at wk 8, 12, 16 and 24 during treatment. Following the completion of treatment, patients were evaluated at wk 4, 12 and 24. On each visit during follow-up, routine hematological workup was done. Besides, relevant investigations were performed as and when necessary. Qualitative HCV RNA was tested after 12 wk of treatment, at end of treatment (24 wk) and 6 mo after completion of treatment. Liver biopsy was not considered mandatory in study protocol and was done in those patients who agreed to undergo the procedure. Side effects of the therapy were carefully recorded during follow-up. Sustained virologic response was defined as normalization of ALT and negative HCV-RNA 6 mo after completion of therapy.

Informed, written consent was taken from all the patients. Our hospital ethics committee approved the study protocol.

Statistical analysis

The quantitative values were expressed as mean ± SD. Fisher's exact test was used for statistical comparison of the data. $P < 0.05$ was considered as significant.

RESULTS

Overall 28 patients (25 males and 3 females) were included in the study. The demographic profile and clinical characteristics of the patients are shown in Table 1.

Fifteen out of 28 patients (54%) were chronic hepatitis and the remaining 13 (46%) were compensated cirrhosis (Child A). Eighteen (64%) of 28 patients had elevated ALT > 1.5 times the upper limit. The pretreatment ALT levels were 89 IU/L ± 28 IU/L. Out of 28 patients, 75%, 18% and 7% were genotype 3, 2 and 1 respectively. Fourteen patients (mass < 60 kg) were administered 50 μg S/C weekly dose of peginterferon alpha 2b plus 80 mg oral daily dose of ribavirin. The mean dose of peginterferon alpha 2b was 0.91 μg/ kg body weight (0.6 μg/kg ± 1.22 μg/kg) in this group.

The second group of 14 patients (mass > 60 kg) received 80 μg S/C weekly dose of peginterferon alpha 2b with daily oral dose of 800 mg ribavirin. The mean dose of peginterferon alpha 2b in this group was 1.23 μg/kg (1.03 μg/kg ± 1.33 μg/kg). One patient discontinued treatment due to severe side effects and another patient lost to follow up after 2 wk. Twenty-six out of 28 patients completed the 24 wk treatment. At the end of 24 wk treatment, 23 patients were negative for HCV RNA and 3 patients tested positive for HCV RNA. On further follow up, one patient tested positive for HCV RNA 6 mo after completion of therapy. Overall, at the end of treatment, 23 (82%) of 28 patients showed response to therapy. The SVR was achieved in 22 (78%) out of 28 patients. Though the dose per kg body weight of peginterferon alpha 2b was significantly different in two groups ($P < 0.002$), there was no difference in response to therapy with respect to dose or genotype (Table 2). During the follow-up of 18.1 ± 6.7 mo, one non-responder patient developed hepatocarcinoma (HCC) and died of liver failure following variceal bleeding.

One patient (3.5%) developed unbearable weakness and burning in urethra and discontinued the treatment. Seven (25%) of 28 patients developed mild leucopenia and thrombocytopenia which required temporary interruption of treatment for 1-2 wk. However, none of these 7 patients discontinued treatment any more and completed the 24 wk treatment.

DISCUSSION

The combination of peginterferon and ribavirin is the mainstay of treatment in chronic hepatitis C. Both forms of peginterferon alpha 2a and alpha 2b in combination with ribavirin have shown SVR rates from 79%-93% in genotype 2 and 3 chronic hepatitis C patients, making it a potentially curable disease[14,15]. In our study, end of treatment response (ETR) and SVR rates were 82%

Table 2 Response of therapy with respect to dose and genotype

Patients (n = 28)	Response to peginterferon alpha 2b Dose 50 mcg (n = 14)		Response to peginterferon alpha 2b Dose 80 mcg (n = 12)[1]	
	Yes	No	Yes	No
Genotype 1 (n = 2)	-	1	1	-
Genotype 2 (n = 5)	3	-	2	-
Genotype 3 (n = 21)	8	2	8	1

[1]Two patients in group 2 did not complete therapy.

and 78% respectively. The mean dose per kg body weight of peginterferon alpha 2b was 0.9 μg/kg and 1.23 μg/kg in the two groups, respectively. Lindsay *et al*[9] have shown similar SVR rates with 1.5 μg/kg and 1 μg/kg of peginterferon alpha 2b as monotherapy.

In a recent study, Zeuzem *et al*[14] have shown SVR rates of 79% and 93% in genotype 3 and genotype 2 chronic hepatitis C patients respectively when treated with peginterferon alpha 2b 1.5 μg/kg S/C weekly plus ribavirin 800-1400 mg/d based on body weight. In the same study, higher virologic response rate was observed in HCV genotype 3 patients with baseline HCV RNA concentration of < 600 IU/L compared to those with baseline HCV RNA > 600 IU/L (85% *vs* 59%). In our study, quantitative HCV RNA assay was not included in the study protocol, hence data could not be analysed based on HCV RNA levels. However, our results are comparable with those reported by Zeuzem *et al*[14], albeit at a much lower dose. One patient (3.5%) reported serious side effects resulting in discontinuation of treatment. The remaining patients tolerated the treatment well. The overall safety profile was much improved compared with earlier studies[16]. One patient who was a non-responder to treatment died during follow-up due to HCC related decompensation, suggestive of progressive disease.

HCV genotypes 1b and 2a are common in China[15]. In Japan, genotypes 1b, 2a and 2b are prevalent. Genotype 3 is also observed in Southeast Asian countries. In India, genotypes 2 and 3 are predominant HCV genotypes[2]. These genotypes 2 and 3 respond well to treatment[11,13,14]. But the cost of the treatment is a major limiting factor in developing countries. Our study has shown that > 80% SVR rates could be achieved in HCV genotype 2 and 3 infected chronic hepatitis C patients with lower than recommended dose of pegylated interferon alpha 2b. In light of encouraging results of our study, a randomized controlled trial is needed to compare the efficacy of lower doses of pegylated interferon alpha 2b, ie, with 1.5 μg/kg body weight of peginterferon alpha 2b in combination with standard dose of ribavirin with specific reference to Asian population.

In conclusion, the present study shows that lower than recommended dose of peginterferon alpha 2b in combination with ribavirin for 24 wk is effective in HCV genotype 2 and 3 chronic hepatitis C patients.

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