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ORIGINAL ARTICLE *Hepatitis C*

Clinical outcome of interferon and ribavirin combination treatment in hepatitis C virus infected patients with congenital bleeding disorders in Iran

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Summary. Hepatitis C virus (HCV) infection is a major cause of morbidity and mortality in patients with inherited bleeding disorders. The results of interferon and ribavirin combination therapy have been reported in a limited number of clinical trials on these patients. Peginterferon is a costly treatment. Conventional interferon and ribavirin therapy is still the main available and affordable antiviral therapy in some countries. The goal of this study was to assess the effectiveness and safety of interferon alfa-2b plus ribavirin in HIV seronegative, non-alcoholic, non-cirrhotic, naïve subjects with congenital coagulopathy. Between May 2003 and August 2007, 103 haemophiliacs were treated consecutively with standard inclusion and exclusion criteria, with interferon alfa-2b (PDferon B®) 3MIU three times a week subcutaneously plus ribavirin, for 24–48 weeks, with appropriate dose adjustments. They were all scheduled to have serial visits and laboratory tests. Among 7(6.8%) female and 96(93.2%) male haemophiliacs, 11(10.68%) cases did not complete the study because of psychological side effects. With intent-to-treat analysis, end-of-treatment response was 63.1%, and sustained virological response (SVR) was 56.3%. There was a significant correlation between SVR and genotype, baseline HCV viral load, rapid virological response, early virological response and BMI. A decrease in the haemoglobin level of two patients required ribavirin dose reduction. One developed thrombocytopenia at the end of treatment, but none had neutropenia. Hypothyroidism was observed in two patients. Interferon plus ribavirin combination therapy in HCV-infected haemophilic patients is well tolerated and treatment outcomes appear to be similar to those seen in the general population.

Keywords: congenital bleeding disorder, haemophilia, hepatitis C, interferon, ribavirin

Introduction

Transmission of hepatitis C virus (HCV) infection was a tragic setback reported in almost 100% of some groups of haemophiliacs [1,2]. HCV infection is a major cause of morbidity and mortality in patients with inherited bleeding disorders [3–6]. Treatment of HCV is one of the important issues in reducing the medical health burden of haemophiliacs.

From 1995, the addition of ribavirin to interferon (IFN) therapy markedly improved the virological response rate to 30–40% among infected patients [7,8]. Posthouwer and *et al.* [9] have evaluated the efficacy of IFN-based antiviral therapy in patients with haemophilia chronically infected with HCV, in a multicentre cohort study. They concluded that IFN-based therapies for chronic hepatitis C are effective in a significant proportion of patients with haemophilia, especially when treated with pegylated form of interferon (peginterferon) and ribavirin.

The introduction of peginterferon increased the efficacy of HCV treatment, especially for genotype 1

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viruses by 50–60%. However, this is a costly treatment. Access to this form of treatment is consequently impossible for some haemophiliacs. Peginterferon was registered in the Iranian Pharmacopoeia by the year 2000, but its cost is eight times more than conventional interferon and it still imposes an intolerable financial burden. Conventional interferon and ribavirin is therefore the main affordable antiviral therapy available to most of Iranian HCV infected patients. Moreover, efficacy of locally manufactured, affordable interferon in Iran (PDferon B®) has been studied previously and the findings showed acceptable and promising response rate of PDferon B® in general population. On the other hand, it seems that adverse events with PDferon are similar to other standard IFNs [10].

In contrast to studies in the general population, the studies of antiviral therapy in haemophilia patients are limited and often include small numbers of patients [11].

The goal of this study was to assess the effectiveness and safety of interferon alfa-2b plus ribavirin in HIV seronegative, previously untreated Iranian patients with congenital bleeding disorders and chronic hepatitis C virus infection.

Materials and methods

This was a prospective, open-label, non-randomized study comprising 103 haemophiliacs treated at the hepatitis clinic of Iranian Comprehensive Hemophilia Care Center (ICHCC) in Tehran, Iran, between May 2003 and August 2007.

Adult patients with inherited coagulation disorders were eligible if they had been positive for serum HCV-RNA and had not been treated before with interferon antiviral therapy. Inclusion criteria were values of haemoglobin (Hb) of ≥ 12 g dL^{-1}, white blood cell (WBC) count $\geq 3 \times 10^3$ mm^{-3}, neutrophil (PMN) count $\geq 1.50 \times 10^3$ mm^{-3}, platelet count $\geq 80 \times 10^3$ mm^{-3} and serum bilirubin, albumin and creatinine within normal limits. Exclusion criteria were decompensated liver disease (jaundice, ascites, encephalopathy or esophageal variceal bleeding) or clinical evidence of liver cirrhosis, severe psychiatric illness, uncontrolled co-morbid disease, alcohol abuse or dependency. We did not do liver biopsies. All the patients were negative for human immunodeficiency virus and hepatitis B virus markers. The study protocol was in accordance with the Helsinki Declaration and was approved by the local Ethical Committee. Informed consent was obtained from all participants.

Eligible patients were treated with interferon alfa-2b (PDferon B®; Pooyesh Darou, Tehran, Iran) 3 MIU three times a week subcutaneously, plus ribavirin (RIBACIP 200®; CIPLA Ltd, Mumbai, India) 800–1200 mg day^{-1} orally, genotype 2/3: 800 mg for 24 weeks, genotype 1: according to body weight (Wt < 75 kg, 1000 mg day^{-1}; Wt ≥ 75 kg, 1200 mg day^{-1}) for 48 weeks.

All patients were scheduled to have clinical visits and blood tests in the course of treatment every 1–2 months and whenever required. Serum levels of HCV RNA were quantitatively measured by real-time polymerase chain reaction (PCR) (lower limit of detection 100 IU mL^{-1}). Therapy was stopped in patients who did not show more than 2 log reduction in the pre-treatment HCV RNA level at 12 weeks, or if the HCV RNA remained detectable by PCR assay at 24 weeks, during treatment. A flow-chart was established in the database for each patient, recording demographic data, clinical changes, serial laboratory results, side effects, dose modifications and decision/reasons for treatment discontinuation.

The analysis was conducted on an 'intent-to-treat' basis. All patients who received medication for at least one month were included in the efficacy analysis. All data were entered into a Microsoft Access database and analyzed using SPSS version 12 software packages (SPSS Inc., Chicago, IL, USA). Continuous data were expressed as means ± SD. Categorical data were expressed as number of subjects or proportion of subjects with a specific feature. Chi-square test was used to compare categorical data. Multivariate logistic regression was performed to identify independent predictors of a sustained viral response (SVR), considering them as the dependent variables. A two-tailed *P*-value of less than 0.05 was required for statistical significance.

Results

Patients' characteristics are shown in Table 1. The mean age of patients was 27.45 ± 12.17, with no meaningful difference between the two main genotype groups (6.8% female and 93.2% male). Genotype distribution was as follows: 1a or 1b, 34 patients (33.01%); 1a and 3a, 2 patients (1.94%); 2a/c, 2 patients (1.94%); 3a, 63 patients (61.17%); 4, 1 patient (0.97%) and not typeable, 1 patient (0.97%). Patients with genotype 1 had higher ALT and AST levels (*P*-value 0.048 and 0.022, respectively). There was no significant difference among the patients with genotype 2/3 ($N = 65$) and genotype 1 ($N = 38$) with respect to gender, age and type of congenital bleeding disorder, baseline HCV RNA

Table 1. Demographic and baseline characteristics.

Patients	Genotype 1 $N = 38$ (36.89%)	Genotype 2/3 $N = 65$ (63.11%)	Total $N = 103$
Gender, *P*-value 0.7			
Male	35 (92.1)	61 (93.8)	96 (93.2)
Female	3 (7.9)	4 (6.2)	7 (6.8)
Age, *P*-value 0.35			
Mean ± SD	25.97 ± 11.84	28.31 ± 12.36	27.45 ± 12.17
Range	10–58	13–58	10–58
Congenital bleeding disorder, *P*-value 0.17			
Haemophilia A	28 (73.7)	48 (73.8)	76 (73.8)
Haemophilia B	5 (13.2)	7 (10.8)	12 (11.7)
von Willebrand	1 (2.6)	8 (12.3)	9 (8.7)
Others	4 (10.5)	2 (3.1)	6 (5.8)
BMI, *P*-value 0.12			
Mean ± SD	22.88 ± 4.0	21.45 ± 4.55	22.0 ± 4.39
Range	15.4–29.3	14.0–38.3	14.0–38.3
ALT before treatment, *P*-value 0.048			
Mean ± SD	81.24 ± 74.01	57.58 ± 41.25	65.80 ± 55.65
Range	28–450	12–209	12–450
AST before treatment, *P*-value 0.022			
Mean ± SD	62.76 ± 56.80	43.45 ± 23.533	50.16 ± 39.29
Range	24–300	11–133	11–300
Viral load (log) before treatment, *P*-value 0.09			
Mean ± SD	5.92 ± 0.82	5.52 ± 0.92	5.67 ± 0.89
Range	3.97–7.23	3.40–7.08	3.40–7.23
WBC before treatment, *P*-value 0.99			
Mean ± SD	5.92 ± 1.84	5.92 ± 1.87	5.92 ± 1.85
Range	3.4–13.9	2–11	2.0–13.9
PMN before treatment, *P*-value 0.25			
Mean ± SD	3.02 ± 0.91	3.41 ± 1.46	3.28 ± 1.31
Range	1.8–5.3	1.5–8.5	1.5–8.5
Hb before treatment, *P*-value 0.42			
Mean ± SD	14.65 ± 1.81	14.29 ± 2.07	14.42 ± 1.98
Range	10.9–17.5	9.4–18.0	9.4–18.0
PLT before treatment, *P*-value 0.24			
Mean ± SD	202.97 ± 54.96	221.90 ± 78.03	215.44 ± 71.26
Range	100–368	109–500	100–500

levels and baseline BMI, WBC, PMN, Hb and PLT count.

In the course of treatment, haemoglobin levels decreased transiently by a mean value of 1.9 ± 2.2 g dL^{-1}, with no significant differences between the two genotype groups (Table 2). Decrease in Hb to less than 10 g dL^{-1} occurred in two patients, in genotype 1, resulted in ribavirin dose reduction. Decreases in platelet counts by a mean value of $22.69 \pm 77.20 \times 10^3$ mm^{-3} and neutrophil counts by a mean value of $1.42 \pm 1.45 \times 10^3$ mm^{-3} did not differ in the two genotype groups. One patient with genotype 2/3 had thrombocytopenia at the end of treatment, but none of them had neutropenia. Hypothyroidism occurred in two patients, one man and one woman, who required thyroid hormone replacement therapy with no need for interferon dose reduction.

Regarding non-laboratory adverse events, general complaints as minor adverse events were more frequent than major adverse events. Major side effects requiring treatment discontinuation by physician were not seen. Eleven patients (10.68%) failed to comply with the treatment regime, mainly because

Table 2. Laboratory abnormalities, N (%).

Side effects	Genotype 1 $N = 38$ (35.92)	Genotype 2/3 $N = 65$ (64.08)	Total $N = 103$
Leucopenia (WBC $< 1500\ mm^{-3}$)	0	0	0
Neutropenia (neutrophil $< 750\ mm^{-3}$)	0	0	0
Anaemia (HB $< 10\ g\ dL^{-1}$)	2 (5.6)	0	0
Thrombocytopenia (PLT $< 75000\ mm^{-3}$)	0	1 (1.5)	1 (1)
ΔWBC ($\times 10^3\ mm^{-3}$) , *P*-value 0.72 Mean ± SD	2.26 ± 2.49	2.10 ± 1.95	2.158 ± 2.15
ΔPMN ($\times 10^3\ mm^{-3}$), *P*-value 0.43 Mean ± SD	1.26 ± 1.27	1.51 ± 1.55	1.42 ± 1.45
ΔHb ($g\ dL^{-1}$), *P*-value 0.35 Mean ± SD	1.62 ± 2.54	2.04 ± 1.99	1.89 ± 2.20
ΔPLT ($\times 10^3\ mm^{-3}$), *P*-value 0.43 Mean ± SD	14.73 ± 87.86	27.30 ± 70.65	22.69 ± 77.20

of intolerance to psychological side effects. No mortality was seen.

We were able to carry out HCV RNA tests on 49.5% of patients (51/103) at the first month of treatment; 52.43% patients (54/103) 3 months after treatment, and 81.55% patients (84/103) at the end of treatment (EOT) (Table 3). Treatment was stopped in seven patients with genotype 1 (7/38, 18.42%), because their HCV RNA levels were not negative after the first 6 months of therapy. An EOT response was achieved in 52 patients with genotype 2/3 (52/65, 80%) and in 13 patients with genotype 1 (13/38, 34.21%) (*P*-value 0.000). Viral relapse occurred in seven EOT responders (6.79%), six with genotype 2/3 and one with genotype 1, 6 months after the end of treatment. Therefore, a sustained virological response (SVR) was ultimately achieved in 58 patients (56.3%), including 46 patients with genotype 2/3 (46/65, 70.77%) and 12 patients with genotype 1 (12/38, 31.58%) by intent to treat analysis (*P*-value 0.000). A biochemical response was detected at the end of treatment in 98.46% and 89.47% of patients with genotype 2/3 and genotype 1, respectively (*P*-value 0.04). Thirty two (56.9%) patients with SVR (10 with genotype 1 and 22 with genotype 2/3) were followed up for the mean period of 21.63 months (12–45 months) after the end of treatment and HCV RNA PCR remained negative in all of them.

There was a significant correlation between SVR and genotype (*P*-value 0.000), baseline HCV viral load (*P*-value 0.01) and BMI (*P*-value 0.009) (Table 4). Multivariate regression analysis determined that hepatitis C genotype was the only main factor in SVR achievement. Rates of SVR did not differ in relation to age, gender, type of congenital bleeding disorder and baseline ALT and AST levels. Patients with SVR had a higher rapid viral response (RVR) rate which is negative HCV RNA PCR result at week 4 and higher early viral response (EVR) rate which is negative HCV RNA PCR or at least a 2 log reduction at week 12 (*P*-values 0.002). Among 42 patients with EVR, 29 patients (64.4%) achieved SVR (*P*-value 0.003). This rate was 77.4% for genotype 2/3 and 35.7% for genotype 1. Among 20 patients with a RVR, 16 patients (80%) achieved SVR (*P*-value 0.004). This rate was 88.9% for genotype 2/3 but 0% for genotype 1.

Discussion

This 'real-world' clinical experience has some specific features:

First, the subjects of our study were patients with congenital bleeding disorder, an understudied group of patients whose response to HCV therapy is insufficiently reported in the literature.

Table 3. Treatment response, N (%).

Treatment response (intent to treat)	Genotype 1	Genotype 2/3	Total
Rapid viral response (RVR), *P*-value 0.00	3 (7.9)	25 (38.46)	28/51 (27.18)
Early viral response (EVR), *P*-value 0.004	14 (36.84)	33 (50.77)	47/54 (45.63)
End of treatment response (EOTR), *P*-value 0.00	13 (34.21)	52 (80)	65/84 (63.1)
Sustained viral response (SVR), *P*-value 0.00	12 (31.58)	46 (70.77)	58/65 (56.31)
End of treatment biochemical response (EOTBR), *P*-value 0.041	34 (89.47)	64 (98.46)	98/103 (95.14)

Table 4. Sustained viral response (SVR), N (%).

Patients	Patients with SVR	Patients without SVR
Genotype, *P*-value 0.00		
Genotype 1	12 (20.7)	23 (69.7)
Genotype 2/3	46 (79.3)	10 (30.3)
Viral load (log) before treatment, *P*-value 0.01		
Mean ± SD	5.39 ± 0.95	6.04 ± 0.75
Range	3.40–6.94	3.97–7.23
Gender, *P*-value 0.47		
Male	55 (94.8)	30 (90.9)
Female	3 (5.2)	3 (9.1)
Age, *P*-value 0.86		
Mean ± SD	26.69 ± 12.445	26.24 ± 11.39
Range	10–58	10–58
Congaenital bleeding disorder, *P*-value 0.81		
Haemophilia A	44 (75.9)	25 (75.8)
Haemophilia B	5 (8.6)	3 (9.1)
von Willebrand	6 (10.3)	2 (6.1)
Others	3 (5.2)	3 (9.1)
BMI, *P*-value 0.009		
Mean ± SD	20.90 ± 3.76	23.38 ± 4.76
Range	14–30.1	15.4–38.3
ALT before treatment, *P*-value 0.96		
Mean ± SD	68.04 ± 66.75	67.33 ± 41.08
Range	12–450	15–196
AST before treatment, *P*-value 0.59		
Mean ± SD	49.79 ± 41.72	54.97 ± 42.0
Range	11–300	17–232
WBC before treatment, *P*-value 0.45		
Mean ± SD	5.87 ± 1.69	6.19 ± 2.01
Range	3.4–11.0	3.6–13.9
PMN before treatment, *P*-value 0.48		
Mean ± SD	3.18 ± 1.36	3.43 ± 1.20
Range	1.5–8.5	1.9–6.1
Hb before treatment, *P*-value 0.66		
Mean ± SD	14.31 ± 1.87	14.52 ± 2.27
Range	10.2–17.7	9.4–18
PLT before treatment, *P*-value 0.47		
Mean ± SD	223.20 ± 82.50	210.41 ± 51.22
Range	109–500	125–368
Rapid viral response (RVR), *P*-value 0.002	16 (66.7)	3 (17.6)
Early viral response (EVR), *P*-value 0.002	29 (100)	15 (71.4)
End of treatment biochemical response (EOTBR), *P*-value 0.001	33 (100)	12 (70.6)

Second, the study population is a captive cohort, naturally compelled to attend the clinic regularly by the nature of their bleeding disorder, not just carefully selected patients who meet specific eligibility criteria enrolled in reported randomized clinical trials (RCTs).

Third, the inclusion and exclusion criteria; the treatment duration; the clinical monitoring, and dose modifications were generally similar to reported RCTs, but our intimate day-to-day clinical contact with these patients ensured their full co-operation and our access to real feedback.

Therefore, we can extrapolate the results of our current study to the real situation among HCV-infected haemophiliacs.

According to ICHCC reports (unpublished data), similar to the haemophilic and blood donor populations of many countries, genotype 1 is predominant [8,12–14] among all Iranian haemophiliacs, but more than half of our present study patients were patients with genotype 2/3 (63.11%). This is because in our daily clinical practice, we encourage all genotype 2/3 patients to undertake treatment, regardless of their liver enzyme test results. Patients with genotype 1 are difficult to treat as a group. In our experience, when counselling prior to treatment, patients with normal liver enzyme tests do not usually accept treatment with the conventional interferon and ribavirin regimen. So, in the genotype 1 group, only patients with elevated aminotransferases level were treated.

Sustained virological response was achieved in 56.3% of all patients: 31.58% with genotype 1 and 70.77% patients with genotype 2/3. This is consistent with the lower response rate of genotype 1 to therapy [2]. In addition, there was no relation between ALT and AST levels and sustained virological response in our study. SVR was mainly associated with HCV genotype 2/3 and a low baseline HCV RNA level as in large RCTs [3], RVR [15], EVR, end of treatment biochemical response (EOTBR) and BMI, but not female gender, although the number of females enrolled in this study was not sufficient for meaningful statistical analysis.

About 10% of patients didnot complete the study, mainly because of intolerance to side effects. To avoid non-compliance, greater psychological support is needed during this arduous therapeutic regime in haemophiliacs.

The overall SVR rate achieved in our study was greater than that in previous studies in haemophilics [15–18] and similar to results in a trial of induction therapy with high dose interferon alfa combined with ribavirin [19]. This may be because of different baseline characteristics of the patients, for example, lower mean age [15] in our study, although, we didnot find any significant correlation between age of

the patients and SVR. Moreover, all the patients participating in our study were as yet untreated and HIV negative. Our results in achieving SVR are comparable to, or even better than the results of studies on patients without congenital bleeding disorders [10,20]. This may be because of more patients with genotype 2/3 participated in our study, and suggests that patients with congenital bleeding disorders are more compliant to therapy than the general HCV-positive population. SVR achievement in our patients with genotype 2/3 was lower than other results [16,21].

As very late responses have been described previously in cases with no viral response at 6 months in the course of a 12-month treatment regime [14], the possibility of delayed response was discussed with such patients and four of them (three without biochemical response) accepted to continue therapy for the full 12 months, but none of them had an EOT response. This may suggest that a favourable biochemical response at 6 months is necessary for continuing therapy in this situation.

Conclusion

In conclusion, treatment responses to interferon plus ribavirin combination therapy in haemophilic patients appear to be similar to those seen in the general population. As treatment with peginterferon and ribavirin has led to better virological responses in the general population, it is also likely to be effective in a proportion of patients with haemophilia.

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Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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