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CLINICAL RESEARCH

Treatment of hepatitis C virus genotype 4 with peginterferon alfa-2a: Impact of bilharziasis and fibrosis stage

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Abstract

AIM: To evaluate pegylated interferon alpha2a (PegIFN-α2a) in Egyptian patients with HCV genotype 4, and the impact of pretreatment viral load, co-existent bilharziasis and histological liver changes on response rate.

METHODS: A total of 73 naïve patients (61 with history of bilharziasis) with compensated chronic HCV genotype 4 were enrolled into: group A (38 patients) who received 180 mg PegIFN-alpha2a subcutaneously once weekly for a year and group B (35 patients) received IFN alpha-2a 3 MU 3 times weekly. Ribavirin was added to each regimen at a dose of 1200 mg. Patients were followed for 72 wk and sustained response was assessed.

RESULTS: Significant improvement in both end of treatment response (ETR) ($P < 0.002$) and sustained response (SR) ($P < 0.05$) was noted with pegylated interferon, where ETR was achieved in 29 (76.3%) and 14 patients (40%) in both groups respectively, and 25 patients in group A (65.8%) and 9 (25.7%) in group B could retain negative viraemia by the end of follow up period. Sustained virological response (SVR) showed a significant negative correlation with age and positive correlation with pretreatment inflammation in patients receiving PegIFN. Viral clearance after 3 mo of therapy was associated with high incidence of ETR and SR ($P < 0.001$), but without significant difference between both forms of interferon. Significant improvement in response was achieved in patients with high grade fibrosis (grade 3 and 4) with PegIFN-α2a, where SR was seen in 5 out of 13 patients in group A, but none in group B. There was no significant difference in response between bilharzial and non-bilharzial patients in both groups. In terms of safety and tolerability, neutropenia was the predominant side effect; both drugs were comparable.

CONCLUSION: PegIFN-α2a combined with ribavirin results in improvement in sustained response in HCV genotype 4, irrespective of history of bilharzial infestation.

Key words: Hepatitis C virus; Genotype 4; Pegasys; Bilharziasis

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INTRODUCTION

Hepatitis C is comparable to a 'viral time bomb'. The WHO estimates that about 200 million people, 3% of the world's population, are infected with hepatitis C virus (HCV) and 3 to 4 million persons are newly infected each year. The striking genetic heterogeneity of RNA genome of HCV is well recognized. Six major genotypes and over 50 subtypes and minor variants referred to as "quasispecies" are described[1]. HCV genotype differences seem to be of considerable clinical significance because they affect the responses to antiviral therapy[2]. HCV genotype 4 appears to be prevalent in the Middle East and Central Africa, where almost 13% of HCV carriers around the world live in the Eastern Mediterranean region. Prevalence rates of HCV genotype 4 ranges from 60% in Saudi Arabia to 90% in Egypt where it has been reported to be frequently associated with cirrhosis and a poor response to interferon (IFN)[3,4].

Concurrent HCV-genotype 4 infection and schistosomiasis result in a much more severe liver disease than that seen with either disease alone. Luckily, the activity of HCV infection seems to be partially suppressed in such patients[5]. The effect of such co-infection on hepatic fibrosis and in turn on response to treatment in HCV patients is however, conflicting. While Helal *et al* in 1989[6] and Shiha *et al* in 2002[7] reported a lack of enhancement

of hepatic pathology in the schistosomal patients, Hassan *et al* in 2002[8] suggested that schistosomiasis is an important risk factor involved in enhancement of nitric oxide levels and virus replication, which in turn may aggravate liver cell injury and hence the development of cirrhosis.

It has been reported that treatment with conventional IFN is less effective in patients with genotypes 1 and 4 than in patients with genotypes 2 and 3[9]. The high rate of HCV turnover coupled with the short half–life of the drug, limits the efficacy of conventional IFN therapy[10]. Pegylated IFN-α2a [Peg-IFN-α2a (40 kDa); Pegasys, Hoffmann-La Roche] is produced by attachment of a 40 kDa branched polyethylene glycol moiety to IFN-α2a by a stable amide bond. It is characterized by prolonged absorption half-life, restricted volume distribution, and decreased clearance compared to standard interferon, which thus increase its therapeutic efficacy with less frequent doses[11]. Recent clinical trials have shown that the response to pegylated interferon α2a plus ribavirin (RBV) therapy for chronic HCV infection is superior to that achieved with standard interferon α2a plus ribavirin therapy or peginteferon-α2a alone with a rapid decline in viral load in the first 12 wk, for all HCV genotypes[12]. Hematological adverse effects in the form of anaemia, neutropenia and thrombocytopenia are the primary laboratory abnormalities experienced during IFN plus RBV combination therapy and may necessitate dose modification and thus potentially impact outcome. This anemia is attributed to both ribavirin dose-dependent hemolysis and direct suppressive effect of interferon on erythropoiesis[13]. Hematopoietic growth factors may be useful in the management of these side effects.

The purpose of this prospective analysis is to compare the effectiveness and safety of Pegasys (40 kDa) IFN-α2a once weekly with IFN-α2a, in compensated HCV genotype 4, in combination with ribavirin. The effect of pretreatment viral load, histological liver changes and schistosomiasis co-infection on response to treatment is also assessed.

MATERIALS AND METHODS

Patients

Adult patients with chronic active hepatitis C as evidenced by positive serological test for HCV-Ab using enzyme linked immunosorbent assay (ELISA) (Ortho Diagnostics, Neckargmun, Germany), detectable serum HCV-RNA by RT-PCR (Amplicor Molecular System, Hoffmann-La Roche, Basel, Switzerland), elevated serum alanine transaminases (ALT) activity more than twice the normal value and histopathological criteria of chronic active hepatitis. Liver histology was classified according to Scheuer score system from 0-4 for both grades (necroinflammation) and stage (degree of fibrosis). Hepatocellular carcinoma was excluded by testing of α-fetoprotein and by ultrasound scanning. None of the female patients was pregnant as evidenced by negative serum pregnancy test. Breast feeders were excluded. All patients had normal serum direct and indirect bilirubin, albumin and creatinine. All patients were genotype 4 detected by the Inno LiPA HCV Ⅱ assay (Innogenetics Inc., GA, USA). Patients were excluded if co-infected with HBV, HIV. Hemochromatosis, Wilson disease or other causes for chronic liver disease were also ruled out. Other exclusion criteria included neutrophil count < 1.5×10^9/L, platelet count < 90×10^9/L or haemoglobin (Hb) < 100 g/L for female and < 110 g/L for male, positive auto-antibodies including antinuclear antibody (ANA), antimitochondrial antibody (AMA), anti-smooth muscle autoantibody (ASMA), patients with a history of severe psychiatric disease, seizure disorder, organ transplantation, or severe cardiac or pulmonary disease. All patients had normal thyroid function prior to the study and all were either non-diabetics or with controlled blood glucose level with hemoglobin A_{1C} < 8.5%. Patients were excluded if they had clinically significant retinal abnormalities, clinical gout, were a substance abuser (alcohol or I.V. drugs) or showed any medical condition requiring systemic steroids.

Safety assessment

Patients were reviewed in the Hepatology Outpatient Clinic weekly during the first month and monthly thereafter along the course of therapy to check for safety, and then followed for at least 6 mo after discontinuation of treatment to assess for sustained response. Epoetin beta (Recormon®. Roche) at a dose of 4000 U/weekly for 2 wk was given when Hb level decrease > 30 mg/L or > 25% from baseline levels. Also Filgrastim (Neupogen®. Amgen. Inc. F. Hoffmann-La Roche Ltd. Basel) 5 μg/kg was given once or twice weekly if neutrophils < 0.7×10^3/μL, while drug was discontinued completely for any patient showing Hb level < 85 g/L, neutrophils < 0.5×10^9/L, platelet < 50×10^9/L, abnormal thyroid function tests, creatinine > 177 μmol/L or ALT/AST double baseline levels. Patients requiring modification of more than 4 doses were excluded.

Efficacy assessment

The primary efficacy end point was sustained response (SR), defined as undetectable HCV RNA and normal ALT level at the end of follow up (24 wk after discontinuation of treatment). The relapse rate was calculated as percentage of patients with an end-of-treatment response in whom HCV RNA was detectable at wk 72. End of treatment response (ETR) was defined as normalization of ALT and loss of detectable serum HCV RNA at the end of treatment.

Study design

This randomized, controlled clinical trial was conducted from February 2002 to November 2004. The study consisted of a screening phase, which began 2 mo prior to the first dose of the drug under evaluation. Examination established eligibility of patients according to inclusion/exclusion criteria. After a written informed consent was obtained in accordance with the Helsinki Declaration of 1979, 80 patients were randomly assigned at a 1:1 ratio to receive either, subcutaneously, once weekly 180 μg of peginterferon-α2a (Pegasys, Hoffmann-LaRoche) or IFN α2a (Roferon®, Hoffmann-LaRoche) 3 MU 3 times. Ribavirin 1200 mg at a daily oral dose was added to both

Table 1 Demographic data of the hepatitis C patients

Variable	Group A (PEG-IFN + RBV) n = 38	Group B (IFN + RBV) n = 35	P
Age (yr) (mean ± SD)	45.5 ± 6.1	45.4 ± 5.8	NS[1]
Gender			
Male	31 (81.6)	33 (94.3)	
Female	7 (18.4)	2 (5.7)	
Body mass (mean ± SD)			
Before treatment	81.9 ± 12.0	73.6 ± 7.7	0.001
After Treatment	78.9 ± 12.5	71.1 ± 7.4	0.002
Weight reduction	2.9 ± 4.3	2.6 ± 2.7	NS[1]
Inflammation stage			
0-1	7 (18.4)	8 (22.9)	NS[1]
2-3	31 (81.6)	27 (77.1)	
Grade of fibrosis			
Mild (0-2)	25 (65.8)	23 (65.7)	NS[1]
Severe (3-4)	13 (34.2)	12 (34.3)	
Bilharzial co-infection No.	31 (81.6)	30 (5.7)	

[1]Not significant.

Table 2 Comparison of response of hepatitis C in both groups

Variable	Group A (PEG-IFN + RBV) n = 38	Group B (IFN + RBV) n = 35	P
After 48 wk			
Responders	29 (76.3)	14 (40.0)	< 0.002
Non-responders	9 (23.7)	21 (60.0)	
After 72 wk			
Among responders			
Sustained response	25 (86.2)	9 (64.3)	0.124
Relapser	4 (13.8)	5 (35.7)	

regimens. Throughout the study, patients were monitored for vital signs, weight, adverse events, medication compliance, thyroid function, haematologic parameters, blood chemistry and serum HCV- RNA levels.

Statistical analysis

The data were coded, and processed on an IBM-PC compatible computer using Statistical Packages for Social Sciences (SPSS). Data were expressed as mean and standard deviation (SD) unless otherwise stated. Student-t-test was used to ascertain the significance of difference between mean values of two continuous variables and Mann-Whitney test was used for non-parametric distribution. Chi-Square analysis was performed to test for differences in proportions of categorical variables between 2 or more groups. In 2 × 2 tables, the Fisher exact test (two-tailed) was used instead of Chi-Square, in particular, when sample size was small. One-way analysis of variance (ANOVA) and non-parametric Kruskal Wallis one-way analysis of variance (ANOVA) was employed for comparison of several group means and to determine the presence of significant differences between group means. The Pearson's correlation coefficient was used to evaluate the strength association between two variables. The level $P < 0.05$ was considered as the cut-off value for significance. Multivariate logistic regression analysis was performed.

RESULTS

Seventy-three patients out of 80 completed the study and follow up periods, and were classified into 2 groups: 38 patients received pegylated IFN and ribavirin (group A) and 35 received non-pegylated IFN and ribavirin (group B). Seven patients (2 in group A and 5 in group B) could not continue the study because of severe side effects or intolerability to treatment. Thyroid dysfunction in one patient in each group, intolerability of the drug's side effect in another one in group A and in 2 patients from group B, in addition to increase of transaminases and thrombocytopenia in 2 patients with cirrhosis in group B were the causes of drug discontinuation. Male gender was predominant in both groups, 31 and 33 respectively. Baseline demographic data and disease characteristics were similar in both groups (Table 1). Thirty-one patients in group A and 30 in group B had a history of bilharziasis treated with either tarter emetic (44 patients) or praziquentel (17 patients). Among these, one had histological pattern of bilharzial granuloma in liver tissue, but none had active bilharziasis prior to treatment.

Patients who received pegylated IFN (29, 76.3%) showed a significant ETR in comparison to those receiving non-peg-IFN (14, 40%) ($P < 0.002$). A significant ($P < 0.05$) improvement in SR was noticed with Peg-IFN, where 25 patients in group A (65.8% of total number of patients who completed the study) and 9 (25.7 %) in group B could retain negative viraemia at the end of follow up period (Table 2). A significant negative correlation between age and sustained response was noted in both groups ($P = 0.015$) without a significant difference between both drugs. There was no correlation between gender, pre-treatment, viraemia or body weight and response rate (Table 3). There was a significant positive correlation between pre-treatment ALT and ETR in patients receiving Peg-IFN but not in patients receiving IFN. Also, a significant positive correlation ($P < 0.05$) was found between stage of hepatic inflammation and response rate in patients treated with peg-IFN, but not with IFN (Table 3). Intent to treat (ITT) analysis showed significant improvement in both of ETR and SR with peg-IFN therapy, where ETR was 72.5% and 35%, respectively, while SR was 62.5% and 22.5% ($P < 0.002$).

Regarding viraemia, there was no significant difference between responders and non-responders in both groups and within the same group. Viral clearance after 12 wk of therapy was associated with high incidence of ETR and SR ($P < 0.001$), but also, without significant difference between both groups. By studying the relation between histopathological activity and response, treatment with peg-IFN showed a significant improvement in response and sustained response in patients with severe fibrosis (grade 3 and 4). Only one patient out of 11 with severe fibrosis showed ETR with conventional IFN therapy and unfortunately relapsed after discontinuation of treatment, while 8 patients out of 13 showed ETR with peg-IFN therapy and 5 of them could retain negative viremia at

Table 3 Comparison between responders and non-responders in both hepatitis C groups (mean ± SD)

Variable	Group A (PEG-IFN+RBV) *n* = 38			Group B (IFN+RBV) *n* = 35		
	R[1]	NR[2]	SR[3]	R[1]	NR[2]	SR[3]
Age (yr)	44.7 ± 5.4	47.8 ± 7.9	44.2 ± 5.8	45.23 ± 5.2	45.6 ± 6.2	42.9 ± 4.6
Body mass (kg)	82.6 ± 10.2	79.7 ± 17.0	82.7 ± 9.8	74.6 ± 9.5	73.1 ± 6.6	77.3 ± 9.6
ALT (μkat/L)						
Before treatment	2.559 ± 1.564	1.524 ± 0.082	2.757 ± 1.607	1.494 ± 0.432	1.810 ± 0.570	1.524 ± 0.515
After 3 mo	1.065 ± 0.980	1.095 ± 0.767	1.084 ± 1.039	0.405 ± 0.112	1.135 ± 0.741	0.487 ± 0.263
Baseline HCV RNA (MU/L)	473 934 ± 373 542	496 256 ± 667 356	472 444 ± 402 109	312 786 ± 185 583	361 857 ± 339 942	346 667 ± 207 364

[1]Responders; [2]Non responder; [3]Sustained response.

Table 4 Comparison of response in both hepatitis C groups according to histopathological changes *n* (%)

Variable	*n*	Responders	Non responders	Among responders	
				Sustained response	Relapse
Severe Fibrosis					
A[1]	13	8 (61.5)	5 (38.5)	5 (62.5)	3 (37.5)
B[2]	11	1 (9.1)	10 (90.9)	0 (0.0)	1 (100.0)
Mild fibrosis					
A[1]	25	21 (84.0)	4 (15.0)	20 (95.2)	1 (4.8)
B[2]	24	13 (54.2)	11 (45.8)	9 (69.2)	4 (30.8)
Severe inflammation					
A[1]	31	22 (71.0)	9 (29.0)	18 (81.8)	4 (18.2)
B[2]	27	7 (25.9)	20 (74.1)	4 (57.1)	3 (42.9)
Mild inflammation					
A[1]	7	7 (100.0)	0 (0.0)	7 (100.0)	0 (0.0)
B[2]	8	7 (87.5)	1 (12.5)	5 (71.4)	2 (28.6)

[1]Group A = PEG-IFN+RBV; [2]Group B = IFN + RBV.

72 wk (Table 4). There was no significant difference in response in bilharzial and non-bilharzial patients in both groups, where SR was achieved in 27 patients co-infected with bilharziasis (60.7%) and in 7 cases of HCV alone (58.3%) (Table 5).

With respect to safety and tolerability, peg-IFN was comparable to conventional IFN. Weight reduction was similar in both groups, where the mean reduction was 2.9 ± 4.3 kg and 2.6 ± 2.7 kg respectively. After flu-like picture, hematological side effects represented the commonest encountered problem (Table 6). Although anemia was seen in 71.1% and 65.7% in both groups respectively, only 39.5% and 37.1% in both groups developed Hb drop more than 30 mg/L or > 30% of baseline level and required growth stimulating factors (These figures were related only to those patients who completed the study). Two patients from group B with cirrhotic changes were withdrawn because of thrombocytopenia. The proportions of patients withdrawn from treatment because of laboratory abnormalities or other adverse effects were similar in both groups and no new or unexpected adverse effects specific to peginterferon were presented. On multivariate logistic regression analysis, no significant predictive values were noted.

DISCUSSION

Hepatitis genotype is now recognized as the most important baseline characteristic determining treatment regimen and the most useful predictor of response[14]. Slow viral dynamics, particularly second-phase decay[15] and limited effectiveness of IFN in blocking the virion have been implicated in poor response to IFN therapy in hepatitis C genotype 4 patients[16], which genotype has been described as a difficult-to-treat one. Unfortunately, this is the predominant genotype in the Middle East where large numbers of affected individuals are reported. A great improvement in response has recently been noted in all genotypes after the introduction of pegylated forms of IFN, whether as monotherapy or combined with ribavirin. Data presented in this study further reinforce the superior efficacy of PegIFN/Ribavirin combination therapy in terms of ETR and SVR in HCV genotype 4 infection. This is in accordance with earlier reports (Thakeb *et al* 2004[17]; Shobokshi *et al* 2004[18]; and Diago *et al* 2004[19]). The lower SR noted compared to that reported by Diago *et al*[19] for western genotype 4 cases (65.8% *vs* 79%) may reflect a difference in sensitivity of genotype 4 subtypes to PegIFN-α2a. The improved response to PegIFN-α2a in genotype 4 compared to conventional IFN and PegIFN-α2a previously reported by us[20,21] can be attributed, at least in part, to a high and persistent trough serum level of PegIFN-α2a in the first 4 wk of treatment which led to rapid viral eradication[22,23], or the recently reported third phase decay with PegIFN-α2a in the first 1-4 wk of therapy[24]. Other causes also include

Table 5 Comparison between responders and non-responders in both hepatitis C groups

Variable	Responders n = 43	Non Responders n = 30	P
Gender			
Male	38 (88.4)	26 (86.7)	NS[1]
Female	5 (11.6)	4 (13.3)	
Body mass (kg, Mean ± SD)			
Before treatment	80.1 ± 10.6	75.1 ± 10.9	NS[1]
After treatment	76.9 ± 10.6	72.9 ± 11.5	NS[1]
ALT			
Pre treatment	141.1 ± 88.9	101.2 ± 41.0	NS[1]
12 wk	56.2 ± 55.0	67.1 ± 44.0	NS[1]
48 wk	38.1 ± 22.7	65.0 ± 30.6	NS[1]
			NS[1]
PCR (No. of viruses in BL; mean ± SD)			
Pre treatment	416 328 ± 341 106	337 321 ± 482 826	0.036
Liver fibrosis			
Grade 1	17 (39.5)	3 (10.3)	0.009
Grade 2	17 (39.5)	11 (37.9)	
Grade 3	8 (18.6)	8 (27.6)	
Grade 4	1 (2.4)	7 (24.1)	
HCV *vs* HCV and Bilharziasis			
Co-infected	37 (84.1)	24 (82.8)	NS[1]
Non Bilharzial	7 (15.9)	5 (17.2)	
Drug used			
Pegasus	29 (67.4)	9 (30.0)	0.002
Non-pegylated IFN	14 (32.6)	21 (70.0)	

[1]Not significant.

Table 6 Comparison of side effects in both hepatitis C groups

Variable	Group A	Group B	P
Flu-like symptoms	40 (100.0)	40 (100.0)	
Discontinuation of drug	0 (0)	0 (0)	NS[1]
Thyroid dysfunction	2	3	NS[1]
Discontinuation of drug	1	2	
Psychological upset and drug intolerability	1	1	NS[1]
Discontinuation of drug	1	1	
Hematological			
Anemia (30% from baseline)	13 (26.0)	12 (24.0)	NS[1]
Neutropenia (< 0.9×10^9/L)	21 (42.0)	19 (38.0)	NS[1]
Thrombocytopenia (< 50×10^9/L)	None	2 (4)	NS[1]

[1]Not significant.

the improved patients' adherence to treatment and the use of erythropoietin and G-CSF, thus overcoming anaemia and neutropenia that have commonly led to halting therapy.

The significant correlation noted in the present study between viral clearance at wk 12 and SVR, regardless of the type of IFN used, confirms a consistent relationship between the rapidity of HCV-RNA suppression and the likelihood of achieving SR[25,26]. Conversely, patients showing positive PCR at wk 12, all failed to achieve SR regardless of ETR seen in 2 of them. This suggests that a positive PCR at wk 12 in genotype 4 cases might be considered as a strong negative predictor of response.

In terms of pretreatment predictors, only patient's age showed a negative correlation with response rate. This is probably not related to age *per se*, but rather to the age of infection, or in other words, the duration of infection, since older patients are known to develop a higher rate of liver fibrosis[27]. The presence of cirrhosis has been shown to be independently associated with decreased SVR in HCV infected patients[28]. In this respect we could demonstrate a superior SR with PegIFN-α2a over non-pegylated IFN (25.7% *vs* 0%) in both advanced fibrosis and compensated cirrhosis genotype 4 patients. Similar results were reported by Heathcote *et al* in 2000[29] and Marcellin *et al* in 2004[30].

In agreement with Tsubota *et al*[31] and contrary to Picciotto *et al*[32], we could not find any correlation between pretreatment viral load and SR, which implies that HCV-RNA levels *per se* are less influential compared to the major impact of genotype that generally determines the rate of SR.

HCV patients co-infected with schistosomiasis exhibited a unique clinical, virological and histological pattern manifested by an increased incidence of viral persistence with high HCV-RNA titers and accelerated fibrosis. This may be attributed to the fact that patients with schistosomiasis have a down regulated immune response to HCV in the form of reduced IFNγ, IL-4 and IL-10 secreted by HCV-specific T cells[33]. In spite of this, we did not find any significant difference in response to either IFN forms in cases of combined infections. This might be explained by the recent observation of El Rafei and colleagues[34] that Schistosoma mansoni by targeting a specific subset of memory CD8 cells, reduces the late differentiated memory T cell population in HCV co-infected individuals. This implies that patients infected with the genotype 4 can still mount HCV-specific T cell responses, despite the prevalence of concomitant schistosomiasis.

As for safety and tolerability, both IFN forms were comparable. As in previous reports, anemia and thrombocytopenia were the commonest haematological adverse events of the combination therapy[35]. Nevertheless, none of our patients experienced bleeding tendency or uncontrolled infection throughout the study period. The use of Epoietin α and G-CSF helped improve patients' adherence to treatment, and minimize dose reduction and discontinuation of treatment in the first 12 wk. Adherence to therapy is increasingly recognized as a key determinant in the outcome of antiviral therapy in chronic hepatitis[36] and although erythropoietin stimulates both erythropoiesis and thrombopoiesis[37], the latter effect was not demonstrated in our patients and 4 had to discontinue treatment because of thrombocytopenia.

We can conclude that concomitant HCV-genotype 4 and bilharzial infections do not seem to affect the improved responses achieved with pegylated interferon α2a plus ribavirin combination therapy. Also, in spite of the improved response in advanced fibrosis and compensated cirrhosis, advanced histopathological changes, coupled with positive viremia after 12 wk of

therapy, still remain the most important negative predictive factor for response in genotype 4 patients. A non-stop and extensive work is still needed to win the battle against HCV. Each new pharmacological modification carries with it more hope for better control of this complicated disease and tells that the difficult to treat genotype 4 will eventually be conquered.

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