Research Article

Response of Patients with Chronic Hepatitis C to Different Types of Pegylated Interferon in El-Minia Province Egypt. A Retrospective Study

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Abstract

Background: Pegylated interferon products have been available: pegylated interferon α-2a and pegylated interferon α-2b ***for treatmet of chroic HCV.*** In 2007, a novel interferon was introduced in Egypt and was approved for the treatment of CHC. It is a Pegylated interferon α-2a linear 20 kD derived from *Hansenula polymorpha*. The cost of this novel interferon is markedly less than that of the existing peginterferons **. Aim of the work**: to compare the rates of sustained virologic response (SVR) and safety achieved by pegylated interferon α-2a, pegylated interferon α-2a (*Hansenula polymorpha derive)*, and pegylated interferon α-2b each type plus weight-based ribavirin in patients with chronic HCV using a large database of hepatitis cases. **Methods t**he study included 400 patients with chronic hepatitis C divided into three groups the group I includes 100 patients treated by pegylated interferon alfa-2a(40KD) group II 200 patients treated with pegylated interferon α-2b group III 100 patients treated with pegylated interferon α-2a (Hansenula polymorpha derive) these patients meet the criteria of national protocol for the treatment of chronic hepatitis C approved by Egyptian ministry of health R**esults:** SVR in patients treated with pegylated interferon alfa-2a(40KD) was 56% and 54% with pegylated interferon α-2b respectively. While patients treated with pegylated interferon α-2a (20KD) the SVR rates was 48% however the difference was not statistically significant **(p** < 0.4). Multivariate logistic regression analysis showed that low viral load, low inflammatory activity and low fibrosis grades were independent variables associated with SVR**. Conclusion:** There was insignificant difference in the SVR rates and safety profile between chronic hepatitis C patients treated with the PEG-IFN alpha-2a (two types) and alpha-2b. Early fibrosis, low activity and low viral load are independent variables of SVR

Key words: Chronic Hepatitis C; Peginterferon-Alpha- 2a; Peginterferon-Alpha- 2b**,** Egypt.

Introduction

Hepatitis C is a disease with a significant global impact. According to the World Health Organization there are about 150 million people chronically infected with hepatitis C virus (HCV), corresponding to 2-2.5% of the world's total population. There are considerable regional differences. In some countries, like Egypt, the prevalence is >10% [(1)].

Hepatitis C virus (HCV) is the leading cause of liver disease in Egypt and is one of the country's major health problems. Genotype 4 is the predominant genotype of HCV in Egyptian patients (up to 91%) [(2)].

Genotype 4 is the least studied HCV genotype, and is prevalent in developing countries in Africa and the Middle East. This particular genotype was considered difficult to treat with the combination of conventional interferon and ribavirin [(3)].

However, after the introduction of pegylated interferon, subsequent studies reported favorable response to treatment with pegylated interferon α-2a and α-2b in combination with ribavirin [(4)]. The optimal duration of treatment for patients with genotype 1 or 4 is 48 weeks. For patients with genotype 2 or 3, 24 weeks has been the standard [(5)].

In the past decade, only two pegylated interferon products have been available: pegylated interferon α-2a (40 KD) and pegylated interferon α-2b (12KD) [(6)]. In 2007, a

novel interferon was introduced in Egypt and was approved for the treatment of chronic hepatitis C. pegylated interferon α-2a derived from *Hansenula polymorpha* is a linear 20 kD. The cost of this novel interferon is markedly less than that of the existing peginterferons [7].

To date, no head-to-head comparative studies of the three PEG-IFNs have been published. We aimed to compare the rates of sustained virologic response (SVR) and safety achieved by pegylated interferon α-2a, pegylated interferon α-2a (*Hansenula polymorpha derive)*, and pegylated interferon α-2b each type plus weight-based ribavirin in patients with chronic HCV using a large database of hepatitis cases.

Patients and Methods

Selection of Patients

Four hundreds patients with CHC were included in the present study during the period from March 2013 to December 2014. The study protocol was in accordance with national protocols for the treatment of CHC approved by the ministry of health in Egypt. All of the pharmaceutical products used were approved by the local health authorities. Inclusion criteria comprised the following: treatment-naive patients, 18 years of age and older, the presence of detectable serum HCV RNA, clinical and laboratory evidence of compensated liver disease (absence of ascites, encephalopathy or esophageal varices, serum bilirubin level of less than 1.5 mg/L, serum albumin level of greater than 3.5 g/L and an international normalized ratio of less than 1.5), acceptable hematological values (hemoglobin level greater than 12 g/L, neutrophil level greater than 1500/mm3 and platelet count of greater than 90,000/mm3), serum creatinine level of less than 1.5 mg/dL and a body mass index of less than 30 kg/m2. Exclusion criteria were as follows: the presence of hepatitis B surface antigen or serum anti hepatitis B core antigen antibodies, HIV infection major depressive illness, solid organ transplant, HCC or concomitant clinically significant disease (uncontrolled diabetes mellitus, significant ischemic heart disease, severe hypertension, autoimmune disorders and uncontrolled thyroid disease).

Study design and assessment of response

This is a retrospective, multicenter, randomized study conducted on 400 chronic HCV patients confirmed with histological examination. Study was conducted on patients attending at outpatient clinics of medical centers for HCV treatment at El-Minia governorate (Health Insurance and One day hospitals). According to METAVIR score, patients with chronic HCV were classified into 4 groups according to the degree of fibrosis, F0, no fibrosis; F1, fibrous portal expansion; F2, bridging fibrosis; F3, bridging fibrosis with lobular distortion; and F4, cirrhosis. Only F1, F2 and F3 were included in the study.

Patients were classified into three groups:

- Group 1 consisted of 100 patients who received pegylated interferon α-2a (40KD) 180μg s.c weekly plus weight-based ribavirin (15mg/kg/day).
- Group 2 consisted of 200 patients who received pegylated interferon α-2b (12KD) 1.5μg/kg s.c weekly plus weight-based ribavirin (15mg/kg/day).
- Group 3 consisted of 100 patients who received pegylated interferon α-2a (20KD) (derived from Hansenula polymorpha), 160μg s.c weekly plus weight-based ribavirin (15mg/kg/day).

Assessment of response

Response to treatment was assessed by measuring follow-up serum HCV RNA levels 12, 24, 48 and 72 weeks after the start of treatment, and defined as the following:

- Early virological response (EVR): 12 weeks after initiation of treatment, undetectable HCV RNA in serum was considered to be a complete EVR (cEVR), while a baseline decrease in serum HCV RNA of 2 log units or greater was considered to be a partial EVR (pEVR).
- End of treatment response (ETR): undetectable serum HCV RNA at the end of treatment (after 48 weeks).
- Sustained virological response (SVR): undetectable serum HCV RNA after 24 weeks from the end of treatment (i.e, 72 weeks from the start of treatment).

Treatment was discontinued if no cEVR was achieved; these patients were defined as non-responders. Early responders continued treatment for a total of 48 weeks.

Assessment of safety

Throughout the entire treatment period, regular patient monitoring for adverse events was performed at the clinical and laboratory levels. Temporary discontinuation of peginterferon was considered if neutrophil counts fell to below 500/mm^3. Dose reduction of peginterferon by 50% was initiated if the neutrophil count was less than 750/mm^3 and/or platelet counts were less than 50,000/mm^3. Adjustment of ribavirin dose was initiated when hemoglobin levels fell to below 10 g/dL. Dose reduction for both drugs was continued until improvement of the adverse event, after which the original dose was subsequently reinstituted. Discontinuation of therapy was considered if adverse events persisted or worsened for more than four weeks without improvement after dose reduction was initiated.

Statistical methods

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version 20.

Descriptive statistics were done for numerical data by mean, standard deviation, minimum and maximum of the range, while they were done for categorical data by number and percentage.

Analyses were done for quantitative variables using one way ANOVA test for parametric data between the three groups and post HOC analysis for each two groups, with Log transformation of non-parametric data.
Paired sample t test was used for parametric data between two variables in each group.

Chi square test was used for qualitative data between groups when the cell contains more than 5. The level of significance was taken at (P value ≤ 0.05).

Result

Demographic, laboratory, virological and histopathological features of the studied patients are shown in Table 1 with no significant differences between them as regard the age, sex and BMI. Regarding to the residence the patient in rural areas were significantly higher than in urban areas (p=0.001). The pretreatment level of viral load showed that Low and high viraemic loads were found in 60% & 40% in group I , 57% & 43% in group 2 and 51% & 49% in group 3 with insignificant statistical differences . The histopathological features showed that the majority of patients in the all three groups had mild inflammatory activity (A1 & A2) (73.%; 74.5%; 68%, respectively) and fibrosis stages (F1& F2) (55%; 46%; 57%, respectively) with insignificant statistical difference.

The other laboratory data of the studied patients showed non significant statistical difference between the studied groups (data not shown).

Regarding the response to treatment cEVR was detected in 84 out of 100 for Peginterferon α-2a; 169 out of 200 showed cEVR for Peginterferon α-2b and 85 out of 100 showed cEVR for Peginterferon α-2a (*Hansenula derived*) with no statistical significance (P=0.8) (table 2)

Also there was insignificant difference between the three groups regarding to ETR and SVR P=0.3 & 0.4 respectively.

Table (3) shows the simple logestic regression analysis of some selected factors to find out its relation to SVR; the age less than 40 years, early fibrosis (F1, F2), low activity (A1, A2) and low viral load all these factors were significantly associated with SVR. However BMI, Ribavirin dose and type of interferon have insignificant association with SVR.

Multivariate logistic regression analysis (reported as odds ratios [ORs] with 95% confidence intervals [CIs]) showed that low viral load, low inflammatory activity and low fibrosis grades were independent variables associated with SVR [P=0.001,0.001, 0.002 respectively) (table 4).

Most side effects were encountered in the first 12 weeks of initiation of therapy and were related to the interferon therapy; however hemoglobin drop was an effect of interferon and ribavirin. Incidence of neutropenia (ANC count

< 750) was significantly high in group 3 treated by pegylated interferon α-2a (*Hansenula polymorpha*) (P=0.03). The other side effects encountered during treatment were: hemoglobin drop, platelets drop, fatigue, depression loss of appetite and retinopathy showed insignificant difference between the three groups (table 5).

Table (1): Baseline data of the studied patients

variable	Group 1 PEG-IFN alfa-2a (N=100)	Group 2 PEG-IFN alfa-2b (N=200)	Group 3 PEG-IFN alfa-2a Hansenula derived (N=100)	P value
Age:				
Mean ± SD	40.7±10.9	43.3±9.2	43.1±8.6	0.080
Sex:				
Male	71 (71%)	145 (72.5%)	70 (70%)	0.895
Female	29 (29%)	55 (27.5%)	30 (30%)	
BMI				
Mean ± SD	25.7±2.7	26.1±2.3	26.1±2.1	0.540
Residence:				
Rural	83 (83%)	101 (50.5%)	49 (49%)	0.001*
Urban	17 (17%)	99 (49.5%)	51 (51%)	
ALT				0.553
Mean ± SD	52.34±24.82	55.17±21.24	54.23±16.73	
AST	53.99±26.66	56±22.73	56.72±18.28	0.672
Mean ± SD				
Viral load before ttt:				
LVL.	60 (60%)	114 (57%)	51 (51%)	0.420
HVL.	40 (40%)	86 (43%)	49 (49%)	
Histological feature				
Activity:				
A1.+A2.	73 (73%)	149 (74.5%)	68 (68%)	
A3.	27 (27%)	51 (25.5%)	32 (32%)	0.206
Fibrosis:	55 (55%)			
F1.+F2.	45 (45%)	92 (46%)	57 (57%)	0.206
F3.		108 (54%)	43 (43%)	0.149

BMI: body mass index; High HCV viral load HVL: High viral load (serum hepatitis C virus RNA level of greater than 600,000 IU/mL); LVL: low virological load serum HCV RNA level of 50 IU/mL to less than 600,000 IU/mL).

Table (2): Virological Response in Relation to the Type of Treatment

	12 week (EVR) N, %	24week(BT) N ,%	48 week (ETR) N, %	72 week (SVR) N, %
PEG-IFN alfa-2a	84 (84%)	8 (8%)	68 (68%)	56 (56%)
PEG-IFN alfa-2b	169 (84.5%)	15 (7.5%)	129 (64.5%)	108 (54%)
PEG-IFN alfa-2a Hansenula derived	85 (85%)	8 (8%)	58 (58%)	48 (48%)
P value	0.84	0.98	0.32	0.48

EVR: early virological response BT24: break through at 24th week; ETR: end of treatment response; SVR: sustained virological response.

Table (3): Simple logistic regression analysis of factors affecting SVR

Variable	AOR	95% CI	P value
Age: ≥ 40 years	0.977	(0.96-0.99)	0.033*
BMI: ≥ 25	1.32	(0.79-2.2)	0.295
Fibrosis: (F_1,F_2)	4.983	(3.18-7.8)	0.001*
Activity(A_1,A_2)	8.687	(5.16-14.61)	0.001*
Low viral load	2.227	(1.47-3.38)	0.001*
Ribavirin dose	1.11	(0.97-1.27)	0.143
Type of interferon **Interferon α-2a(40KD)** **Interferon α-2b** **Interferon α-2a(20KD)**	1 1.4 0.92	------ (0.78-2.51) (0.44-1.89)	------ 0.256 0.809

OR: odds ratio; CI: confidence interval; LVL: low viral load
*Statistically significant

Table 4: Multiple logistic regression analysis of variables affecting SVR

	OR	(95 % CI)	P value
Age	0.996	(0.97-1.02)	0.785
Viral load (LVL)	2.378	(1.47-3.87)	< 0.001*
Fibrosis (F1,F2)	2.666	(1.61-4.42)	< 0.001*
Activity (A1,A2)	6.15	(3.45-10.96)	< 0.002*

OR: odds ratio; CI: confidence interval; LVL: low viral load
*Statistically significant

Table 5: Major adverse events of treatment

	PEG-IFN alfa-2a (N=100)	PEG-IFN alfa-2b (N=200)	PEG-IFN alfa-2a Hansenula derived (N=100)	P value
Hb gm/dl 8.5-10	20 (20%)	42 (21%)	18 (18%)	0.829
ANC <750	3 (3%)	4 (2%)	8 (8%)	0.03*
Platelets <80,000	2 (2%)	6 (3%)	0 (0%)	0.216
Fatigue	60(60%)	116(58%)	61(61%)	0.869
Depression	15(15%)	32(16%)	16(16%)	0.792
Loss of appetite	30(30%)	58(29%)	32(32%)	0.866
Retinopathy	13(13%)	22(11%)	11(11%)	0.863

Discussion

Hepatitis C is a disease with a significant global impact. According to the World Health Organization there are about 150 million people chronically infected with the hepatitis C virus (HCV), corresponding to 2-2.5% of the world's total population. There are considerable regional differences. In some countries, e.g., Egypt, the prevalence is >10%[1].

In the past decade, pegylated interferon (PEG-IFN) in combination with ribavirin has been the standard of care for HCV in all international guidelines. These guidelines do not discriminate between the two available forms of PEG-IFN α-2a (40KD) and PEG-IFN α-2b (12KD)[8-10].

Multiple previous non comparative and head to head comparative studies were performed to assess the efficacy and safety profiles of PEG-IFN α-2a (40KD) and PEG-IFN α-2b (12KD). The results of these studies are discrepant[11].

In 2007, a novel interferon was introduced in Egypt and was approved for the treatment of CHC. It is a linear 20 KD pegylated interferon α-2a derived from *Hansenula polymorpha*. The cost of this novel interferon is markedly less than that of the existing peginterferons[12].

In our study regarding the demographic data, there were insignificant differences between the three groups regarding age, sex and BMI. The difference between the three groups regarding residence was significant as the rural patients were 83%, 50.5% and 49% for groups 1, 2 and 3 respectively. This is because the data of the patients were collected from 2 centers serving different locations.

Other data including, baseline laboratory data, histopathological data and viral loads, differences between the three groups were not statistically significant.

In our study, as regard the EVR, ETR there were insignificant difference between the three treated groups. The SVR response to pegylated IFN α-2a (40KD) was better than the response to pegylated IFN α-2b (12KD) and linear pegylated IFN α-2a (20KD) (novel type) with SVR rates 56%, 54% and 48% for the three groups respectively but the differences were not statistically significant. This goes with the study done by McHutchison et al., (2009) who reported SVR rates of 40.9% and 39.8% for PEG-IFN α-2a (40KD) and PEG-IFN α-2b (12KD) respectively[13]. The previously published Egyptian trials that compared both PEG-IFN types showed that PEG-IFN α-2a (40KD) was significantly better than PEG-IFN α-2b (12KD) for SVR rates. The first study conducted on 196 patients showed that the SVR rates in the PEG-IFN α-2a group vs. PEG-IFN α-2b group were 64.4% vs. 53.2%, respectively; P value 0.04 [14],the second study was conducted on 217 patients and showed that the SVR rates were 70.6% vs. 54.6%, respectively; P value 0.017[15]. The third trial was a large retrospective cohort of 3718 Egyptian chronic HCV patients in a real life comparison and showed that the SVR rates were 59.6% vs. 53.9% respectively;

p value < 0.05[16]. These data support a Greek trial also comparing both types of PEG-IFN in the treatment of 177 HCV genotype 4 patients and it also showed that PEG-IFN α-2a was better than PEG-IFN α-2b with SVR rates of 47.5% vs. 38.1%[17].

As mentioned before, there were no head to head trials comparing the three types of IFN, but the previously published clinical trials regarding linear pegylated IFN α-2a (20KD) (derived from *Hansenula polymorpha*.) reported SVR rates of 56% [18], 53.4% in the study conducted by Amer et al., 2010[19]), and 60.7%[12].

The lower overall SVR in our study may be explained by lower percentage of patients with F_{1-2} stages of fibrosis than any of the previously mentioned studies. In the current study, overall patients with F_{1-2} of the three groups were 51% of all patients while they comprised 91% of all patients in the study conducted by El Raziky et al.,[16] and 72% in the study conducted by Esmat and Fattah[18], 67.5% in the study conducted by Gad et al.,[14], and 79.4% in the study conducted by Taha et al.,[12].

In our study, EVR was not statistically significantly different for the three groups. EVR was achieved in 84%, 84.5% and 85% of patients for groups 1, 2 and 3 respectively with p value 0.846. This goes with other investigators who reported EVR of 89.1% and 87.7% for groups 1 and 2 respectively[16] and others who reported EVR of 87.8% for group 3[12].

In the present study, ETR was achieved in 68%, 64.5% and 58% of all patients for groups 1, 2 and 3 respectively with p value 0.3. This goes with previous study that reported ETR of 72.5% and 70.4% for groups 1 and 2 respectively with p value 0.76[15]; however, other study reported ETR of 64% and 58% for groups 1 and 2 respectively with p value < 0.05[16].

Previous non comparative studies regarding PEG-IFN alfa-2a *Hansenula derived* reported ETR of 64%[18], 60.8%[19] and 72.9% [12].

The probability of achieving an SVR in the present study was tested against several factors including the age , the degree of liver fibrosis and baseline viral load, and type of pegelated interferon. Of these factors the degree of fibrosis F1, 2 and activity A1, 2 and the low viral load were independent variables associated with SVR however the age, BMI, dose of ribavirin and the type of interferon treatment not affecting the SVR. The degree of liver fibrosis was widely studied as a pretreatment predictor of response to therapy in patients with CHC. Generally, the higher the degree of fibrosis, the lower the likelihood of response[20–22]. This could be explained on the basis of insufficient delivery of peginterferon due to reduced peripheral portal flow[23] or decreased expression of hepatic interferon receptors with the progression of fibrosis [24]. In our study, the rate of SVR was significantly higher in patients with Metavir F1 and F2 liver fibrosis; this finding was related to both the lower rate of SVR and higher rates of relapse in patients with a higher degree of fibrosis.

There was impact of baseline virological load on the rate of SVR in the present study in accordance to many other authors who recognized viral load to be one of the pre-treatment predictors of response to therapy, where low viral load was associated with the SVR .The adverse events that occurred in our patients were not sufficiently serious to discontinue treatment, which suggests good drug tolerability. Most of these events were mild to moderate and responded to the dose adjustment required. Neutropenia was significantly higher in group treated by pegylated interferon α-2a (20KD) 8% than the other groups 3%, 2% P=0.03. As regard the thrombocytopenia, anemia, fatigue depression, loss of appetite and retinopathy there was insignificant statistically difference between the three groups. These findings are consistent with previous reports[26-27] regarding the safety of a combination peginterferon and ribavirin regimen in patients with CHC.

We concluded that the novel pegylated interferon α-2a (20KD) is as effective as the other two interferons pegylated interferon α-2a (40KD), pegylated interferon α-2b (12KD) with statistically insignificant difference in SVR rates between them. Also it is well tolerated and safe

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