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Original Investigation

Efficacy of regimens containing pegylated interferon and ribavirin in the treatment of chronic hepatitis C: A retrospective overview

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ABSTRACT

Objective: We aimed to evaluate the response to interferon treatment, factors affecting permanent response, and recurrence in patients with chronic hepatitis C (CHC).

Methods: This retrospective study included 305 patients with CHC. They received either pegylated interferon alfa-2A (PEG IFNα-2A) + ribavirin (RIB) treatment or pegylated interferon alfa-2B (PEG IFNα-2B) + RIB treatment for 48 weeks.

Results: At the 48th week of treatment, hepatitis C virus ribonucleic acid (HCV RNA) clearance was seen in 151 (49.5%) of the 305 patients as end-of-treatment response (ETR). ETR was observed in 70 (50.7%) patients treated with PEG IFNα-2A + RIB and in 81 (48.5%) patients treated with PEG IFNα-2B + RIB ($p>0.05$). After 6 months of treatment, sustained virological response (SVR) was observed in 138 (45.2%) patients. SVR was observed in 63 (45.7%) patients treated with PEG IFNα-2A+RIB and in 75 (45.9%) patients treated with PEG IFNα-2B+RIB ($p>0.05$). After treatment, recurrence occurred in 35 (11.6%) patients.

Conclusion: The long-term prognosis of CHC infection is positively affected by the treatment regimen. PEG IFNα-2A + RIB and PEG IFNα-2B + RIB treatment regimens have not yet increased HCV RNA clearance to the desired level. Thus, new treatment regimens are required.

Keywords: Pegylated interferon alfa-2A + ribavirin, pegylated interferon alfa-2B + ribavirin, hepatitis C virus ribonucleic acid

INTRODUCTION

More than 200 million people across the world are estimated to have been infected with hepatitis C virus (HCV). Every year, 250,000 people die due to cirrhosis or hepatocellular carcinoma caused by HCV (1). HCV infection leads to complications such as chronic hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma (HCC). Important advancements have been made in the treatment of HCV-related liver disease over the last 20 years. Sustained virologic response (SVR) defined as hepatitis C virus ribonucleic acid (HCV RNA) levels that cannot be detected in 24 weeks after the end of treatment is associated with recovery in patients without cirrhosis (2).

In general, while SVR was 29% in patients using pegylated interferon (PEG-IFN) only for 48 weeks, it increased to 44-56% in patients receiving PEG-IFN and ribavirin (RIB) combination treatment (3). In various studies, the PEG-IFN α-2A and PEG-IFN α-2B success rate was found to be similar. In treatment-naive patients the SVR rate is 54-56%, which is highly associated with the HCV genotype. SVR was found to be 42-46% in genotype 1 patients and 76-82% in genotype 2-3 patients (4).

Low level of HCV RNA, HCV types except for genotype 1, absence of cirrhosis, being under 40 years of age, being female, absence of fatty liver, absence of obesity, and being white increases the SVR rates (5). The strongest predictive factor known is the genotype of the virus, and determining the genotype prior to treatment is an important step for the selection of treatment type. Apart from that, body mass index over 30, insulin resistance, IL28B genetic polymorphism localized on chromosome 19, and advanced liver fibrosis are defined as the other negative predictive factors (6).

In patients with SVR, no progress is seen in fibrosis, and even a regression can be observed in the existing fibrosis. Survival rates associated with liver failure and HCC were higher in cirrhotic patients with SVR compared to unresponsive patients. Therefore, the ultimate target in HCC treatment must be the eradication of the virus (7).

In accordance with the previous Health Practice Communique (SUT), PEG-IFN and RIB treatment were given to chronic hepatitis C (CHC) patients. In this study, we aimed to evaluate the response

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to treatments with interferon, factors affecting sustained viral response and recurrence in CHC patients who were followed-up and treated in our clinic.

METHODS

Patient Group

305 patients with CHC who applied to our polyclinic between April 2008 and February 2012 were included in the study retrospectively. CHC diagnosis was established with serologic and molecular examinations. Patients were given pegylated interferon alpha-2A (PEG-IFN α-2A) + ribavirin (RIB) or pegylated interferon alpha-2B (PEG-IFN α-2B) + RIB treatment for 48 weeks. The baseline alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), albumin, hemogram and Child-Pugh scores of patients were evaluated. The results of the PEG-IFN α-2A /2B + RIB treatment were examined. Anti-HCV was studied with the enzyme-linked immunosorbent assay (ELISA) method serologically. In the molecular laboratory, HCV RNA levels in the serum of patients were determined using the real time polymerase chain reaction (PCR) method (COBAS Taqman HCV, Roche Diagnostic Systems, Inc., Branchburg, NJ, USA). HCV RNA was accepted as 15 IU/mL quantitatively, and the above results were considered positive. In patients who were determined as HCV RNA positive, HCV genotyping was studied with real time PCR method in the Abbott m2000r (Abbott Molecular Diagnostic, USA) system.

The inclusion criteria for the study were as follows: I) Being over 18, II) Anti-HCV positive result in enzyme-linked immunosorbent assay (ELISA), III) Serum HCV RNA measured quantitatively and detected as positive, IV) Having received 48 weeks of PEG-IFN α-2A 2B + RIB treatment. The exclusion criteria for the study were as follows: I) Being HCV RNA negative, II) Diagnosed with cirrhosis, HCC and auto-immune liver disease.

The study was undertaken in accordance with the 1975 Declaration of Helsinki Principles as revised in 2008 and the Approval of the Clinical Trials Ethics Committee Commission dated/numbered 16.05.2016/149. Written patient consent was taken from all the patients included in the study.

Statistical Analysis

The Kolmogorov-Smirnov test was used in the conformity check of continuous variables to normal distribution. Student's T-Test and Mann Whitney U were used in the comparison of two independent groups of variables with normal distribution, and two independent groups of variables without normal distribution, respectively. The Chi-Square Test was used together with descriptive statistics. SPSS for Windows version 22.0 package (IBM Corp.; 2011 IBM Corp. Armonk, NY, USA) was used for statistical analysis, and $p< 0.05$ was considered statistically significant.

RESULTS

The treatment responses of 305 patients who were treated with CHC infection diagnosis in our clinic were evaluated at the end of month 18. Table 1 shows the age, gender, baseline ALT levels, baseline HCV RNA levels of the genotype sub-groups, and distribution of patients who were diagnosed with advanced fibrosis as a result of biopsy (ISHAK 3-6). Advanced fibrosis was detected in 37 (66%) of a total of 56 patients and in 33 (64.7%) of 51 genotype 1b patients (Table 1).

Of the 305 patients in our study, 133 were female (43.6%), and 172 were male (56.4%) (p=0.967). Factors affecting SVR were investigated. There was no significant difference between the age

Table 1. General distribution of genotype sub–groups in patient group

Variable	Number (n)	Genotype 1b %	Genotype 1 %	Genotype 1a %	Genotype 1 ve 1b %	Genotype 3A %	Genotype 4A %	Genotype 5 %
Total	305	284 (93,1)	13 (4,3)	4 (1,3)	1 (0,3)	1 (0,3)	1 (0,3)	1 (0,3)
Female	133 (43,6)	121 (42,6)	8 (61,5)	2 (50)	0	1 (100)	0	1 (100)
Male	172 (56,4)	163 (57,4)	5 (38,5)	2 (50)	1 (100)	0	1 (100)	0
Age	55,8±12,8	55,8±12,9	54,7±13,3	62±4,5	62	46	32	66
Baseline ALT level (U/L)	43,3±33,6	42,71±33,76	49±24	84±49,74	30	24	30	26
Baseline HCV RNA Level (IU/mL)	4207225,8± 3687669,52	4238402,6± 3729767,86	3130977,6± 2761167,17	6675000± 3004857,17	226000	1900000	7900000	2100000
KC Bx performed	56	51	5	0	0	0	0	0
Severe fibrosis detected (ISHAK score 3–6	37 (%66)	33 (%64,7)	4 (%80)	0	0	0	0	0

ALT: alanine aminotransferase; HCV RNA: hepatitis C virus ribo nucleic acid; KC Bx: liver biopsy

Table 2. Factors affecting sustained virologic response

Variable		Number (n)	SVR, n (%)	p
Gender	Female	133	78 (45.3)	0.967
	Male	172	60 (45.1)	
Age group	Under 40	38	19 (50)	0.167
	Between 40–49	36	21 (58.3)	
	50 and Over	231	98 (42.4)	
HCV genotype	1b	284	129 (45.4)	0.255
	1	13	7 (53.8)	
	1a	4	0	
	1 and 1b	1	1 (100)	
	3a	1	1 (100)	
	4a	1	0	
	5	1	0	
Diabetes,	Yes	31	11 (35.5)	0.249
Prediabetes	No	274	127 (46.4)	
Baseline	<500000	37	17 (45.9)	0.586
HCV RNA	≥500000 <3000000	74	37 (50)	
(IU/mL)	≥3000000	193	83 (43)	
Presence of Fibrosis	Yes	37	15 (40.5)	0.713
	No	17	6 (35.3)	
Baseline	<40	185	109 (58.9)	0.000
ALT level	40– <80	88	24 (27.3)	
(U/L)	80– <120	20	3 (15)	
	120+	12	2 (16.7)	
Baseline	<14	247	108 (43.7)	0.271
Hb Level	≥14	58	30 (51.7)	
Baseline	<4000	21	6 (28.6)	0.112
WBC Level	≥4000	284	132 (46.5)	
Baseline	<200	100	38 (38)	0.206
PLT level	200– <300	141	69 (48.9)	
(10^3/μL)	≥300	64	31 (48.4)	

SVR: Sustained virologic response; HCV: hepatitis C virus; HCV RNA: hepatitis C virus ribo nucleic acid; ALT: alanine aminotransferase; Hb: Hemoglobin; WBC: white blood cells; PLT: platelet

groups of below 40, 40-49, and over 50 (p=0.167). The number of genotype 1 patients, one of the HCV genotype sub-groups, was 284 (93.1%). No significant difference was observed between other genotype sub-groups (p>0.255). SVR showed no significant effect on baseline HCV RNA levels (p=0.586). Presence or absence of advanced fibrosis in patients was not found as a significant risk factor for SVR (p=0.713). Baseline white blood cell, hemoglobin, and platelet levels were not considered a risk factor for SVR, either. Baseline ALT levels <40 IU / mL were determined as positive factors on SVR, which was a significant result (p=0.000) (Table 2).

Table 3. Sustained virologic response levels according to treatment regimen and genotype

Treatment regimen	PEG–IFN α–2A + RIB, n (%)	PEG–IFN α–2B + RIB, n (%)	p
Number of patients	138	167	–
Sustained virologic response	63 (%45.7)	75 (%45.9)	0.897
Genotype 1b, SVR	58/124 (%46.8)	71/160 (%44.4)	0.126
Genotype 1, SVR	3/7 (%42.9)	4/6 (%66.7)	
Genotype 1a, SVR	0/4 (%0)	0	
Genotype 1 and 1b, SVR	1/1 (%100)	0	
Genotype 3a, SVR	1/1 (%100)	0	
Genotype 4a, SVR	0	1/1 (%100)	
Genotype 5, SVR	0/1 (%0)	0	

PEG–IFN α–2A + RIB: Pegylated interferon α–2A + ribavirin; PEG–IFN α–2B + RIB: Pegylated interferon α–2B + ribavirin; SVR: sustained virologic response

Table 4. Response status of pegylated interferon alpha–2A / 2B + ribavirin treatment by genotype sub–group

Genotype	Number (n)	Sustained virologic response (%)	Unresponsiveness to treatment (%)	Recurrence cases (%)
Genotype 1b	284	129 (45,4)	86 (30,3)	35 (12,3)
Genotype 1	13	7 (53,8)	3 (23,1)	0
Genotype 1a	4	0	3 (75)	0
Genotype 1 and 1b	1	1 (100)	0	0
Genotype 3a	1	1 (100)	0	0
Genotype 4a	1	0	1 (100)	0
Genotype 5	1	0	1 (100)	0

Sustained virological response rates of the treatment regimen (PEG-IFN α-2A + RIB and PEG-IFN α-2B + RIB) were investigated according to the genotype sub-groups. There was no significant difference between both treatment regimen for SVR (p>0.05). Accordingly, SVR was found in 63 (45.7%) of 138 patients receiving PEG-IFN α-2A + RIB. SVR was detected in 75 (45.9%) of 167 patients receiving PEG-IFN α-2B + RIB. SVR was seen in 58 (46.8%) of 124 patients receiving PEG-IFN α-2A + RIB treatment in genotype 1 group. In 71 (44.4%) of 160 patients receiving PEG-IFN α-2B + RIB, SVR was observed. The SVRs of other groups were

Table 5. Distributions of patients' response to treatment

Response status	Number	Percentage (%)
Primary unresponsiveness	118	38.7
Partial virologic response	36	11.8
End–of–treatment virologic response	151	49.5
Sustained virologic response	138	45.2
Recurrence	35	11.6

evaluated individually. A significant difference was not seen in either branches of treatment in terms of all genotypes ($p<0.05$) (Table 3).

With regards to the response status of PEG-IFN α-2A + RIB and PEG-IFN α-2B + RIB treatment in genotype sub-groups, among 284 patients with genotype 1; SVR, unresponsiveness to treatment, and recurrence were seen in 129 (45.4%), 86 (30.3%), and 35 (12.3%) patients, respectively. Responses of other genotype sub-groups to treatment are shown in Table 4.

The patients' unresponsiveness to treatment was evaluated. 118 patients (38.7%) had primary unresponsiveness. Partial virologic response was seen in 36 patients (11.8%). ETVR was seen in 151 patients (49.5%). SVR was observed in 138 (45.2%) of the patients. 35 (11.6%) patients experienced recurrence (Table 5).

According to the laboratory, adverse effects of PEG-IFN α-2A + RIB and PEG-IFN α-2B + RIB treatment in month 3, anemia, high ALT, leucopenia, and thrombocytopenia were observed in 133 (43.6%), 116 (38%), 16 (5.2%), and 50 (16.4%) patients, respectively. There was no significant difference in terms of all adverse effects in either branches of treatment ($p>0.05$). According to the laboratory, adverse effects of PEG-IFN α-2A + RIB and PEG-IFN α-2B + RIB treatment in month 12, anemia, high ALT, leucopenia, and thrombocytopenia were observed in 110 (36.1%), 128 (42.8%), 18 (6%), and 66 (22.1%) patients, respectively. There was no significant difference in terms of all adverse effects in either treatment arms ($p>0.05$).

The common clinical side effects of PEG-IFN α-2A + RIB and PEG-IFN α-2B + RIB treatment were detected to be weakness and fever. But there was no statistically significant difference when all clinical side effects were observed ($p>0.05$).

DISCUSSION

During the last 10 years, important advancements have been made in the treatment of HCV infections with the emergence of PEG-IFN (8). The aim of the treatment is suppression of viral replication, and prevention of late complications such as cirrhosis and HCC. Success criteria targeted with antiviral treatment in CHC treatment were normalization of ALT and AST as the biochemical response, negativity of HCV RNA as the virologic response, and decrease of necroinflammation in the liver as the histological response (3).

Among the studies where ETVR has been evaluated, Manns et al. (4) found that ETVR was 65%, 56% and 54% in the group receiving high dose PEG-IFN α-2B + RIB combination treatment, low dose PEG-IFN α-2B and RIB combination treatment, and INF α–2B + RIB combination treatment group, respectively. In a multi-centered study with 531 patients who evaluated the efficiency and reliability of PEG-IFN α-2A, PEG-IFN α-2A was applied subcutaneously at a dose of 180μg/kg once a week for 48 weeks, and ETVR was found to be 69%. This rate is significantly higher than the 28% obtained with IFN α-2A treatment (9). In the study conducted by Fried et al. (3) on chronic HCV patients, the ESVR rate was found to be 69%, 52%, and 59% in patients taking PEG-IFN α-2A and RIB combination, INF α-2B + RIB combination, and PEG-IFN α-2A and placebo combination, respectively.

In month 12 of the treatment regimen (PEG-IFN α-2A + RIB and PEG-IFN α-2B + RIB) we gave in our study, ESVR was observed in 151 (49.5%) of all the patients. HCV RNA clearance was detected in 70 (50.7%) of the patients using PEG-IFN α-2A, and 81 (48.5%) of the patients using PEG-IFN α-2B + RIB. There was no significant difference in either of the branches of treatment ($p>0.05$). The ESVR rates we obtained were lower than in some publications, but similar to some studies in the literature. The lower ETVR rates compared to some publications may be attributed to the fact that the majority of the patients are genotype 1 and genotype 1b.

In our study, SVR levels were also examined by genotype sub-group of the treatment regimen (PEG-IFN α-2A + RIB and PEG-IFN α-2B + RIB), and SVR was found in 63 (45.7%) of 138 patients that received PEG-IFN α-2A + RIB. SVR was detected in 75 (45.9%) of 167 patients receiving PEG-IFN α-2B + RIB. In genotype 1b group, SVR was observed in 58 (46.8%) of 124 patients who were treated with PEG-IFN α-2A + RIB. In 71 (44.4%) of 160 patients receiving PEG-IFN α-2B + RIB, SVR was observed. Regarding other studies where SVR has been evaluated; in a study conducted by Reddy et al. to determine the dose of PEG-IFN α-2A in patients with CHC who had not received INF treatment before, SVR was 10% with a dose of 45μg once a week, and they reported that there was not a significant difference in terms of SVR when compared to IFN α-2A treatment administered in three doses a week. In 180μg PEG-IFN α-2A administered once a week, this rate was 36%, and it was stated that the most suitable dose of PEG-IFN α-2A was 180μg

once a week (10). In a study carried out by Zeuzem et al. (9), as a result of PEG-IFN α-2A 180μg administration once a week, SVR was 39%. This rate is significantly higher than the 19% obtained with IFN α-2A treatment. In a study conducted by Olut et al. (11), 50 treatment-naive CHC patients infected with genotype 1 received PEG-IFN α-2B 1.5 μg/kg/week, and RIB 1000-1200mg/day depending on the weight of patient. The ultimate target of the treatment was absence of HCV RNA in the serum 24 weeks after the end of treatment. SVR was seen in 30 of 50 patients (60%). In a study performed by Goncalves et al. (12) with 141 patients, ETVR and SVR were found in 77 (54.6%) and 56 (39.7%) patients. In our study, SVR rates were similar to those in the literature. The reason behind higher SVR rates found in some studies in the literature might be the difference and broadness of the patient population.

There are very few studies in the literature that show which of the PEG-IFN α-2A and PEG-IFN α-2B preparations is more effective on SVR. In a study carried out in Italy, it was reported that SVR rates obtained with PEG-IFN α-2A and RIB combination were significantly higher than the SVR rates obtained with PEG-IFN α-2B and RIB combination both in genotype 1-4 and genotype 2-3 patients; however, the adverse effects observed in patients in both branches of treatment were similar (13).

With regards to the response status of PEG-IFN α-2A / 2B + RIB treatment in genotype sub-groups, among 284 patients with genotype 1b; SVR, unresponsiveness to treatment, and recurrence were seen in 129 (45.4%), 86 (30.3%), and 35 (12.3%) patients, respectively.

It was shown that in patients with HCV RNA level < 400,000 IU/mL, sustained viral response was higher compared to patients with higher viral load. In a clinical study, it was reported that low sustained viral response rate was obtained with HCV RNA level > 600,000 IU/mL, whereas high viral load decreased the sustained viral response rate (14, 15). It was observed that significantly higher sustained viral response was obtained with a regimen including interferon in patients with low serum viral load (< 800,000 IU/mL) (16, 17). In some studies, on the other hand, higher sustained viral response was received from patients with high viral load (> 850,000 IU/mL) compared to those with low viral load (9, 18-21). In a study conducted by Fried et al. (3), when patients receiving PEG-IFN α-2A were compared to those receiving PEG-IFN α-2B, higher SVR was observed in patients with a > 800,000 IU/mL HCV RNA level treated with PEG-IFN α-2A. In a study carried out by Berg et al. (22) on 260 patients, < 130,000 IU/mL HCV-RNA level was reported to respond better to treatment. However, there is no clear HCV-RNA level that can predict the response to treatment. The latest studies on PEG-IFN α-2A have shown that SVR rates vary depending on the HCV genotype independently from the viral load (23). However, there was no significant difference between baseline HCV RNA values and SVR, and it did not affect SVR. In our study, HCV RNA clearance was determined in 151 (49.5%) of all patients in month 12 of the treatment regimen (PEG-IFN α-2A and PEG-IFN α-2B). In 70 (50.7%) of the patients using PEG-IFN α-2A + RIB, and 81 (48.5%) of the patients using PEG-IFN α-2B + RIB, HCV RNA clearance was detected. In month 18, SVR was found in 138 (45.2%) of all patients. SVR was detected in 63 (45.7%) of the patients using PEG-IFN α-2A + RIB, and 75 (45.9%) of the patients using PEG-IFN α-2B + RIB. There was no significant difference in either of the branches of treatment ($p>0.05$).

In a study performed on recurrence after treatment, HCV RNA was determined in 7 (2%) patients out of 400, 5 of them were followed-up, and HCV RNA was found again in 2 patients (0.5%) 12 months after the treatment (24). On the other hand, there are studies in which late recurrence rates were high: Lee JE et al. (25), Reichard et al. (26), and Khokhar et al. (27) reported the rates as 7.4%, 8%, and 8.8%, respectively. These inconsistencies result from PCR methods used in varying sensitivity and patient populations. As a result, continuity of the sustained viral response and optimal follow-up time are not known (28). With regards to the response status of PEG-IFN α-2A + RIB and PEG-IFN α-2B + RIB treatment in genotype sub-groups in our study, among 284 patients with genotype 1b; sustained viral response, unresponsiveness to treatment and recurrence were seen in 129 (45.4%), 86 (30.3%), and 35 (12.3%) patients. No recurrence was observed in other genotype sub-groups. The lower numbers of recurrence compared to the literature were attributed to the short follow-up period and insufficient number of patients.

Undesired adverse effects are often observed in patients receiving IFN treatment. One adverse effect is seen in at least 75% of the patients receiving IFN and RIB treatment. Flu-like complaints and depression are observed less in PEG-IFN treatment compared to classic interferons (29). In our study, clinical adverse effects of PEG-IFN α-2A / 2B + RIB treatment, weakness and fever were common. Furthermore, in terms of the adverse effects such as flu-like symptoms, muscular pain, loss of appetite, nausea, headache, rash, and depression, it was observed that the adverse effects seen in both treatment groups were similar and there was no significant difference.

CONCLUSION

The long-term prognosis of patients is positively affected by treatments given for CHC infection. The desired level could not be reached in HCV RNA clearance with PEG-IFN α-2A + RIB and PEG-IFN α-2B + RIB treatment.

Ethics Committee Approval: Ethics committee approval was received for this study from Gaziantep University School of Medicine Clinical Research Ethics Committee (16.05.2016/149).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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