Evaluation of Dual Therapy in Real Life Setting in Treatment-Naïve Turkish Patients with HCV Infection: A Multicenter, Retrospective Study

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Background: Before the introduction of direct-acting antivirals in the treatment of chronic hepatitis C patients, the combination of peginterferon alpha and ribavirin was the standard therapy. Observational studies that investigated sustained virological response (SVR) rates by these drugs yielded different outcomes.
Aims: The goal of the study was to demonstrate real life data concerning SVR rate achieved by peginterferon alpha plus ribavirin in patients who were treatment-naïve.

Study Design: A multicenter, retrospective observational study.
Methods: The study was conducted retrospectively on 1214 treatment naïve-patients, being treated with peginterferon alpha-2a or 2b plus ribavirin in respect of the current guidelines between 2005 and 2013. The patients' data were collected from 22 centers via a standard form, which has been prepared for this study. The data included demographic and clinical characteristics (gender, age,

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body weight, initial Hepatitis C virus RNA (HCV RNA) level, disease staging) as well as course of treatment (duration of treatment, outcomes, discontinuations and adverse events). Renal insufficiency, decompensated liver disease, history of transplantation, immunosuppressive therapy or autoimmune liver disease were exclusion criteria for the study. Treatment efficacy was assessed according to the patient's demographic characteristics, baseline viral load, genotype, and fibrosis scores.

Results: The mean age of the patients was 50.74 (±0.64) years. Most of them were infected with genotype 1 (91.8%). SVR was achieved in 761 (62.7%) patients. SVR rate was 59.1% in genotype 1, 89.4% in genotype 2, 93.8% in genotype 3, and 33.3% in genotype 4 patients. Patients with lower viral load yielded higher SVR (65.8% vs. 58.4%, p=0.09). SVR rates according to histologic severity were found to be 69.3%, 66.3%, 59.9%, 47.3%, and 45.5% in patients with fibrosis stage 0, 1, 2, 3 and 4, respectively. The predictors of SVR were male gender, genotype 2/3, age less than 45 years, low fibrosis stage, low baseline viral load and presence of early virological response. SVR rates to each peginterferon were found to be similar in genotype 1/4 although SVR rates were found to be higher for peginterferon alpha-2b in patients with genotype 2/3. The number of patients who failed to complete treatment due to adverse effects was 33 (2.7%). The number of patients failed to complete treatment due to adverse effects was 33 (2.7%).

Conclusion: Our findings showed that the rate of SVR to dual therapy was higher in treatment-naïve Turkish patients than that reported in randomized controlled trials. Also peginterferon alpha-2a and alpha-2b were found to be similar in terms of SVR in genotype 1 patients.

Keywords: Hepatitis C, peginterferon alpha-2a, peginterferon alpha-2b, ribavirin, therapy

Hepatitis C virus (HCV) infection is a common disease all over the world, affecting nearly 3% of the world's population (1). The prevalence has been reported to be approximately 0.5-1% in the studies conducted in Turkey (2,3). In a clinical series, the prevalence of cirrhosis within 20 years after detection of chronic hepatitis was found to be 24% (4). The annual risk of hepatocellular carcinoma (HCC) is between 2-6% in patients who develop cirrhosis as a result of HCV infection (5). It has been demonstrated that sustained virological response (SVR) achieved with treatment in chronic hepatitis C patients and even in patients with advanced-stage liver fibrosis decreases the risk of hepatic insufficiency and liver-related mortality (6). In a meta-analysis, it was demonstrated that development of HCC could be prevented in patients receiving interferon, even if SVR has not been achieved (7).

The purpose of the treatment of chronic hepatitis C (CHC) is to achieve a virological cure. Before direct-acting antiviral drug-including regimes, SVR rates achieved in the first pivotal study performed using the combination of peginterferon alpha and ribavirin, which was the standard therapy for CHC patients, were found to be as follows: 54% in all genotypes (GTs), 42% in GT 1, and over 80% in GT 2/3 (8,9). In a similar study performed with peginterferon alpha-2a plus ribavirin, SVR rates were found to be 56% in overall GTs, 46% in GT 1 , 76% in GT 2 and 3 patients (10). GT 1 appears to be the most difficult to treat GT and more than 90% of Turkish patients are GT 1 (11).

Beside GT and HCV RNA levels, patient-related factors such as interleukin-28B polymorphism, age, body weight, ethnicity, steatosis, fibrosis, and insulin resistance affect SVR rates in patients receiving dual therapy (9,10,12). If HCV RNA is undetectable at the fourth week of treatment, which is known as rapid virological response (RVR), SVR rate is around 90% (13). In recent years, real life data reported from various countries revealed different SVR rates from pivotal studies, and the reasons for these differences were discussed by authors. The present multi-center study has been conducted to obtain real life data regarding treatment outcomes in treatment-naïve CHC patients receiving dual therapy in Turkey.

MATERIALS AND METHODS

The present study was designed as a multicenter, retrospective study by the members of Viral Hepatitis Study Group which was formed within the body of Turkish Society of Clinical Microbiology and Infectious Diseases, between 2005 and 2013. The data of treatment-naïve CHC patients treated with peginterferon alpha plus ribavirin were collected. Twenty-two centers from different regions of Turkey participated in the study. Thirty researchers from the member centers of the group shared the data of 1214 patients, who met the predefined criteria, over the standard form that was delivered. The study protocol was approved by Dışkapı Yıldırım Beyazıt Training and Research Hospital, Ethics Committee for Clinical Researches. Considering patient privacy, patient information was recorded by coding.

Study design

A form was developed for eligibility criteria and shared with the group members. Baseline data of treatment-naïve patients receiving peginterferon alpha-2 (a or b) plus ribavirin for CHC, treatment protocol and doses, follow-up during treatment, data at the end of treatment and post-therapy follow-up were collected. Age, gender, liver histopathology, alanine aminotransaminase (ALT) and aspartate aminotransferase (AST) levels, HCV genotype, RVR, early virological response (EVR), end of treatment response (ETR), and SVR rates were recorded.

Patient selection

The study comprised treatment-naïve patients, who were over 18 years of age and had anti-HCV positivity and detectable HCV RNA for longer than six months. Twenty one patients co-infected with hepatitis B virus were also included. Patients with renal insufficiency, decompensated liver disease, history of transplantation, immunosuppressive therapy or autoimmune liver disease were not included in the study. Patients with a leucocyte count less than $3000/mm^3$ or neutrophil $<1500/mm^3$ and thrombocyte count $<90000/mm^3$ before therapy were also excluded. Patients in whom peginterferon plus ribavirin dose adjustment due to adverse events had not been performed in accordance with the guidelines, were not included in the study.

Baseline parameters

Patients' age, gender, pretreatment body weight, height, underlying diseases, baseline biochemical parameters (ALT, AST, total protein, albumin, alkaline phosphatase), complete blood count, prothrombin time, HBsAg, Anti-HIV, liver histopathology, HCV RNA, genotype, and history of diabetes were recorded. HCV RNA levels were recorded quantitatively in IU/mL. Results from the centers that measured HCV RNA quantification in copy/mL were transformed into IU/mL using the transformer factor of the test. Liver biopsy was evaluated in accordance with the Metavir scoring system (14,15): F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; and F4, cirrhosis. HCV RNA levels of the patients were analyzed at the beginning of treatment, at the fourth, 12th and 24th weeks over the course of treatment, at the end of treatment, and at the 24th week after treatment. Complete blood count was analyzed at the second and fourth weeks and every four weeks thereafter over the course of treatment, whereas biochemical analyses were performed every four weeks. The doses of peginterferon and ribavirin, reasons for dose adjustments if any, and adverse effects were recorded.

Treatment and defining the response

The dose and duration of the dual combination therapy were in compliance with national and international guidelines: Weekly peginterferon alpha-2a (Pegasys; Hoffmann-la Roche, Switzerland) 180 µg subcutaneously (SC) plus oral daily ribavirin (Copegus; Hoffman-la Roche, Switzerland) or peginterferon alpha-2b (Pegintron, Merck & Co., Inc.; New Jersey, USA) 1.5 µg/kg SC per week plus oral daily ribavirin (Rebetol; Merck & Co., Inc.; New Jersey, USA). Ribavirin dose was adjusted according to body weight in line with the recommendations of the manufacturers. Treatment durations were 24 weeks for HCV GT 2 and 3 or 48 weeks for HCV GT 1 and 4 patients.

Undetectable HCV RNA at the end of treatment was considered ETR, whereas undetectable HCV RNA at the 24th week after treatment was considered to SVR. Undetectable HCV RNA at the 12th week of treatment was considered as EVR. Treatment was discontinued in those patients who had decline in viral load less than 2 log at the 12th week or who had detectable HCV RNA at the 24th week of treatment since they were accepted as unresponsive. Undetectable HCV RNA at the fourth week of treatment was considered RVR. HCV RNA <50 IU/mL was considered a loss of HCV RNA. Patients from the centers that had difficulty in accessing HCV RNA test and therefore could not perform HCV RNA analysis at the fourth or 12th week were also included in the study, but effects of RVR and EVR on SVR could not be evaluated for those patients.

Statistical analysis

Baseline data of the patients were calculated as mean±SD or median. Categorical data were presented as numbers and ratio. Relation of baseline data with SVR was analyzed by using student's t-test and Mann–Whitney U-test or chi-square test The results were considered statistically significant if p<0.05. Variances that reached statistical significance in univariate analysis were evaluated by multivariate logistic regression analysis. Stepwise and multivariate logistic regression models were used to explore the independent factors that could be used to predict SVR. Statistical analysis was carried out using SPSS program for Windows, version 15.0 J (SPSS; Chicago, IL, USA).

RESULTS

All of the participants were Caucasians and females accounted for the majority (57.7%). The mean age of the patients was 50.74 years (±0.64). Of the patients, 8.7% were diabetic and 1.8% had hepatitis B co-infection. Since the study was retrospective and primarily aimed to determine SVR rates, 267 pa-

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tients with undetermined GT, 316 patients without biopsy, and 490 patients for whom body mass index could not be calculated were also included in the study. GT1 was found to be the predominant genotype (91.8%) among those patients who underwent genotyping.

Histological findings of the liver were available for 898 patients; cirrhosis was present in only 2.4% of the patients with known fibrosis. Baseline demographic characteristics and laboratory findings of the patients are shown in Tables 1 and 2.

In all GTs, the percentage of patients with SVR was 62.7%. While SVR was 58.5% in GT 1/4, it was found to be 90.7% in GT 2/3 (p=0.001). SVR rate was considerably higher in GT 2/3 patients compared to GT 1/4 patients (p=0.001). EVR was 73.7%, whereas ETR rate was found to be 79.0%.

SVR was evaluated according to the baseline characteristics of the patients. While SVR was 75.8% under the age of 45 years, it was found to be 58.1% over the age of 45 years (p=0.001). ALT elevation was found in 54.7% of the patients. SVR rates were lower in the patients with higher ALT levels than those with normal ALT levels (59.2% vs. 67.8%). Likewise, SVR was also lower in the patients with higher AST levels (67.6% vs. 56.1%). HCV RNA level ≥800,000 IU/mL

TABLE 1. Baseline Characteristics of Study Subjects (n=1214)

Characteristic	Number of patients and values
Gender, Male/Female	513/701 (42.3%/57.7%)
Age (Mean)	50.74 (±11.68)
<45	314 (25.9%)
=>45	900 (74.1%)
Body Mass Index (n=724)	
<25	248 (34.3%)
≥25-<30	338 (46.7%)
≥30	138 (19.1%)
Fibrosis stage (n=898)	
0	127 (14.1%)
1	419 (46.7%)
2	182 (20.3%)
3	148 (16.5%)
4	22 (2.4%)
Genotype (n=947)	
1	869 (91.8%)
2	38 (4%)
3	16 (1.7%)
4	24 (2.5%)
Peginterferon alpha-2a/2b	618/596 (50.9%/49.1%)
Diabetes mellitus	106/1214 (8.7%)
Hepatitis B surface antigen positivity	21/1198 (1.8%)
ALT, U/L (n=1214)	
Mean	68.73 (±50.96)
Normal	525 (43.2%)
Above upper limit of the normal	689 (56.8%)
Hepatitis C virus RNA,	
Median (min.-max.)	625,500 (372-5,200,000,000)
≥8×105 IU/mL	510/1214 (42%)

ALT: alanine aminotransaminase

TABLE 2. Demographic characteristics of the patients receiving peginterferon alpha-2a and 2b

	Peginterferon alpha-2a n (%)	Peginterferon alpha-2b n (%)	Total	p
Gender				
Male	276 (44.6%)	237 (39.8%)	513 (42.3%)	
Female	343 (55.4%)	358 (60.2%)	701 (57.7%)	p=0.094
Total	619 (100%)	595 (100%)	1214 (100%)	NS
Age				
<45	170 (27.5%)	144 (24.2%)	314 (25.9%)	
45-59	310 (50.1%)	288 (48.4%)	598 (49.3%)	p=0.111
≥60	139 (22.5%)	163 (27.4%)	302 (24.9%)	NS
Total	619 (100%)	595 (100%)	1214 (100%)	
BMI				
Normal	124 (34.9%)	124 (33.6%)	248 (34.3%)	
Overweight	171 (48.2%)	167 (45.3%)	338 (46.7%)	p=0.346
Obese	60 (16.9%)	78 (21.1%)	138 (19.1%)	NS
Total	355 (100%)	369 (100%)	724 (100%)	
Genotype				
1, 4	447 (94.3%)	446 (94.3%)	893 (94.3%)	p=0.994
2, 3	27 (5.7%)	27 (5.7%)	54 (5.7%)	NS
Total	474 (100%)	473 (100%)	947 (100%)	
Fibrosis				
0	65 (14.3%)	62 (14.0%)	127 (14.1%)	
1	209 (45.9%)	210 (47.4%)	419 (46.7%)	
2	99 (21.8%)	83 (18.7%)	182 (20.3%)	p=0.807
3	72 (15.8%)	76 (17.2%)	148 (16.5%)	NS
4	10 (2.2%)	12 (2.7%)	22 (2.4%)	
Total	455 (100%)	443 (100%)	898 (100%)	
HCV RNA				
<800000	350 (56.5%)	354 (59.5%)	704 (58.0%)	p=0.297
≥800000	269 (43.5%)	241 (40.5%)	510 (42.0%)	NS
Total	619 (100%)	595 (100%)	1214 (100%)	
Diabetes				
No	555 (89.7%)	553 (92.9%)	1108 (91.3%)	p=0.043
Yes	64 (10.3%)	42 (7.1%)	106 (8.7%)	S
Total	619 (100%)	595 (100%)	1214 (100%)	

NS: not significant, S: significant, BMI: body mass index

was considered as high viral load; accordingly, high viral load was detected in 42% of the patients. Median HCV RNA level was 625,500 IU/mL. SVR was higher in those patients with lower viral load (65.8% vs. 58.4%, p=0.09).

Patients who had low fibrosis accounted for the majority of the study group; the frequencies of fibrosis stages were as follows: stage 0, 14%; stage 1, 46.7%; stage 2, 20.3%; stage 3, 16.5%; and stage 4 (cirrhosis), 2.4%. SVR rates according to fibrosis stages (0 through 4) were found to be 69.3%, 66.3%, 59.9%, 47.3%, and 45.5%, respectively.

Two hundred and fifty-four patients (20.92%) could not complete the treatment because of unresponsiveness to therapy or adverse effects. Treatment was discontinued at the 12th or 24th week due to complete or partial non-response in 186 (15.32%) and due to breakthrough in 35 (2.88%) patients, whereas 33 (2.71%) patients failed to complete the study due to adverse events. While SVR rate was 47.2% in diabetic patients, it was found to be 64.2% in non-diabetic patients (p=0.001). Any effect of HBsAg positivity on SVR was not determined.

Rapid virological response was evaluated in only 645 patients and was determined in 43.3% of these patients. SVR was higher in those with RVR (79.6% vs. 43.2%, p=0.001). SVR was achieved in 78.1% of the patients with EVR and in 8.7% of those without EVR (p=0.001). Relationship between SVR and demographic and clinical features of the study group are given in Table 3.

In the study group, 50.9% of the patients received peginterferon alpha-2a and 49.1% received peginterferon alpha-2b. We found no differences between two interferons in terms of SVR (63.0% vs. 62.4%, p=0.814). We also evaluated per-genotype differences in SVR rates according to the type of peginterferon used (Table 4). Peginterferon alpha-2b appears to be associated with higher SVR rates in GT 2/3 patients when compared with alpha-2a (96.3% versus 85.2%, p>0.001), although we could not find any statistically significant difference between two drugs in patients with GT 1/4 (p=0.891).

Multivariate logistic regression analysis revealed positive correlation between SVR and male gender, EVR and the age under 45 years (Table 5).

The most common adverse effects were weight loss, myalgia, fever and headache. While 27% of the patients required dose reduction for ribavirin due to anemia, the dose of peginterferon was reduced in 7% patients due to neutropenia. Treatment discontinuation was required due to adverse events in 2.7% of the patients. Common adverse effects are presented in Table 6.

DISCUSSION

Although the seroprevalence of CHC is about 1% in Turkey, HCV is ranked second in the etiology of HCC after

TABLE 3. Relationship between demographic and clinical characteristics and SVR (n=1214) (Chi-Square tests)

Demographic and clinical characteristics	SVR (%)	p
Age		
<45	75.8	p=0.001
=>45	58.1	
Gender		
Male	63.7	p=0.515
Female	61.9	
Body Mass Index		
<25	68.1	
≥25-<30	58.9	p=0.010
≥30	53.9	
Diabetes Mellitus	47.2	p=0.001
Non diabetics	64.2	
Genotype		
1, 4	58.5	p=0.001
2, 3	90.7	
Fibrosis (Metavir)		
0	69.3	
1	66.3	
2	59.9	p=0.001
3	47.3	
4	45.5	
HCV RNA		
≥800,000	58.4	p=0.09
<800,000	65.8	
HBV Co-infection		
Yes	66.7	p=0.444
No	62.5	
Peginterferon		
Alpha-2a (n=619)	63.0	p=0.814
Alpha-2b (n=595)	62.4	
ALT, U/L		
Normal	67.8	p=0.02
Above upper limit of the normal	59.2	
AST, U/L		
Normal	67.6	
Above upper limit of the normal	56.1	p=0.001
Rapid virological response		
Yes	79.6	p=0.001
No	43.2	
EVR		
Yes	78.1	p=0.001
No	8.7	

SVR: sustained virological response; HBV: hepatitis B virus; ALT: alanine aminotransaminase; AST: aspartate aminotransferase; EVR: early virological response; HCV: hepatitis C virus

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TABLE 4. Comparison of peginterferon alpha-2a vs. peginterferon alpha-2b according to SVR

	SVR (%)	p
All genotypes		
Peginterferon alpha-2a (n=619)	63.0	p=0.814
Peginterferon alpha-2b (n=595)	62.4	
Genotype 2, 3		
Peginterferon alpha-2a (n=27)	85.2	p<0.001
Peginterferon alpha-2b (n=27)	96.3	
Genotype 1, 4		
Peginterferon alpha-2a	58.9	p=0.891
Peginterferon alpha-2b	58.4	

SVR: sustained virological response

TABLE 5. Multivariate Logistic Regression analysis to identify factors associated with SVR after peginterferon plus ribavirin therapy in treatment-naïve chronic hepatitis C patients with HCV genotype 1

Factor	OR	95% CI	p
Male gender	1.956	1.107-3.453	0.021
Age <45 years	3.630	1.689-3.020	0.002
EVR	24.111	3.915-19.083	0.001
RVR	1.490	0.802-2.770	0.207
ALT	0.770	0.359-1.651	0.502
AST	0.750	1.597-0.455	0.455
HCV-RNA	0.758	0.406-1.306	0.287
Genotype	3.203	0.712-14.416	0.129
Fibrosis 1	1.157	0.432-3106	0.773
Fibrosis 2	0.852	0.279-2.605	0.779
Fibrosis 3	0.565	0.173-1.846	0.345
Fibrosis 4	2.048	0.283-14.796	0.477

OR: odds ratio; CI: confidence interval; HCV: hepatitis C virus; EVR: early virological response; RVR: rapid virological response; ALT: alanine aminotransaminase; AST: aspartate aminotransferase

TABLE 6. Frequency of adverse events for peginterferon alpha plus ribavirin

Adverse Events	%
Fever	50
Headache	50
Myalgia	56
Weight loss	59
Injection site inflammation	13
Arthralgia	11
Nausea	18
Alopecia	10
Depression	13
Insomnia	12
Hyperthyroidism	4
Hypothyroidism	0.2
Anemia (<10 gr/dL)	27
Neutropenia (<750 cell/mm³)	7
Thrombocytopenia (<50,000/mm³)	2

hepatitis B virus (16-18). Therefore, the treatment of such patients is important to prevent the development of cirrhosis or, if it has already developed, progression to HCC or hepatic insufficiency, and accordingly to reduce liver-related mortality. Long-term follow-up shows that response is permanent in 99% of the patients with SVR (19,20). In the pivotal studies performed using standard therapy, which consists of peginterferon plus ribavirin, SVR rate was 54-56% for overall genotypes in treatment-naïve patients and it was reported that SVR rate was 42-52% for GT 1 patients (9,10,13). Real life data indicate that SVR rates are usually higher than pivotal studies. Park et al. (21) conducted a study in Korea and evaluated the data of 758 patients; they found SVR rate to be 59.6% in all GTs, 53.6% in GT 1, and 71.4% in GTs 2/3. Similar results were obtained in two studies conducted in Ar-

gentina and Italy (22,23). In France, the outcomes obtained by Bourliere et al. (24) were similar to the pivotal studies. In Turkey, there has been no large-scale study published regarding the results of dual therapy. Yenice et al. (25) conducted a study with 74 GT 1 treatment-naïve patients and determined the rate of SVR to be 48.6% in those treated with peginterferon alpha-2a and 35.1% in those treated with peginterferon alpha-2b. Dogan et al. (26) found 57.0% and 52.3% SVR rate in those treated with peginterferon alpha-2a and peginterferon alpha-2b, respectively, in a study consisting of 151 CHC patients with GT 1. In this multicenter study, we have found SVR rate of 59.1% in GT1 patients, which is higher than both the pivotal studies and the studies published previously in Turkey.

As shown in many studies, SVR rate in GT 2/3 patients is higher than for GT 1 patients (9,10,13). As is expected, we also have found higher SVR rates in GTs 2/3 as compared to GTs 1/4 (90.7% vs. 58.5%, p=0.001). Another factor that enhances SVR was low viral load before treatment (9,13,24). In the present study, SVR rate was also higher (65.8%) in patients with low viral load than those of higher viral load (58.4%) (p=0.09). Other patient-related factors that positively affect SVR were found to be young age, low body weight and low fibrosis stage. It is known that SVR rate is low in patients with advanced–stage fibrosis, particularly with cirrhosis (27). The rate of cirrhotic patients was 2.4% in this study. This rate was found to be 29% by Manns et al. (9) and 12% by Fried et al. (10). We conclude that the lower number of cirrhotic patients in this study group is one of the important reasons for higher SVR rates found in our study.

Diabetes and insulin resistance are more common in patients with CHC and the presence of insulin resistance leads to rapid progression of fibrosis and reduction in SVR rates (28-31). While SVR rate was 47.2% in our diabetic patients, it was 64.2% in non-diabetic patients. SVR rate was found to be lower in the patients in whom ALT was above the upper limit of normal. The effect of HBV co-infection on SVR could not be demonstrated.

The probability of SVR correlates with the rapidity of HCV RNA suppression (32). Logistic regression analysis revealed that EVR was one of the three independent factors that influenced SVR.

Either peginterferon alpha-2a or alpha-2b is recommended together with ribavirin in the standard dual therapy for CHC (33,34). In the pivotal studies, no substantial difference regarding SVR was detected between these two drugs (9,10). Many studies, being conducted later on, evaluated whether these two drugs were superior to each other. Asconi, Rumi and Awad found that peginterferon alpha-2a was superior to peginterferon alpha-2b (35-37). However, in other studies carried out by McHutchison et al. (38) and Jin et al. (39), no difference was found between peginterferon alpha-2a and 2b in terms of SVR. In two studies conducted in GT 1 patients in Turkey, no difference was found between two peginterferons. Our study is one of the largest series seeking for the SVR differences between two drugs and we have found peginterferon alpha-2a and 2b to be similar in terms of the SVR (25,40). Different SVR rates have also been shown between two peginterferons according to genotypes (41). In this study, higher SVR rates were obtained in GTs 2/3 with peginterferon alpha-2b, but no difference has been shown in GTs 1/4 patients.

It is known that gender usually has no effect on SVR (22,23). In our study, multivariate analysis showed higher SVR rates in males. There are also studies suggesting that response is better in male gender (21,25,35).

Treatment discontinuation due to laboratory abnormality and adverse events was encountered in 2.7% of the patients. This rate is lower than 10 and 11%, which were obtained in the pivotal studies performed for peginterferon alpha-2a and 2b. We think that this is related to the low rate of patients with advanced fibrosis (9,10,42).

Dual therapy with peginterferon alpha plus ribavirin has been being replaced by triple combinations of direct-acting antiviral drugs with peginterferons in many countries. Although SVR rates obtained by new therapies are better than standard therapy, it will be difficult for new antiviral therapies to replace the standard therapy in many countries due to the cost of new treatment regimes. Moreover, the fact that telaprevir and boceprevir, included in the triple therapy, are used in only GT 1, leads to more adverse events than dual therapy, dis-

play interactions with many drugs, and cause resistant strains. Dual therapy may be preferred in young and treatment-naïve patients, with low fibrosis and low viral load, particularly in resource limited settings.

In conclusion, this study comprises the "real life" results of peginterferon alpha plus ribavirin therapy in a large group of treatment-naïve Turkish patients. Our data suggest that the rate of SVR to peginterferon alpha plus ribavirin therapy was higher than those reported in randomized controlled trials. SVR rates to peginterferon alpha-2a and alpha-2b treatments were found to be similar in GTs 1/4 although SVR rates were found to be higher for peginterferon alpha-2b in patients with GTs 2/3.

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