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ORIGINAL ARTICLE

The follow-up results with sustained virologic response in chronic hepatitis C patients in Şanlıurfa/Turkey

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ABSTRACT

Objectives: The aim of the study was to evaluate sustained virological response (SVR) after treatment and factors that influence SVR among patients treated for chronic hepatitis C (CHC).

Materials and methods: The study was conducted in patients with CHC between April 2007 and March 2011, who had achieved SVR following treatment. They were treated with PEG IFN-α and ribavirin. Patients, whose end of treatment responses were obtained without a SVR, received a second course of treatment.

Results: A total of 124 patients, 61 female (49.2%) were enrolled in the study. The distribution of genotypes was: 102 patients with genotype 1 (82.3%) and 22 with genotype 2 (17.7%). SVR was achieved in 78 patients (62.9%) (67 during the first course and 11 in the second) were followed up for a mean duration of 18.4±8.5 months. Positive predictive factors on SVR were female gender (P=0.01), low initial viral load (P=0.01), early virological response (EVR) development (P<0.001) and infection with genotype 2 (P<0.001).

Conclusions: In conclusion, there was no recurrence of HCV infection beyond follow-up of 24 months in any of the patients who obtained SVR. Female gender, low initial viral load, development of EVR and infection with genotype 2 was determined to have a positive impact on SVR. *J Microbiol Infect Dis 2012; 2(1): 14-20*

Key words: Chronic hepatitis C, genotype, sustained virological response, therapy.

Şanlıurfa'da Kalıcı Virolojik Yanıtlı Kronik Hepatit C Hastalarının Takip Sonuçları

ÖZET

Amaç: Bu çalışmada, kronik hepatit C (KHC) hastalarında tedavi sonrası kalıcı virolojik yanıt (KVY) ve KVY'yi etkileyen faktörlerin değerlendirilmesi amaçlanmıştır.

Gereç ve yöntem: Çalışma, Nisan 2007 ile Mart 2011 tarihleri arasında KHC tanısı alan ve tedavi sonrasında KVY gelişen hastalarda yapıldı. Hastalar PEG-IFN-α ve ribavirin ile tedavi edildi. Tedavi sonrasında KVY elde edilmeyenlere ikinci bir tedavi kürü uygulandı.

Bulgular: Çalışmaya, 61'i (% 49,2) kadın toplam 124 hasta dahil edildi. Genotip dağılımları: 102 hastada (% 82,3) genotip 1 ve 22'sinde (% 17,7) idi. Kalıcı virolojik yanıt elde edilen 78 hasta (% 62,9) (67'si ilk tedavi küründe ve 11'i ikinci tedavi küründe) ortalama18,4±8,5 ay 1 takip edildi. Kadın cinsiyet (P=0,01), düşük viral yük (P=0,01), erken virolojik yanıt (EVY) gelişimi (P<0,001) ve genotip 2 ile infeksiyon (P<0,001) KVY'yi olumlu yönde etkileyen faktörler idi.

Sonuç: Sonuç olarak, KVY elde edilen hastalarda 24 ay takip sonrasında rekürrens gelişmedi. Kadın cinsiyet, düşük viral yük, EVY gelişimi ve genotip 2 ile infeksiyon KVY'yi olumlu yönde etkilemektedir.

Anahtar kelimeler: Kronik hepatit C, genotip, kalıcı virolojik yanıt, tedavi.

INTRODUCTION

Currently, hepatitis C virus (HCV) infection is a major cause of chronic liver disease worldwide.[1] It is estimated that 3% of the world's population, approximately 130-220 million individuals, are infected with HCV.[1,2] During long-term follow-up, HCV infection may lead to chronic hepatitis that either progresses with minimal changes or causes various clinical states that may progress to cirrhosis with or without generalized fibrosis and hepatocellular carcinoma (HCC).[3] While the

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mortality rate due to complications associated with cirrhosis is approximately 4%, the incidence of HCC development in the same group varies between 1-5%.[4]

During the progression of HCV to a chronic state, genetic sequence differentiations develop due to rapid viral replication and RNA transcription defects, and these differentiations lead to the development of HCV genotypes. Six major genotypes and more than 100 subtypes have been determined for HCV.[5] While genotype 1 (subtypes 1a and 1b) is commonly seen around the world, genotype 3 is only found in certain European regions.[6]

The current standard therapy for chronic hepatitis C is a combination of pegylated interferon-alpha (PEG-IFN α) and ribavirin. Duration of treatment is 24 weeks for patients infected with genotypes 2 and 3 and 48 weeks for genotype 1. In addition, lower doses of ribavirin are recommended for genotype 2 and 3 patients for the same duration.[7,8] Treatment success is determined in terms of sustained virological response (SVR), which is described as undetectable HCV RNA in patients during the first six months after treatment.

Currently, the rate of SVR varies according to virus genotype and host factors but is approximately 50%.3 The leading factors that influence SVR in patients include host genetic polymorphisms adjacent to the region that codes the IL28B (interferon lambda 3) gene, HCV genotype and degree of fibrosis. In addition, other important predictive factors include host factors such as basal HCV RNA levels, dose and duration of treatment, body mass index (BMI), age, insulin resistance, gender, liver enzyme levels, including ALT and GGT, and co-infection with HIV or other hepatotropic viruses.[9] A significant problem in the treatment of chronic hepatitis C patients following achievement of SVR is disease progression during long-term follow-up, and whether positivity reoccurs in viral load during this stage.

In this study, the aim was to evaluate SVR and the factors that influence SVR in patients treated for chronic hepatitis C. In addition, the secondary objective was to determine the development of relapse during long-term follow-up of patients who achieved SVR with treatment.

METHODS

Study population

This study was a retrospective analysis of 124 adults with chronic hepatitis C (CHC) who were admitted to the Department of Infectious Diseases and Clinical Microbiology at Harran University Medical Faculty between April 2007 and March 2011.

Anti-HCV and HCV RNA-positive patients with findings of chronic liver disease as determined by liver biopsy were diagnosed with chronic hepatitis C regardless of the presence of high levels of liver enzymes.[10] Patients diagnosed and treated with CHC and followed up for at least one year following treatment were evaluated in terms of treatment results.[2]

Quantitative determination of HCV RNA was performed by polymerase chain reaction (PCR) with a commercial kit (RealTime HCV, Abbott Molecular Inc. IL, USA).[11] HCV genotyping was performed with a line probe assay (Inno-LiPA HCV II, Bayer Diagnostics, USA)[12] or with an in-house method.[13] Pre-treatment alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, γ-glutamyl transferase, urea, creatinine, bilirubin, platelets, complete blood count, HBsAg, anti-HBs, anti-HDV, anti-HIV and autoantibodies were determined in patients. In addition, body mass index (BMI, kg/m2) was calculated for each patient.

In cases where no contraindication was present and upon the informed consent of the patient, pre-treatment liver biopsies were performed. Although liver biopsy was recommended for all participants, some patients rejected the procedure. Biopsy samples of patients were stained with hematoxylin eosin, reticulin, and mason-trichrome, and slides were evaluated according to the Modified Knodell system as recommended by Ishak.[14] Cases were classified into four groups as indicated below according to severity of inflammation in terms of the following hepatic activity index (HAI) scores: a minimal group with scores of 1-3, a mild group with scores of 4-8, a moderate group with scores of 9-12 and a severe group with scores of.[13-18]

According to the degree of fibrosis, patients were classified into the following three groups: cases with no fibrosis and mild fibrosis with

scores of 0-2, moderate fibrosis with scores of 3-4 and severe fibrosis with scores of.[5-6]

The exclusion criteria were as follows: patients with co-infections (i.e., HBV, HIV), chronic liver diseases (decompensated cirrhosis, hemochromatosis, Wilson's disease, and autoimmune hepatitis), patients presenting with findings of HCC with ultrasonographic or computerized tomography, immunosuppressive patients and pregnant women. As for treatment, subcutaneous PEG IFN-α 2a (180 μg/week) or PEG IFN-α 2b (1.5 μg/ kg/week) and oral ribavirin (1000-1200 mg/day) were administered to genotype 1 patients for 48 weeks. For genotype 2 patients, PEG IFN therapy and ribavirin (800 mg/day) were administered for 24 weeks. Treatment responses were evaluated according to HCV RNA levels. At least a 2-log decrease or negativity in HCV RNA at the twelfth week of treatment was regarded as early virological response (EVR), while achievement of negative HCV RNA at the end of treatment was regarded as end of treatment response (ETR), and sustained negative HCV RNA at the sixth month following treatment was regarded as SVR. Patients with severe adverse events associated with treatment and patients who failed to achieve ETR were regarded as treatment failures. Patients who voluntarily stopped treatment or who were lost to follow-up were not included in the evaluations.

In the first section of the study, achievement of SVR and the variables influencing this response were evaluated. During monitoring of patients, the dose of ribavirin was decreased when hemoglobin values fell below 10 g/dL, and the agent was discontinued in cases with hemoglobin levels below 8.5 g/dL. Pegylated interferon was decreased to half of the initial dose when the neutrophil count was below 750 cells/mm^3 and the platelet count <50,000 cells/mm^3. A decrease of the neutrophil count below 500 cells/mm^3 and the platelet count below 25,000 cells/mm^3 led to discontinuation of treatment. Patients who achieved SVR were followed up. Recurrence of disease during the follow-up period was regarded as relapse. The development of time-dependent relapse in patients who were being followed up and the factors that influenced relapse constituted the second section of the study.

This study was approved by the Ethical Committee of Harran University Medical Faculty, and written informed consent was obtained from all patients.

Statistical analysis

The dependent variable of the study was sustained virological response. The continuous independent variables of the study were age of patients, ALT, AST, platelet,3 leukocyte, neutrophil and hemoglobin levels. The independent categorical variables were age (≤39/≥40), gender, initial HCV RNA status (high viral load ≥600,000 IU/mL), at least a 2-log decrease or negativity of HCV RNA levels at the twelfth week of treatment, genotype status (genotype 1/genotype 2), treatment protocol (peg IFN α2a/2b), HAI rating status (≤8/≥9), fibrosis staging status (≤2/≥3) and BMI (≤24.99/≥25).

At the twelfth week of treatment, negativity of HCV RNA or a decrease in the level of ≥ 2 log was regarded as negativity. To indicate the effect of independent variables on SVR, a t test and chi square test were performed. Statistical analysis was performed using the SPSS 11.5 package program.

RESULTS

A total of 124 patients, 61 female (49.2%) and 63 male (50.8%), were enrolled in this study. The mean age of patients was 49.6±12.9 (range 18-74) years. Regarding age, 16.9% (n=21) of patients were under 40 years of age. In terms of initial body mass index, 21.7% of patients (n=27) were within normal weight ranges; 72.6% (n=90) were overweight and 5.7% (n=7) were obese.

The mean hemoglobin value was 14.1±1.5 (min-max 11-19) mg/dL and platelet count was 229.3±68.7 (min-max 90-406) x103/μL. The mean ALT value was 75±56 (min-max 13-268) U/L and the mean HCV RNA level was 5.4x106±1.2x106 (min-max 2.7x10 4-1.0x108) IU/ mL. Regarding initial viral load, 55 of 124 patients (44.3%) had a low viral load (<600,000 IU/ml) and 69 (55.6%) presented with a high viral load. The distribution of genotypes was as follows: genotype 1 was 82.3% (n=102) (80.7% 1b, 1.6% 1a) and genotype 2 was 17.7% (n=22) (13.7% 2b, 3.2% 2a/2c and 0.8% 2a/2c). Liver biopsy was performed in 97 patients (78.2%). Classification according to the degree of inflammation and fibrosis in the liver biopsies is shown in Table 1. In total, 66.1% (n=82) of patients were treated with PEG IFN-α

2a and 33.9% (n=42) were treated with PEG IFN-α 2b.

Table 1. Classification according to the degree of inflammation and fibrosis in the liver biopsies

Degree of inflammation	N (%)
Minimal (1-3)	6 (6.2)
Mild (4-8)	71 (73.1)
Moderate (9-12)	18 (18.6)
Severe (13-18)	4 (2.1)
Degree of Fibrosis	
1 (F0-2)	64 (66.0)
2 (F3-4)	25 (25.8)
3 (F5-6)	8 (8.2)

The evaluation of treatment outcomes revealed the following: ETR was achieved in 74.1% (n=92) of patients, 19.3% (n=24) of patients were evaluated as unresponsive, 5.6% (n=7) of patients discontinued treatment due to serious adverse events and one patient (0.8%) died due to an unrelated cause.

SVR was achieved in 54.0% of patients (n=67). The rate of SVR was 49.0% in genotype 1 patients (n=50), while it was 77.3% among genotype 2 patients (n=17). Among patients with ETR responses, relapse developed in 25 cases (five cases of genotype 2 and the remaining twenty cases were genotype 1. A second course of treatment was administered in these patients. Following the second course of treatment, SVR was achieved in 44.0% of patients (11/25) (seven cases of genotype 1 and four cases of genotype 2). In total, SVR was achieved in 78 patients (62.9%), 67 during the first course of treatment (Figure 1) and 11 in the second course (Figure 2), and these patients were followed up for a mean duration of 18.4±8.5 (12-48) months. During this follow-up period, HCV RNA negativity was observed to be sustained.

The evaluation of factors with an influence on SVR revealed that among the dependent variables, age, initial ALT, AST, hemoglobin, platelet, leukocyte and neutrophil levels, were found to have no effect on SVR (P>0.05) (Table 2). The initial BMI of patients, treatment and biopsy results of HAI and fibrosis were determined to have no impact on SVR (P>0.05). Factors with an impact on SVR were gender (positive effect for female gender), initial viral load (response was good if initial load was low), at least a 2-log decrease or negativity in viral load at the twelfth week and genotype (P<0.05 for all) (Table 3).

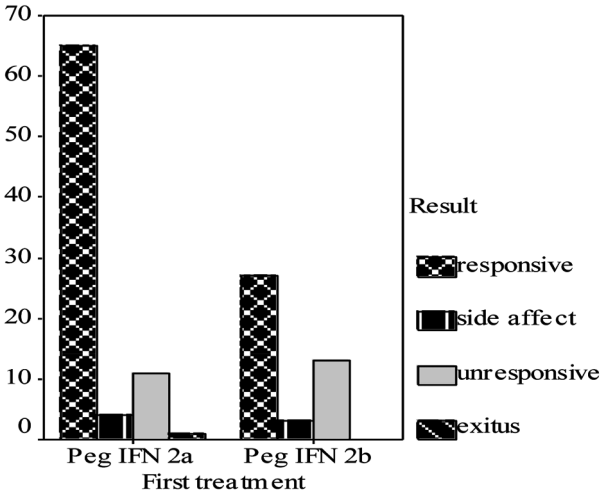

Figure 1. First treatment results

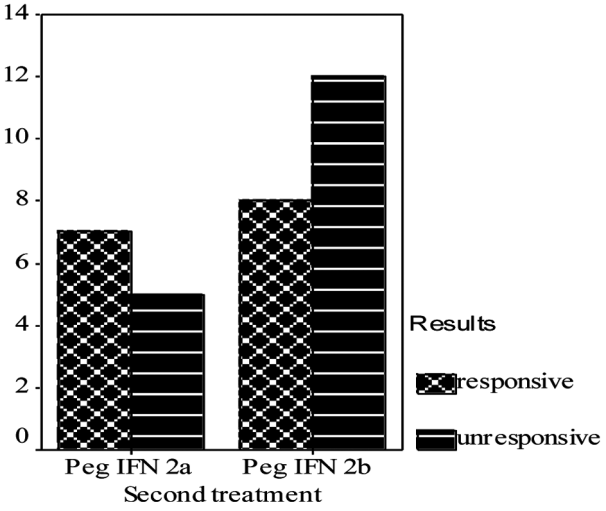

Figure 2. Treatment results of relapse cases

Table 2. Dependent variables with an impact on sustained virological response in patients

			CI % 95	
	t	P	Lower	Upper
Age	-1.34	0.18	-7.9	1.5
AST	0.08	0.93	-14.7	15.9
ALT	0.40	0.68	-16.1	24.8
PLT	0.42	0.67	-27.7	42.7
Hemoglobin	-1.30	0.19	-0.93	0.19
Leukocyte	0.75	0.45	-336.6	748.4
Neutrophil	1.02	0.30	-262.6	818.8

CI: Confidence Interval, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, PLT: Platelet

Table 3. Distribution of independent variables in terms of SVR and results of analysis

		SVR positive	SVR negative		
Risk factor		N (%*)	N (%*)	X^2	P
Gender	Female	47 (77.0)	14 (23.0)	9.13	0.003
	Male	31 (49.2)	32 (50.8)		
BMI	<25	16 (59.3)	11 (40.7)	0.04	0.82
	≥25	62 (63.3)	35 (36.1)		
HCV RNA 1	≥600000 IU/mL	36 (52.2)	33 (47.8)	6.67	0.01
	<600 000 IU/mL	42 (76.4)	13 (23.6)		
HCV RNA 2	>2 log/ negative	50 (80.6)	12 (19.4)	15.2	<0.00
	< 2 log	28 (45.2)	34 (54.8)		
Genotype	1	57 (54.9)	45 (45.1)	13.8	<0.00
	2	21 (95.4)	1 (4.5)		
Treatment	PEG IFN-α 2a	55 (67.1)	23 (54.8)	1.31	0.25
	PEG IFN-α 2b	23 (54.8)	19 (45.2)		
HAI	≥9	14 (70.0)	6 (30.0)	0.14	0.70
	<9	48 (62.3)	29 (37.7)		
Fibrosis	≥3	19 (57.6)	14 (42.4)	0.50	0.47
	≤2	43 (67.2)	21 (52.8)		

* Row percentage

BMI: Body mass index, RNA 1: HCV RNA levels at the beginning of treatment,

HCV RNA 2: HCV RNA levels at the twelfth week of treatment, HAI: Hepatic activity index

DISCUSSION

Hepatitis C (CHC) occurs in 70-80% of individuals who contract the virus. Following the progression of HCV to a chronic state, complications, including cirrhosis, hepatic failure, portal hypertension and HCC, are seen during the first 20-30 years in the majority of4 patients.[15] A recent study showed that HCV-infected persons have death rates three times higher than those persons in the age-matched general population.[16]

Treatment is essential to prevent the development of these complications among CHC patients. Guidelines prepared in accordance with published studies3,[17] recommend standard therapy of PEG-IFN α -2b 1.5 mg/kg/week or PEG-IFN α -2a 180 mg/week combined with low doses (800 mg/day) of RBV for 24 weeks for patients with genotype 2 (G2) and genotype 3 (G3) CHC, and PEG-IFN α (2a or 2b) with high doses (1,000-1,200 mg/day) of RBV for 48 weeks for patients with genotype 1 CHC.

Determining viral genotypes and subtypes is critical in terms of choice of treatment, response to treatment and establishing disease prognosis.[18] Among the six well-known genotypes of HCV and more than 100 subtypes, 1a, 1b, 2a, 2b and 3a are the most common types worldwide.[5,6]

In a study conducted by Gokahmetoglu et al. that showed the distribution of HCV genotypes in Turkey, 96.5% of 57 cases were reported to be infected with genotype 1b, while 3.5% were infected with genotype 1a.19 Similarly, in another study conducted in 2008, in 345 cases genotype 1b was the most frequent (87.2%), and the respective distribution of the remaining genotypes was as follows: 1a (9.9%), 3 (1.4%), 2 (0.9%) and 4 (0.6%)20. In a recent study, genotype 1b was the most frequent (81.7%) followed by the other genotypes as follows: 1a (5.2%), 2 (1.7%), 3 (6.1%) and 4 (3.5%).[21] In the current study, the frequency of genotype 1 was found to be similar to other studies, although the percentage of genotype 2 patients was higher than in previous

studies. Our study was conducted in the southeast region of Anatolia. We believe that this discrepancy is due to inter-regional differences. In a previous study conducted in this region on 30 patients, genotype 1a was found in 5 patients (22.7%), genotype 1b was found in 16 patients (72.8%) and genotype 3a was found in 1 patient (4.5%).[22] Our study covers a larger series with a greater number of patients. Based on these results, genotype 2 is common in this region.

Although the aim of treatment is to prevent the development of cirrhosis, hepatic failure and HCC in CHC patients, the primary goal of treatment in CHC is to obtain a SVR.23 Rates of SVR among HCV patients vary according to genotype. While the rate of SVR is 42-50% among patients infected with genotype 1, an SVR rate of approximately 80% is achieved in cases of genotypes 2 or [3.10,15,24] The results of the current study, which cover patients infected with genotypes 1 and 2, are similar to the results of previous studies. In a study conducted on genotype 1 patients, the rate of SVR was reported to be 48% (47/98) during the first course of treatment and 58% (11/19) during the second course of treatment.[25] SVR rates achieved in the current study during the second course of treatment were lower than the rates achieved during the first course. Most of the relapsing patients were infected with genotype 1. In a similar study, Mathew et al.[26] achieved an 8% SVR rate among genotype 1 patients who received a second course of treatment, while the rate of SVR in relapsing patients was reported to be 34%. In chronic HCV infection, HCV genotype 1, high viral load, greater body weight, advanced age, male gender, high pre-treatment liver fibrosis scores and noncompliance with treatment were suggested as factors having a negative impact on treatment response.[27] In another study in which genotype 2 and 3 patients were analyzed, older age, male gender, advanced fibrosis or cirrhosis, high baseline viral load, and metabolic factors were indicated as the most significant negative predictive factors for SVR among G2 and G3 CHC patients.[28] Similar to results in the literature, in the first and second courses of treatment in the current study, the negative predictive factors for SVR were genotype 1 infection, high viral load (HCV-RNA> 600,000 IU) and male gender. In addition, the rate of SVR was found to be significantly high among patients who developed EVR.

In a study evaluating the impact of treatment on SVR known as the IDEAL study, or5 Individualized Dosing Efficacy versus Flat Dosing to Assess Optimal Pegylated Interferon Therapy, no difference was found in terms of SVR between treatments of PEG IFN-α 2a and 2b (the study arm that received 1.5 μg/kg/week) combined with ribavirin.[29] In a recent meta-analysis, a successful result in favor of PEG IFN-α 2a was found.[30] In this study, selected interferon was observed to have no impact on SVR; however, the number of patients was lower than the indicated studies. Because the numbers of patients in the two arms of the study were not equal, it is not possible to draw a definite conclusion based on these results.

A significant problem in the treatment of chronic hepatitis C patients following achievement of SVR is disease progression during long-term follow-up and whether positivity reoccurs in viral load during this stage. In a study conducted by Desmond et al., patients were followed up for a mean duration of 2.3 years, and no virological recurrence was observed except in one patient (146/147 patients).[31] In another study by Ferreira et al., 77.0% of 174 follow-up patients received one course of treatment, 16.7% received two courses, and 6.3% received three courses. The distribution of HCV genotypes was as follows: genotype 1 (40.2%), genotype 3 (40.8%) and genotype 2 (10.3%). The genotype was undetermined in 8.7% of cases. Among these patients, long-term follow-up following SVR did not reveal any detectable GCV RNA in any of the patients.[32] Similarly, in the current study, no relapse was seen in patients who achieved SVR with two courses of treatment. No development of cirrhosis or HCC was observed during the follow-up period. We believe that this finding may be associated with non-advanced stages of disease as indicated by the pre-treatment biopsy results.

In conclusion, there was no recurrence of HCV infection in any of the 124 patients on antiviral therapy who obtained SVR after a mean follow-up of 19 (12-48) months. Female gender, low initial viral load, development of EVR and infection with genotype 2 was determined to have a positive impact on SVR. We believe that it is of the utmost importance to initiate appropriate treatment prior to the advancement of disease and the development of liver damage. Relapse is not common during the long-term follow-up of patients who achieve SVR, but the final decision

on this issue should be based on the follow-up of patients for much longer durations.

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