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ORIGINAL ARTICLE

The Success Rate of Interferon-Based Treatments in Chronic Viral Hepatitis C Patients and Factors Affecting Treatment Success

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Abstract

Introduction: To examine the treatment success and the factors affecting the treatment success in patients with chronic viral hepatitis C.

Methods: This retrospective study was conducted by scanning the files of patients with chronic viral hepatitis C, who were followed in Infectious Diseases and Gastroenterology outpatient clinics. Demographic and clinical characteristics (presence of hepatomegaly or splenomegaly, comorbidity treatment protocols, and side effects) were examined.

Results: 418 patients were included in the study. The mean age of the patients was 48.4 (min: 27-max:76) years. 40.4% (n=169) of the patients were male. Fifty patients had hepatomegaly and 45 had splenomegaly. While 79.9% of the patients had no comorbid disease, 13.4% had diabetes, 5.3% had thyroid dysfunction, and 1.4% had both. Hepatocellular carcinoma was observed in 4 patients, cirrhosis was observed in 29 patients, and side effects were observed in 33 patients. Four patients received ribavirin, 32 patients received classical interferon, 13 patients received pegylated interferon, 69 patients received classical interferon+ribavirin, 297 patients received pegylated-interferon+ribavirin, and three patients received classical interferon+ribavirin+pegylated-interferon. Of the patients, 12 resulted in "exacerbation under treatment," 14 with "partial response," 89 with "relapse," 124 with "no response," and 179 with "sustained virologic response (SVR)." Overall, the most success-

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ful results were obtained in patients treated with pegylated interferon+ribavirin. In univariate comparisons, younger age, absence of splenomegaly, and absence of cirrhosis were significant in patients with SVR. In multivariate analysis, combined therapy was found to be independently significantly successful among patients with SVR.

Discussion and Conclusion: In our study, the response rate of patients to interferon-based treatment was 42.8%, while young age, female gender, and absence of organomegaly were determined as factors that increased this rate, and according to multiple analyses, it was determined that combined treatment alone was effective on SVR independently.

Keywords: Chronic hepatitis C; cirrhosis; hepatocellular carcinoma; interferon; pegylated interferon; ribavirin.

Chronic hepatitis C virus (HCV) infection is a serious, life-threatening condition that causes cirrhosis and hepatocellular carcinoma (HCC). It is common globally. An estimated 71 million people worldwide are infected with the chronic HCV. It is estimated that approximately 399,000 people died in 2016 from hepatitis C, mostly from cirrhosis and HCC (primary liver cancer)[1].

Although vaccine studies against hepatitis C continue, there is no effective vaccine yet. This poses a major challenge for the control of HCV worldwide[1,2].

Treatment options currently used for the treatment of hepatitis C infection are: sofosbuvir, sofosbuvir + ledipasvir, paritaprevir + ritonavir + ombitasvir, dasabuvir, daclatasvir, simeprevir, grazoprevir + elbasvir, sofosbuvir + velpatasvir, sofosbuvir + velpatasvir + voxilaprevir, glecaprevir + pibrentasvir and ribavirin[3].

Prior to the discovery of direct-acting antivirals (DAAs), interferon-based treatment options were used for hepatitis C infection. Interferon therapy has been promising for the treatment of patients with hepatitis C, with sustained virologic response (SVR) rates of 40–50% for genotype 1 chronic hepatitis C patients until the introduction of DAAs[4, 5].

In our study, it was aimed to determine the epidemiological data of chronic hepatitis C patients followed in Infectious Diseases and Clinical Microbiology and Gastroenterology Outpatient Clinics of our hospital and to evaluate their effects on treatment success.

Materials and Methods

This study included 418 patients aged 18 years and over, who were followed up with the diagnosis of chronic hepatitis C in Medeniyet University Faculty of Medicine, Göztepe Training and Research Hospital, Infectious Diseases and Clinical Microbiology and Gastroenterology outpatient clinics between August 24, 1993 and October 13, 2013. File data of patients diagnosed with chronic hepatitis C were uploaded to the Microsoft Office Access Database program and patients were scanned through this system. The study was designed retrospectively.

The cases in which classical interferon monotherapy, classical interferon and ribavirin combined treatment, pegylated-interferon monotherapy, or pegylated-interferon and ribavirin combined treatment were initiated, were evaluated. The data of patients were evaluated in terms of age, gender, presence of hepatosplenomegaly, accompanying thyroid dysfunction and/or diabetes, cirrhosis, or HCC. Response rates and factors affecting response to interferon treatment, treatment-related side effects, and duration of treatment were examined.

Exclusion Criteria

1. Patients that were followed without treatment
2. Patients whose treatment was interrupted due to side effects or because the patient could not tolerate it
3. Patients on treatment at the time of the study
4. Patients whose outcome is unknown because treatment was started but they did not show up for follow up
5. Cases whose HCV-RNA result was negative at the end of the treatment, but it is not known whether they formed a permanent viral response because the 24th week result is unknown.

Permission for this study was obtained from the Ethics Committee of the Ministry of Health, Istanbul Medeniyet University Göztepe Training and Research Hospital (Decision No: 2013/0088), and the study was conducted in accordance with the Helsinki criteria.

Definitions[6]

SVR

Negative HCV-RNA measured at 24 weeks after the end of treatment.

Null Response

HCV-RNA level decreased by<2 log10 from baseline at 12 weeks of treatment.

Partial Response

Drop at HCV-RNA level by more than 2 log10 from baseline at week 12 of treatment, but HCV-RNA remaining at detectable levels between weeks 12 and 24.

Exacerbation Under Treatment

Increase in HCV-RNA levels back to a measurable level at any time during treatment after virological response has been achieved with treatment.

Relapse

Negative HCV-RNA at the end of the treatment, however, reaching a measurable level again at 24 weeks after the treatment is finished. In accordance with the definition above, if the patients' HCV-RNA level decreased by <2 log10 from the initial value at week 12 of their treatment, the patients were considered unresponsive to treatment and their treatment were discontinued at week 12. If the HCV-RNA level fell more than 2 log10 compared to the initial value but was not negative at the 12th week of their treatment, the HCV-RNA level was re-measured between the 12th and 24th weeks, and the patients were considered partial responders if the HCV-RNA remained at detectable level, and their treatment was discontinued at 24 weeks. Treatment of patients who experienced exacerbation under treatment was discontinued when an increase in HCV-RNA level was detected. Treatment of other patients was completed in 48 weeks.

Statistical Analysis

The data of the study were entered into the statistics program by cross-examination from the database. Stata 12.1 (Stata corp., Texas, USA) was used in this study. Student's t-test was used for continuous variables, Pearson's Chi-square test or Fisher's exact test was used for binary variables. The independent variables that may be effective in the formation of SVR were estimated in the logistic regression model. A value of "p<0.05" was considered statistically significant.

Results

A total of 252 patients were registered in the Infectious Diseases outpatient clinic records, and 181 patients were registered in the Gastroenterology outpatient clinic records. 15 patients were followed up from both outpatient clinics. After removing duplicate records, 418 patients were included in the study.

A total of 472 patients were not included in the study. The reasons for exclusion and distribution of these patients are shown in Figure 1. Of the 418 patients included in the study, 40.4% (n=169) were male and 59.6% (n=249) were female; their ages ranged from 27 to 76 years, and the mean age was 48.4±11.3 years. The presence of hepatosplenomegaly, underlying diseases, development of cirrhosis and HCC,

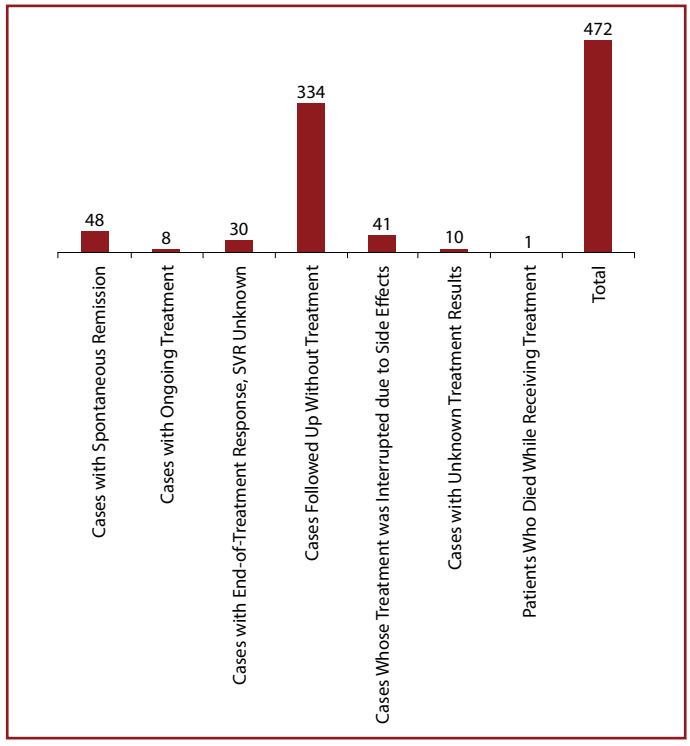

Figure 1. The reasons of exclusion.

and treatment-related side effects are listed in Table 1.

Of the patients, 12 (2.9%) resulted in exacerbation under treatment, 14 (3.3%) had partial response, 89 (21.3%) resulted in relapse, 124 (29.7%) resulted in null response, and 179 (42.8%) resulted in SVR. In univariate analysis, young age, absence of splenomegaly, and absence of cirrhosis were highly significant to induce a SVR (p≤0.001, p=0.02, p=0.003) (Table 1).

According to multiple statistical analysis (logistic regression), age, male gender, and underlying disease were not found to be significant variables. Combined therapy was found to be effective very limited (OR: 1.45), but significant (Table 2).

The relationship between the treatment options; monotherapy, interferon + ribavirin, and pegylated-interferon+ribavirin and SVR is shown in Figure 2. Accordingly, pegylated-interferon+ribavirin has the highest effect.

Discussion

Our treatment goal in a patient with chronic hepatitis C is to obtain SVR. SVR is associated with negative HCV-RNA at the end of treatment and negative HCV-RNA at 6 months post-treatment[7].

Obtaining SVR results in a reduction in all HCV-related liver-related deaths, the need for liver transplantation, the rate

Table 1. Factors influencing sustained viral response

Factors influencing sustained viral response	All patients		Sustained viral response		p
	n	%	Absent (n=239) (%)	Present (n=179) (%)	
Age, median (IQR)	48.4	-	51 (45, 58)	47 (37, 54)	<0.001
Gender (Male)	169	40.4	88 (36.8)	81 (45.3)	0.082
Hepatomegaly	50	12	34 (14.2)	16 (8.9)	0.099
Splenomegaly	45	10.8	33 (13.8)	12 (6.7)	0.02
Underlying disease					
Absent	334	79	183 (76.6)	151 (84.4)	0.12
Diabetes	56	13.4	40 (16.7)	16 (8.9)	
Diabetes+TD	6	1.4	4 (1.7)	2 (1.1)	
TD	22	5.3	12 (5.0)	10 (5.6)	
HCC	4	1	4 (1.7)	0 (0.0)	0.14
Cirrhosis	29	6.9	24 (10.0)	5 (2.8)	0.003
Side effect		21 (8.8)	12 (6.7)	0.43	
Treatment					
Ribavirin	4	1	4 (1.7)	0 (0.0)	0.054
IFN	32	7.7	21 (8.8)	11 (6.1)	
IFN+PegIFN+Rib	3	0.7	0 (0.0)	3 (1.7)	
IFN+Rib	69	16.5	45 (18.8)	24 (13.4)	
PegIFN	13	3.1	8 (3.3)	5 (2.8)	
PegIFN+Rib	297	71	161 (67.4)	136 (76.0)	
Combined therapy					
Mono T	49	11.8	33 (13.8)	16 (8.9)	0.069
IFN+Rib	69	16.5	45 (18.8)	24 (13.4)	
PegIFN+Rib	297	71	161 (67.4)	139 (77.7)	

Mono T: Monotherapy; IFN: Interferon; Rib: Ribavirin; PegIFN: Pegylated interferon; TD: Thyroid dysfunction; HCC: Hepatocellular carcinoma.

Table 2. The final logistic regression model

The final logistic regression model	OR*	Confidence Interval		p
		Lower	Upper	
Age	0.99	0.97	1.01	0.213
Male gender	1.36	0.90	1.01	0.213
Underlying disease[1]	0.95	0.72	1.24	0.685
Combined therapy	1.45	1.07	1.96	0.017
Constant	0.61	0.25	1.51	0.289

*OR: Odds ratio; [1]The definitons of the variables are as in Table 1.

of HCC development, and liver-related complications [8, 9]. In many studies on interferon-based therapies performed to date, SVR rates have been shown to differ according to genotypes. It was determined as 40-50% for genotype 1, 80% for genotypes 2 and 3, 50–70% for genotype 4, 60% for genotype 5 and 60–80% for genotype 6[4-14].

In a randomized controlled study, SVR rates were compared by applying different treatment protocols to a total of 1530 patients (90% Caucasian, 68% genotype 1, and 68% HCV-RNA>2,000,000 copies/ml). SVR rates were calculated as 47% with classical interferon+ribavirin combination, 47% with pegylated interferon alfa 2b (1.5 mcg/kg/week for the first 4 weeks, continued with 0.5 mcg/kg/week)+ribavirin, 54% with pegylated interferon alfa 2b (1.5

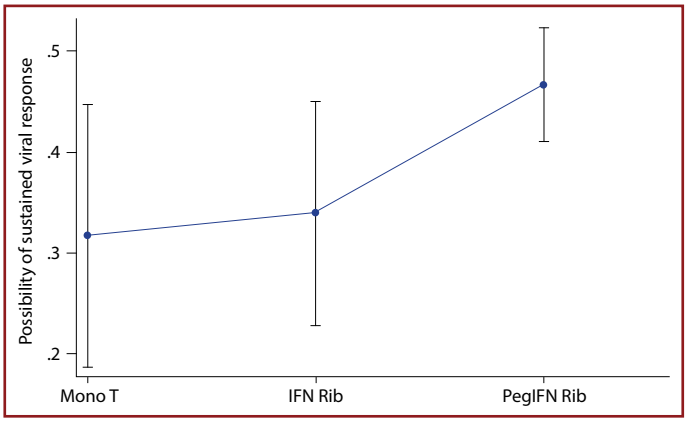

Figure 2. Effect of treatment protocols on sustained viral response.

mcg/kg/week)+ribavirin combination [5]. In our study, SVR was detected in 0% of those receiving ribavirin, 34% of those receiving classical interferon monotherapy, 35% of those receiving classical interferon+ribavirin, 38% of those receiving pegylated interferon monotherapy, and 46% of those receiving pegylated interferon+ribavirin.

In the literature, the rate of SVR in genotype 1 infected patients treated with the combination of pegylated interferon alfa and ribavirin was approximately 50%, while this rate was found to be 70-90% in patients infected with genotypes 2 and 3[15]. In this study, our overall SVR rate was found to be 42.8%, which is consistent with the literature.

While the rates of SVR were found to be high in patients under the age of 45, it was low in those over the age of 65[16]. In this study, a statistically significant correlation was found between young age and SVR ($p \leq 0.001$) (Table 1).

Complications associated with the HCV are more common in males. Spontaneous remission is more common in women who develop HCV infection. If chronic infection develops, the progression of liver disease is more slowly in women than men. The progression of HCV infection in women varies by years. Fibrosis is less common in women of reproductive age. This is because estradiol and estrogen receptors in the liver protect hepatocytes from oxidative stress, inflammatory damage, and cell death that contribute to fibrosis. However, postmenopausal women have a higher risk of developing fibrosis due to the loss of the protective effect of estrogen. As a result, liver disease in women progresses more slowly and viral clearance is greater[17]. In our study, while no statistically significant relationship was found between gender and SVR, it was found that female gender had a positive effect on treatment (Table 1).

The presence of portal hypertension was found to be an independent risk factor for pegylated interferon and ribavirin therapy[18]. The ultrasonographic finding of splenomegaly in both portal hypertension and cirrhosis, which adversely affects the response to treatment, is a guide for us. In this study, patients could not be evaluated in terms of portal hypertension, since ultrasound results were not available for most of the patients. However, it was observed that the presence of cirrhosis and splenomegaly was less in those who developed SVR (Table 1).

When the treatment protocols in the literature are examined, pegylated interferon+ribavirin treatment is seen to be superior to classical interferon+ribavirin treatment[5]. Moreover, 48 weeks of treatment is superior to 24 weeks of treatment, while standard-dose ribavirin treatment is superior to low-dose ribavirin[19]. In this study, when the treatment protocols according to SVR were examined, SVR did not occur in any of the patients who received ribavirin monotherapy, while three of the patients who started with classical interferon and continued with pegylated interferon and used interferon+ribavirin combination, developed SVR. The rate of SVR was found to be higher in the combination of pegylated interferon+ribavirin (Table 1). This is consistent with the literature data[5].

In this study, when the duration of treatment was examined, it was found that the duration of treatment was significantly longer in patients with SVR in the group treated with pegylated interferon+ribavirin. However, according to the decrease in HCV-RNA levels in the follow-ups of our patients, since the group with null response received 12 weeks of treatment and the group with partial response received treatment for 24 weeks, we did not encounter any outcome as unresponsive or partial response in long-term treatment, and the rate of SVR in those receiving long-term treatment increased significantly.

Our study has limitations. In this retrospective study, the lack of data as a result of the inability to find back many patients led to a decrease in the number of patients included in the study. In addition, the effect of the dose on the treatment could not be included in the study because there were changes in the treatment doses and these doses have not been mentioned in the file. Since there is no restriction on the start date of the treatment of the patients included in the study, various treatment protocols are encountered. In addition, initial viral load, genotype, and liver biopsies could not be included in the study because standardization could not be done in the tests. These data could not be standardized because different units were used in viral load measurements over the years and genotypes could not be analyzed in most of the patients. Another limitation of our study is that the patients could not be classified in terms of fibrosis stages and the presence of cirrhosis since the pathology reports of liver biopsies performed before the treatment could not be accessed and the data in the file

could not be standardized. In addition, since the treatment with DAAs was newly introduced at the time the study was initiated, and there were no patients who concluded this treatment, DAAs were not included in our study.

Conclusion

In the literature, the response rate of HCV genotype 1 patients to interferon-based therapy is approximately 50%[4, 5]. In this study, the response rate was found to be 42.8%.

According to the results of this study, it was found that the young age, the absence of splenomegaly, and the absence of cirrhosis had a positive effect on SVR. According to multiple analyses, it was determined that combined therapy was effective independently on SVR.

Ethics Committee Approval: The Ethics Committee was approved by the Istanbul Medeniyet University Göztepe Training and Research Hospital Clinical Research Ethics Committee with the decision number 2013/0088 on 20.11.2013.

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Conflict of Interest: None declared.

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