Gastroenterology and Hepatology From Bed to Bench.

ORIGINAL ARTICLE

Evaluated outcomes in patients with Chronic Hepatitis C

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ABSTRACT

Aim: The objective of this study was to evaluate the real outcomes of chronic hepatitis C patients, who treated with interferon plus ribavirin (INF-RBV) and peg-interferon plus ribavirin (PEG-RBV).

Background: Despite the PEG-RBV has become a standard treatment of hepatitis C virus (HCV) around the world; and in Iran too, but in developing countries like as Iran, INF-RBV is still used among some patients for treating HCV, due to the high costs of treatment with PEG-RBV.

Patients and methods: The present cross-sectional study was conducted on 77 naïve patients referred to a private gastroenterology clinic between years 2007 through 2009 in Tehran. Patients had participated in this study taking two types of combination therapies, based on standard protocol of the Iranian Ministry of Health. At the end of the treatment, sustain virological response (SVR) rate was evaluated.

Results: The outcomes showed in INF-RBV treatment; 11.6%, 16.3% and 34.9% patients were suffered from relapse, lost follow-up their treatment and non-responder, respectively, and finally 37.2% of the patients reached SVR. In PEG-RBV treatment outcomes were as follows; 2.9%, 14.7% and 14.7% patients were non-responder, lost follow-up their treatment and suffered from a relapse, respectively, and 67.6% of the patients reached SVR. The multivariate-adjusted odds ratios of outcomes showed that treated with PEG-RIB and also genotype 3a than the others genotypes in this treated had more chance to achieved SVR.

Conclusion: The findings of the present study showed that the rate of SVR in patients who treated with PEG-RBV significantly was higher than patients who treated with INF-RBV. Also in PEG-RBV the chance of achieving SVR is higher among the patients with genotype 3a than among those with other genotypes.

Keywords: chronic hepatitis C, Interferon, Peg-interferon, Sustain Virological response.

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Introduction

Hepatitis C virus (HCV) infection has a large prevalence worldwide (1-4). HCV is one of the most common causes of chronic liver disease, and the third leading cause of death in end-stage renal disease patients (5-8). The patients suffering from chronic HCV for an average 15 years have 15% risk of developing cirrhosis and 1-5% risk of developing heaptocellular carcinoma (HCC) (9, 10). The treatment regimen of chronic hepatitis C has changed significantly over the past decades around the world. In the mid-1990s, monotherapy with interferon administered by an injection 3 times weekly for 6 to 12 months was associated with an overall sustained virological response (SVR) of 6% to 10% (11-14). The addition of ribavirin to interferon (INF-RBV) in the late 1990s was associated with an increase in SVR to approximately 40-45% (15-17). Currently, the

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combination of peg-interferon plus ribavirin (PEG-RBV) is the treatment for patients with chronic HCV infection (18-20). PEG-RBV has produced overall SVR rates of up to 66% in HCV mono-infected patients (21-23), and 50% in patients with human immunodeficiency virus (HIV)-HCV co-infection (24, 25).

The objective of therapy is to eradicate the virus and prevent potential complications from CHC infection. The primary goal of treatment in chronic hepatitis C patients is to achieve a SVR, which is operationally defined as the absence of HCV RNA (detectable through PT-PCR) within six months of treatment termination (26). Achievement of SVR has been associated with improvement in liver histology and health related quality of life, as well as a reduced risk of HCC and liver-related mortality (27-30). The degree of response depends on a variety of factors and these may also differ in various patient populations (31). Viral genotype, viral load, patient age, BMI, race, environment and several other factors have been shown to correlate with SVR (32-34).

Despite that the PEG-RBV has become a standard treatment of HCV around the world (35) and in Iran too (36) but in developing countries like as Iran, INF-RBV is still used for treating HCV, due to the high costs of treatment with PEG-RBV (37, 38). So, the main purpose of this study was evaluated the outcomes based on genotype in the both of treatment.

Patients and Methods

All data for this cross-sectional study were collected from medical records of 77 naïve patients with chronic hepatitis C, who referred to private gastroenterology clinics between years 2007 through 2009 in Tehran. The selected patients had chronic hepatitis C, evidenced by a liver biopsy. A sample of 77 naïve HCV patients with a minimum age of 17 was selected.

Exclusion criteria included simultaneous infection with hepatitis B or HIV, active liver disease, and existence of liver disease with a cause other than hepatitis C, HCC, liver transplantation history, uncontrolled diabetes mellitus, sever cardiac or pulmonary disease, autoimmune disorders, retinopathy, severe depression, uncontrolled psychotic disorders and existing drug addiction.

A checklist was designed to gather information from medical records of HCV patients, it's including ; age, gender, marital status, HCV genotype, HCV risk factors, the type of combination treatment and the duration of treatment. Patients had participated in this study taking two types of combination therapies. One was conventional interferon (Roche® Products Ltd, Switzerland) and ribavirin (Copegus®, Roche) and another was peg-interferon α-2a (Pegasys®, Roche,Switzerland) and ribavirin (Copegus®, Roche), based on standard protocol of the Iranian Ministry of health. This protocol consisted of, conventional interferon (3 MU three times a week) plus ribavirin (800-1200 mg per day) was for 24 weeks (genotypes 2, 3) or 48 weeks (genotype 1 and 4). And peg-interferon α-2a in a fixed dose of 180 micrograms per week plus ribavirin (800-1200 mg per day) was for 24 weeks (genotypes 2, 3) or 48 weeks (genotype 1 and 4). In addition, patients were followed up six months after the intervention for complications, the rate of SVR.

Outcome Measurement

The HCV RNA was measured at the outset of the treatment, in weeks 12, 24, 48 and also six months after the end of treatment. The main outcome was SVR level which is defined as no virus present (undetectable HCV RNA) in a blood sample 6 months after completion of therapy.

The secondary outcomes included; early viral response (EVR), as undetectable HCV RNA or a decrease of more than 2 logs IU compared to the level at the 12th week of the treatment and the end of treatment response (ETR), undetectable HCV RNA at the end of treatment. On the basis of the obtained outcomes, patients were divided into four groups; non-responder patients with no EVR, relapse patients with ETR but without SVR, patients who had SVR and patients who had lost follow-up their treatment because of side effects of the medications such as; fatigue, muscle aches, depression, headache, flu like, fever, itching, GI symptoms, hair loss, rash, insomnia and dry skin.

Statistical analysis

Data analysis was performed using statistical package for social sciences (SPSS) 16.0 software (SPSS Inc., Chicago, IL, USA). Descriptive statistics and frequency distribution such as mean, standard deviation and percentage were employed. A chi-square test was used to compare the qualitative variables. $P< 0.05$ was considered as statistically significant.

Results

In total, seventy seven naïve patients with chronic HCV were enrolled in this study out of which 58 (75.3%) were male. The mean age was 49.1± 10.2 (± standard deviation) years. Majority of patients 68 (88.3%) were married. Intravenous drug user (IVDU) and blood transfusion were the commonest risk factors for HCV. In terms of history, 6 (7.8%) of patients were IVDU and 4 (5.2%) patients had blood transfusion. The most common virus genotype was 1a (61%). All the patients were treatment-naïve. Table 1 shows patients characteristics at the outset of the study. In term of outcomes in 43 chronic HCV patients who treated with INF-RBV results showed; 5 patients (11.6%) suffered from a relapse, 7 patients (16.3%) did lost follow-up their treatment, 15 patients (34.9%) were non-responders and 16 patients (37.2%) had reached SVR. Outcomes in 34 chronic HCV patients who treated with PEG-RBV are as follows: one patient (2.9%) was non-responder, 5 patients (14.7%) did lost follow-up their treatment, 5 patients (14.7%) suffered from a relapse and 23 patients (67.6%) had reached SVR. Table 2 shows antiviral treatment outcomes in HCV patients based on genotype.

Table1. Basic characteristic of patients (n=77)

Patients characteristics	No (%)
Male	58(75.3)
Female	19(24.7)
Age, y, mean ± SD	49.1± 10.2
Age range	21-78
Marital status	
Single	9(11.7)
Married	68(88.3)
Genotype	
1a	47(61)
1b	11(14.3)
3a	19(24.7)
HCV risk factors	
IVDU	6(7.8)
Blood transfusion	4(5.2)
Needle stick	3(3.9)

Abbreviation: IVDU, Intravenous drug user

The chance of achieving SVR in patients who had been treated with PEG-RBV was more than those treated with INF-RBV (OR=3.528, CI95 %=1.367-9.105) (Table 3). Treated with PEG-RIB the overall SVR is 67.6%, compared with a rate between 37.2% with INF-RIB ($P< 0.05$). According to the results of this table, we did not reach statistical significance differences between achieving SVR and different genotypes in INF-RBV (table 3).

Table 4 shows the outcomes of re-treatment of HCV patients who not achieved SVR in the first course of treatment. As can be seen, SVR mostly occurs in patients who were non-responder because many patients (34.9%) have not responded to therapy with INF-RBV. So in re-treating they treated with PEG-RIB instead of INF-RBV and 8 patients (61.5%) from 13 patients sustained SVR. And finally the percent of patients who achieved SVR in re-treatment was (46.16%).

Table 2. Treatment outcomes based on genotype

Treatment	Genotype	SVR	Lost follow-up	Relapse	Non-responder	Total
INF-RBV	1a	10 (23.3)	5 (11.6)	3 (7)	9 (20.9)	27 (62.8)
	1b	4 (9.3)	0	1(2.3)	3 (7)	8 (18.6)
	3a	2 (4.7)	2(4.7)	1 (2.3)	3 (7)	8 (18.6)
	Total	16 (37.2)	7 (16.3)	5 (11.6)	15 (34.9)	43 (100)
PEG-RIBV	1a	13(38.2)	4 (11.8)	3 (8.8)	0	20 (58.8)
	1b	2 (5.9)	1 (2.9)	0	0	3 (8.8)
	3a	8 (23.5)	0	2 (5.9)	1 (2.9)	11 (32.4)
	Total	23 (67.6)	5 (14.7)	5 (14.7)	1 (2.9)	34 (100)
Total		39 (50.6)	12 (15.5)	10 (12.9)	16 (20.7)	77 (100)

Abbreviation: SVR, Sustained Virological Response; INF-RBV, Interferon and Ribavirin; PEG-RIBV, Peg-interferon and ribavirin

Table 3. Multivariate Analysis results between patients with and without Sustain Virological Response (SVR)

Treatment	Genotype	SVR	Non-SVR	P-value	OR	95% CI for OR
INF-RIB	1a	10(37.0)	17(63.0)	0.372*	1	-
	1b	4(50.0)	4(50.0)		4	0.416-38.454
	3a	2(25.0)	6 (75.0)		0.8	0.191-3.347
PEG-RIB	1a	13(65.0)	7(35.0)	0.906*	1	-
	1b	2(66.7)	1(33.3)		0.714	0.063-8.150
	3a	8(72.7)	3(27.3)		1.286	0.237-6.963
INF-RIB		16(37.2)	27(62.8)	0.008*	1	-
PEG-RIB		23(67.6)	11(32.4)		3.528	1.367-9.105

Abbreviation: SVR, Sustained Virological Response; OR, odds ratio. *chi square test, $P< 0.05$ was considered as statistically significant

Table 4. Re-treatment outcomes

	SVR N (%)	Non SVR N (%)	Total N (%)
Previous history			
Non-responder	8(61.5)	5(38.5)	13(100)
Relapse	4(50)	4(50)	8 (100)
Lost follow-up	0	5(100)	5 (100)
Total	12(46.1)	14(53.8)	26(100)

Abbreviation: SVR, Sustained Virological Response

Discussion

The findings of the present study show that the rate of SVR in patients who treated with PEG-RBV was (67.6%) and these rates were different among the various genotypes. The highest SVR was observed in patients with genotype 3a, while the lowest SVR was identified in patients with genotype 1a in treated with PEG-RBV. In addition, the chance of achieving SVR in patients who had been treated with PEG-RBV was more than those treated with INF-RBV (OR=3.528, CI95 %=1.367-9.105). And also the chance of attaining SVR is higher among the patients with genotype 3a than among those with other genotypes (OR=1.286, CI95 %=0.237-6.963). But in treated with INF-RBV the rate of SVR in genotype 3a was lower than genotype 1a and 1b; one might assume that the number of patients with genotype 3a was very lower than the other genotypes in INF-RBV. Therefore, we did not reach statistical significance differences between achieving SVR and different genotypes in INF-RBV.

The overall, the results of this study confirm other studies that showed the using PEG-RBV instead of INF-RBV in treatment of HCV patients leads to improved treatment outcomes in these patients with ETR and SVR rates increasing to 69% and 56% respectively in different genotypes (21, 39, 40). Genotypes has been the most important predictors in a variety of studies (32,

41). In comparison to other genotypes, genotype 1 has been associated with lower SVR (15, 16, 22). Also in this study, genotype 1 in PEG-RBV therapy had low SVR.

Despite all these studies about the efficacy and safely of treatment with PEG-RBV; in developing countries like as Iran, INF-RBV is still used for treating HCV. Use this treatment just because it has a low cost than the PEG-RBV (4,403 PPP$ vs. 20,010 PPP$) (37), but the SVR rate is very low in this treatment, especially in genotype 1 that known as difficult to treat. Another problem is more side effects of interferon than the peg-interferon (19); so many patients are not able to tolerate these side effects and thus leave their treatment (as called as lost follow-up in this study). As the results of this study indicated that most people who leaved their treatment was treated with INF-RBV (16.3%).

In general, reaching an SVR in patients with a prior history of treatment has been reported to be 20-30% (42). In the study by Alavian et al. SVR in naïve patients was found to be 62.9% and in non-responder or relapsing patients it was found to be 35.3% (43) and the study by Namazee et al. showed an SVR proportion of 56%, 60% and 28% in naïve, relapse and non-responder patients using conventional interferon, respectively (44). Our study showed an SVR proportion in naïve patients is 67.6%, 37.2% using PEG-RBV and INF-RBV, respectively. Our study also showed the SVR rate in re-treatment is 61.5% in non-responder and 50% in relapsing patients. The most non-responder in this study at first were treated with INF-RBV and then re-treated with PEG-RBV and they achieved SVR.

The primary goal of re-treatment was to achieve a SVR. Secondary goals include the prevention of progressive histologic diseases, the regression of fibrosis, a decrease in the risk of HCC, and potentially a reduction of the risk of hepatic decomposition. According to the other studies; The SVR in INF-RBV non-responders re-treated with PEG-RBV between 4% and 12%. Unfortunately, re-treatment options are limited, and their efficacy is low (42, 45, 46).

Despite improvements in antiviral therapy in recent years, the treatment of chronic hepatitis C is still a challenging endeavor requiring significant improvement, especially in developing countries like as Iran.

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