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Efficacy of 24-Week Pegylated Interferon Alpha and Ribavirin Combination Therapy in Highly Selected Patients Infected With Hepatitis C Virus Genotype 1

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Background: Previous studies using pegylated interferon (Peg-IFN) and ribavirin (RBV) combination therapy suggested that patients with hepatitis C virus (HCV) genotype 1 and low pretreatment HCV RNA level who achieved rapid virological response (RVR) can be treated for 24 weeks without compromising sustained virological response (SVR) rate.
Objectives: The current study aimed to investigate the efficacy of Peg-IFN-alfa-2a plus RBV administered for a 24-week treatment course in patients with chronic HCV genotype 1 infection and possessing the following criteria: low baseline serum HCV RNA level, absence of significant fibrosis and achievement of RVR.
Patients and Methods: In this case-control study, 20 patients with HCV genotype 1 infection and favorable baseline characteristics and on-treatment response were treated with Peg-IFN and RBV for 24 weeks as the case group. Furthermore, 23 patients with the same characteristics who underwent a 48-week treatment course were selected as the control group.
Results: The majority of patients had no fibrosis on liver elastography. There was no statistical difference regarding age, gender, alanine transaminase (ALT) level, rs12979860 polymorphism and the level of fibrosis between the two studied groups. All patients in the 24-week treatment course achieved SVR and all the subjects who received the 48-week treatment course achieved SVR as well ($P > 0.99$).
Conclusions: The current study confirmed that the efficacy of a 24-week regimen of Peg-IFN-alfa-2a plus RBV was similar to the 48-week treatment in the patients infected with HCV genotype 1, and low baseline HCV RNA level who achieved RVR. Response guided therapy can be efficient and cost-effective among the selected HCV genotype 1-infected patients.

*Keywords:*Hepatitis C; PEG-interferon alfa-2A; Viral Load

1. Background

Hepatitis C is a major health problem affecting approximately 2%-3% (130-170 million) of the world population. The major burden of hepatitis C virus (HCV) infection comes from squeals of chronic infection including liver cirrhosis and liver cancer (1). Given that hepatitis C treatment and achieving sustained virological response (SVR) improve the survival rate in the patients, and prevent disease progression and hepatocellular carcinoma (HCC), the treatment of chronic hepatitis C is highly recommended (2, 3). The recommended treatment for chronic hepatitis C infection is a 24- or 48-week course of pegylated interferon-alpha-2b (Peg-IFN-α-2b) or Peg-IFN-α-2a combined with ribavirin (RBV) (4). Several host and viral factors are attributed to the probability of response with combination therapy. Among the host factors, age, IFN lambda (IFNL) polymorphisms, liver fibrosis, liver steatosis and insulin resistance are associated with SVR rate (5-7). Viral factors including HCV genotype and HCV RNA level are the most important parameters which affect achieving SVR. Numerous studies demonstrated that HCV genotype 1 and high HCV RNA level negatively affect the treatment with Peg-IFN and RBV combination therapy (7-9). Patients with HCV genotype 1 have lower SVR rate compared to HCV-infected patients with other HCV genotypes (60% in HCV genotype 1 infection compared to 80% in HCV genotypes 2 and 3 infections), and consequently should be treated for a longer duration of 48 to 72 weeks (10). Moreover, it was recommended that some patients with HCV genotype 1 can be treated with a short course (24-week) of Peg-IFN and RBV combination therapy successfully (11).

2. Objectives

The present study aimed to investigate the efficacy of Peg-IFN-alfa-2a plus RBV administered for a 24-week treatment course in the patients with chronic HCV genotype 1 infection and possessing the following characteristics: low baseline serum HCV RNA level, absence of significant fibrosis, and achievement of rapid virological response (RVR).

3. Patients and Methods

3.1. Study Population

Twenty patients with HCV genotype 1 infection and possessing the following criteria: baseline HCV RNA level > 50 IU/mL and less than 400,000 IU/mL for more than six months, achievement of RVR after Peg-IFN and RBV combination therapy (12), and the absence of significant fibrosis (≤ F3) were selected as the case group. Moreover, 23 patients with HCV genotype 1 and the mentioned criteria that were treated for 48 weeks were selected as the control group. All the patients in the case group were treated with Peg-IFN and RBV for 24 weeks in Tehran Blood Transfusion Hepatitis Clinic (Tehran, Iran) and the subjects in the control group were treated for 48 weeks in Tehran Hepatitis Center, Clinical Department of Baqiyatallah Research Center for Gastroenterology and Liver Disease (BRCGL)-(Tehran, Iran) from 2011 to 2013. All the study population successfully completed the treatment course. The subjects had not received any antiviral therapies for hepatitis C infection, prior to the study. Patients coinfected with hepatitis B virus (HBV) and human immunodeficiency virus (HIV) were excluded from the study. Other exclusion criteria were: acute hepatitis C, HCC, liver transplantation, creatinine clearance < 50 mL/minute, poorly controlled psychiatric disease, poorly controlled diabetes, malignant or neoplastic disease, severe cardiac or chronic pulmonary disease, active substance abuse, immunologically mediated disease, retinopathy and the presence of clinical and laboratory evidences of liver decompensation. The participants signed informed consent and the study design was approved by the Ethics Committee of BRCGL. The study protocol conforms to the ethical guidelines of the 1975 declaration of Helsinki.

3.2. Treatment Regimen and Treatment Response Definition

The treatment regimen of subcutaneous, once a week injection of 180μg Pegaferon® (PegIFN-alpha-2a by Pooyesh Darou, Tehran, Iran), and Ribabiovir® (Ribavirin by Bakhtar Bioshimi, Kermanshah, Iran) was given orally at a dose of 1000 mg daily to the patients weighing 75 kg or less, and 1200 mg daily to those weighing more than 75 kg as a combination therapy of chronic hepatitis C infection. Undetectable HCV RNA (< 10 IU/mL) at the end of fourth week of treatment was considered as RVR. Undetectable HCV RNA (< 10 IU/mL) six months after the treatment cessation was considered as SVR which determined the treatment success. During the treatment course, the patients were closely monitored. Complete blood cell count and liver function tests were checked at regular intervals. Serum HCV RNA level was measured at fourth, 12^{th}, 24^{th}, and 48^{th} weeks of the treatment, and 24 weeks after the treatment cessation.

3.3. Laboratory and Histological Assessments

Assessment of HCV RNA level was carried out using COBAS® TaqMan® HCV Test v2.0 (Roche Diagnostics) with the detection limit of 10 IU/mL. In the current study, rs12979860 polymorphism was assessed as the most common *IFNL* polymorphism. The detailed previously described protocol of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was used to genotype the rs12979860 polymorphism (13). Liver stiffness was assessed by transient elastography using FibroScan 502 machine (EchoSense, Paris, France) for all patients and the results were defined as F0-F4.

3.4. Statistical Analysis

Categorical variables were expressed by frequency and percentage. Continuous variables with normal distribution were expressed by mean ± standard deviation (SD) and continuous variables deviated from the normal distribution by median (interquartile range). Fisher-exact test was used to analyze the categorical variables, t-test for continuous variables with normal distribution, and Mann-Whitney U test for continuous variables deviated from the normal distribution. P-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 17.

4. Results

Patients' demographics, and clinical and laboratory characteristics are shown in Table 1. The majority of study population was male. The HCV genotype 1a was the most prevalent HCV genotype. The majority of patients had no fibrosis on liver elastography. There was no statistically significant difference regarding age, gender, level of alanine transaminase (ALT) and the level of fibrosis between the two studied groups. The HCV RNA level was higher in the control group than in the case group; although the difference was not statistically significant. The distribution of rs12979860 genotypes varied between the two studied groups and there was a lower prevalence of CC genotype and higher prevalence of TT genotype in the case group compared to the control group; however, the difference was not statistically significant (P = 0.469). All the patients in the 24-week, and 48-week treatment groups achieved SVR (P > 0.99).

Table 1. Characteristics of the Study Population [a]

	Patients Treated for 24 Weeks (n = 20)	Patients Treated for 48 Weeks (n = 23)	P Value
Gender [b]			0.687 [c]
Male	16 (80.0)	20 (87.0)	
Female	4 (20.0)	3 (13.0)	
Age, y [d]	39.5 ± 9.7	37.0 ± 11.5	0.458 [e]
ALT, IU/L [f]	60.5 (142.8)	45.0 (51.6)	0.401 [g]
Fibrosis [b]			0.557 [c]
F0	12 (60.0)	10 (43.5)	
F1	5 (25.0)	6 (26.1)	
F2	3 (15.0)	6 (26.1)	
F3	0 (0)	1 (4.3)	
HCV RNA level, Log IU/mL [f]	4.9 (4.9)	5.2 (5.3)	0.077 [g]
HCV Subtype [b]			0.669 [c]
HCV-1a	18 (90.0)	19 (82.6)	
HCV-1b	2 (10.0)	4 (17.4)	
rs12979860 genotypes [b]			0.469 [c]
CC	6 (30.0)	10 (43.5)	
CT	10 (50.0)	11 (47.8)	
TT	4 (20.0)	2 (8.7)	

[a] Abbreviation: ALT, alanine transaminase
[b] Data are presented as No. (%)
[c] Fisher-exact test
[d] Data are presented as mean ± SD
[e] t-test
[f] Data are presented as median (interquartile range)
[g] Mann-Whitney U test

5. Discussion

The current study demonstrated excellent virological response to Peg-IFN and RBV in a group of patients with HCV genotype 1 infection. On the other hand, all the subjects who were treated for 24 weeks achieved SVR. The patients in this study were selected according to the favorable baseline characteristics and on-treatment response. Some studies showed that a subgroup of patients with HCV genotype 1 infection who had low baseline HCV RNA level and became serum HCV RNA negative at the fourth week of treatment, achieved an excellent SVR rate (11, 14, 15). The reasons for the high success rate in the current study can be the relatively younger age of the subjects, high compliance to antiviral therapy, low baseline HCV RNA level and absence of cirrhosis and previous antiviral therapy in the patients. Despite the higher rate of SVR provided by the new generation of hepatitis C antiviral agents, it remains that conventional dual therapy may result in the achievement of SVR in 40%-50% of the naïve patients with HCV genotype 1 infection. Identifying the patients with HCV genotype 1 infection susceptible to achieve high SVR rate following dual therapy appears clinically valuable and appropriate for cost-effectiveness reasons. Besides economic reasons, interferon has several adverse effects and shortening the treatment duration exposes the patients with HCV genotype 1 infection to less treatment adverse events. Response guided therapy with Peg-IFN and RBV dual therapy for the patients with HCV genotype 1 infection with favorable baseline characteristics who achieved RVR can improve the quality of life and be cost-effective.

Cirrhosis is one of the negative predictive factors of response to therapy. Patients with cirrhosis have lower RVR rate, more frequent relapses, and always require long-term therapy. In a recent study, among the subgroup of the patients with HCV infection and cirrhosis, SVR rate was 25% including all HCV genotypes and 18% when only HCV genotype 1 was considered (16). Another study showed that liver cirrhosis was the only baseline predictor of treatment failure. Moreover, in the patients with cirrhosis and *IL28B* CC, the achievement of RVR identified those who still had high rates of SVR to Peg-IFN/RBV therapy (17). However, the study by Ferenci et al. (11) showed that the presence of advanced fibrosis (METAVIR stage F3 or F4) at the baseline did not affect either the rate of relapse or SVR in the patients with HCV genotype-1 or -4 who were treated with Peg-IFN and RBV for 24 weeks and achieved RVR.

Rapid virological response has known as a determining factor for achieving SVR. A study by Andriulli et al. on a large cohort of 1045 patients with HCV infection demonstrated that achieving RVR was dominant over all other variables to determine the likelihood of achieving SVR following Peg-IFN and RBV therapy (18). Another study found that the patients with HCV genotype 1 and low baseline viral level (< 200,000 IU/mL or 200,000 - 600,000 IU/mL) were significantly more likely to attain RVR than the patients with higher baseline HCV RNA level (> 600,000 IU/mL). As a result, these groups of patients are appropriate to receive a shortened treatment regimen (19). A theory was proposed that viral kinetic, which is assessed by RVR, can predict SVR stronger than baseline predictors. Previously, it was assumed that *IL28B* polymorphisms could be an alternative to RVR, but according to the obtained experiences, it seems that RVR is a reflection of all known and unknown predictors of treatment outcome and cannot be replaced by *IL28B* polymorphism (20).

It is proved that the impact of rs12979860 polymorphism on the probability of achieving SVR depends on the concomitant predictive factors such as plasma HCV RNA level. Some studies showed that the HCV-infected patients with rs12979860 CC genotype had a higher chance to achieve RVR and SVR compared to the ones with rs12979860 non-CC genotypes (21, 22). In a study, on the patients with HCV genotype 1 infection harboring the rs12979860 CC genotype, 71% of the individuals with HCV RNA level < 600,000IU/mL reached SVR, versus 49% of those with a higher HCV RNA level (23). The present study showed that in spite of achieving RVR in all the patients in the case group, the prevalence of rs12979860 CC genotype was lower and the prevalence of unfavorable TT genotype was higher in this group compared to the control group patients and the similar groups of the Iranian patients with chronic HCV infection (24, 25), which can be resulted from the small number of patients in the case group.

Several direct acting antiviral agents (DAAs) are developed that show potent activity against HCV and incrementally improve the rates of SVR, even in patients with difficult-to-treat chronic hepatitis C. The problems with these agents are the high cost, and consequently they cannot be affordable in the developing countries. On the other hand, conventional dual therapy should be preserved for HCV-infected patients with favorable pretreatment characteristics and on-treatment responses for cost-effective reasons.

The main limitation of the present study was the small sample size; thus it is advisable to design a large multicenter study to evaluate the efficacy of short course treatment. Shortened courses of treatment may be beneficial if the adverse effects or costs are issues and particularly valuable in the patients who experienced substantial adverse effects that may pose a health risk if the treatment is continued.

In conclusion, individualization of antiviral therapy is not only feasible according to the baseline parameters, but also according to the on-treatment responses. With the availability of more potent antiviral agents, it can be anticipated that individualizing the treatment according to RVR will gain further importance.

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Authors' Contributions

Heidar Sharafi, Seyed Moayed Alavian, and Maryam Keshvari designed the study. Seyed Moayed Alavian and Maryam Keshvari contributed in sample collection. Heidar Sharafi, Seyed Moayed Alavian and Maryam Keshvari performed the study. Heidar Sharafi analyzed the data. Heidar Sharafi and Maryam Keshvari prepared the manuscript.

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