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Evaluation of response to treatment with Ribavirin plus Peginterferon in patients with chronic hepatitis C genotype 1b

Abolfazl Pourhasan[1] and Neda Zamen Milani[2]*

[1]Infectious and Tropical Diseases Research center, Tabriz University of Medical Sciences, Tabriz, Iran

[2]Department of Infectious Diseases, Faculty of Medicine, Tabriz University of Medical Sciences, Tabriz, Iran

Corresponding author

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A B S T R A C T

Chronic infection with hepatitis C virus is a global health problem that can lead to cirrhosis, hepatic disease and hepatic cancer. One of the standard treatments for hepatitis C genotype 1b is Peginterferon plus Ribavirin for 48 weeks that has different response to treatment. Response to treatment could be influenced by different factors. In this study we aim to evaluate the factors related to response to treatment and the rate of response to treatment with Ribavirin plus Peginterferon in patients with chronic hepatitis C genotype 1b. In this analytical cross-sectional study, 90 patients including 44 male and 46 female with mean age of 38.01±11.10 years with the definite diagnosis of Hepatitis C who were treated with Ribavirin plus Peginterferon were included and followed for 48 weeks. In all patients demographic findings, underlying disease and social habits were recorded. Response to treatment was defined at weeks 12, 24 and 48 and different factors were evaluated between groups. Response to treatment was observed in 68 cases (75.6%), recurrence in 16 cases (16.7%) and treatment cessation in 7 cases (7.7%). Opium was used in 1.1%, alcohol in 7.8% and smoking in 22.2%. Also, hepatitis B in 2.2% and diabetes in 6.7% were observed. There were no significant differences between cases with and without response to treatment regarding age, gender, weight, alcohol use, smoking or diabetes. Results of current study showed that treatment with Ribavirin plus Peginterferon in patients with chronic hepatitis C genotype 1b unlike previous studies accompanies with higher response to treatment (75.6%) and different factors have no significant influence in the response to treatment.

Introduction

Chronic infection with HCV is a global health problem that can lead to cirrhosis of the liver and liver cancer (1). Cirrhosis of the liver caused by HCV is the most common indication for liver transplantation and is a major factor contributing in the increasing incidence of HCC. One hundred and thirty to 150 million people worldwide are chronically infected and 300-500 thousand people annually die due to the

infection of hepatitis C (3-2). Successful treatment of HCV is associated with achieving SVR (4-5). Patients reaching the SVR can enjoy long-term benefits associated with improved fibrosis, reduced complications of chronic liver disease, and improved quality of life (6).

One of the standard treatments for hepatitis C genotype 1 is performed with a combination of Interferon α-2b and Ribavirin and 48-41% of patients under treatment reached SVR and it seems that it is lasting for a long period and is associated with long-term benefits (8 and 7). It is shown that the combination of Peginterferon and Ribavirin has improves this response rate up to 54%. Furthermore, a retrospective study showed a 61% response when Peginterferon and Ribavirin doses are assessed based on the patient's weight. Treatment by the combination of interferon α -2bor Peginterferon α2b and Ribavirin requires a balanced treatment regimen including subcutaneous injection, oral prescription twice a day, frequent visits along with blood tests to assess the health and side effects in almost all patients (9).

In patients with genotype 2 and 3, 24-week treatment with 180 g / w Peginterferon in combination with 800 mg / day Ribavirin resulted in SVR in approximately 80% of patients. It has not proven that higher doses of Ribavirin and prolonged treatment improve the response of the patient. However, in positive-HCV patients with the genotype *1b*, higher doses of Ribavirin 1000-2000 mg / day and 48-week treatment period to reach at least 50% SVR are necessary (10). Therefore, treatment of patients with HCV genotype 1 seems difficult and a stronger regimen is recommended to achieve maximum virologic response (11). In most treatment regimens, successful treatment is associated with more contact with medicine. Being exposed to a drug depends on the drug's pharmacokinetic properties and the patient's capability to tolerate the extent to the treatment regimen in which the drug is prescribed for a particular period (11).

Recently, new drugs and different regimes have been introduced for the treatment of hepatitis C. New drugs contain combinations of Sofosbuvir and Ledipasvir, Simeprevir, Daclatasvir, Ritonavir, Paritaprevir and Ombitasvir and Dasabuvir combination. However, due to the high cost and lack of access to new drugs, Peginterferon and Ribavirin standard regimen is often used (12). According to what mentioned, this study aimed to investigate the factors influencing the response to treatment and the amount of response to interferon and Ribavirin treatment in patients with hepatitis C.

Materials and Methods

In a cross-sectional study conducted in Tabriz on patients with hepatitis C, the response to the combination of Ribavirin and Peginterferon treatment in patients with genotype *1b* hepatitis C was evaluated. In this study, all patients who were diagnosed with hepatitis C during the 2014s and referred to the infectious disease clinics for treatment were included and treated by Ribavirin and Peginterferon. In this period, 120 patients were evaluated.

Exclusion criteria

1. Patients with genotypes other than 1b.
2. Patients with no further reference and their evaluation remained incomplete.
3. Patients with discontinued treatment due to lack of response to the treatment.
4. Patients who regressed by this treatment regimen and their treatment was replaced by Pegasys.

All patients enrolled in the study were first evaluated using a checklist.

Underlying diseases including hepatitis B, AIDS, and diabetes were considered. Participants were also asked about their smoking habit, alcohol drinking, and drug injection. HCVRNA, AIT, AST were evaluated at baseline, three months and six months after treatment and at the end of the treatment. PCR was analyzes through sending samples to the Keyvan Virology Laboratory in Tehran and using the COBAS-TaqMan.48 Analyzer and Roche-Applied-Science kits made in Germany.

Ethical Considerations

Written consent was collected from all patients before the study. No additional costs were imposed on patients and all the required tests were provided by the approved project. Patients' names and addresses are mentioned nowhere and their information remained confidential. Moreover, biopsy of the liver was not performed because of its potential risks.

Statistical Analysis

The collected data were analyzed by SPSS-17 statistical software. The collected data were expressed as percentage and mean ± SD. Continuous (quantitative) variables were compared by Independent samples and Paired t test. Categorical (qualitative) variables were compared by contingency tables and Chi-square test or Fisher's exact test. P-value ≤ 0.05 was considered statistically significant.

Results and Discussion

In the present study, 20 out of 120 studied patients were suffering from genotype other than *1b* who were excluded from the study. Ten patients had no further reference and their examination remained incomplete. Finally, the study continued with 90 patients. Of 120 patients, 15 cases regressed by this treatment regimen and their treatment was replaced by Pegasys and 7 cases discontinued treatment due to lack of response to the treatment and 68 cases responded to this treatment. The response to the treatment was 75.6 percent.

Forty-four cases (48.9%) were males and 46 (51.1%) were female. The mean age of patients was equal to 11.10 ± 38.01 years. Patients' weight mean was 14.15 ± 73.32 kg. There were also observed opium consumption in one case (1.1%), alcohol drinking in 7 cases (7.8%) and smoking in 20 cases (22.2%).

There were Hepatitis B in 2 cases (2.2%) and diabetes in 6 cases (6.7%). At the treatment week 12, respond to treatment was observed in all patients.

At the treatment week 24, there was treatment discontinuation for 4 patients (4.4%) and disease recurrence in 9 patients (10%) with changed treatment. At the treatment week 48, among the remained 77 patients, there was treatment discontinuation for 3 patients (3.9%) and disease recurrence in 6 patients (7.8%) with changed treatment. The average age of patients responsive to the treatment was 11.73 ± 37.73 years and the average age of patients unresponsive to the treatment was 9.08 ± 38.86 years. Despite the lower age of patients responsive to the treatment, the difference between two groups was not statistically significant (P=0.68). The average weights of patients responsive to the treatment and patients unresponsive to the treatment were 14.50 ± 72.91 and 13.35 ± 74.59 kg, respectively. In this case, despite the lower weight of patients responsive to the treatment, the difference between two groups was not statistically significant (P=0.63). Both

patients with hepatitis B and the patient with the habit of taking opium had responded to treatment.

Figure 3-4 shows the frequency rate of alcohol drinking among cases responsive and unresponsive to the treatment. As it can be observed in this figure, patients responsive to the treatment had lower levels of alcohol consumption than those unresponsive to the treatment; however, the difference was not statistically significant (P=0.23).

Figure 4-4 shows the frequency rate of smoking among cases responsive and unresponsive to the treatment. As it can be observed in this figure, patients responsive to the treatment had higher smoking frequency than those unresponsive to the treatment; however, the difference was not statistically significant (P=0.6).

In this study, there were diabetes in 4 patients with therapeutic response (5.9 %) and 2 patients unresponsive to the treatment (9.1%). Despite the higher frequency of diabetes in patients unresponsive to the treatment, the difference between two groups was not statistically significant (P=0.63).

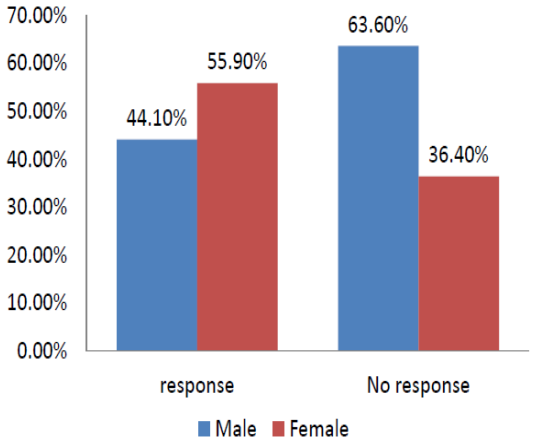

Chart.1 Frequency of patient's gender between response and no response groups

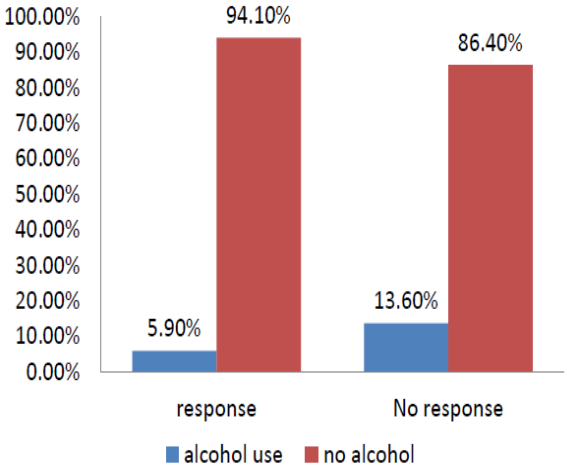

Chart.2 Frequency of alcohol usage between response and no response groups

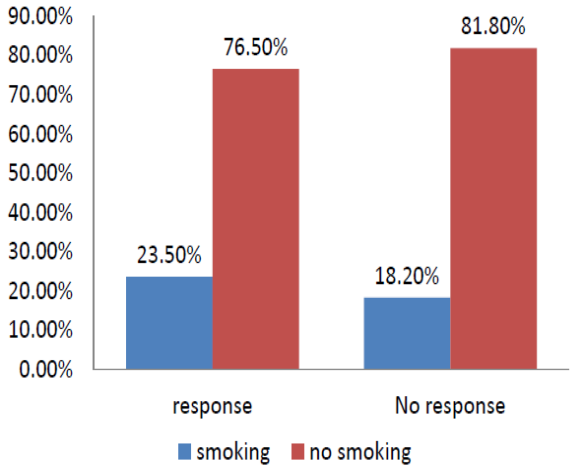

Chart.3 Frequency of Cigarette usage between response and no response groups

The primary goal of hepatitis C treatment is improving infection. A sustained virologic response (SVR) is determined by undetectable HCV RNA at week 12 or week 24 after treatment completion. Infections are improved in more than 99% of patients who reach SVR. SVR in patients without cirrhosis is generally associated with improved liver disease. Patients with cirrhosis are at risk of life-threatening complications. However, liver fibrosis may progress by SVR and the risk of complications such as liver failure and hypertension ports may decrease (25 and 24).

Until 2011, the combination of Peginterferon Alpha and Ribavirin was approved for 24 or 48 weeks of treatment in chronic hepatitis C (26). With this regimen in patients with hepatitis C genotype 1, SVR rate reached 40% in North America and 50% in West Europe. Higher SVR rates were reached in patients with hepatitis 2, 3, 5 and 6. The average rate of SVR was achieved in patients with genotype 4 hepatitis C (27).

In 2011, Telaprevir and Boceprevir were approved to be used for Hepatitis C genotype 1. These two medicines are a part of the first generation of DAA drugs. Both drugs must be prescribed in combination with Peginterferon Alpha and Ribavirin. In phase III of Telaprevir and Boceprevir trial, among patients with Hepatitis C genotype 1 with no pre-treatment, three-drug treatment regimen compared to two-drug regimen with Ribavirin and Peginterferon achieved higher SVR. However, three-drug treatment regimen had greater side effects and costs (31-28).

In 2014, three new DAA drugs were confirmed to be used as a part of combination therapy for hepatitis C infection. Sofosbuvir, Simeprevir, and Daclatasvir were confirmed in January 2014, May 2014, and August 2014, respectively.

Each of these drugs can be used as a part of a three-drug combination regimen with Peginterferon Alpha and Ribavirin. Regarding the used drug, the genotype of hepatitis C, drug resistance, and liver disease severity, SVR will vary from 40% to 100% (12).

With the arrival of these three new drugs, interferon-free treatment regimens have been widely used in Europe since 2014. The combination of Ribavirin and Sofosbuvir in patients with hepatitis C genotypes 2 (12

weeks) or genotype 3 (14 weeks) resulted in 80-95% SVR. The combination of Simeprevir and Sofosbuvir in patients with hepatitis C genotypes 1 resulted in 93-100% SVR. The combination of Sofosbuvir and Simeprevir with or without Ribavirin in patients with hepatitis C, genotype 1 resulted in 93-100% SVR (1). The combination of Sofosbuvir and Daclatasvir with or without Ribavirin is widely used in Europe for patients with advanced liver disease. It resulted in 95-100% SVR in patients with hepatitis C genotype 1(32).

Existing drugs consist of Peginterferon Alpha, Ribavirin, Sofosbuvir, Sofosbuvir and Ledipasvir combination, Simeprevir, Daclatasvir, Ritonavir, Paritaprevir and Ombitasvir and Dasabuvir combination.

Six treatment regimens for patients with hepatitis C genotype 1 were suggested in 2015 (12). These show that new drugs would lead to achieving an ideal high SVR. However, some differences in the economy and health care system of communities make the treatment by Ribavirin and Peginterferon regimens continue without new drugs.

In the present study, due to the unavailability of these drugs, treatment responses to Ribavirin and Peginterferon were assessed. In the present study, we evaluated the treatment response to Interferon and Ribavirin in patients with hepatitis C genotype 1 and its affecting factors. It was observed that more than three-quarters of patients (75.6%) responded appropriately to treatment at the end of 48 weeks.

Unlike the current study, the treatment response was reported up to 60% in previous studies. In a research study, Vadim et al. found that the SVR in Genotype *1b* 1 was 46.1% (19). In another study conducted by Zeuzem et al., SVR was 50% (21). In Urbanek's study, the observed treatment response in genotype *1b* was equal to 55% (33).

However, there was only one study with results similar to the results of the present study. Ma et al. in their study observed that the response at the end of 48 weeks of treatment by Peginterferon and Ribavirin in genotype 1 was 73.6% (34).

In different studies, different factors have been considered involved in the response to a treatment. The main factors effective in the antiviral treatment of Hepatitis C can be divided into two major categories: Factors related to the virus including virus genotype, baseline virology, virologic response during treatment, and host factors such as age, sex, race, obesity, alcohol consumption, and the degree of liver fibrosis (16).

In the present study it was observed that cases responsive to the treatment, compared unresponsive cases, had lower mean age and weight, were mainly females, consumed less alcohol and smoked more, and suffered from diabetes to a lesser extent. However, there was no significant statistical difference between two groups.

Javier et al. observed that older age is associated with a lower rate of response to treatment (18). Vadim et al. also concluded that the SVR rate in patients younger than 40 years old, compared to older people, is higher (19). Zeuzem et al. in their study found that, some predictive factors including age, base HCV-RNA and the duration of treatment were significantly associated with SVR; however, it has no significant relationship with gender, race, weight, source of exposure, duration of exposure, the dose of Ribavirin, Metavir and Knodell scores (21). Berg et al. also reported that, in

the 48-week treatment, there is no significant relationship between race, gender, height, fibrosis, and ALT and the treatment results. However, age, weight, blood glucose level, and HCV-RNA had significant correlation with those results (22).

Depending on the sample size of patients and patients' specifications, different studies have suggested various factors in the response to the treatment. However, none of these factors had a significant role in this study. This treatment should be considered for all patients with chronic liver disease associated with hepatitis C, who have not been treated so far or have already experienced treatment and have no contraindication for treatment.

Prior to the treatment, other causes chronic liver disease or factors affecting the progression of liver disease should be assessed and all patients should be checked for other hepatotoxic viruses, particularly hepatitis B and immunodeficiency viruses. Alcohol consumption should be assessed and its discontinuation shall be recommended. Possible comorbidities including autoimmune disease, metabolic or genetic liver diseases (eg, hemochromatosis, diabetes, obesity) and drug hepatotoxicity should be assessed (12).

Prior to the treatment, assessing the severity of the liver disease with regard to cirrhosis or advanced fibrosis is also important. Evaluation of fibrosis in patients with clinical evidence of cirrhosis is not necessary and these patients do need to be evaluated in terms of hepatocellular carcinoma. Over many years, liver biopsy has been an acceptable method for determining the phase of histologic progress and disease activity. Liver stiffness measurement contributes in the estimation of liver fibrosis in patients with hepatitis C. Biomarkers representing fibrosis can also be used. Using the combination of these methods reduce the need for the liver biopsy. It would also be useful for patients with coagulation disorders (36 and 35).

Quantifying RNA HCV in patients under treatment has indications and shall be carried out a reliable and sensitive method and expressed in IU/mL. HCV genotype and the subtype of genotype 1 should be determined prior to treatment. Determining genotype and subtype must be done by a method which would accurately distinguish between subtypes *1a* and *1b* (37).

Test of resistance to first-line drugs is not required since resistance has no high impact on treatment and the outcome of the treatment, except for patients infected with subtype *1a* who were treated by Peginterferon Alpha, Ribavirin and Simeprevir (12).

Cirrhotic patients achieving SVR should be examined by ultrasonography for HCC every 6 months and by endoscopy for esophageal varices, if they were with esophageal varices prior to the treatment. Non-cirrhotic patients achieving SVR shall be evaluated for HCV RNA during the week 48 after treatment and if the HCV RNA is still not recognized, infection can be considered cured. There is no need to re-check HCV-RNA (25 and 24).

Despite what mentioned, following points are important in making decision:

Treatment of chronic hepatitis C is contraindicated by the regimens containing Peginterferon Alpha and Ribavirin in uncontrolled depression, psychosis, convulsion of pregnant women or couples who do not use safe contraceptive methods, severe simultaneous, diseases, comorbidities including retinal disease, thyroid disease,

autoimmune disease, and decompensated liver disease. The use of Peginterferon Alpha in patients with neutrophils less than 1500 or platelets less than/ equal to 90,000 is not recommended. Sofosbuvir in patients with severe renal insufficiency should be used with caution. The combination of Ritonavir, Paritaprevir, Ombitasvir and Dasabuvir in patients with decompensated cirrhosis Child-Pugh-C is contraindicated (12).

Peginterferon Alpha and Ribavirin side effects include neutropenia, anemia, thrombocytopenia, and lymphopenia. These parameters shall be checked in weeks 1, 2 and 4 of therapy and then in each 4-8 weeks (12).

Conclusion

Results of this study showed that, unlike previous studies, treatment using the combination of Ribavirin and Peginterferon therapy in the treatment of patients with hepatitis C genotype 1 b is associated with greater rate of response to the treatment (75.6%) and various factors have no significant impact on the treatment response.

Recommendations

According to the results of this study, using the combination of Ribavirin and Peginterferon therapy in the treatment of patients with hepatitis C genotype 1 b is recommended. However, further studies with larger sample sizes can provide more accurate results in this regard.

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