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Assessment of the Response to Treatment in Patients with the Hepatitis C Virus Infection: A Quantitative Study by Focusing on Virologic and Biochemical Responses

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Abstract

Objectives: The main goal of the treatment of the hepatitis C virus (HCV) infection is reduction and elimination of viruses as well as achieving high sustained viral response (SVR). The present study aimed to assess response to treatment of HCV infection by focusing on virological and biochemical aspects.

Methods: This study was performed in Hamadan, Iran on HCV infected patients who were referred between 2009 and 2013. All participants were under the treatment with Pegylated Interferon (PEG-IFN) and Ribavirin (RBV). The duration of treatment varied based on the HCV genotype as 24 weeks for genotypes 2 and 3, and 48 weeks for other genotypes.

Results: Of the 186 patients with HCV infection, 52.8% had a genotype of 3a and 35.6% had a genotype of 1a/b. Three months after treatment, 75 patients were willing to do quantitative PCR and early virologic response was observed in 58 cases (78.4%). Also, 112 patients were assessed after completing the treatment (75 patients in 24 weeks and 37 patients in 48 weeks treatment protocol) and the end-of-treatment response (ETR) was 94.7% and 86.5% respectively. Amongst the 103 patients with ETR, 76 were followed up six months after treatment and the PCR was negative in 71 cases (SVR = 93.4). With the progress and completion of the treatment, improvement is observed in liver function tests.

Conclusions: Even with the introduction of new drugs and interferon free protocols in treatment of hepatitis C infection it seems that the IFN-based treatment is still used in low/middle income countries for treatment-naive patients with HCV genotype 3.

Keywords: Hepatitis C, Treatment Outcome, PEG- IFN, Ribavirin

1. Background

According to the world health organization report, more than 3% of the world's populations (170 million people) are now infected with hepatitis C virus (HCV) (1). Each year, 3 to 4 million people are infected with this virus responsible for 350,000 annual deaths (2). Many of the hepatitis C patients are asymptomatic and are realized randomly with routine blood tests indicating increased level of serum aminotransferases. In total, specific serologic tests such as detection of serum HCV antibody (anti HCV) is necessary to assess the HCV infection. HCV antibody can be measured in more than 95% of patients during the chronic phase; however, the level of this antibody cannot be measured in 5% - 10% of patients in the acute phase. In this regard, the gold standard for the diagnosis of the HCV infection is detection of HCV-RNA using the polymerase chain reaction (PCR) method (3). Also, liver biopsy is the most reliable method used to determine the extent of liver damage and fibrosis (4). Regarding the disease progression, the disease in its acute phase can be recovered spontaneously in 20% of cases, but 70% - 80% of cases can continue as the chronic phase to be a cause varying degrees of liver inflammation, fibrosis or even cirrhosis (5). In less than 5% of the affected ones, this infection progression may lead to hepatocellular carcinoma (6).

Until recent years the best treatment for HCV infection is a combination of interferon α (PEG-IFN-α 2b / 2a) and ribavirin (RBV) for 24 - 48 weeks (7). In recent protocols interferon free regimens have been introduced (8, 9). However, still PEG-IFN and ribavirin is used in low/middle income countries.

Response to treatment in these patients is assessed from three virologic (viral load), biochemical (parameters

of liver function test) and histological (liver biopsy) aspects. The main goal of treatment is reduction and elimination of viruses as well as sustained viral response (SVR) that is determined with normal aminotransferase levels and the absence of serum HCV RNA during 24 weeks after the end of treatment (7). However, the recurrence of infection and also treatment side effects are also common findings needing more assessment of treatment protocol.

2. Objectives

The present study aimed to assess the response to treatment of HCV infection to PEG-IFN/RBV regimen by focusing on virological and biochemical aspects.

3. Methods

This retrospective study was performed at the Imam Khomeini clinic in Hamadan, Iran on record files of 186 consecutive patients with positive HCV infection who were referred between 2009 and 2013. All of the patients are above 18 years old and posses positive HCV RNA (PCR) in addition to the positive serology for the hepatitis C infection. The relevant information is entered to the checklist from the patients' file.

All participants were under the treatment with PEG-IFN-α 2b / 2a and RBV. The exclusion criteria include: incomplete record files, those who did not complete the course of treatment and those who were treated with anything other than the PEG-IFN/RBV regimen. All study information including demographic information, genotype of virus, residency, co-infection with HIV, liver function parameters (AST, ALT, ALP, Bill total/direct, PT, INR) and time of treatment was collected from recorded files of the patients.

In this study, AST, ALT < 40 IU/L, Bilirubin direct < 1.5 mg/dl, Alkaline phosphatase < 306 IU/L is considered in normal limit.

The treatment method for genotype 1, HCV infection is 48 weeks course of the following regimen:

- PEG IFN-α2b (1.5μg/kg) + RBV (weight based and range from 800-1400 mg) or

-PEG IFN-α2a (180-μg) + RBV (weight based and range from 1000-1200 mg)

The treatment of genotype 2 and 3, is similar doses of PEG IFN-α2b or PEG IFN-α2a with 800 mg of RBV for 24 weeks (9).

The study endpoint was to assess virologic and biochemical responses to treatment protocol by assessing quantitative PCR results and liver function parameters respectively after the two 24 and 48 weeks treatment protocols.

In this study, early virologic response (EVR) was defined when the levels of HCV RNA becomes undetectable or decreased at least two logs after 12 weeks of therapy. If HCV RNA was undetectable at the end of treatment this was considered as end-of-therapy response (ETR). A sustained virologic response (SVR) was considered when HCV RNA in the serum was negative at the end of treatment and 6 months later (9).

For statistical analysis, the trend of the changes in diagnostic parameters during the treatment was assessed using the repeated measure ANOVA test. The statistical software SPSS version 16.0 for Windows (SPSS Inc., Chicago, IL) was used. P values of 0.05 or less were considered statistically significant.

4. Results

The mean age of patients was 46.84 $\pm$ 1.34 years (ranged 19 to 79 years) and 91.8% were male. Furthermore, 91.0% were resident in urban areas. Regarding various genotypes of HCV, 52.8% had genotype 3a, 35.6% had genotype 1a/b, 3.9% had a genotype of 2 and the rest were other genotypes. Co-infection with HIV was reported in 3.4%. Duration of treatment varied based on HCV genotypes as 24 weeks for genotypes 2 and 3, and 48 weeks for other genotypes. The change of liver functional parameters within 6 months of treatment in genotypes 2 and 3 is summarized in Table 1. As shown, a downward trend in serum level of liver enzymes (ALT, AST) was revealed within 6 months of treatment, while the trend of the change in total and direct bilirubin as well as protrombin time (PT) remained unchanged. Regarding the change in liver function indices in HCV genotypes other than 2 and 3 (Table 2), the decreasing trends in liver function parameters specified to ALT, AST and bilirubin within one year after beginning treatment. In the group treated for 24 weeks (genotypes 2 and 3), no significant association was found between the change in serum level of AST and ALT and baseline parameters of gender (P = 0.99), age (P = 0.96), type of genotype (P = 0.82) residency (P = 0.52) and co-infection with HIV (P = 0.41). However, the trend of the changes in the levels of AST (P = 0.03), PT (P < 0.001) and total bilirubin (P < 0.001) was related to the residency of patients. Also, different trends of the change in direct bilirubin were observed between men and women (P = 0.045).

Of the 186 patients, 75 were willing to do quantitative PCR three months post treatment and virologic response was observed in 58 cases (EVR = 78.4%). Also, 112 patients were assessed after completing the treatment, 75 patients in the group with 24 weeks treatment protocol (ETR = 94.7%) and 37 patients in the group with 48 weeks protocol (ETR = 86.5%). Amongst the 103 patients with ETR,

Table 1. Mean Level of Liver Function Parameters in Patients with HCV Genotypes 2 and 3

Parameter	On Admission	3 Months Later	6 Months Later	P Value
ALT (IU/L)	76.06	40.49	34.15	< 0.001
AST (IU/L)	58.58	36.24	32.05	< 0.001
ALP (IU/L)	227.22	214.81	191.52	0.006
Direct Bilirubin (mg/dL)	0.25	0.257	0.27	0.509
Total Bilirubin (mg/dL)	0.947	0.976	0.874	0.523
PT (Sec)	12.99	12.99	12.70	0.078

Table 2. Mean Level of Liver Function Parameters in Patients with HCV Genotypes other than 2, 3

Parameter	On Admission	3 Months Later	1 Year Later	P Value
ALT (IU/L)	76.32	40.86	33.76	< 0.001
AST (IU/L)	58.41	35.79	34.42	< 0.001
ALP (IU/L)	227.55	215.18	203.31	0.162
Direct Bilirubin (mg/dL)	0.23	0.25	0.43	< 0.001
Total Bilirubin (mg/dL)	0.95	0.97	0.77	0.020
PT (Sec)	12.199	13.00	12.86	0.052

76 were followed up six months after treatment and the PCR was negative in 71 cases (SVR = 93.4). In fact, 78.4% of patients in both treatment groups (6-month and 1-year groups) achieved EVR, three months after the beginning of treatment; while 94.7% of patients in 6-month treatment group and 86.5% of those in 1-year treatment group achieved ETR after completing their treatment schedule. In the present study, the trend of the change in PCR negativity was significant in females, younger ages, in those who resident in urban area and also in those with negative HIV.

5. Discussion

In our observation, the most frequent genotype was genotype 3a, which was similar to the result presented by Rafiei et al. in Iran (10), but partially higher than that was reported by Mchutchison et al. (7) in the United States and Keyvani in Iran (11). The distribution of various genotypes of HCV is different according to the ethnical and geographical varieties. Taherkhani and Farshadpour have mentioned the increasing prevalence of genotype 3a and decreasing prevalence of genotype 1a / 1b in recent years in Iran (12). In our study, achieving SVR was reported in 93.4% of patients with ETR, which was similar to the rate reported by Alavian (13) and Akhoondi (14), but considerably higher than the rates reported by Mchutchison (7). The difference in the rate of SVR might be due to the difference in immune system status, difference in genotypic pattern of virus and also more use of alcohol in the western areas. Also, the obtained ETR in our survey was similar to the Alavian et al. report (15) (85.0%), but was contrary to the rate by Pearlman et al. in Atlanta (16). Also, the obtained EVR in our study (78.4%) was near the rate of Alavian et al. as 91.0% (15), but was higher than the rate reported by Ocker et al. as 72.0% (17). It seems that the rate of SVR is directly associated with some determinants such as female gender, low level of HCV RNA, lack of fibrosis and lower body mass index. In Asian societies such as Iran, the BMI and the prevalence rate of its complication such as hypertension and diabetes are lower than western countries and thus the prognosis of HCV infection can be better. As indicated by Bafandeh et al. in Iran (18), achieving SVR was reported high in various genotypes of the virus.

In the present study, the trend of the change in PCR negativity was significant in females, in those who resident in urban areas and also in those with negative HIV. In a study by Mauss et al. in Germany (19) and contrary to our study, significant trends were revealed in positive HIV patients. However, similar to our study, Conjeevara et al. showed higher SVR in females than in male patients (20). Regarding association between SVR and type of genotype, we could not find a relationship similar to the Bafandeh et al. study (18), but in another study by Alavian et al. (15), the achieved SVR was higher in the genotype of 1 a/b and 3a. It is obvious that achieving SVR is higher in the younger population rather than in the old patients due to a higher

prevalence rate of chronic diseases such as hypertension and diabetes as well as a higher rate of immunodeficiency conditions in older people. This was shown in our survey.

Although the increase in liver enzymes is an indicator for progression to cirrhosis and liver damages, several studies could not indicate a significant association between the increased level of these markers and severity of liver lesions (18). In our study, the changes in ALT and AST were significant in the genotypes of 2 and 3. The change in bilirubin, AST and ALT was also significant in other genotypes that indicate the presence of all types of genotypes that can predispose liver to damage. Furthermore, with the progress and completion of the treatment, improvement is observed in liver enzymes in both treatment groups of 24 and 48 and this refers to the possibility of improving liver activity.

Due to the retrospective nature of the study, it was not possible to follow up on all patients. For this reason some files were left out of the study and EVR and SVR investigations were not possible for all patients. Lack of considering treatment side effects and lack of comparison of treatment response with other treatment regiments were another limitation of this study.

5.1. Conclusion

Despite the introduction of interferon free regimen to treat of hepatitis C in recent years, it appears that the PEG-IFN/RBV combination is suitable on treatment-naive patients with HCV genotype 3 in areas that do not have easy access to new drugs or because of the high cost, drugs cannot be used. Naturally protocol should change to the new drugs if it is more accessible.

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Footnotes

Authors' Contribution: Peyman Eini was involved in the study concept and design, the study supervision, analysis and interpretation of data; Fatemeh Keshavarz and Abbas Moradi participated in the study design and analyzed the data; Mojgan Mamani was involved in the study concept and design, abstracted data, wrote and prepared the manuscript; All authors provided comments and approved the final manuscript.

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