Baseline Predictors of Sustained Virological Response to Pegylated Interferon and Ribavirin in Egyptian Patients Infected with Viral Hepatitis C

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Abstract

Background: Egypt represents the highest prevalence of HCV worldwide. Identifying Predictive factors for response to antiviral therapy in patients with chronic hepatitis C virus (HCV) infection especially those with genotype 4 may provide information to optimize and/or individualize the treatment of HCV genotype 4 infected patients, thus improving antiviral response.

Aim: To analyze the data from Egyptian chronically infected patients with HCV treated for 48 weeks with a course of Peg interferon alfa-2a and alpha-2b plus Ribavirin, to determine the baseline factors associated with SVR.

Patients and Methods: Retrospective data of 3719 patients with chronic HCV who had received pegylated interferon/Ribavirin therapy in the context of the national program at Cairo-Fatemia Hospital, Egypt were retrieved. Different baseline demographic, laboratory, histological [grade and stage (Metavir score)] and virological parameters were recorded before initiating treatment and response to treatment was evaluated by PCR at 12, 48 and 72 weeks of treatment.

Results: The estimated sustained virological response (SVR) at week 72 was 54%. On doing Univariate and multivariate analysis of the base line factors related to SVR, the most significant factors detected for achievement of sustained virological response were male gender and the grade of inflammation (Grade 2, 3) at a p-value <0.01, <0.01 respectively and the most significant factors related to failure of SVR achievement were base line ALT >40u/1 at a p-value <0.05, as well as Viremia if >600x10^3 IU, baseline AFP >10ng/ml and stage of fibrosis (F2, F3, F4,) with at p<0.01 respectively.

Conclusion: Male gender, high grade of inflammation, were found to be significant factors in achievement of SVR, however, higher stages of fibrosis and higher level of viremia, ALT and AFP at base line were found to be the predictive factors that play a significant role in failure of achievement of sustained virological response to HCV.

Key Words: Baseline — Predictors — SVR — HCV therapy.

Introduction

CHRONIC hepatitis C is endemic in most regions of the world though prevalence rates vary widely. Over 170 million people are infected with HCV worldwide (about 3% of the global population). Egypt has among the world's highest prevalence rates of HCV (10-15% having HCV antibodies in rural areas). HCV is major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma and represents most common cause of liver transplantation in the US and Europe III.

Egypt represents the highest prevalence worldwide. According to the Egyptian Demographic Health Survey (EDHS), 15% among the survey responders had antibodies to HCV whereas 10% were found to have active infection [2]. The heavy burden of liver disease due to chronic HCV infection is attributed to the personal history of parenteral anti-schistosomal therapy. In general, HCV genotype 4 (HCV4) is predominant in Africa and the Middle East. In Egypt, where hepatitis C is highly endemic, 91% of the patients were infected with HCV genotype 4. Liver disease is thus the second-commonest cause of death in Egypt, after heart disease and deaths from liver disease are predicted to peak in 2010-2012 [2].

PEG-IFN has become the cornerstone of therapy as it extends the duration of therapy and reduces adverse effects and when combined with Ribavirin, the rate of sustained virological response (SVR) has dramatically improved even in patients with high HCV RNA level [3,4].

Given the significant side-effects and healthcare costs associated with interferon therapies, identifying patients who are less likely to respond is highly desirable to predict the rate of achieving
SVR in the individual patient, before initiating treatment. Both virus and host-related elements have been reported as factors correlated to therapeutic effects of combination therapy. A particular focus has been placed on age, gender, Body mass index (BMI), degree of activity and fibrosis of the liver and HCV RNA level [5,6].

Baseline factors that have been shown to predict SVR to peg interferon alfa-2a plus Ribavirin include HCV genotype, age (<40 years) and body weight (075 kg) [7].

Identifying these factors may provide information to optimize and/or individualize the treatment of HCV genotype 4 infected patients, thus improving antiviral response. This is of particular importance because these difficult to treat populations have a high prevalence of HCV infection and comprise a large proportion of the HCV-infected population in Egypt.

We, therefore, retrospectively analyzed the data from Egyptian patients treated for 48 weeks with a course of Peg interferon alfa-2a or alpha-2b plus Ribavirin, to examine the baseline factors associated with SVR to treatment.

Patients and Methods

In 2006, the Egyptian Ministry of Health and Population (MOHP) has created the National Committee for Control of Viral Hepatitis. The committee had organized a network of 21 National Treatment Reference Centers that provide care for viral hepatitis patients according to standardized guidelines and at subsidized costs.

The study population included 3719 Egyptian chronic HCV patients, who had been treated with Peg-IFN/RBV between the years 2007 and 2010 at Cairo-Fatemic Hospital (one of the largest National Treatment Reference Centers, Cairo, Egypt). The study population included IFN naïve chronic HCV patients who were diagnosed by anti-HCV antibodies, HCV-RNA by reverse transcription-polymerase chain reaction (RT-PCR) in addition to the histological evidence of chronic hepatitis. Adult patients, age ranged from 18-60 years, of both sexes, who received combined antiviral therapy were included and were evaluated for their response by PCR at 12, 24, 48 and 72 weeks. The study was approved by the ethical committee of the MOHP and all patients were consented for the blood sampling and possible data application in future research.

Data studied included full clinical examination, Ultrasonographic examination and laboratory evaluation (Hematological tests, Liver function tests and PCR for detection of HCV viremia); liver biopsy was done for all patients prior to treatment to assess the grade of inflammation and the stage of fibrosis according to the METAVIR scoring system to decide whether included or excluded from treatment.

Patients were included according to the national guidelines of National Committee, being adult, naïve, non obese (BMI <30) of both sexes with no co-morbid conditions and —ve HBsAg, having no contraindications for IFN/RBV therapy and with METAVIR score F2 if ALT is persistently normal or F1 if ALT is above upper limit normal.

Results

3719 patients were recruited in this retrospective study, 713 females and 3006 males. They received 180ug once weekly of Peg interferon alpha2-a or 1.5ug/kg once weekly of peg interferon alpha 2-b and a weight-based dose of Ribavirin: 15 mg/kg body weight per day as a treatment for HCV for 48 weeks and were evaluated for their response at 12 weeks (EVR), 24 weeks, 48 weeks (ETR) and at 72 weeks (SVR) by PCR. Among 3719 patients the ETR was 63% and the SVR was 54% and non-responders were (46%) including 428 patients (19%) who discontinued the treatment either due to side effects or non-compliance.

Among 713 females 313 (43.9%) achieved SVR and among 3006 male patients 1703 (56.7%) were sustained virological responders with a statistically significant difference of <0.01. The BMI and the mean age were nearly the same in both responders and non-responders with no statistical significant difference.

On analyzing the baseline demographical, biochemical, and hematological characteristics of the 3719 patients shown in Table (1), a statistical significant difference <0.05 was noted in response between males and females; age and BMI were of no significance between responders and non-responders. Among the biochemical and hematological findings of our patients; only Blood glucose, AFP, ALT show a statistical significant difference between responders and non-responders with a p-value <0.01 and <0.05 respectively.

Univariate analysis of the baseline factors associated with failure where failure is the dependent factor, showed that the most significant base line factors with response were male gender p-value <0.01, and the grade of inflammation (A2,A3) with a p-value <0.05, however the most significant
factors with failure of response were Viremia if >600x10^3 IU with p<0.01, base line ALT >40u/l with p<0.05 and with ap<0.01 the baseline of AFP >10ng/ml and the stage of fibrosis (F2, F3, F4.). On doing the multivariate analysis of these univariate analysis significant base line factors, the most significant factors related to response were male gender and the grade of inflammation (A2, A3) with a p<0.01, and those related to failure of response were Viremia >600x10^3 IU, baseline ALT >40, stage of fibrosis (F2, F3, F4) and baseline AFP >10ng/ml with a p-value <0.01.

Table (1): Demographic, biochemical and hematological characteristics of the studied patients in relation to response.

<table>
<thead>
<tr>
<th>Attribute</th>
<th>SVR</th>
<th>NR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1703 (57%)</td>
<td>1303 (43%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Female</td>
<td>313 (44%)</td>
<td>400 (56%)</td>
<td></td>
</tr>
<tr>
<td>Age (Mean y±SD)</td>
<td>42±10</td>
<td>42±10</td>
<td>0.06</td>
</tr>
<tr>
<td>BMI (Mean±SD)</td>
<td>28±4</td>
<td>28±4</td>
<td>0.68</td>
</tr>
<tr>
<td>Blood glucose (Mean±SD)</td>
<td>98±27</td>
<td>101±30</td>
<td>0.001</td>
</tr>
<tr>
<td>ALT (Mean±SD)</td>
<td>64±44.8</td>
<td>60.8±40</td>
<td>0.02</td>
</tr>
<tr>
<td>AST u/L (Mean±SD)</td>
<td>56±36</td>
<td>59±50</td>
<td>0.31</td>
</tr>
<tr>
<td>Albumin (Mean±SD)</td>
<td>4±0.5</td>
<td>4±0.5</td>
<td>0.23</td>
</tr>
<tr>
<td>Prothrombin (Mean±SD)</td>
<td>86±11</td>
<td>87±10</td>
<td>0.08</td>
</tr>
<tr>
<td>Bil(total) (Mean±SD)</td>
<td>0.8±0.3</td>
<td>0.8±0.3</td>
<td>0.93</td>
</tr>
<tr>
<td>AFP (Mean±SD)</td>
<td>8±15</td>
<td>32±1208</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>HB g/dl</td>
<td>14±1</td>
<td>14±1.5</td>
<td>0.33</td>
</tr>
<tr>
<td>WBCx10^3</td>
<td>6±2</td>
<td>6±2</td>
<td>0.35</td>
</tr>
<tr>
<td>Plateletx10^3</td>
<td>214±61</td>
<td>213±64</td>
<td>0.64</td>
</tr>
</tbody>
</table>

NR: Failure of response or break through or relapse or discontinuation of treatment due to side effects or non compliance.

Table (2): Univariate logistic regression analysis for baseline factors associated with failure of treatment.

<table>
<thead>
<tr>
<th>Univariate</th>
<th>OR</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;50</td>
<td>1.0</td>
<td>0.8</td>
<td>1.3</td>
<td>0.81</td>
</tr>
<tr>
<td>BMI</td>
<td>0.93</td>
<td>0.83</td>
<td>1.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Male gender</td>
<td>0.65</td>
<td>0.51</td>
<td>0.83</td>
<td>0.001</td>
</tr>
<tr>
<td>Viremia &gt;600x10^3 IU</td>
<td>1.7</td>
<td>1.3</td>
<td>2.2</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Baseline AST &gt;40 u/l</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.90</td>
</tr>
<tr>
<td>Baseline ALT &gt;40u/l</td>
<td>1.0</td>
<td>0.99</td>
<td>0.99</td>
<td>0.049</td>
</tr>
<tr>
<td>Baseline AFP &gt;10ng/ml</td>
<td>1.1</td>
<td>1.0</td>
<td>1.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Baseline ALP &gt;290 u/l</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
<td>0.21</td>
</tr>
<tr>
<td>METAVIR A (2,3)</td>
<td>0.47</td>
<td>0.37</td>
<td>0.59</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>METAVIR F (2,3,4)</td>
<td>1.5</td>
<td>1.2</td>
<td>1.9</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Discussion

Given the significant side-effects and healthcare costs associated with interferon therapies of HCV being the major cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma among Egypt, this retrospective study was conducted, to evaluate the base line predictors of sustained virological response at 72 weeks (SVR) before initiating treatment, among 3719 patients with chronic hepatitis C of genotype 4.

In our study, the response in males was better than females, however Martinot-Pegnoux et al. [8] reported that females respond better than males and Koruk et al. [9] reported that males are negative predictors of SVR. This difference in our study may be due the larger number of males included compared to females.

A better response between higher grades of inflammation and positive SVR in our study, is consistent with the finding of Derbala MF et al., who reported positive correlation (p-value <0.05) between higher grades of inflammation and response rate (SVR positive) in HCV genotype 4 patients treated with Pegylated Interferon and Ribavirin for one year Rob These findings are also biologically plausible. HCV activates the cytotoxic
T-lymphocytes which causes liver inflammation in CHC patients. III. Grade of liver inflammation correlates with the underlying immune response of the host i.e. Higher the immune response to HCV infection, higher is the liver inflammation [12]. Pegylated Interferon a is a cytokine that has two modes of action: Direct antiviral effect as well as it acts as an immune modulator to clear HCV infection [13]. Therefore high grades of liver inflammation depicts higher immune response to HCV which responds more to immune modulation effect of Interferon a compared to low grades of inflammation and this finding remains true for our patients with higher grades of inflammation who achieved better SVR.

The most significant baseline factors related to failure of response were high viremia, elevated ALT >40u/1, advanced stage of fibrosis and elevated AFP >10ng/ml. Our findings were in agreement with De Careaga [14] who reported a positive correlation between the base line ALT levels and the probability of a better response to treatment and that a baseline AST/ALT quotient of 0.5 or lower is predictive of a better response to treatment as well Kim [15] in a study on the effect of ALT dynamics on the prediction of SVR in chronic HCV patients found that patients with elevated baseline ALT levels had remained high ALT levels and patients with normal range of baseline ALT levels experienced high ALT during treatment and both groups had a low probability of SVR.

Abdo and Sanai [16] cited that a higher AFP level is associated with a negative treatment outcome in chronic hepatitis C patients of genotype 4 and Gad et al. [17] reported that in genotype 4 patients, treatment with both alfa-2a and alfa-2b forms of pegylated interferon has shown lower AFP levels to be predictive of SVR.

De Careaga [14] reported that patients with hepatitis C and cirrhosis have lower rates of sustained responses even with the absence of cirrhosis, the degree of response to treatment decreases with the increase of stage of fibrosis and this was in agreement with our study finding that the advanced stage of fibrosis is a negative predictor of SVR.

Baseline low viremia was a good predictor of SVR and this was in agreement with Izumi et al. [18] and Koruk et al. [9]; who found that base line viremia >600x10^3 IU is a negative predictor of SVR however it is therefore difficult to predict the virological response solely from the amount of HCV RNA before starting the treatment [18].

In our study due to the selection of our patients at base line before initiating treatment at a BMI <30kg/m^2, there was no correlation between BMI and achievement of SVR, however in the literature, Bressler et al. [19] demonstrated that obesity, defined as BMI >30kg/m^2, is a risk factor for non-response to antiviral treatment, regardless of genotype and the presence of liver cirrhosis. BMI was not significantly associated with SVR, as well in other studies [20-22].

From our study we can conclude that proper evaluation of the base line predictors of SVR before initiating treatment such as gender, ALT level, stage of fibrosis, grade of inflammation, PCR, Alpha fetoprotein, is important in determining the possibility of achievement of SVR and also in reducing the burden of cost and the side effects of chronic HCV treatment for patients who are not likely to achieve SVR.

Study limitations: Being a retrospective study, it was difficult to randomize the number of males and females included in this study and this makes that males achieved a SVR better than females.

Acknowledgement: Special thanks to Cairo Fatemic Hospital and the Ministry of Health, for their active participation in the practical part of this work and their active cooperation in giving the permission for the collection of data of chronic HCV patients who were subjected to proper evaluation and treatment of HCV.

References

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