Original Article

Extent of Liver Injury as a Predictor of Response to Interferon Combination Therapy

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Abstract

Background: To determine the value of extent of liver injury as a baseline predictor of response to conventional interferon plus ribavirin for chronic hepatitis C Genotype 3.

Methods: In this descriptive study treatment naive hepatitis C patients (n=489) underwent serum Alanine Aminotransferase (ALT) measurement and a liver biopsy to assess for hepatic steatosis and Histology Activity Index (HAI). Six months conventional interferon plus ribavirin therapy was given to all and the significance of above mentioned parameters as predictors of response in terms of Sustained Virological Response (SVR) and End of Treatment Response (ETR) was analyzed. Chi-square test and regression analysis were used to calculate the results with a significant P value < 0.05.

Results: Male individuals constituted 31.1% (n=152) of the population while 68.9% (n=337) were females. Mean Alanine Aminotransferase level was 73.74 ± 65.27 IU/l. SVR was achieved by 61% (n=298) individuals while ETR by 83.4% (n=408). Mild hepatic inflammation and fibrosis i.e., low HAI (≤8) turned out to be a significant predictor of both a good ETR (p=0.00) and SVR (p=0.00). Minimal to mild degree of steatosis (≤33%) was a predictor of better SVR (0.00). Baseline ALT level was not significantly associated with response rate (p=0.76).

Conclusion: Lower extent of hepatic steatosis (≤33%) and low HAI (≤8) is a significant predictor of better response to conventional interferon combination therapy for HCV Genotype 3. Hepatic steatosis >66% and HAI > 12 predicts failure to respond.

Key Words: Conventional interferon, Ribavirin, Histological Activity Index, Steatosis, End of Treatment Response, Sustained Virological Response, Hepatitis C.

Introduction

It is impossible to really know the origins of hepatitis C. However given the nature of the evolution of all viruses, hepatitis C has probably been around for hundreds of thousands of years or more. Chronic infection with hepatitis C virus (HCV) is a global health problem and is estimated to affect up to 3% of the world population. Treatment of HCV infected patients with interferon combination therapy remains suboptimal. Various clinical, laboratory and histological parameters are used to predict non-response to treatment. Age, gender, Body Mass Index, steatosis, biochemical markers and Histological Activity Index (HAI) are some of them. The role of baseline biochemical parameters and hepatocyte injury towards achieving better response is a debatable topic.

The objective of our study was to determine the importance of hepatic steatosis, serum Alanine Aminotransferase (ALT) levels and Histological Activity Index as a predictor of response to conventional interferon plus ribavirin therapy in treating chronic HCV infection in Pakistan. This has become important because predictors of response to therapy serve as a decision tool for physicians to help identify patients who are likely or unlikely to achieve a Sustained Virological Response (SVR). This will help to consider pre-treatment counseling in those patients with a reduced likelihood of successful therapy via risk stratification considering financial constraints of general population exposed to HCV in Pakistan. Moreover, such patients can be offered newer antivirals right at the beginning.

Patients and Methods

Interferon naïve adults of both gender and all ages seen at liver clinic, KRL hospital with chronic Hepatitis C genotype-3 infection were included in the study. Patients were required to have a detectable serum HCV RNA (ribonucleic acid) on Polymerase Chain Reaction (PCR) at presentation. They were also required to have a negative pregnancy test and having minimum values for hemoglobin of 120 g/l for women and 135 g/l for men; leukocyte count ≥ 4x10⁹/l and platelet count ≥ 150 x 10⁹/l . It was also required that they have normal bilirubin, albumin, urea and creatinine levels. Patients were excluded if they had decompensated cirrhosis, other causes of liver disease and/or were Hepatitis B surface antigen or Human Immunodeficiency Virus positive. Alcoholics, patients
with seizure disorders, cardiovascular disease, hemoglobinopathies, thyroid disease, clinically relevant depression or any other psychiatric disease were also excluded. Other exclusion criteria included hemophilia, poorly controlled diabetes, autoimmune disease, previous organ transplant and/or being unable to use contraception.  

The primary measure of efficacy was Sustained Virological Response. The other parameter used to depict effectiveness was End of Treatment Response (ETR). Extent of liver injury was assessed on the basis of HAI, degree of steatosis and biochemical marker for hepatocyte damage i.e., Alanine Aminotransferase levels.

Treatment naïve, HCV RNA positive patients with chronic hepatitis C were given conventional interferon alpha 2b (3 Million IU) thrice weekly plus ribavirin (1000-1200 mg/day) for 24 weeks. Treatment was stopped in 3 individuals due to serious side effects. Rest of the 36 either did not come for follow-up or had important data missing and were excluded from the study results. Response to treatment was assessed via ETR. Extent of liver injury was assessed via the classification described by Kleiner et al. 9

The extent of liver inflammation and fibrosis was defined using the Histologic Activity Index (HAI) i.e., no (0), minimal (1-4), mild (5-8), moderate (9-12) or severe (13-18). 10 Multivariate analysis was done by forward stepwise logistic regression keeping a significant p value < 0.05.

Results

Male individuals constituted 31.3% (n=152) of the population while 68.9% (n=337) were females. Mean age of the cohort was 44.33 ± 9.11 years and mean BMI was 27.51 ± 7.04 kg/m². Mean base line hemoglobin was 13.2 ± 1.84 g/l, platelet count was 227 ± 84 x 10⁹ /l and mean leukocyte count was 6.7 ± 1.75 x 10⁹ / l. Mean Alanine Aminotransferase level was 73.74 ± 65.27 IU/l. Sustained Virological Response was achieved by 61% (n=298) individuals while End of Treatment Response by 83.4% (n=408) (Table 1 &2). All subjects had some degree of steatosis and hepatic inflammation on biopsy. None had minimal HAI. The spectrum of HAI varied from 'mild' to 'marked' while that of steatosis from 'minimal' to 'severe' (Table 3). On univariate analysis, mild hepatic inflammation and fibrosis i.e., low HAI (≤8), moderate/severe (≥9) or presence of steatosis, minimal to mild (≤33%), moderate (>33%-66%) or severe (≥66%) grade of hepatic steatosis was a significant predictor of both a good ETR as well as SVR. Minimal to mild degree of steatosis (≤33%) was a predictor of better SVR but not ETR (Table 3).

On multivariate analysis, mild hepatic inflammation and fibrosis (HAI≤8) was a significant predictor of good ETR and SVR. Minimal to mild degree of steatosis (≤33%) was a predictor of both a good ETR as well as SVR. Minimal to mild degree of steatosis (≤33%) was a predictor of better SVR but a poor predictor of ETR (Table 2 &3). Baseline Alanine Aminotransferase level was not significantly related to either SVR (p=0.11) or ETR (p=0.76). Grades of hepatic steatosis varied from mild to severe (Figure 1). Grades of hepatic inflammation and fibrosis varied from minimal to marked (Figure 2).

Table 1: Outcome at end of treatment response (ETR)

<table>
<thead>
<tr>
<th>Response</th>
<th>No (%)</th>
</tr>
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<tbody>
<tr>
<td>Complete response</td>
<td>408 (83.4)</td>
</tr>
<tr>
<td>Breakthrough non responders</td>
<td>69 (14.1)</td>
</tr>
<tr>
<td>Non responders</td>
<td>12 (2.4)</td>
</tr>
</tbody>
</table>
Discussion

Chronic infection with hepatitis C virus is a global health problem. The burden of disease in our region is far more than the western community. 1 Treatment of chronic HCV infection with interferon plus ribavirin combination therapy remains suboptimal. Different studies describe predictors of response to interferon combination therapy to select patients who would benefit most from the treatment. 2 Our study describes significance of hepatic steatosis, hepatic inflammation and fibrosis and serum ALT level as a predictor of response to interferon therapy. According to different researchers, hepatic steatosis has a negative influence on SVR. SVR for patients with significant steatosis is lower. 3,11 In our study, univariate analysis showed that lower degree of hepatic steatosis (≤33%) is a significant predictor of achieving better SVR (p=0.00). However, it was found to be a poor predictor of ETR (p=0.99). Multivariate analysis yielded similar results.

According to Kojima et al. (2001), histological...
improvement is more rapid in patients who achieve SVR than in those who biochemically improve but remain seropositive for HCV. 5 Only the ones with SVR exhibit complete cure histologically. While in patients whose ALT level decrease but SVR is not achieved, liver fibrosis remains unchanged or shows progression. 5, 6 Univariate analysis for our study showed mild hepatic inflammation and fibrosis i.e., low HAI (≤8) to be a significant predictor of better ETR (p=0.00) as well as better SVR (p=0.00) (Table 2). Low HAI (≤8) was found to be a significant predictor of achieving better ETR and SVR on multivariate analysis as well (p=0.00) (Table 2). On the other hand, high HAI i.e., >12 was associated with a higher chance of eventually ending up (at SVR stage) as a non-responder (p=0.00) (Table 2).

Table 4: Baseline hepatocellular inflammation and fibrosis (HAI) as a predictor of response to interferon combination therapy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HAI as predictor of ETR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR % (n)</td>
<td>BTN % (n)</td>
</tr>
<tr>
<td>Minimal to mild</td>
<td>88.7 (362)</td>
<td>17.3 (12)</td>
</tr>
<tr>
<td>Moderate</td>
<td>9.0 (37)</td>
<td>26.0 (18)</td>
</tr>
<tr>
<td>Marked/Severe</td>
<td>2.2 (9)</td>
<td>56.5 (39)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (69)</td>
<td>100 (12)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HAI as predictor of SVR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CR % (n)</td>
<td>R % (n)</td>
</tr>
<tr>
<td>Minimal to mild</td>
<td>77.5 (231)</td>
<td>29.0 (32)</td>
</tr>
<tr>
<td>Moderate</td>
<td>15.1 (45)</td>
<td>32.7 (36)</td>
</tr>
<tr>
<td>Marked/Severe</td>
<td>7.3 (22)</td>
<td>51.8 (42)</td>
</tr>
<tr>
<td>Total</td>
<td>100 (298)</td>
<td>100 (110)</td>
</tr>
</tbody>
</table>

ETR=End of Treatment response; SVR=Sustained Virological Response.CR=Complete Responders; BTN=Break-Through Non-Responders; NR=Non-Responders; R=Relapsers; * = statistically significant; U=univariate; M=multivariate.

According to Hung et al. (2002), delayed normalization of serum ALT levels does not predict SVR in patients treated with combination of interferon plus ribavirin. 4 They showed that there is no difference in SVR between patients with or without early normalization of ALT level. 4 To our observation, the significance of baseline ALT as an independent predictor of response has not been studied previously in South-East Asia where viral characteristics differ from rest of the world i.e., genotype 3 is more common. In our study, baseline ALT was not a significant predictor of either achieving an ETR (p=0.76) or SVR (p=0.11). The value of this biochemical marker has been controversial 2, 4 in the past and based on our results, we would like to make the comment that baseline ALT is a poor predictor of response to interferon combination therapy.

A lower degree of steatosis and HAI can significantly predict a better response to antiviral therapy. Greater extent of baseline hepatic damage i.e., higher HAI (>12) and marked steatosis (>66%) are associated with a higher possibility of failure to achieve an SVR. Based on these observations, pre-treatment counseling can be done in patients unlikely to achieve an SVR and better antivirals can be opted for in the first place. This will not only serve to reduce the cost of treatment but also spare them of the untoward effects of multiple treatments that might have to be used in case of failure of one type. Moreover, such patients can be offered newer antivirals right at the beginning with the aim to achieve better outcomes including sofosbuvir. By having a predictive risk assessment via baseline HAI and steatosis, risk stratification can be done and patients can be offered treatment accordingly as all patients in a third world country like Pakistan cannot afford to follow best available treatment strategy. Such a risk categorization can help reduce the burden of cost on poor community while providing them intelligently with suitable treatment plans.

Conclusion

Lower extent of steatosis (≤33%) and low HAI (≤8) is a significant predictor of better response to conventional interferon combination therapy for HCV Genotype 3. Hepatic steatosis >66% and HAI >12 predicts failure to respond.

References


