RESPONSE TO STANDARD INTERFERON A2b AND RIBAVIRIN
COMBINATION THERAPY IN CHRONIC HEPATITIS C
TREATMENT NAÏVE PATIENTS

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Background: Treatment of Chronic Hepatitis C is now well established with conventional interferon or pegylated interferon in combination with ribavirin. Peginterferon Alfa and Ribavirin for 6 to 12 months is currently approved initial therapy, which is expensive. Response of our patients to standard Interferon-alpha-2b and ribavirin for 24 weeks have been studied. The objective of this study was to assess Sustained Viral Response (SVR) with standard Interferon A2b and Ribavirin combination treatment in chronic Hepatitis C patients. Methods: This quasi-experimental study was conducted at Combined Military Hospital, Quetta from Jan 2006 to Jun 2007. One hundred and three patients, with 20–60 years of age suffering from chronic Hepatitis C were selected on the basis of raised ALT, positive anti-HCV antibodies, evidence of viraemia by quantitative PCR for HCV RNA and liver biopsy. All patients were started on same brand of Interferon alpha-2b, 3 MIU subcutaneously, thrice weekly and oral Ribavirin (1,000–1,200 mg/day) for 24 weeks. End treatment response (ETR) after completion of treatment and SVR six months after ETR were recorded. Results: The 103 patients, 85 males and 18 females with mean age of 21–48 years completed the treatment for 24 weeks. Mean ALT was 96.17 (SD±49.98). End treatment response (ETR) was 89.3% (p=0.032). Sustained Viral Response after 6 months of treatment was 86.4% (p=0.034). Conclusion: Standard Interferon and Ribavirin had excellent SVR. It is effective as well as economical treatment in Chronic Hepatitis C patients.

Keywords: Chronic Hepatitis C, Interferon A2b, Ribavirin, SVR

INTRODUCTION

Hepatitis C virus (HCV) is an important causative agent of parenteral non-A-non-B hepatitis. Choo and co-workers of Chiron Co-operation Group discovered HCV as a new viral agent in 1989. The World Health Organization estimates that approximately 3% of the world population has been infected with HCV. There are about 170 million patients with HCV worldwide and three to four million individuals are newly diagnosed each year. In Pakistan, the prevalence of HCV varies widely, but generally is in the range of 3–13%. It is estimated that approximately ten million people (6% of the population) have been living with HCV infection.

Diagnostic test for chronic hepatitis C is persistently raised serum ALT levels; however it is non-specific and is not a reliable indicator of the disease. Elevated serum ALT levels indicate active disease of liver but 25% of chronic hepatitis C patients may have normal or widely fluctuating levels. Serologic and nucleic acid-based molecular assays are available for the diagnosis of hepatitis C. Serologic tests are sufficient when chronic hepatitis C is expected, with a sensitivity of more than 99% in the 3rd generation assays. Positive serologic results require PCR in order to discriminate between chronic hepatitis C and resolved HCV infection from the past. Liver biopsy, an invasive procedure though not necessary for diagnosis, but assess necroinflammatory damage to liver parenchyma and shows severity of the disease. Liver biopsies are scored by various scoring systems, e.g., Knodell Histopathological Index (HPI) based on inflammatory, necrotic and fibrotic changes.

The treatment of CHC is now well established with conventional interferon or pegylated interferon in combination with Ribavirin. Patients with chronic hepatitis C, response rates to interferon-based therapy are heterogeneous and in ‘easy-to-treat’ genotypes 2 and 3, SVR is observed in about 80% of patients with just 24 weeks of therapy, a lower dose of Ribavirin, and either standard interferon or peginterferon.

The aim of this study was to determine the response of standard Interferon A2b and Ribavirin in Chronic Hepatitis C patients in our setup.

METHODOLOGY

This quasi-experimental study was conducted at Combined Military Hospital Quetta from Jan 2006 to Jun 2007. One hundred and three patients (80 males and 27 females) who were treatment naïve and non cirrhotic were included. Age ranges between 18–48 years were included by non-probability convenience sampling while reporting to outpatient department. Written informed consent was taken from all patients. Patients with persistently raised serum ALT (>42 IU/L), positive HCV antibodies by 3rd generation ELISA, positive HCV RNA by polymerase chain reaction by HCV Real-TM Quant SC were included. Liver biopsy compatible with
the diagnosis of chronic Hepatitis C on the basis of Knodell HPI scoring system was also done. Patients co-infected with HBV, decompensated cirrhosis, anaemia, other medical illnesses, depression and pregnancy were excluded from this study.

All patients were hospitalised for one to two weeks or longer if required to see safety and tolerance of treatment. After detailed history and physical examination, blood complete picture, liver function tests, coagulation profile and chest x-rays were done. Liver biopsy was done earlier with written consent after ultrasound marking and Knodell HPI was recorded. All patients were started on same brand of medicines with Injection Interferon (IFN) A2b (3 MIU subcutaneously, thrice weekly) and oral Ribavirin (1,000–1,200 mg/day) were given for 24 weeks. The medicines were provided free of cost by the institution. All patients were advised fortnightly regular follow up in out patient department. Biochemical and haematological profiles were done to see compliance and complications. After completion of treatment PCR for HCV RNA was done to see end treatment response (ETR) and six months later for sustained viral response (SVR) which is our primary end point.

Statistical analysis was done using SPSS-15. Descriptive statistics like mean and standard deviation was calculated for quantitative variables like age while frequency with percentages was used for qualitative data like gender, ETR and SVR. Chi-square test was applied to compare PCR findings. Statistical significance was determined at p<0.05 for all comparisons.

RESULTS

One-hundred-three treatment naïve patients completed the treatment for 24 weeks (Table-1). They were followed up for 6 months after treatment to see sustained viral response (SVR). Patients who declined to undergo treatment or follow up were excluded.

Eighty-five (82.5%) patients were males and 18 (12.5%) were females with age ranged from 21–48 years. The mean age was 31.75±5.87 years. ALT levels ranged from 44 to 385 U/L with mean value of 96.17±49.98.

Measurements of disease activity (grade) and fibrosis (stage) were calculated on liver biopsy by Knodell Histopathological Index (HPI) scoring system. Liver inflammation was graded as no inflammation (0) to minimal (1–4), mild (5–8), moderate (9–12) and marked (13–18). Out of 103 patients, 7 patients (6.8%) had minimal disease, 67 patients (65%) had mild disease while 29 patients (29%) had moderate disease on liver biopsy. None of them had advanced disease. Similarly liver fibrosis was scored as stage 0 to stage 4. Stage 0 or no fibrosis, was present in 3 (2.9%) patients, mild fibrosis (Stage-1) was seen in 94 (91.3%) patients and stage-3 (severe fibrosis) was present in 6 (5.8%) patients. Stage-4 or cirrhosis was not seen in our patients.

Baseline PCR for HCV RNA showed level of viraemia as low, moderate and high grade. 21 (20.3%) patients had low grade viraemia, 57 (55.3%) patients had moderate grade and 25 (24.3%) patients had high grade viraemia. End Treatment Response (ETR) was achieved in 92 patients (89.3%) with p-value 0.03 (chi-square). There were 75 (81.5%) males and 17 (18.5%) females. There were 11 patients (10.7%) who were non responder, i.e., detectable PCR at the end of 24 weeks of treatment. SVR (sustained viral response) was seen in 89 patients (86.4%) with p value of 0.034 (χ2-test). There were 89 patients, 72 (80.8%) males and 17 (19.2%) females.

Table 1: Patients’ demography and baseline features

<table>
<thead>
<tr>
<th>Variables</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients (n)</td>
<td>103</td>
</tr>
<tr>
<td>Males</td>
<td>85 (82.5%)</td>
</tr>
<tr>
<td>Females</td>
<td>18 (17.5%)</td>
</tr>
<tr>
<td>Mean±SD age (years) (range 21–48)</td>
<td>31.75±5.87</td>
</tr>
<tr>
<td>Mean±SD ALT IU/L (range 44–385)</td>
<td>96.17±49.98</td>
</tr>
<tr>
<td>HCV RNA/ Viraemia Grade</td>
<td></td>
</tr>
<tr>
<td>Low Grade</td>
<td>21 (20.4%)</td>
</tr>
<tr>
<td>Moderate Grade</td>
<td>57 (55.3%)</td>
</tr>
<tr>
<td>High Grade</td>
<td>25 (24.3%)</td>
</tr>
<tr>
<td>Biopsy Grading (Inflammation)</td>
<td></td>
</tr>
<tr>
<td>Minimal Grade</td>
<td>07 (6.8%)</td>
</tr>
<tr>
<td>Mild Grade</td>
<td>67 (65%)</td>
</tr>
<tr>
<td>Moderate Grade</td>
<td>29 (28.2%)</td>
</tr>
<tr>
<td>Biopsy Staging (fibrosis)</td>
<td></td>
</tr>
<tr>
<td>No Fibrosis</td>
<td>3 (2.9%)</td>
</tr>
<tr>
<td>Mild Fibrosis</td>
<td>94 (91.3%)</td>
</tr>
<tr>
<td>Moderate Fibrosis</td>
<td>06 (5.8%)</td>
</tr>
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</table>

ALT=Alanin Amino-Transferase, SD=Standard Deviation

DISCUSSION

HCV is a tremendous health problem not only in Pakistan but also worldwide. Prevalence of hepatitis C is increasing worldwide. Adherence to therapy, decreased viral load, genotype 3, female sex, young age and lower body weight are associated with better viral response to therapy.12 In all prospective treatment studies, genotype is the strongest predictor of response.10 In published reports of distribution of different HCV genotypes in Pakistani population, the most predominant HCV genotype is genotype 3 (75–90%), followed by genotypes 1, 2, and 5.13,14 Peginterferon Alfa (PEG-IFN) and Ribavirin (RBV) for 6–12 months is currently approved initial therapy for patients with chronic HCV infection, which is expensive. But our study was conducted with conventional Interferon Alfa-2b and Ribavirin for 6 months to assess the end of treatment as well as sustained viral response.

In our study, 103 patients after completing 24 weeks of treatment, ETR was 89.3% (p=0.03). Ninety-two (89.3%) patients showed no detectable virus in serum. There were 75 (81.5%) males and 17 (18.5%) females. Our results are not only comparable to but also showed better response when compared with the local results. Agha Babar Hussain et al15 reported ETR of
86.5%, Amina Nadeem12 84%, Javed Iqbal Farooqi16 86.3% and Sundeep Mukarjee20 reported a response rate of 90%.

Pegylated interferon, now a days is becoming the interferon of choice in developed countries.7 However in our setting, standard interferon gives better sustained viral response of more than 80%.8 Sustained response reported by various local studies, e.g., Ashraf et al9, Sarwar et al14, and Javed Iqbal Farooqi16 was 79%, 82%, and 85.3% respectively. Sundeep Mukarjee20 also reported response rate of 80% (Table-2). SVR in our study was primary outcome. It was 86.4% (p=0.034) which was statistical significant. Like ETR, our study also showed better sustained response. This could be due to the fact that our patients were young, and probably due to treatment responsive genotype 3 in our patients.12

Table-2: Comparison of our work with others

<table>
<thead>
<tr>
<th>Study</th>
<th>ETR</th>
<th>SVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Our Study</td>
<td>89.3%</td>
<td>86.4%</td>
</tr>
<tr>
<td>Amina Nadeem12</td>
<td>84%</td>
<td>81–86%</td>
</tr>
<tr>
<td>Agha Baber Hussain13</td>
<td>86.5%</td>
<td>76%</td>
</tr>
<tr>
<td>Javed Iqbal Farooqi16</td>
<td>86%</td>
<td>81–86%</td>
</tr>
<tr>
<td>Sundeep Mukarjee20</td>
<td>90%</td>
<td>80%</td>
</tr>
</tbody>
</table>

Table-2: Comparison of our work with others

Our study showed that younger patients with early liver disease having mild inflammation and fibrosis on liver biopsy had better response to combination therapy as compared to patients with advanced disease.10 This observation is supported by Nauman Kashif and Batool.2 They showed that patients with early liver disease as evidenced by stage 1 and 2 (mild to moderate fibrosis) on liver biopsy had better response to standard Interferon combination therapy as compared to patients with advanced fibrosis (stage 3 and 4).

CONCLUSION

Chronic Hepatitis C patients had better sustained viral response to cheaper standard Interferon and Ribavirin therapy.

REFERENCES


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