RELATIONSHIP BETWEEN FIBROSIS SCORE AND RESPONSE TO INTERFERON ALFA & RIBAVIRIN COMBINATION THERAPY IN CHRONIC HCV INFECTION

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ABSTRACT

Objective: To compare the response to Interferon Alfa (IFN) and Ribavirin (RBV) combination therapy in patients of chronic HCV infection with fibrosis stage 1 (F1) & stage 2 (F2) with fibrosis stage 3 (F3) & stage 4 (F4).

Study Design: Quasi-experimental study.

Place and Duration of study: Military Hospital, Rawalpindi, from Jan 2004 to Jun 2004.

Patients and Methods: Forty patients of chronic hepatitis C were selected on the basis of raised ALT, presence of anti-HCV antibodies, detection of viral RNA on PCR and liver biopsy. They were divided into 2 groups on the basis of stage of fibrosis. Group A constituted 20 patients with fibrosis stage 1 & 2 and group B constituted 20 patients with fibrosis stage 3 & 4. Interferon Alfa 03 Million units subcutaneously three times a week and Ribavirin 1200 mg orally per day in divided doses for patients who weigh 75 kg and 1000 mg for those weighing less than 75 kg for six months was administered. Polymerase chain reaction (PCR) for HCV RNA was performed at 0 and 6th months at Armed Forces Institute of Pathology Rawalpindi.

Results: At completion of treatment, HCV–RNA levels in serum were not detectable in 14 of 20 (70%) patients in group A as compared to 07 of 20 (35%) patients in group B who received interferon alpha and ribavirin combination therapy.

Conclusion: Patients with early fibrosis on liver biopsy have better response to IFN-Ribavirin therapy compared to patients with advanced fibrosis.

Keywords: Chronic hepatitis C, Interferon Alfa, Ribavirin, PCR.

INTRODUCTION

Hepatitis C virus (HCV) infects an estimated 170 million persons worldwide, approximately 3% of the world's population and thus represents a viral pandemic [1,2]. Infection can result in both acute and chronic hepatitis. Liver disease caused by the hepatitis C virus progresses in stages, generally speaking inflammation is the precursor to fibrosis, the critical transition point in the development of chronic liver disease. Fibrosis, more than inflammation, predicts the progression to irreversible liver disease.

The presence of bridging fibrosis or cirrhosis markedly reduces the expected response rate to antiviral therapy [3]. Cirrhosis is found in approximately 29% of unselected cases of HCV infection that come to biopsy. Patients with stage 0 and 1 fibrosis very rarely progress to cirrhosis and patients with stages 2, 3, and 4 with advancing fibrosis are the patients that should be targeted and treated. In principle, all patients with chronic HCV infection are candidates for antiviral therapy [4]. The primary goal is to eradicate the hepatitis C virus which can be achieved in over 50% of patients and in patients with genotypes 2 or 3, well over 80% of patients [5].

Combination therapy with Ribavirin and Interferon alfa-2b for six months is approved for the treatment of patients with chronic hepatitis C who have compensated liver disease previously untreated with Alfa Interferon or who have relapsed following interferon monotherapy [1]. Combination therapy has better response rate in the treatment of Chronic Hepatitis C than Interferon monotherapy [6-8] and it is not

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associated with increased side effects [9]. No significant differences were observed between 24 and 48 weeks of therapy in patients infected by genotype 2 or 3 [10,11]. Sustained responders (SR) to treatment have an actual reduction in fibrosis and even non-sustained responders (Non-SR) appear to have a slower rate in the progression of fibrosis [12-14].

The population in Pakistan is having the problem at larger scale as compared to the western world [15], and is the major cause of HCC compared to HBV infection.

The purpose of this study was to compare the response to Interferon Alfa and Ribavirin combination therapy in patients of chronic HCV infection with fibrosis stage 1 and stage 2 with fibrosis stage 3 and stage 4.

PATIENTS AND METHODS

This quasi-experimental study was conducted in the department of Gastroenterology unit-III, Military Hospital Rawalpindi, from Jan 2004 to Jun 2004. Forty patients of chronic hepatitis C were selected and they were divided into 2 groups on the basis of stage of fibrosis. Group A constituted 20 patients with fibrosis stage 1 & 2 and group B constituted 20 patients with fibrosis stage 3 & 4. All the patients reporting in out-patient department aged 20-60 yrs of both sexes, having positive Anti HCV antibodies, presence of HCV RNA by PCR (table 1), with Knodell Histological stage 1-4 on liver biopsy (table 2) and acceptance to participate in the study by informed consent were included in the study. Patients simultaneously infected with Hepatitis B Virus or HIV infections, patients already treated with Interferon therapy, patients with other chronic illnesses like chronic renal failure, anaemia, cardiac failure & malignancy, patients with decompensated cirrhosis and pregnancy were excluded from the study.

All patients received a detailed history and clinical examination to evaluate co-morbidity. PCR for HCV RNA was performed at 0 and 6th months at AFIP Rwp. Sera were collected from brachial veins of all patients under strict aseptic measures and Liver function test and full blood counts were performed at AFIP Rwp on fortnightly basis to monitor response to treatment and adverse effects of therapy. All the HCV PCR positive patients were subjected to liver biopsy to document the activity and stage of the disease. Both of these groups were treated with conventional Interferon Alfa 3 MU subcutaneously thrice weekly and 1200 mg of Ribavirin orally in divided doses for patients who weigh 75 kg or more and 1000 mg orally for those weighing less than 75 kg daily for 06 months.

The data was compiled and analyzed by using Statistical Package for Social Sciences (SPSS) version 10.0. Rational descriptive statistics, frequency and percentage were computed for presentation of qualitative variables like sex, lab finding like PCR for HCV RNA before and after Interferon & Ribavirin therapy etc. Qui square test of significance was applied to compare PCR finding before and after Interferon & Ribavirin therapy at $p < 0.05$ level of significance. Qualitative variables like age etc. were percentages by means +/- standard deviation.

RESULTS

In this study a total of 40 patients were enrolled of proven Chronic Hepatitis C infection at Military Hospital Rawalpindi. The mean age was 37.09 year with SD 12.78 in group A and 40.20 with SD 12.16 in group B with almost equal distribution in both the groups. The males were 75% while females being 25%. At the end of 06 months of therapy PCR for HCV RNA was performed in both groups, as predictor to response to Interferon & Ribavirin therapy. In 14 out of 20 treated patients from group A (70%), PCR for HCV RNA became negative indicating end of treatment response (Table 3). In group B 07 out of 20 patients (35%) who received treatment became HCV PCR negative indicating ($p=0.027$). This value is statistically significant ($p<0.05$).

Treatment with interferon and ribavirin was the strongest predictor of a response. End of treatment response was unrelated to age, sex. Regardless of the viral load at base line or

the presence of cirrhosis or bridging fibrosis at base line, the response was better in patients who were treated with interferon and ribavirin.

Normalization of serum alanine aminotransferase values was associated with undetectable levels of serum HCV RNA in most patients who had end of treatment responses. Serum ALT level came down to normal in 18 of 20 patients (90%) in group A and 14 of 20 patients (70%) in group B.

evidenced by stage 1 & 2 (mild to moderate fibrosis) on liver biopsy have better response to Interferon therapy as compared to patients with advanced fibrosis (stage 3 & 4).

Results of this study are comparable to the results of the study conducted by Moriyama et al [5], in which patients were treated with Interferon alpha-2b (IFN) and Ribavirin (RBV), had sustained virological response (SVR) of 34.9% in genotype 1 and 82.5% in genotype 2 and 3.

Table-1: Interpretation of Hepatitis C Testing

Anti-HCV	HCV RNA (PCR)	Interpretation
Negative	Negative	No infection
Positive	Positive	Acute or chronic infection
Negative	Positive	Early infection Chronic infection in immunosuppressed
Positive	Negative	Resolved infection Chronic infection with low-level viremia False-positive-antibody Passively acquired antibody

(Reference: National Institutes of Health Consensus Development Conference Statement: management of hepatitis C: Hepatology 2002; 36: S3-S20.)

Table-2: Common Histologic Grading and Staging Scales

Scales	Necroinflammation	Fibrosis	Total Score
Histology Activity Index (HAI)	0 to 18	0 to 4	0 to 22
Ishak Modified HAI	0 to 18	0 to 6	0 to 24
Metavir	0 to 3	0 to 4	0 to 7

(Reference: National Institutes of Health Consensus Development Conference Statement: management of hepatitis C: Hepatology 2002; 36: S3-S20.)

Table-3: Recovery With Treatment Group – A & B Crosstabulatuion

	Groups		Total
	Group A	Group B	
Recovered	14	07	21
Not Recovered	06	13	19
Total	20	20	40

Group A: Fibrosis Stages 1 & 2: Group B: Fibrosis Stages 3 & 4

DISCUSSION

Infection with the HCV can result in both acute and chronic hepatitis. Sixty to eighty percent of cases develop chronic hepatitis, cirrhosis occurs in up to 50 percent of chronically infected patients, and about 15-20 percent will finally develop hepatocellular carcinoma (HCC) [4]. The currently approved initial therapy for patients with chronic HCV infection consists of treatment with Peginterferon alfa (PEG-IFN) and Ribavirin (RBV) for 06 to 12 months. This study was conducted with conventional Interferon Alfa and Ribavirin for 06 months duration to asses the end of treatment response. This study shows that patients with early liver disease as

Results of this study are also comparable to the results of the study conducted by Schalm, et al [9], in which patients without cirrhosis who were treated with IFN-RBV had sustained virologic response rate of 33% in genotype 1 and 65% in genotype 2 and 3. While in patients with cirrhosis, sustained virologic response with IFN-RBV was 7% in genotype 1 and 24% in genotype 2 and 3.

Our study shows better response to Interferon Alfa-Ribavirin combination therapy compared to studies conducted by McHutchison, et al (16) and Davis, et al (17). In studies conducted by McHutchison and Davis the sustained virologic response ranged

from 31-38% with Interferon Alfa combination therapy.

The confounding factors in our study which led to the better response to interferon Alfa combination therapy were, the end point that was end of treatment response rather than sustained virologic response in our study and prevalence of genotype 3 in this part of the world [1]. Further the group B included patients with advanced liver disease which included both patients with marked fibrosis and early cirrhosis. The response rate to Interferon combination therapy in genotype 2 and 3 ranges from 50-70% and no significant differences were observed between 24 and 48 weeks of therapy in patients infected by genotype 2 or 3 [10,11].

The results of our study show better response with IFN-RBV than results shown by three large trials of Peginterferon and Ribavirin conducted by Manns, et al, Fried, et al, and Di Bisceglie, et al [18-20]. Sustained viral eradication rates in patients who received PEG-IFN and RBV ranged between 48% and 56%, and rates of 29% to 47% among those who received standard IFN and ribavirin.

The study results are also better than shown by Heathcote, et al [3] in his study, in which treatment lasted for 48 weeks and was followed by a 24-week follow-up period. The response rate was 8% at 72 weeks in IFN-Ribavirin treated group.

Although no local study is available which directly compares the response to IFN-RBV with reference to fibrosis stage on liver biopsy, two local studies which showed the response rate of IFN-RBV therapy in our population are from Niaz [7] and Shaikh, et al [8]. In his study Shaikh achieved a response rate of 71.4% to combination therapy, while it was 75% in study by Niaz [7].

CONCLUSION

Interferon alfa and ribavirin has better response rate in patients of chronic hepatitis C with early fibrosis on liver biopsy compared to patients with advanced fibrosis on liver biopsy.

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