

## EFFICACY OF COMBINED INTERFERON ALPHA AND RIBAVIRIN THERAPY IN PATIENTS OF CHRONIC HEPATITIS C

Amina Nadeem, Muhammad Aslam, \*Tassawar Hussain, Muhammad Mazhar Hussain, \*\*Saadat Ali Khan,

Department of Physiology and \*Medicine, Army Medical College, Rawalpindi, \*\*Department of Physiology, Foundation University Medical College, Rawalpindi.

**Background:** This study was carried out to determine the efficacy of combined interferon alpha and ribavirin therapy in patients of chronic hepatitis C. **Methods:** This study was conducted at Military Hospital Rawalpindi and Army Medical College, Rawalpindi from January 2006 to Feb 2007. One hundred and sixty seven non cirrhotic chronic hepatitis C patients were studied. The patients were grouped into study group (n=107) and control group (n=60). The patients had persistently raised serum aminotransferase (ALT), positive HCV antibodies by 3<sup>rd</sup> generation ELISA, positive HCV RNA by polymerase chain reaction. Study group patients had positive histopathological findings on liver biopsy on basis of Knodell histopathological index (HPI). At weeks 0, 12 and 24, blood samples were taken for the assay of serum alanine transferase (ALT) and serum aspartate transferase (AST) levels in both the groups. Study group patients underwent 24 weeks Interferon and Ribavirin combination therapy and subsequently followed up for the response to treatment by the assay of HCV RNA by polymerase chain reaction at weeks 24. Control group included the patients without treatment plan but they also underwent screening for the same liver function tests. **Results:** Patients of chronic hepatitis C (80 males and 27 females) had age range 18-48 years. After 24 weeks of INF and ribavirin therapy, 86% patients showed favourable response to treatment manifested by negative HCV RNA polymerase chain reaction. **Conclusions:** Treatment with Interferon and ribavirin combination therapy for 24 weeks produces significant virological response in patients of chronic hepatitis C at the end of treatment.

**Keywords:** Chronic hepatitis C, interferon, ribavirin.

### INTRODUCTION

According to World Health Organization, approximately 170 million individuals of the world population are diagnosed as infected with Hepatitis C virus (HCV).<sup>1</sup> Approximately four million individuals in the United States of America are suffering from this disease and it is the most common blood-borne infection in USA.<sup>2</sup> The prevalence rate of anti HCV antibodies in Pakistan reported mostly by hospital based studies in patients, blood donors and in general population is 1 to 25.7%.<sup>3-9</sup>

National Institute of Health (NIH) has recommended interferon (INF) as the standard therapy for chronic hepatitis C.<sup>13</sup> It is given subcutaneously at doses of three million units three times a week for 24 weeks.<sup>10</sup> Exogenous INF is a group of cytokines that exhibit antiviral effects via immunomodulation and ribavirin is a guanosine analogue.<sup>11</sup> Combination therapy with INF- alpha and Ribavirin has resulted in two to three folds improvement in virological response to the disease.<sup>12-13</sup> Response rates have been found to be favorable in 80-85% of CHC patients with genotypes 2 and 3 as is predominant in Pakistan.<sup>14</sup> In genotypes 1 and 4 as is prevalent in America and Europe, response rates have been found to be 60-70% with INF and Ribavirin and may require 48 weeks treatment.<sup>15</sup>

Pegylated interferon has now replaced standard interferon alpha for chronic hepatitis C patients. Because of the predominance of genotypes 2 and 3 in Pakistan, the response rate to combination therapy with interferon plus Ribavirin is close to the result achieved with pegylated interferon.<sup>16</sup> It is therefore recommended to use pegylated interferon not routinely but only for non-responders.<sup>16</sup>

The aim of this study was to evaluate the efficacy of combined interferon alpha and ribavirin therapy in patients of chronic hepatitis C.

### MATERIAL AND METHODS

This prospective study was conducted at Military Hospital, Rawalpindi and Army Medical College, Rawalpindi from February 2006 to January 2007. Patients (167) of chronic hepatitis C had age range between 18 and 48 years. They had persistently raised serum amino transferase (ALT), positive HCV antibodies by 3<sup>rd</sup> generation ELISA and positive HCV RNA by polymerase chain reaction. Study Group patients had positive histopathological findings on liver biopsy consistent with diagnosis of chronic hepatitis C on basis of Knodell Histopathological Index (HPI). Exclusion criteria was, those treated previously with IFN and/or ribavirin, history of neoplastic, autoimmune, severe cardiac or pulmonary

disease, those currently using immunosuppressant and/or steroids and pregnant patients.

Subjects (n=167) were divided into two groups, study group comprising of 107 patients with planned treatment regimen of INF therapy, and control group comprising of 60 patients without treatment plan. Study group patients were treated with combination of Interferon alpha 2-b (INF) three million units subcutaneously three times a week and ribavirin 800-1200 mg orally daily for 24 weeks. Result values of serum alanine transferase (ALT) and S. Aspartate transferase (AST) levels were determined at weeks 0, 12 and 24 in both groups. Study group patients subsequently were followed up for response to treatment by HCV RNA by polymerase chain reaction at the end of treatment.

## RESULTS

In study group, among 107 patients of chronic hepatitis C (80 males and 27 females) had age range 18-48 years, 90 patients (86%) of chronic hepatitis C showed favorable response to combined Interferon and Ribavirin therapy depicted by HCV RNA by PCR at the end of 24 weeks treatment. Among those patients who responded to treatment, 88% at 12 weeks and 97% at the end of 24 weeks treatment showed normalization of S. Amino transferase ( $p$  value= 0.001) and Amino aspartate levels ( $p$  value= 0.001). In study group, baseline S. ALT ranged between 13 to 383 U/L (Mean= 93), at 12 weeks, between 14-201 U/L (Mean= 38 U/L) and at 24 weeks 11-170 U/L (Mean= 33 U/L). In control group mean S. ALT was 69, 63 and 68 U/L at weeks 0, 12 and 24 respectively. Seventeen patients (13 males out of 80 males and 4 females out of 27 females) did not respond to treatment after 24 weeks as depicted by positive HCV RNA by PCR. There was no statistically significant relation between response to treatment and gender of the patients. All the patients completed the 24 weeks regimen and none had to discontinue the therapy due to any of the side effects.

## DISCUSSION

Combination therapy with INF- alpha and ribavirin has been recommended<sup>10</sup> as the standard therapy for chronic hepatitis C and is given subcutaneously at doses of three million units three times a week for 24 weeks. The treatment response to INF mono therapy for 6 months is considerably less than the combination with INF and Ribavirin and is reported to vary from 20-35%.<sup>11</sup> The sustained virological response with INF mono therapy is reported to be 15-20% which can be increased to 30-35% with continuing treatment for 12 months.<sup>17</sup> Oral Ribavirin was tried as a single drug for HCV infection and

sustained response were not achieved although decrease in S. ALT was observed with Ribavirin.<sup>17</sup> Higher sustained responses were achieved with the combination of INF and Ribavirin in subsequent studies.<sup>18</sup>

**Table-1: S. Alanine aminotransferase levels in study and control groups at weeks 0, 12 and 24 of therapy**

S. ALT (U/L)	Study group (n=107) Mean $\pm$ SD	Control group (n=60) Mean $\pm$ SD	$p$
ALT-1 (Baseline)	92.82 $\pm$ 62.83	69.77 $\pm$ 41.36	0.06
ALT-2 (At 12 weeks)	38.6 $\pm$ 30.74	63.68 $\pm$ 30.08	0.001
ALT-3 (At 24 weeks)	33.85 $\pm$ 24.02	68.18 $\pm$ 54.6	0.001

**Table-2: S. Aspartate aminotransferase levels in study and control groups at weeks 0, 12 and 24 of therapy**

S. ALT (U/L)	Study group (n=107) Mean $\pm$ SD	Control group (n=60) Mean $\pm$ SD	$p$
AST-1 (Baseline)	59.65 $\pm$ 42.47	55.46 $\pm$ 34.7	0.07
AST-2 (At 12 weeks)	37.56 $\pm$ 18.03	52.56 $\pm$ 37.26	0.001
AST-3 (At 24 weeks)	33.80 $\pm$ 15.14	54.33 $\pm$ 32.50	0.001

**Table-3: Frequency of treatment response in patients of study group**

HCV RNA by PCR	Number of Patients	Male:Female	Percent	Valid%
Negative	90	66:24	86%	86%
Positive	17	14:03	14%	14%
Total	107	80:27	100%	00%

In our study, 90 out of 107 (86%) patients of chronic hepatitis C showed favorable response to combined Interferon and ribavirin therapy depicted by negative HCV RNA by PCR at the end of 24 weeks of treatment. Among those who responded to treatment, 88% at 12 weeks and 97% at the end of 24 weeks treatment showed normalization of S. Amino transferase and amino aspartate levels. The clearance of HCV RNA at 24 weeks instead of 12 weeks in serum is not related to non response and treatment should be continued for 06 months despite the persistence of HCV RNA at 12 weeks.

Our study supports a number of earlier studies<sup>11,13-15</sup> which showed that combination therapy is significantly effective in patients of chronic hepatitis C in our part of the world probably because of prevalence of genotypes 2 and 3. The definite evidence is not available as genotyping was not done in this study because of financial constraints. Ashraf *et al*<sup>17</sup> have reported 79 % of response rate at the end of 24 weeks. A sustained virological response of 71.4% with combination therapy has been reported by Wazir *et al*.<sup>11</sup> Sarwar *et al*<sup>12</sup> discovered a response

rate of 82% in their study. Farooqi *et al*<sup>14</sup> detected a response rate of 87.83% in HCV patients in their study. The low response rate of 65% reported by Herrine *et al*<sup>18</sup> may be due to genotype 1 which is predominant in European countries and is related to poor response rate and relapse of the disease. HCV is the major health problem and timely treatment should be given to achieve a favorable response.

## CONCLUSION

Combined Interferon and ribavirin therapy for 24 weeks produces significant virological and biochemical response in chronic hepatitis C patients. However, there was no relation between gender and the response to treatment.

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## Address for Correspondence:

**Dr. Amina Nadeem**, Department of Physiology, Army Medical College, Abid Majeed Road, Rawalpindi. Pakistan.

**Email:** nadeemamina@yahoo.com