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END OF TREATMENT AND BIOCHEMICAL RESPONSE TO INTERFERON AND RIBAVIRIN THERAPY IN CHRONIC HEPATITIS C PATIENTS

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ABSTRACT

OBJECTIVE: *To ascertain Biochemical and End of treatment response to interferon and Ribarvirin therapy in chronic hepatitis C patients.*
STUDY DESIGN: *Interventional and descriptive.*
PLACE AND DURATION: *The data was collected from district hospitals of various areas of Hyderabad from January 2008 to December 2008.*
MATERIAL AND METHODS: *Hepatitis C patients during the period from Jan 2008 and December 2008 were included. All studied patients were HCV RNA positive by PCR. Complete blood cell count, prothrombin time, ALT and serum albumin were done. None of the patients were cirrhotic as determined clinically and by ultrasound examination and co infected with hepatitis B virus. All studied patients received standard interferon 3 miu subcutaneously three times a week and ribavirin 1000 – 1200 mg/day for provided by Government of Sindh. HCV RNA was repeated after 12 weeks and 24 weeks of treatment. Biochemical, early virological and End of treatment response were assessed.*
RESULTS: *Out of 800 patients 766(95.8%) completed the 24 weeks of therapy. 34(4.2%) patients discontinued treatment in within 02 months. Early virological response was achieved in 735(95.9%) patients by negative HCV RNA while in 31(4.04%) patients HCV RNA remained positive at 12 weeks of therapy. End of treatment response was achieved in 740(96.6%) of patients by negative HCV RNA while 26(3.3%) of patients HCV RNA remained positive. There was a significant correlation between EVR and ETR (P value = 0.001, r = 0.913). Serum ALT becomes normal in 694(90.6%) at 12 weeks and 739(96.5%) of patients at 24 weeks of therapy. Statistically analysis was evaluated in statistical program SPSS version 16.0.*
CONCLUSION: *Chronic hepatitis C patients who have not been previously treated had excellent End of treatment and biochemical response to interferon and ribavirin therapy.*

KEYWORDS: Interferon, Ribavirin, chronic hepatitis C

INTRODUCTION:

Hepatitis C virus infection is the major cause of chronic hepatitis in Pakistan.[1,2] Chronic infection with Hepatitis C virus (HCV) is estimated to affect 170 million individual worldwide[3,4], and is one of the leading cause of chronic liver disease and related complications such as cirrhosis and Hepatocellular carcinoma.[5] The current prevalence in Pakistan varies from 3 to 7 percent in different parts of the country.[6] The problem in developing countries is compounded by the poor economical status of the patients who are unable to afford the expensive therapy.

National Institute of Health (NIH) has recommended interferon (INF) as the standard therapy for chronic hepatitis C[7] It is given subcutaneously at doses of three miu three times a week for 24 weeks[8]. Exogenous INF is a group of cytokines that exhibit antiviral effects via immunomodulation and ribavirin is a guanosine analogue[9]. Combination therapy with INF alpha and ribavirin has resulted in two to three folds improvement in virological response to the disease.[7, 10]

Response rates have been found to be favorable in 80 – 85% of CHC patients with genotype 2 and 3 as is predominant in Pakistan.[11] In genotype 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 required 48 weeks treatment1.[12] Pegylated interferon has now replaced standard interferon alpha for chronic hepatitis C patients. Because of the predominance of genotype 2 and 3 in Pakistan, the response rate to combination therapy with

interferon Plus ribavirin is close to the result achieved with pegylated interferon.[13] It is therefore recommended to use pegylated interferon not routinely but only for non responder.[13]

The aim of this study was to evaluate the biochemical and End of treatment response to interferon alpha and ribavirin therapy in Patients of chronic Hepatitis C.

PATIENTS AND METHODS:

In this study data was collected from district hospitals of various areas of Hyderabad from January 2008 to December 2008. 800 patients fulfilled the criteria for treatment. Age ranges between 15 to 55 years with no previous history of interferon and ribavirin therapy. They had persistently raised serum amino transferase (ALT), positive HCV antibodies by 3rd generation ELISA and positive HCV RNA by polymerase chain reaction. Liver biopsy was not mandatory. Exclusion criteria, those previously treated with IFN and ribavirin therapy, HBSAg positive, cirrhosis of liver, blood dyscrasia, sever cardiac or pulmonary disease. Auto immune disorders, preexisting psychiatric conditions and pregnancy, serum albumin less than 35 g/L, prothrombin time exceeding the normal limits or significant cytopenia were also excluded from this study. Hemoglobin level was more than 10gm / dl.Written informed consent was taken from all the patients. Patients were given combination of interferon 3 miu subcutaneously three times a week and ribavirin 1000-1200 mg/day for 24 weeks provided by Government of Sindh.

All patients were assessed in out patients setting for safety, tolerance and efficacy at the end of week 1, 2 than every 4 weeks for 24 weeks. Biochemical and Hematological profiles were checked initially fortnightly and than monthly for 24 weeks. Serum HCV RNA was done after 12 weeks and 24 weeks of treatment. The purpose of this study was to ascertain early virological and End of treatment response, defined as absence of HCV RNA at 12 weeks and 24 weeks of treatment while subjects positive for HCV RNA at the end of treatment were defined as non responder and normalization of serum ALT in these patient's.

TABLE NO. 1
DEMOGRAPHIC DETAILS OF PATIENTS (N = 766)

	Male (n = 214)	**Female (n = 552)**	**P value**
Age (in years)	34.8 + 11.98	33.7 + 10.30	0.19
Anti HCV Positive	214(100%)	552(100%)	1.0
PCR (HCV RNA)	214(100%)	552(100%)	1.0
Hb%(gm/dL)	12.06 + 0.86	11.44 + 0.77	0.001*
SGPT (IU/litre)	106.41 + 40.928	105.48 + 41.315	0.78
Prothrombine time (seconds)	13.02 + 0.86	13.02 + 0.85	0.98
Albumin (gm/dL)	3.72 + 0.22	3.72 + 0.21	0.95

* P value is statistically significant

TABLE NO. 2
12 WEEK THERAPY (N = 766)

	Male (n = 214)	**Female (n = 552)**	**P value**
PCR HCV RNA: Negative Positive	 199(93.0%) 15(7.0%)	 536(97.1%) 16(2.9%)	 0.014
SGPT: < 49 > 49	35.43 + 14.88 193(90.2%) 21(9.8%)	34.14 + 15.06 501(90.8%) 51(9.2%)	0.28 0.78

Results are expressed as Mean + Standard deviation

TABLE NO. 3.
24 WEEK THERAPY (N = 766)

	Male (n = 214)	**Female (n = 552)**	**P value**
PCR HCV RNA: Negative Positive	 201(93.9%) 13(6.1%)	 539(97.6%) 13(2.4%)	 0.015
SGPT: < 49 > 49	30.19 + 9.93 207(96.7%) 7(3.3%)	31.21 + 10.31 532(96.4%) 20(3.6%)	0.21 0.99

Results are expressed as Mean + Standard deviation

STATISTICAL ANALYSIS:

The data were evaluated in statistical program SPSS version 16.0. Qualitative data (frequencies & percentages) were presented as n(%) and X^2 test was applied to compare the proportions among the male and female. Continuous parameters were expressed as Mean + standard deviation and student t test (2 tailed) was used to compare the means among the male and female patients. A P value < 0.05 was considered as statistically significant level for all comparisons.

RESULTS:

800 patients fulfilled the criteria for interferon and ribavirin therapies were included in this study. Of these 230(28.75%) were male and 570(71.25%) were female. The mean age of male patients was 34.84 + 11.9 and of females 33.71 + 10.3 (P value = 0.19). 766(95.8%) patients completed the 24 weeks of therapy while 34(4.2%) discontinued therapy within to 02 months. Out of

766(95.8%) patients who completed the 24 weeks therapy 214(27.9%) were male and 552(72.06%) were female.

Early virological response was achieved in 735(95.9%) of patients of these 199(25.9%) were male and 536(69.9%) were females (P value 0.014). While 31(4.0%) were not responded to achieve EVR, out of which 15(1.95%) were male and 16(2.08%) were females. End of treatment response was achieved in 740(96.6%) patients of which 210(26.2%) were male and 539(70.3%) were female(P value 0.015), while 26(3.3%) were not responded to therapy. Five (16.12%) patients out of 31 patients who did not achieve EVR became negative while 26(83.8%) remained HCV RNA positive after 24 weeks of therapy. There was a significant correlation between EVR and ETR (P value = 0.001, r = 0.913).All 735 (95.9%) patients with negative HCV RNA at 12th weeks of therapy remained negative at the end of 24 weeks of therapy. The ALT decreased during treatment and it become normal at 12 weeks in694 (90.6%) patients with no significant difference in male and female level (p value 0.28) and at 24 weeks in 739(96.5%) patients with non significant difference in male and female value (p value 0.99). All patients tolerated the treatment well except for 34(4.2%) patients who discontinued the therapy due to adverse effects. Dosage reduction of Ribavirin was made in 25 patients due to drop in hemoglobin below 10gm/dl. All these patients completed the treatment with adjusted dosage. The side effects were mostly influenza like syndrome.

DISCUSSION:

HCV is a major health problem and timely treatment should be given to achieve favorable response and prevent from cirrhosis and hepatocellular carcinoma. In Pakistan the majority of genotype 3 patients are treated with standard interferon due to economic reasons and Pakistan Society of Gastroenterology and GI endoscopy also found the use of standard interferon in genotype 3.[14] Government is also providing standard interferon via a special prime ministers initiative for a viral hepatitis program. We had collected a data from District hospital of various areas of Hyderabad and observe the biochemical and end of treatment response after 24 weeks of therapy.

Combination therapy with INF alpha and ribavirin has been recommended[8] as the standard therapy for chronic hepatitis C and is given subcutaneously at doses of three million unites three times a week and 1000 – 1200 mg /day of Ribavirin for 24 weeks. The treatment response of interferon monotherapy for 06 months is considerably less than the combination with interferon and ribavirin and is reported to vary from 20 – 35%.[9] The sustained virological response with INF monotherapy is reported to be 15 -20%, which can be increased to 30-35% with continuing treatment for 12 months.[15] oral ribavirin was tried as a single drug for HCV infection and sustained response were not achieved although decrease in serum ALT was observed with ribavirin [15]. High sustained response were achieved with the combination of INF and ribavirin in subsequent studies.[16]

In our study out of 766(95.8%) patients who had completed the 24 weeks therapy Early virological response was achieved in 735(95.9%) of patients of these 199(25.9%) were male and 536(69.9%) were females. While 31(4.0%) of patients were not responded to achieve EVR. Out of which 15(1.95%) were male and 16(2.08%) were females while 740(96.6%) out of 766 patients responded to therapy at 24 weeks of these 20(26.2%) were males and 539(70.3%) were females. Five (16.12%) out of 31 patients who did not responded at 12 weeks because HCV RNA negative at 24 weeks of therapy. While 26(83.8%) patients remains positive at the end of 24 weeks. The clearance of HCV RNA at 24 weeks instead of 12 weeks is not related to non response and treatment should be continued for 06 months despite the persistence of HCV RNA at 12 weeks. All patients with negative serum HCV RNA at 12 weeks had also negative serum HCV RNA at the end of treatment. Among those who responded to treatment 694(90.6%) patients at 12 weeks and 739(96.5%) patients at the end of 24 weeks treatment showed normalization of ALT level. Kenneth K Yar et al[17] showed 81% of End of treatment in Asians and SVR 73% in genotype I CHC patients. Amina Nadeem [18] showed a response rate of 86% at the end of 24 weeks. Similarly Ashraf et al[15] have reported 79% of response rate, while sustained virological response of 71.4% with combination therapy has been reported by Wazir et al[10] and Sarwar et al[7] discovered a response rate of 82% in their study.Farooqi et al[11] detected a response rate of 87.3% in HCV patients like wise Zagham Abbas[19] in his study showed a response rate of 90.6% and normalization of ALT in 97% of patients at the 24 weeks of therapy. Likewise Nasir Khokhar[20] in his study showed a response rate of 83% at 24 weeks of therapy. The low response rate of 65% reported by Herrin et al[21] may be genotype 1 which is predominant in Europe countries and is related to poor response rate and relapse of the disease.

In our study, the overall response rate of combination therapy is higher as compared to other international studies.[22, 23] But it was almost similar to the published data from Pakistan.[24,25] The better response rate in our patients might be due to genotype 3, which is common in our country[26] but definite evidence is not available as genotyping was not done because of financial problem. Because of the poor follow up we do not comment on the sustained virological response which is a more reliable evidence of effectiveness of the therapy.

CONCLUSION:

Our study shows that chronic hepatitis C patients who have not been previously treated had excellent End of treatment and biochemical response to interferon and ribavirin therapy. We recommended the conventional combination therapy as the first line treatment for chronic hepatitis C patients in our set up.

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