ORIGINAL ARTICLE

ROLE OF INTERFERON AND INTERFERON PLUS RIBAVIRIN IN THE MANAGEMENT OF CHRONIC HEPATITIS C

Wazir Muhammad Shaikh, Majid Ahmed Shaikh, G.A. Solangi and B.F. Zuberi

ABSTRACT

Objective: Chronic hepatitis due to C virus may regress with Interferon-alpha-2b (INF) therapy. Forty percent cases have an initial response to this therapy, but most relapse after stopping therapy. Because of this limited response, alternative forms of therapy including combining interferon with other antiviral agents have been investigated. Hence this study was conducted to evaluate the safety and efficacy of INF alone or in combination with ribavirin.

Design: A prospective study.

Place and Duration of Study: Department of Medicine, Chandka Medical College Hospital, Larkana from July 1996 to June 2001.

Patients and Methods: A total of 82 patients with biopsy proven chronic liver disease due to HCV and raised serum amino-transferase (ALT) present for at least a period of 6 months were included in this study. Forty patients received INF therapy alone (group I) and 42 received INF alongwith ribavirin (group II) for 6 months.

Results: HCV RNA showed sustained response for HCV RNA in 11 (27.5%) and 30 (71.4%) patients of groups I and II respectively. While as sustained response with sernm ALT was noted in 5 (12.5%) and 18 (42.9%) patients of each group. Twenty-eight patients of group I, 32-patients of group I and II underwent repeat liver biopsies after 6- months of the stoppage of treatment. The histologic activity index score improved in 11 (39.3%) and 21 (65.6 %) patients of group I and II respectively (Odds ratio 2.5, 95% C.I. $p < 0.001$).

Conclusion: : The current study supports the hypothesis that INF plus ribavirin has greater efficacy than INF alone.

KEY WORDS: *Chronic Hepatitis C.* *Interferon.* *Ribavirin.*

INTRODUCTION

Nearly 200 million people globally are infected with hepatitis C virus.[1] Of these, approximately 70% have chronic hepatitis and 15-20% will eventually have cirrhosis liver (CL) and hepatocellular carcinoma (HCC).[2-4] Chronic hepatitis C is the most common cause of chronic liver disease (CLD) and is the strong reason for liver transplantation[5] in western countries. INF was first evaluated in chronic hepatitis C in 1986.[6] Since then there have been numerous trials, which suggest that this drug is an effective treatment.[7,8] Several studies[9,10] have analyzed INF therapy, comparing doses and duration of treatment, but do not offer any significant difference in the outcome. However, low dose of 3 million units thrice a week for 6 months have gained recognition. Few studies have suggested[6,11] superiority of 12-month duration treatment, though many patients still relapse.[9,12] In approximately 40% of patients normalization of serum ALT is frequent and HCV.RNA disappears, but most of the patients relapse soon after stopping treatment.[9,11] Other therapeutic options are potential adjuncts to INF in order to improve the response.[13,14] Among such options, ribavirin, an oral guanoside analogue is found effective against many viruses. It reduces serum ALT but is little effective against HCV RNA in chronic hepatitis.[15] Various studies[16,17] do suggest that combination therapy (INF and ribavirin) increases the initial response and also reduce relapse rate as compared to INF alone. Therefore this prospective study was conducted to evaluate the safety and efficacy of INF alone or in combination with ribavirin in our region.

Department of Medicine, Chandka Medical College, Larkana.

Correspondence: Prof. Wazir Muhammad Shaikh, Prof. of Medicine, Chandka Medical College, Larkana. E-mail profwazir@yahoo.com

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PATIENTS AND METHODS

This prospective and open trial was conducted in the department of medicine, Chandka Medical College Hospital Larkana during the period from July 1996 to June 2001. A detailed proforma was prepared and proper study protocol was designed with special emphasis on identification of risk factors. A full laboratory work-up included blood complete picture, LFTs, prothrombin time, activated partial thromboplastin time, virological markers like HBs, HCV, Pan- abdominal ultrasound and liver biopsy. Follow up liver biopsy 6 months after stoppage of treatment was a part of protocol. An independent histopathologist assessed liver biopsy specimens obtained before and after treatment using the Knodel histologic activity index.[18] Scores for this index can range from 0 (normal) to 22 (severely abnormal). This represent the sum of four histologic components; the severity of periportal necrosis (range of score 0 to 10), intralobular necrosis (range of scores 0 to 4), portal inflammation (range of scores 0 to 4) and fibrosis (range of scores 0 to 4). Elisa kit for detection of Anti-Hepatitis C Virus (HCV RNA diagnostics Reedleg CA 93654) was used with Multi-scan MS EIA Analyzer (by Lab systems Finland) the reagents. HCV 1-6 genotype was performed on 28 patients only. EIA Basel Murex serotyping 1-6 kit performed the assay. Patients of either sex age with between 18 and 65 years, HCV positive, raised serum alanine aminotransferase (ALT) for a

minimum period of 6 months duration and biopsy proof of chronic hepatitis were enrolled for study. Exclusion criteria were cirrhosis of liver, HCC, variceal bleeding, platelet counts less than 70000, or total leukocyte count less than 4000 per cmm. Age below 18 and above 65 years, positive test for HBs or HIV, previous use of INF therapy, pregnancy, failure to provide a written informed consent, a history of major depression, underlying autoimmune disorders, and alcoholic consumption. A total of 564 patients of chronic active hepatitis (CAH) were screened, of which 152 patients **(Table I)** met the entry criteria, hence included in this study. Mode of transmission was noted **(Table II).** Fifty-two patients withdrew before receiving treatment because of non-affordability of price of drugs. Forty eight patients placed in group I while 52 in group II. Patients' age, sex and other basic characteristics matched in two groups (I and II). Group I was assigned to receive INF alone and group II to receive INF and ribavirin. The treatment consisted of 6 months subcutaneous INF 3 million units, three times a week and ribavirin administered orally twice daily at a daily dose of 1000 mg for the patients whose weight was 75 Kg or less or 1200 mg for the patients who weighted more than 75 Kg. The patients were evaluated after 2, 4 weeks and thereafter every 3 months. We lost 8 and 10 patients from group I and II respectively during the first 3 months of therapy. All patients were followed at the end of 6 months after stoppage of treatment, which was given for 6 months. HCV 1-6 genotype was performed on 28 patients only. The sample was reactive in all cases for antigen HCV serotype-3. HCV 1-6 genotype was performed on 28 patients only. End points were predefined and strictly carried out. These were as defined by National Institutes of Health consensus development conference[19] on hepatitis C conventional end points like a response at the end of treatment (defined as a partial response as normal serum ALT concentration and undetectable HCV RNA where as complete or sustained response that persists for at least 6 months after stoppage of treatment). So the primary end points were the disappearance of HCV RNA from serum, normal concentration of serum ALT and histologic improvement in the inflammation score of at least 2 points at the end of 6 months therapy. Secondary end points were development of cirrhosis of liver or HCC.

STATISTICAL ANALYSIS

All stastical tests were two- tailed. The base line characteristics and response of treatment group were compared with the use of chi- square test, Student's T test, Haenszel test or analysis of variance (for the liver biopsy specimens).

RESULTS

Out of 564 screened patients of chronic hepatitis C **(Figure I),** 332 (59%) turned up as HBs positive cases, 80 (27%) as unidentifiable and 152 (27%) patients of HCV who were included in this study **(Table I).** Fifty two patients refused treatment because of non-affordability for drugs and 18 were lost during the first 3 months of evaluation. The remaining 82 patients were assigned as 40 and 42 in group I (INF alone) &II (INF + ribavirin) respectively **(Table II).** There was no significant difference between the groups at the beginning of study. Main risk factor so far identified in the spread of disease was history of (H/o) reuse of syringes in 66.5% **(Table III).**

Serum hepatitis C RNA virus became undetectable by the end of treatment in 19 (47.5%) of 40 patients (group I) and 35 (83.3%) of 42 patients in group II respectively. A sustained response was observed in 11 (27.5%) and 20 (47.6%) patients of group II and I respectively. Serum alanine aminotransferase concentrations became normal by the end of treatment in 23 (57.5%) and 38 (90.5%) patients of group I and II respectively. In this study serum HCV RNA remained detectable after treatment despite persistently normal serum ALT concentration in 5 patients (12.5%) of group I and 6 patients (14.3%) in group II respectively. In all patients in whom HCV RNA became undetectable had normal serum ALT concentrations. Sustained response was noted in 5 (12.5%) and 18 (42.9%) patients of group I and II respectively **(Table IV).** In all 60 patients underwent repeat liver biopsies after the 6- months of stoppage of treatment, as 22 did not turn up. Twenty-eight and 32 patients of group I and II respectively underwent repeat liver biopsies. The histologic activity index score improved in 11 (39.3%) and

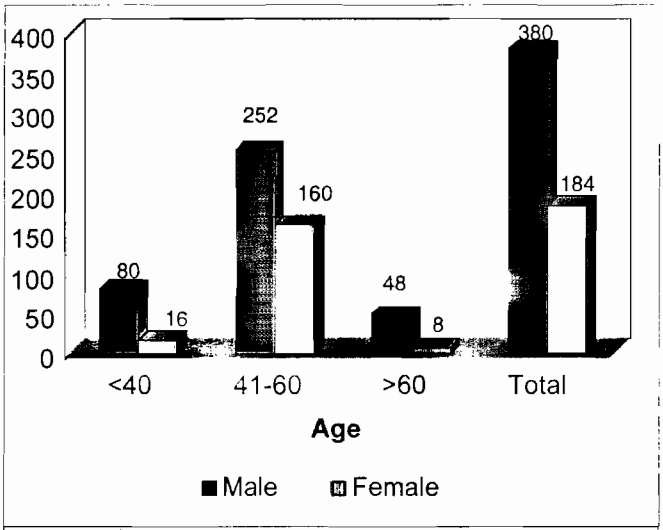

Figure I: Distribution of 564 cases of chronic hepatitis C according to age and sex

TABLE I Distribution of anti HCV +ve 152 cases according age and sex

Age	Male	Female
< 40	31	17
41-59	52	37
> 60	11	04
Total	94	58

TABLE II Mode of transmission

Risk factor	No. of patients	%
H/o Injections	101	66.50
H/o Blood transfusion	5	3.30
H/o Operations	5	3.30
H/o Shaving by barber	7	4.63
Tatooina	5	3.30
Contact	7	4.63
Health employee	4	2.63

TABLE III Distribution of 82 cases according to group

	Interferon			Interferon + Ribavirin		
Age years	< 40	41 - 60	> 60	< 40	41 - 60	> 60
Male	8	15	3	8	16	4
Female	3	10	1	3	9	2
Total	11	25	4	11	25	6

21 (65.6 %) patients of each group (Odds ratio 2.5, 95% C.I. p < 0.001). A logistic regression analysis that took into account the serum ALT concentrations at 6 months after stoppage of treatment showed that the patients in group II had better histologic response than group I.

ADVERSE EVENTS

Flu like symptoms including headache, fatigue, fever with rigors, myalgia and arthralgia were most frequent side effect reported by both groups **(Table V).** Neutropenia was observed in 20% in group I and 36% in group II. Thrombocytopenia was noticed in 15% in group I and 28% in group II respectively. The side effects became evident after 4 weeks of start of therapy. Significant leukopenia, decrease in haemoglobin and thrombocytopenia were present in group II. Life threatening side effects were not observed. Moreover the side effects disappeared after 8 weeks of stoppage of treatment.

TABLE IV Response of therapy at the end of 6 months and 6 months after the stoppage of treatment

Duration	Group I	(no) %	Group II	(no) %
HCV-RNA disappearance				
6 Months	19	47.50	35	83.30
12 Months	11	27.50	20	47.60
S. Alt				
6 Months	23	57.50	38	90.50
12 Months	05	12.50	18	42.90
Histologic improvement		28 patients	23 patients	
12 Months		41%	63%	
Inflammatory score reduction (Knodel)		2.4	2.8	

TABLE V Adverse effects of therapy

Symptoms	Group I (%)	Group-II (%)
Flu like	14 (35%)	15 (35-70)
Leukocyte count < 4000 per cmm	08 20%	14 35%
Haemoglobin < 10 gms %	6 15%	12 28%
Thrombcytopenia	6 (15%)	12 (28%)
Gastro-intestinal		
Anorevia	4 (10%)	5 (16%)
Nausea	7 (17%)	9 (21%)
Diarrhoea	1 (2%)	1 (2%)
Psychiatric Depression		
Insomnia	2 (5%)	3 (7%)
Respiratory		
Cough	2 (5%)	3 (7%)
Dyspnoea	1 (2%)	0 (0%)
Dermatologic		
Rash	1 (2%)	0 (0%)
Pruiritis	2 (5%)	3 (7%)

DISCUSSION

In this study, INF therapy resulted in normalization of serum ALT concentration, loss of detectable HCV RNA in serum and histologic improvement in 47% patients with chronic hepatitis C, but majority relapsed. Sustained response was observed only in 27% for HCV RNA loss and 12.5% in normalization of serum ALT concentration. Our findings correspond to studies reported in world literature.[17,20] Ribavirin, a synthetic guanosine analogue, when given alone to patients with chronic hepatitis C, decreases serum aminotransferase concentration, but has no antiviral effect.[21,22] Meanhile it has improved action when combined with interferon. Hence, treatment with combination of INF plus ribavirin resulted in sustained loss of HCV RNA (47.6%) and normalization of serum ALT (42.9%) concentration and histologic (65.6%) improvement in nearly half of the patients. These findings are consistent with the many studies[23-30], which reported around 49-51% response. Davis *et al*[31], in a multicenter trial demonstrated a sustained virological response of 49% in patients with chronic hepatitis C. Similar observation (43%) was also noted by Albert *et al*.[32] In Pakistan[33] it has been reported as 65% response rate with INF plus Ribavirin therapy for 26 weeks. This clearly establishes that combination therapy have superiority as compared to INF alone. In our country, HCV genotype 3 is very prevalent, as evident from our patients group, the combination of INF and ribavirin enhances the sustained virologic and biochemical response rates and leads to improvement in the histologic markers of inflammation. Treatment regimens for both groups (I and II) were safe and reasonably well tolerated. The only important adverse event in group II was haemolytic anaemia as had been observed with trials of ribavirin alone[30-32] world over. Anti-viral activity is based on the inhibition of all phases of viral interactions within the cells including viral activity, viral uncoating and synthesis of messenger RNA proteins and act as antifibrotic.[34,35]

CONCLUSION

The classical primary goals are to achieve sustained viral eradication, biochemical and histological reversibility. At present, available therapy/ies do not fulfill our aims. Despite a low sustained response rate, interferon therapy can be safe and effective form of therapy in patients with chronic hepatitis C, therefore, it should be considered. Combination therapy seems to exert a synergistic effect between ribavirin and interferon, achieving a sustained response. Management of chronic hepatitis C is a great challenge, and is expected that over the next few years, new drugs should be available to improve the sustained response.

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