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CHRONIC HEPATITIS C;
RESPONSE TO INTERFERON AND RIBAVIRIN COMBINATION

DR. SHAUKAT ALI
Department of Medicine
Combined Military Hospital
Bahawalpur Cantt,

DR. ATIQ UR REHMAN SLEHRIA
Department of Diagnostic Radiology
Combined Military Hospital
Bahawalpur Cantt,

DR. SYED KHURRAM SHAHZAD
Department of Medicine
Combined Military Hospital
Bahawalpur Cantt,

ABSTRACT...Objectives: To know efficacy of combination of standard interferon α2b and ribavirin in chronic hepatitis C. **Design:** Prospective and analytical. **Setting:** CMH Bahawalpur. **Period:** Nov 2008 to Dec 2009. **Materials and methods:** A total of 126 patients, 104 males and 22 females, fulfilling inclusion and exclusion criteria were started combination treatment. Of these, 110 (87.3%) completed the treatment while 16 (12.7%) patients could not complete the treatment so they were dropped out of this study. Patients were started on Interferon α2b in a dose of three million units sub-cutaneous (s/c) thrice a week along with daily Ribavirin 1000 milligram (mg) and 1200 mg orally for patients weighing less or more than 75 kilogram (kg) respectively. The primary outcomes, normalization of ALT and undetectable HCV-RNA by PCR, were determined at end of three and six months of treatment. **Results:** From Nov 2008 to Dec 2009, a total of 110 patients were treated with combination of Interferon α2b and Ribavirin for 24 weeks. Sixty eight patients (62%), 52 males and 12 females showed "end of treatment response" (ETR). **Conclusions:** Results of the study show effectiveness of the combination therapy of standard interferon and ribavirin for Chronic Hepatitis C. Results of this study are comparable to local and international studies.

Key words: Chronic hepatitis C, Interferon, Ribavirin

INTRODUCTION

Hepatitis C virus infection is an important cause of chronic liver disease worldwide despite significant developments/advances in the knowledge regarding diagnosis, treatment and prevention of this disease. At present, hepatitis C virus infects an estimated 180 million people worldwide[1]. Of these, approximately 70% have chronic hepatitis and 20-30% will eventually develop cirrhosis[2]. Once cirrhosis is established, the risk of developing hepatocellular carcinoma is 1 to 4 percent per year[3].

Transmission of disease is parenteral. The common modes of transmission are injection drug use, blood transfusion (unscreened or before the prescreening era), and sexual exposure. Following discovery of HCV in 1989 and subsequently the availability of tests for antibodies against HCV in 1992, the rate of new cases of hepatitis C has fallen by more than 80% in the Western world[4].

The fact that no vaccine is as yet available has become a stumbling block in the efforts to combat this disease through primary prophylaxis. In less developed and poor countries like Pakistan, it remains a problem of greater magnitude, mostly unmapped, due to wide spread poverty, rudimentary health facilities and ignorance among masses regarding mode of its transmission. Presently, it is the most common cause of chronic liver disease in Pakistan as well as developed world as indicated by various studies[5,6,7].

The therapy for chronic hepatitis C is evolving steadily since alpha interferon was first used in this disease more than 10 years ago[8]. Presently, the agreed upon optimal treatment is 24- or 48-weeks course of the combination of pegylated interferon alpha and ribavirin. However, standard interferon α2b along with ribavirin for 24-48 weeks, depending upon hepatitis C virus genotype and pretreatment viral load, remains a viable option for less developed countries[9].

Aim of present study was to evaluate the efficacy of standard interferon α2b & ribavirin administered for 24 weeks in naïve chronic hepatitis C patients.

METHODS & MATERIALS

Patients

Adult patients, 18 years or older, both males and females, with compensated chronic HCV infection who had detectable levels of serum HCV RNA and persistently raised serum ALT levels for six months or more were eligible for the study. Exclusion criteria included decompensated cirrhosis, hepatitis B virus coinfection, anemia, neutropenia, thrombocytopenia, severe psychiatric conditions, hemoglobinopathy, autoimmune disease, poorly controlled diabetes mellitus and an inability or unwillingness to practice contraception during and six months after completion of treatment.

Study Design and Treatment

The study was analytical one and was conducted at CMH Bahawalpur. The treatment comprised of 24 weeks of interferon α2b and ribavirin. Interferon was administered in a dose of 3 million units s/c three times a week while ribavirin was administered twice daily at a total daily dose of 1000 mg (for patients weighing 75 kg or less) or 1200 mg (for those weighing more than 75 kg).

All patients were assessed clinically and biochemically for base line parameters at entry into study. Exclusion and inclusion criteria were checked. All patients were reassessed after 2^{nd}, 4^{th}, 12^{th} and 24^{th} weeks to check for any side effects of medications. Biochemical and hematological tests were done. All biochemical and hematological tests were performed in the department of pathology CMH Bahawalpur. PCR for HCV RNA was done in Armed Forces Institute of Pathology Rawalpindi prior to the start, end of 12th and 24th weeks of treatment by qualitative reverse transcription polymerase chain reaction by using commercial kit of Amplicor (Roche).

Limitation of the study

Due to financial constraints, viral genotyping and quantitative assay of HCV RNA could not be done. These two parameters could have further enhanced the depth of study.

Objectives

The objectives were defined as disappearance of HCV-RNA by PCR and normalization of serum aminotransferase levels after the therapy.

Statistical Analysis

Data was analyzed by using SPSS software version 15. Chi-square test was applied assuming Null hypothesis to be true. Data obtained from the study was tabulated as under:-

	Normal ALT	Abnormal ALT	Total
Negative HCV-RNA	66 (24.72)	02 (9.27)	68
Positive PCR	14 (15.27)	28 (5.72)	42
	80	30	110

$X^2 = E\,(O-E)^2/E = 26.6$ where
O=Observed value
E = Estimated value
Tabulated (Critical) value of X^2 for (2-1) x (2-1) = 1, with degree of freedom at 5% level of significance is 3.841.

Conclusion

Since calculated value of X^2 is greater than the tabulated value, it is significant at 5% level of significance so null hypothesis is rejected. Hence it is concluded that there is significant number of patients showing normal ALT and negative HCV RNA by PCR at end of 24 weeks of therapy.

RESULTS

Characteristics of the Patients

Between November 2008 and December 2009, one hundred and twenty six patients satisfying inclusion and exclusion criteria were started treatment with interferon α2b and ribavirin for a period of six months. Out of these, 110 patients (87%) completed the treatment. Treatment was discontinued in 16 (12.7%) of 126 patients. Out of these, ten patients were lost to follow up due to individual reasons while rest discontinued treatment due to development of depression, neutropenia and hyperthyroidism.(Table-I).

Response to Therapy

Serum HCV RNA levels became undetectable by the end of treatment in 68 of 110 patients (62 percent). Out of these 68 individuals, 58 had undetectable HCV RNA at the end of three months also.

Table-I. Characteristics of patients

Characteristics	Values
Total patients	110
Males	88
Females	22
Age	
Mean	38 ± 12
Male	46 ± 17
Female	40 ± 10
Weight	
Male	62 ± 18
Female	55 ± 19
Source	
Transfusion (single)	28
Transfusion (multiple)	06
Unknown source	76
Demography	
Sindh	26
Punjab	56
N.W.F.P	18
Balochistan	02
Kashmir	08

Serum ALT level became normal by the end of treatment in 80 of the 110 patients (73 percent). Sixty of these patients had normal ALT at the end of three months of treatment. At the end of 24 weeks of treatment, 14 patients out of 80 having normal ALT were positive for HCV RNA. While two patients with abnormal ALT level showed disappearance of HCV RNA.(Table II).

Adverse Events

The mean hemoglobin concentration fell from 13.2± 1.2 g per deciliter to 11.2 ± 1.6 g per deciliter during the first month of treatment, remained stable thereafter throughout the treatment. The values fell below 10 g per deciliter in 10 patients and below 9 g per deciliter in 3 patients. Later three patients were given growth factor as per standard doses thrice weekly till their counts rose to more than 11 g per deciliter. White blood cells decreased by 35 percent and neutrophil count reduced by 25 percent with nadir after 4 weeks of treatment. The platelet counts also fell by seven percent only in five patients. Most patients had minor symptoms like flu and fever and were treated symptomatically.

Table-II. Date of patients treated

At the end of six months	Normal ALT	Abnormal ALT	Total
Negative HCV-RNA	66	02	68
Positive HCV-RNA	14	28	42
	80	30	110

DISCUSSION

This study has shown that combination of interferon α2b and ribavirin is effective in controlling hepatitis C virus infection. The efficacy was evident at the end of six months of treatment as defined in terms of normalization of serum ALT level and negative PCR for HCV RNA in a significant number of treated patients. Response was proven statistically. End of treatment response rate was 62 percent. This compares well with the results reported in the literature[10,11]. There are many local and international studies on this subject. Response rate in international studies is generally lower as compared to this study while it is on higher side in local studies[12,13,14] except one by Shafi MS et al[15] in which daily interferon injection for first six weeks followed by thrice weekly was compared with thrice weekly interferon from the day one. Both limbs used in addition ribavirin in a dose of 1200 mg per day. Later limb of this study resembles to our study closely and it showed response rate of 65% compared to 62% in our study[16].

The combination therapy was largely safe and effective for treatment of patients with chronic hepatitis C. The only significant side effect was occurrence of anemia. The fall in hemoglobin concentration occurred in the first eight weeks of treatment thus emphasizing the need for careful monitoring of hematological parameters during treatment.

The study was closed after six months however long term follow up for sustained response to establish durability of biological response and reduction in development of cirrhosis remains to be determined. Although, this was a small study, however, the patients represented a cross section of population from all over Pakistan as all the

patients were armed forces personnel and their families belonging to all regions of the country. (Table I)

Considering the wide spread nature of hepatitis C in Pakistan and mortality associated with its complications, this study represents the hope in optimal treatment of this disease.

CONCLUSIONS

It can be concluded from this study that combination therapy with standard interferon and ribavirin for chronic hepatitis C is a safe and cost effective option, however, new version of interferon, Peginterferon has shown even better response in chronic hepatitis C patients and is currently the agreed upon therapy. But Peginterferon is more costly, so in our country, even standard interferon remains a viable option.

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Correspondence Address:
Lt. Col. Shaukat Ali
Department of Medicine
Combined Military Hospital
Bahawalpur Cantt,
chshaukatali@yahoo.com

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