Interferon Alpha 2b in Combination with Ribavirin as a Treatment for Chronic Hepatitis C

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ABSTRACT

Objective: To know the response of interferon and Ribavirin as initial treatment of Chronic Hepatitis C and to know the efficacy of interferon and Ribavirin provided in the Prime Minister program in Balochistan.
Methods This study was conducted in the; National Program for Hepatitis; and Department of Gastroenterology Bolan Medical Complex Hospital Quetta from 12-9-2006 to 15-5-2008. HCV antibodies were detected by Elisa Third Generation and HCV RNA Hybridization method in Aga khan University Hospital central lab and shoukat khanum memorial hospital Lahore. . The males to females ratio participated in this study were slightly higher. The majority of them were from the very poor socioeconomic group and lower middle Class. This is because the treatment was free in the National Program for Hepatitis, and the investigations were funded from the Government Zakat fund.
Results: A Total of 223 Patients were enrolled 128(57.39%) were males and 95(42.60%) were Females. Early Virolgical Response (RNA not detected after 12 wk of therapy) was achieved in 79(61.71%) in male patients and 88(92.63%) in female patients. Non responders (HCV RNA detected after three months of treatment) 13(10.15%) patients were males and 4(4.21%) were females. 30 (23.43%) male patients and 16(16.8%) female patients were absconder. End of the Treatment Response (ETR) was 82(64.06%) in male patients and 66(51.15%) was in female patients. SVR was achieved in 10(7.88%) in male patients and 11(8.59%) in female patients. The Relapsers were 4(3.12%) and 5 (5.16%) were in males and females respectively.
Conclusion: The SVR is about between 7-9%, without knowing the genotype, and viral load. And despite of ethnic, racial and geographical variations, SVR in our study, which is near about the same and is comparable to the results of the trials of National and International level.
Key words: Interferon Ribavirin Hepatitis C

INTRODUCTION

Chronic Hepatitis C is a world wide global health problem. Approximately 170 Million (3%) people of the whole world are involved1.

Antiviral therapy either interferon alpha or peg interferon alpha combination with Ribavirin has been shown to be effective.2. A lower sustained Virolgical response (SVR) to Interferon based therapy has been predicted in HCV infected individuals with history of substance abuse as compared to those HCV infected individuals who are not known drug abuser.3... Published repots have strongly proposed the notion, that HCV RNA may be expressed in the liver and extra Hepatic reservoir in the absence of circulating viremia The virus may be active and will lead to Chronic Liver Disease and its complications like Cirrhosis and HCC.3 If the HCV RNA becomes negative but the ALT is still high this means that the virus is still persisting in the liver and extra hepatic sites and ALT is the criteria to asses this effect. The therapeutic effect of Interferon treatment varies depending on the Genotype. Chronic Hepatitis C Genotype 1b is resistant to Interferon and most frequently seen world wide (37%-80%).5-6.Hepatitis C Genotype 3b is most sensitive to Interferon which is most prevalent in Pakistan. The SVR to Interferon mono therapy in HCV 1b patients is low as 10%-20% in Japan and 10% or less in Europe and United States.7.SVR to Interferon mono therapy in patients of HCV 1b with age 40,50 and 60 years were 37.1%, 29.1% and 8.2% respectively8.As the age increases, the response rate to mono therapy decreases significantly. So Interferon is more effective in young individuals as compared to the old individuals. Determinants of pathogenesis are barely known, and include Age at infection, Disease duration, sex, modes of transmission, monogenetic variables and viral heterogeneity, but these factors account for only a small part of the clinical variability of the disease. Dietary factors, inherited metabolic defects, Hemochromatosis, Alcohol consumption can also modulate Chronic Hepatitis C progression.9-10.

MATERIAL AND MEYHODS

This study was conducted in the National Program for Prevention and Control of Hepatitis and the Department Of Gastroenterology of Bolan Medical Complex Hospital Quetta, during the Period from 12-9-2006 to 15-5-2008. The blood was collected in the in the samle collection centre of Aga khan LAB situated in the vicinity of Bolan medical complex hospital Quetta, and sample collection centre of shoukat Khanum LAB and were sent to the central labs of the above said Hospitals.HCV antibodies were detected by Elisa Third Generation and HCV RNA Hybridization method in Aga khan University Hospital central lab and shoukat khanum memorial hospital Lahore**.** . This was a descriptive study.. and the confedence interval was 95%. The majority of them were from the very poor socioeconomic group and lower middle Class. This is because the treatment was free in the National Program for Hepatitis, and the investigations were funded from theGovernmentZakatfund. Patients were introduced 3MU of interferon alpha 2b thrice a week plus daily Ribavirin twice daily for 24weeks. Patients weighing 75 Kg or less received RBV 1000 mg orally per day, and those over 75Kg received 1200 mg day. All the patients tested for HCV RNA by Polymerase chain reaction (PCR) at entry, week 12, week 24, and 24week after discontinuation of therapy. If HCV RNA was detectable at 24 week, therapy was discontinued, if treatment was discontinued prior to 24 week with undetectable HCV RNA, a 24 week follow up PCR was obtained. The primary end point was sustained Virolgical response (SVR), defined as the absence of detectable HCV RNA 24 wk of follow up. EVR (HCV RNA became negative at 3month of treatment) and ETR (HCV RNA became negative at the end of the treatment) were also noted. Safety and tolerance were evaluated (by appearance of side effects like anemia, pancytopenia, fever, general body aches and pains, major depression, suicidal tendencies, and hypothyroidism which may lead to the termination of therapy) at week 1,2,4,8 and then every 4 wk during treatment and at wk 4,8, 12 and 24 following the end of therapy.

Eligible Subjects were adult patients with Chronic Hepatitis C (CHC) who were positive for HCV antibody, treatment naïve and detectable HCV RNA by Polymerase Chain Reaction (PCR) assay. Patients were eligible if they were 15 years of age and had a normal or abnormal ALT at 12 week or more prior to the entry visit and at entry visit which occurred with in 4 week of initiation of therapy.

Patients were excluded from the participation, if they had decompensate liver disease, substance abuse (alcohol or drugs) with in last year, Neutrogena,(ANC>1500/mm^3) thrombocytopenia, (platelets<100000/mm^3), anemia (hemoglobin<12g/dl in females, hemoglobin <13g/dl in males) Hepatocellular carcinoma , concomitant liver disease, HIV infection, poorly controlled psychiatric disease, serum creatinine more than 1.4 mg / dl or other comorbitities.

RESULTS

A total of 223 patients were enrolled, 128(57.39%) were males and 95(42.60%) were females. A total No of 46 patients with 30 (23.43%) male patients and 16(16.8%) of female did not complete the therapy. They were labeled as absconders.

Early Virolgical Response (RNA not detected after 12 wk 0f therapy) was achieved in 79(61.71%) in male patients and 88(92.63%) in female patients. Non responders (HCV RNA detected after three months of treatment) 13(10.15%) patients were males and 4(4.21%) were females. 30 (23.43%) male patients and 16(16.8%) female patients were absconder. End of the Treatment Response (ETR) was 82(64.06%) in male patients and 66(51.15%) was in female patients. SVR (HCV RNA undetectable after 6 months of treatment) was achieved in 10 (7.881%) male patients and 11(8.59%) in female patients. The releasers (SVR did not achieved after 24 wks of treatment) 4(3.12%) and 5 (5.16%) were males and females respectively. The mentioned data is given in the following Table 1& 2

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Table 1. Response of interferon and Ribavirin according to Gender.

Description	**HCV Antibodies**		**Total**
	Male	**Female**	
Total No of HCV Positive patients	128(57.39%)	95(42.60%)	223
Responders :Early Virolgical Response	79(42.60%)	88(92.63%)	167
Non responders (RNA detected at 3 months during therapy.	13(10.15%)	4(4.21%)	17

Absconders.	30(23.43%)	16(16.8%)	46
End of the treatment response(ETR)	82(64.06%)	66(51.15%)	148
Sustained Virolgical Response	10(7.81%)	11(8.59%)	21
Relapsers (SVR did not achieve after 6 month of treatment.	4(3.12%)	5(5.26%)	9

Table 2 Response of HCV to Interferon and Ribavirin according to age and gender.

15-24 Years		**25-44 Years**		**45-64Years**		**64 and above**		**Total**	
Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
15(11.71%)	8(8.42%)	81(63.2%)	53(55.78%)	30(23.43%)	32(33.68%)	3(2.34%)	3(3.15%)	128(57.39%)	95(42.60%)
23		134		62		6		223	

EVR and ETR were very good in both male and female patients. But SVR was low which is comparable to the national and international trials conducted previously. But no such trial has been conducted in Balochistan before this. In the beginning of the study, the majority of the patients had no idea about the causative factors, preventing measures, treatment and complications, Which Indicates a very pathetic situation of hepatitis patients in Balochistan, and shows the over all awareness of the population about this fatal viral infection.

DISCUSSION

In our study the Early Virolgical Response to the combination of interferon 3 MIU and Ribavirin according to body weight is 42.60% in males, and 92.63% in females. The EVR (HCV RNA became negative at 3 month of treatment) is very good in females as compared to males. This may be due to good compliance, low weight, and difference in physiology and hormonal changes in females. End of the treatment response (ETR)(HCV RNA became negative at the end of the treatment) is 64.06% in males and 51.15% in females. The (ETR) increased in males and has decreased in females quite significant statistically. . Sustained Virolgical Response (SVR) is 7.81% in males and 8.15% in females. The SVR has decreased quite significantly in both males and females, as compared to ETR in both the sexes.

The treatment of Hepatitis C has advanced considerably since 1990. Initial therapies with interferon mono therapy were only successful in about 10-15% of patients.11 The Lee and Sherman in a small uncontrolled pilot study of normal or near normal ALT level who were treated with interferon alpha 2b and RBV and reported an over all SVR rate of 47%.12.Lee and Sherman used a high dose of interferon in their study and this may have contributed to their high response rate of 47%.This rate is quite higher than in our study. This may be due to the fact that we have used interferon for shorter duration of 24 wks as per instructions of the government for this program for Hepatitis'.

Gordon et al reviewed data from two prospective randomized controlled trials comparing interferon mono therapy with combination interferon and RBV therapy. And found SVR rate 15%,13. The SVR rate showed in this study is slightly higher than in ours study. In an other study 343 (89%) completed the prescribed treatment schedule, among these ETR was reached in 186(56%) 50, 15% of these went on to SVR while 136(40%) relapsed, and non responders were 157(46%).14.In a study in the United States by wk 24, 34 inmates (58%) responded which was higher in Caucasians compared to Africans Americans. SVR was also higher in cacasians15.This shows that interferon response has racial variation as our study shows lowest SVR as compared to other races of America and Pakistan.

The treatment duration varies depending on the HCV genotype. For patients infected with HCV1, the recommended treatment duration is 48 weeks. Where as patients infected with HCV2or HCV3, The recommended treatment duration is 24weeks.16, 17.The Genotypes 2 and 3 are prevalent in Pakistan .As per recommendation we provided the treatment for 24 weeks in our centre. Our patients were none affording for doing genotypes. So this low response also shows that the genotype prevalent in Balochistan may be resistant to interferon and Ribavirin therapy, and may require high dose and long duration of therapy. So further studies are needed with known genotype on large number of patients.

The other purpose of our study was to know the efficacy of interferon and Ribavirin provided in the Prime Minister Program prevention and control of Hepatitis. The low SVR shown in our study may be due to the low efficacy of the interferon and Ribavirin provided in the Prime Minister program. The cold chain

may have not been maintained properly during transportation or storage. This is a fact, because it has been usually observed that strict rules for the maintenance of cold chain are not followed in the government hospitals of our country, and there is no pertinent test available to check the potency of the drugs.

The studies from Europe have shown that for patients with HCV2or HCV3 who had a rapid Virolgical response (RVR) at 4weeks, a shorter duration of treatment over 12- 16 wks is as effective as 24 wks treatment regimen.18 -20. This strategy may be very useful for our poor people .This strategy will decrease economic burden and will decrease the incidence of side effects of interferon and Ribavirin.

Ethnic and Racial factors have been shown to influence the Virolgical response even when Peg interferon/ Ribavirin are given for the standard duration of treatment.21.22. Geographical variation of HCV by the emergence of quasispecies may have influenced the Virolgical response.23.The low SVR in our Study was low due to Ethnic, Racial and geographical variations.. So further studies are needed on patients with known genotype and viral load.

CONCLUSION

The SVR is about between 7-9% without knowing the genotype , viral load, and despite of ethnic, racial and geographical variations, SVR in our study which is near about the same and is comparable to the results of the trials of National and International level published in the medical literature,

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