RESPONSE TO STANDARD INTERFERON AND RIBAVIRIN COMBINATION IN THE TREATMENT OF PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

Background: Chronic hepatitis C is common in our country and before development of decompensation, it is treated with interferon and ribavirin. This is a costly treatment and many patients remain untreated due to financial constraints. **Objective:** To determine end of treatment response (ETR) to combination of standard interferon and ribavirin (non original brands) provided through Prime Minister program for prevention and control of hepatitis in management in chronic hepatitis C in our setup. **Patients and Methods:** This interventional study was carried out in medical outpatient clinic of Sheikh Zayed Hospital, Rahim Yar Khan, from August 2006 to February 2009. Adult patients (more than 18 years of age) suffering from HCV RNA positive chronic hepatitis were enrolled. Patients were given standard interferon 3 mu s/c thrice a week and ribavirin 800-1200 mg per day for 24 weeks. Four different brands of drugs were used. HCV RNA by qualitative PCR was tested at the end of treatment. End of treatment response was defined as absence of viral RNA. **Results:** 260 patients of chronic hepatitis C were enrolled. 148 patients were male and 112 were female. Their mean age was 34.11 ± 9.18 years. Mean baseline serum ALT of these patients was 91.44 ± 63.00. 217 patients (83.5 %) achieved ETR. There was no statistically significant difference in ETR between various brands of interferon and ribavirin. Moreover, there was no significant difference in gender, age and ALT between patients who achieve ETR and those who did not achieve it. **Conclusion:** Combination treatment with non original brands standard interferon and ribavirin provided through Prime Minister program for prevention and control of hepatitis is effective in our patients with chronic hepatitis C.

Keywords: Hepatitis C, Interferon, Ribavirin, End of treatment response

INTRODUCTION

Chronic hepatitis C is common in our region and affects 3-10 % of our population.[1] Cirrhosis occurs in 25 to 50 percent of chronically infected patients, some of whom develop hepatocellular carcinoma.[2] Interferon along with ribavirin is the mainstay of treatment for chronic hepatitis C. Although, standard interferon has generally been supplanted by pegylated interferon in western countries, standard interferon is still used in our country due to its low cost.

Four types of alpha interferon have been evaluated in clinical trials for patients of chronic hepatitis C- alfa 2a, alfa 2b, alfacon-1 (consensus interferon), and alfa-n1.[3] The last one has never been marketed. Several uncontrolled studies and more than 70 randomized controlled trials have documented the efficacy of interferon for the treatment of chronic hepatitis C infection.[4]

Ribavirin is a nucleoside inhibitor which has broad spectrum antiviral activity.[5] A meta analysis has concluded that its monotherapy is not effective in treatment of chronic hepatitis C.[6] Studies have also shown that combination therapy with interferon and ribavirin is more effective than interferon given alone.[7-10] Interferon is contraindicated in patients with active major depression as these patients may commit suicide during treatment. Ribavirin is contraindicated during pregnancy. Alcohol abuse reduces responsiveness to chronic hepatitis C treatment, so alcoholics should be counselled not to drink alcohol. Hepatitis C virus (HCV) is an extremely heterogeneous family of viruses; at least six genotypes and numerous subtypes have been identified.[11] HCV genotype is a strong predictor of response to interferon and ribavirin treatment. In genotype 2 and 3, the combination therapy has as high as 80 % sustained virological response (SVR) rate.[12] Genotype 3 is the most prevalent genotype in Pakistan.[1] The objective of this study was to determine the end of treatment response (ETR) to combination treatment with standard interferon and ribavirin in patients with chronic hepatitis C.

PATIENTS AND METHODS

This open label uncontrolled interventional study was carried out in medical outpatient clinic of Sheikh Zayed Hospital, Rahim Yar Khan, from August 2006 to February 2009. Patients more than 18 years of age, presenting with chronic hepatitis C were included in the study. Patients with clinical, biochemical or ultrasonographic evidence of cirrhosis were

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excluded from the study. Other excluding criteria were concomitant chronic hepatitis B, pregnant females, autoimmune hepatitis, hepatocellular carcinoma, severe depression, alcoholism, hypo-/hyper-thyroidism and severe cardiopulmonary disease.

At presentation, detailed history was taken from every patient and thorough examination was done. Complete blood count, liver function tests, serum albumin, prothrombin time, ultrasound abdomen and hepatitis C RNA by qualitative PCR (polymerase chain reaction) were advised. Facilities for quantitative PCR and HCV genotyping were not available in the institute. No patient underwent liver biopsy.

Patients eligible for treatment were given interferon 3mu subcutaneously thrice a week and ribavirin for 24 weeks. Dose of ribavirin was 800 mg per day for those having weight less than 65 kg and 1200 mg per day, if weight of patient was more than 65 kg. These drugs were provided by Government through Prime Minister program of prevention and control. Patients were followed every 4 weeks during treatment and at the end of treatment. Complete blood count and serum ALT were done at each visit and hepatitis C RNA by qualitative PCR at end of treatment. ETR meant undetected HCV RNA (PCR) at the end of 24 week treatment. Responders meant patients who achieved ETR and non responders who did not achieve ETR.

Data was analyzed by using SPSS 16.0 software. Quantitative data was recorded in mean ± standard deviation, and compared using student's t test. Qualitative data was recorded as percentage and compared using chi-square test. A p value of <0.05 was considered significant.

RESULTS

Two hundred and sixty patients of chronic hepatitis C were treated with interferon and ribavirin. Mean age of patients was 34.11 ± 9.18 years with a range of 11 to 61 years. 198 patients were less than 40 years of age. 148 (57 %) patients were male and 112 (43 %) were female. Baseline serum ALT was 91.44 ± 63.00, with 62 (23.8 %) patients having ALT within normal range. All patients were from Rahim Yar Khan District.

All the patients completed 24 weeks treatment. At the end of treatment, 217 patients (83.5%) achieved ETR. Demographic data and baseline serum ALT of patients who achieve ETR and those who do not achieve ETR is shown in Table I. Patients having age more than 40 years and those with higher baseline ALT achieved higher ETR, but this was not significant statistically.

Table I: Comparison of gender, age and baseline serum ALT between patients who achieve ETR* and those who do not achieve ETR

Parameters	ETR positive n(%)	ETR negative n (%)	P- value
Gender			
Male	123 (83.11 %)	25 (16.89 %)	1.000
Female	94 (83.93 %)	18 (16.07 %)	
Age (mean ± Sd†)	33.74 ± 8.91	35.95 ± 10.33	0.015
Age			
≤ 40 years	169 (85.35 %)	29 (14.65 %)	0.170
> 40 years	48 (77.41 %)	14 (22.59 %)	
ALT(mean ± SD)	±93.81 ± 65.67	79.46 ± 46.01	0.173
ALT			
≤ ULN ††	47 (75.80 %)	15 (24.20 %)	0.078
> ULN	170 (85.86 %)	28 (14.14 %)	

† standard deviation †† upper limit normal
ETR: End Treatment Response

DISCUSSION

Chronic hepatitis C is treated with a combination of interferon and ribavirin. This combination is more effective than either drug given alone.[8, 9, 13] Pegylated interferon has higher response rate in genotype 1 and 4, but in genotype 2 and 3 both standard and pegylated interferons have same efficacy.[14] In Pakistan, we usually use standard interferon due to its lower cost and because genotype 3 is the most common genotype in our country.

In international literature, an ETR of upto 80 % is described in genotype 2 and 3.[12] In our study, ETR was 83.5 % and it is comparable to other local studies which have shown an ETR of 81-89 %.[15-19] Only one study by Masood N, et al from District Hospital Hyderabad reported a higher ETR (96.6 %).[20] There are many factors that predict the response to interferon and ribavirin combination therapy in chronic hepatitis C. The most important factors are HCV genotype and baseline viral load (higher response with genotype 2 & 3 and lower viral load).[21,22] We did not measure both these factors in our study. Other predictors that are associated with higher response rate are younger age, low body weight, absence of diabetes, cirrhosis and significant (> 33 %) steatosis.[23] None of our patients was diabetic

and we excluded cirrhotic patients from our study. Bhutta SI et al also reported a poor response to combination therapy in diabetics, smokers and older (> 40 years of age) patients.[24] In our patients, ETR was less in patients older than 40 years (77 % vs 85 % in those younger than 40 years) but this difference was not significant statistically. Studies did not reveal any gender difference regarding response to combination therapy similar to our study.[25, 26] The efficacy of interferon plus ribavirin in patients with normal serum ALT appears to be similar to the efficacy in patients with elevated ALT.[27, 28] Apparent difference in ETR in our study regarding this parameter had no statistical significance.

Another important point to note is that we used brands of interferon which had non-original cheaper sources including Chinese sources. Due to this factor these brands are generally considered to have lower efficacy. However, our results are comparable to internationally reported response rates revealing that these brands are as effective as original brand. This issue was also studied by another group (Aziz S, et al) showing that there was no difference in ETR and SVR between FDA approved and non-FDA approved brands.[29] We could not test SVR because most of our patients were lost in follow up.

CONCLUSION

Combination treatment with standard interferon and ribavirin (non-original brands) for 24 weeks in chronic hepatitis C patients is effective. Keeping in view that the factors like quantitative analysis, geno typing and liver biopsy were not done in our study so our results cannot be extrapolated. A larger sample size and a more extensive study is required to compare the efficacy of FDA and non-FDA approved brands.

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Prophet Mohammed ﷺ Said:

"The most excellent Jihad is that for the conquest of self."