ORIGINAL ARTICLE

Conventional Interferon Alfa-2b and Ribavirin for 12 Versus 24 Weeks in HCV Genotype 2 or 3

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ABSTRACT

Objective: To determine the efficacy of 12 weeks therapy with conventional interferon and ribavirin in chronic hepatitis C genotype 2 and 3 naive patients.

Study Design: A randomized clinical trial.

Place and Duration of Study: Postgraduate Medical Institute, Lady Reading Hospital, Peshawar, from January 2005 to October 2006.

Methodology: Two hundred and twenty seven patients with chronic hepatitis C genotype 2 or 3 naive patients were enrolled in the study. All the patients were started on conventional Interferon 3 MIU, S/C, three times a week plus Ribavirin 800 to 1200 mg in divided doses daily. HCV-RNA qualitative PCR was determined after 4 weeks. In case of undetected PCR, patients were randomized to Group-I (where antiviral therapy was given for 12 weeks, n=81) or Group-II (where antiviral therapy was given for 24 weeks, n=81). In case of detected PCR, patients were given 24 weeks antiviral therapy, n=65 (Group-III). HCV-RNA PCR was determined at the end of respective therapies and after 6 months later on. Efficacy was defined as number of patients who achieved Sustained Virological Response (SVR) i.e. HCV-RNA PCR remained undetected 6 months after the end of antiviral therapy.

Results: SVR was achieved in 66 patients (81.48%) in Group-I, 64 patients (79.01%) in Group-II, and 49 patients (75.35%) in Group-III. SVR rate was better in genotype 2 than genotype 3 in all the three groups (p=0.031, OR = 1.52).

Conclusion: Conventional Interferon and Ribavirin combination therapy remains an effective therapy in chronic hepatitis genotype 2 and 3 naive patients in our region. Determination of HCV-RNA qualitative PCR at 4 weeks seems to be an important predictor of SVR and should be used to tailor antiviral therapy to 12 or 24 weeks.

Key words: *Chronic hepatitis C. Naïve patients. Conventional interferon. Ribavirin. Sustained virological response. Genotype 2. Genotype 3.*

INTRODUCTION

Hepatitis C has become one of the major health problems and a leading cause of chronic liver disease. More than 170 million are infected with HCV.[1] HCV infected individuals are at increased risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma.[2-8] Mean prevalence of HCV in Pakistan is 2.34% in healthy blood donors,[9-11] 48.78% in patients with chronic hepatitis,[6,7] 51.09% in liver cirrhosis,[5,8,12,13] and 67.86% in hepatocellular carcinoma.[14]

Current recommendations suggest that patients with chronic hepatitis C virus (HCV) genotype 2 or 3 infection, antiviral therapy should be administered for a period of 24 weeks to ensure a Sustained Virologic Response (SVR).[15] Viral kinetics have demonstrated that decline in HCV viremia is eight times faster in patients with genotypes other than genotype-1.[16,17]

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Mangia *et al.* reported that a shorter course of therapy of 12 weeks with Peg-interferon alfa-2b and Ribavirin is as effective as a 24-week course for patients with HCV genotype 2 or 3 in whom HCV-RNA PCR becomes undetected in 4 weeks (Rapid Virologic Response, RVR).[18]

Antiviral therapy with Interferon and Ribavirin combination therapy is associated with many side-effect, which not only adversely affect the quality of life of the patients but also necessitate reducing or stopping the therapy at time, which results in non-response or relapse of the disease. Peg-interferon-based therapy has become the first choice therapy worldwide, but it is an expensive one. Most of the patients are poor, and cannot afford even conventional interferon-based therapy. Shorter duration therapy will not only reduce the cost but also the side-effects.

The aim of this study was, therefore, to find out whether RVR can predict SVR in genotype 2 and 3 patients treated with conventional Interferon and Ribavirin combination therapy, and whether 12 weeks antiviral therapy may be an option in patients who achieve RVR.

METHODOLOGY

This randomized, clinical trial was conducted in Postgraduate Medical Institute, Khyber Medical

University, Peshawar, from January 2005 to October 2006, without any financial support from industry. Inclusion criteria consisted of chronic hepatitis C naive patients of 18-55 years age, anti-HCV antibodies reactive by ELISA-III, HCV-RNA detected by PCR, HCV genotype 2 or 3, and raised serum Alanine Amino-transferase (ALT) levels. Exclusion criteria included previous antiviral therapy, a leukocyte count lower than 3000 per cubic millimeter, a platelet count lower than 80,000 per cubic millimeter, a hemoglobin level lower than 12 g/dl for women and lower than 13 g/dl for men, co-infection with hepatitis B and/or human immuno-deficiency virus, and the presence of drug abuse, psychiatric disease, autoimmune disease, or pregnancy and lactation.

Informed consent was taken from all included patients. All the patients were started on conventional Interferon 3 MIU, S/C, 3 times a week plus Ribavirin 800 to 1200 mg in divided doses daily. HCV-RNA qualitative PCR was determined after 4 weeks. In case of undetected PCR, patients were randomized to Group-I (where antiviral therapy was given for 12 weeks) or Group-II (where antiviral therapy was given for 24 weeks). In case of detected PCR, patients were given 24 weeks antiviral therapy (Group-III). HCV-RNA PCR was determined at the end of respective therapies and after 6 months later on. The efficacy was defined as a Sustained Virologic Response (SVR); i.e. HCV-RNA remained undetected at 6 months after treatment was stopped.

Blood samples were collected at weeks 4, 12 and 24 during treatment and at week 24 of follow-up, and hematologic and virologic testing was performed within 10 days after collection on samples stored at –20°C (–4°F). Serum levels of HCV-RNA were evaluated qualitatively at each time by Polymerase-Chain-Reaction (PCR) assay (Amplicor HCV test, version 2.0, Roche Diagnostics). HCV genotyping was performed with the use of a hybridization technique (Innolipa HCV, Innogenetics).

Rapid Virological Response (RVR) was defined as HCV-RNA becoming negative after 4 weeks of antiviral therapy. End-Treatment Response (ETR) was defined as HCV-RNA PCR negative at the end of antiviral therapy i.e. 12 weeks in group-I, and 24 weeks in group-II and III. Response was defined as HCV-RNA PCR negative during and/at the end of therapy, and 6 months negative after the end of therapy. Non-Response was defined as HCV-RNA PCR positive during as well as at the end of therapy. Breakthrough was defined as HCV-RNA negative during therapy initially but later on positive at the end of therapy. Relapse was defined as HCV-RNA negative during or at the end of therapy but positive within/or after 6 months of therapy.

Adverse events were graded as mild, moderate, or severe. When severe events other than anemia occurred, the interferon alfa-2b was temporarily stopped for a week or so and the dose of ribavirin was lowered to 800 mg daily; full doses were resumed when the event abated. If the event persisted, both agents were discontinued. In the presence of anemia, the dose of ribavirin was lowered to 800 mg per day if hemoglobin levels were lower than 9.5 g/dl, and ribavirin was discontinued if the concentrations fell below 8.0 mg/dl.

Patients, who achieved RVR were randomized to Group I (where antiviral therapy was given for 12 weeks) or Group II (where antiviral therapy was given for 24 weeks). Those patients who did not achieve RVR were given 24 weeks antiviral therapy (Group III). HCV-RNA PCR was determined at the end of respective therapies and after 6 months later in those patients who had achieved ETR.

The study was designed to compare the standard-duration (24 weeks) and short-duration (12 weeks) strategies. Randomization was performed centrally without stratification according to genotype. Patients who dropped out of the trial were classified as not having a virologic response. No interim analyses were performed, and the analyses included all randomized subjects for whom there were outcome data. Differences in baseline characteristics between the two groups were assessed with the use of the Chi-square test with Yates's correction for discrete variables and the analysis of variance (ANOVA) test for continuous response variables, with confidence intervals set at 95%. The primary comparison was between patients in the standard-duration group treated for 24 weeks and those in the variable-duration group treated for either 12 or 24 weeks. Stepwise logistic-regression analysis was performed to compare p-values and odds ratios for the effect of prognostic factors and length of treatment on the response. At the start of the analysis, all considered variables were included in the model. Statistical analysis was performed using SPSS for Windows, version 11.0.

RESULTS

Patients in the three treatment groups were well matched for baseline characteristics. Male to female ratio was 58:23 (71.60%:28.40%) in groups I and II, 46:19 (70.77%:29.23%) in group III (p=0.45). Genotype 3 to 2 ratio was 65:16 (80.25%:19.75%) in group I, 64:17 (79.01%:20.99%) in group II, and 55:10 (84.61%: 15.39%, p=0.28) in group III. Mean age was 45 ± 3 years in group I, 44 ± 5 years in group II, and 46 ± 4 years in group III, (p=0.76). Mean serum ALT was 95 ± 8 IU/L in group I, 90 ± 11 IU/L in group II, and 99 ± 4 IU/L in group III, (p=0.77).

As detailed in Table I, SVR was achieved in 66 patients (82%) in group-I, 64 patients (79%) in group II, and 49 patients (75%) in group III, results in group I were statistically better than group III (p=0.033). SVR rates

were statistically better in genotype-2 than genotype-3 in all the three groups (p=0.045).

Patients in groups I and II had negative PCR at week-4; therefore, Non-Response could be determined in group III only, where it was seen in genotype-3 patients only. Breakthrough rates were comparable in all the three groups (Table II), but statistically less in group I than group III in genotype-2 patients. Relapse rates were comparable in all the three groups (Table III), but statistically less in group I than group III in genotype-2 patients (p=0.012).

All the three groups were comparable regarding side-effects profile. No patients were dropped due to side-effects.

DISCUSSION

In the past 10 years, enormous progress has been made in the management of patients with chronic hepatitis C. A Sustained Virological Response (SVR) is achieved in 80-85% of patients infected with Hepatitis C Virus (HCV) genotype 2 or 3 after 24 weeks of treatment with peginterferon-alpha and ribavirin.[15,16] Treatment durations of less than 24 weeks have been tried to reduce adverse effects and costs compared with longer-term therapy without compromising efficacy. Studies comprising patients with HCV genotype-2 or 3, with different baseline patient characteristics have shown that 12-16 weeks of treatment can be as effective as 24 weeks of treatment.[18,19] In all the three trials, undetectable HCV-RNA 4 weeks after the start of

Table I: Details of sustained virologic response.

Genotypes	Gender	Group I	Group II	Group III	P-value	Odds ratio
Overall	n=227	n=81	n=81	n=65	group I vs. group III	group I vs. group III
	Male (n=162)	48 (83%)	47 (81%)	37 (80%)	0.061	1.22
	Female (n=65)	18 (78%)	17 (74%)	12 (63%)	0.043	2.08
	Total (n=227)	66 (82%)	64 (79%)	49 (75%)	0.031	1.52
Genotype-3	n=184	n=65	n=64	n=55	group I vs. group III	group I vs. group III
	Male (n=132)	38 (81%)	38 (83%)	30 (77%)	0.053	1.27
	Female (n=52)	14 (78%)	12 (67%)	12 (75%)	0.061	1.18
	Total (n=184)	52 (80%)	50 (78%)	42 (76%)	0.055	1.26
Genotype-2	n=43	n=16	n=17	n=10	group I vs. group III	group I vs. group III
	Male (n=30)	9 (82%)	11 (92%)	5 (77%)	0.05	1.36
	Female (n=13)	5 (100%)	3 (60%)	2 (75%)	0.061	-
	Total (n=43)	14 (88%)	14 (82%)	7 (70%)	0.045	3.14

Table II: Details of breakthrough.

Genotypes	Gender	Group I	Group II	Group III	P-value	Odds ratio
Overall	n=227	n=81	n=81	n=65	group I vs. group III	group I vs. group III
	Male (n=162)	5 (8.62%)	9 (15.52%)	5 (10.87%)	0.064	0.79
	Female (n=65)	4 (17.39%)	5 (21.74%)	4 (21.05%)	0.053	0.77
	Total (n=227)	9 (11.11%)	14 (17.28%)	9 (13.85%)	0.051	0.78
Genotype-3	n=184	n=65	n=64	n=55	group I vs. group III	group I vs. group III
	Male (n=132)	5 (10.64%)	6 (13.04%)	4 (10.26%)	0.061	1.27
	Female (n=52)	3 (16.67%)	5 (27.78%)	2 (12.50%)	0.055	1.50
	Total (n=184)	8 (12.31%)	11 (17.19%)	6 (10.91%)	0.065	1.10
Genotype-2	n=43	n=16	n=17	n=10	group I vs. group III	group I vs. group III
	Male (n=30)	1 (9.91%)	0	1(14.28%)	0.001	0.57
	Female (n=13)	0	1 (20%)	0	-	-
	Total (n=43)	1 (6.25%)	1 (5.89%)	19 (10%)	0.055	6.67

Table III: Details of relapse.

Genotypes	Gender	Group I	Group II	Group III	P-value	Odds ratio
Overall	n=227	n=81	n=81	n=65	group-I vs. group III	group-I vs. group III
	Male (n=162)	5 (8.62%)	2 (4.35%)	3 (7.69%)	0.064	2.37
	Female (n=65)	1(5.56%)	1 (5.56%)	1 (6.25%)	0.045	0.65
	Total (n=227)	5 (7.69%)	3 (4.69%)	4 (7.27%)	0.038	1.18
Genotype-3	n=184	n=65	n=64	n=55	group-I vs. group III	group-I vs. group III
	Male (n=132)	4 (8.51%)	38 (83%)	30 (77%)	0.056	1.14
	Female (n=52)	14 (78%)	12 (67%)	12 (75%)	0.051	0.82
	Total (n=184)	52 (80%)	50 (78%)	42 (76%)	0.058	1.36
Genotype-2	n=43	n=16	n=17	n=10	group-I vs. group III	group-I vs. group III
	Male (n=30)	1 (9.09%)	1 (8.33%)	1 (14.28%)	0.04	0.61
	Female (n=13)	0	1 (20%)	1 (33.33%)	0.001	-
	Total (n=43)	1 (6.25%)	2 (11.76%)	2 (20%)	0.035	0.25

treatment was defined as Rapid Virological Response (RVR) and short-term therapy was given only in patients with RVR.

Present results are consistent with the results of Mangia *et al.*, who treated a total of 283 patients with Peginterferon alfa-2b plus ribavirin.[18] Out of these, 70 patients were assigned to the 24-week regimen (standard-duration group) and 213 patients to a variable regimen (variable-duration group) of 12 or 24 weeks, depending on whether tests for HCV-RNA were negative or positive at week 4. Fifty-three patients (76%) in the standard-duration group and 164 patients (77%) in the variable-duration group had a SVR. Overall, the rate of SVR was 80% among patients with HCV genotype-2 and 66% among those with genotype-3.

In another Norwegian study that did not employ a control group, 85 of 95 patients (89%) with HCV genotype-2 or 3 achieved SVR with 14 weeks therapy with Peginterferon alfa-2b and ribavirin therapy.[19] In this study, SVR was achieved in 49 patients (75.35%) with standard-duration therapy and in 66 patients (81.48%) with 12 weeks duration. SVR rate was better in genotype-2 than genotype-3 in both the groups. These two studies and present study differed in the type of interferon alfa-2b: these two studies used Peginterferon, whereas we used conventional interferon.

In a meta-analysis of outcome of antiviral therapy in HCV genotype-2 and genotype-3 infected patients with chronic hepatitis, Andriulli, *et al.* found that in RVR patients, HCV-3 patients respond to short-treatment as well as HCV-2 patients, irrespective of basal viremia.[20] Patients without RVR might need longer treatment than the recommended 24 weeks. According to review by Dalgard and Mangia, among patients with HCV genotype-2 or 3, achieving an RVR to interferon-based treatment is common and a criterion to reduce the duration of treatment.[21] In patients with genotype-2 and RVR, 12 weeks of therapy with peginterferon-alpha and ribavirin is recommended. For patients with genotype-3, a univocal recommendation on treatment duration cannot be made. However, ongoing trials will probably clarify this aspect.

It has recently been reported that antiviral therapy is more beneficial in patients with HCV genotype-2 than those with genotype-3;[22] and data from the present trial also support these findings in case of female gender. Response rates were 100% and 78% respectively in patients with these two genotypes. However, the present findings suggest that stopping therapy after 12 weeks in patients with a response at 4 weeks is appropriate for patients with either genotype, because the rates of sustained virologic response were similar in patients with genotype-2 or 3, who had an early response and who were treated for 12 or 24 weeks. In keeping with a preliminary report from the DITTO study after early viral clearance has been obtained, the role of genotype appears to be relatively small.[23] From the current trial, it is evident that prolonging treatment in patients with detectable HCV-RNA at week 4 of therapy achieved higher rates of response in those with genotype-2 than those with genotype-3; among patients who did not have an early response and were treated for 24 weeks, the rate of sustained virologic response was higher among those with HCV genotype-2 than among those with genotype-3.

In HCV-2 or -3, the HCV-RNA status after 4 weeks of therapy may guide treatment duration. HCV-2 and HCV-3 patients with severe fibrosis are less likely to experience both rapid virologic response and sustained virologic response, and more frequently relapse after a 12 or 14 weeks duration of antiviral therapy.[24]

CONCLUSION

The findings of this trial suggest that patients with HCV genotype-2 or 3 infection, who have undetectable HCV-RNA after 4 weeks of treatment with conventional interferon alfa-2b and ribavirin, achieve high response rates with 12 weeks of therapy and do not require 24 weeks of treatment. Tailoring the treatment to a shorter course, those with any early response, may make therapy more appealing to the patients without adversely affecting outcomes.

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