ORIGINAL ARTICLE

Response to Combination Therapy in Hepatitis Virus C Genotype 2 and 3

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ABSTRACT

Objective: To determine Sustained Viral Response (SVR) to Interferon (IFN) and ribavirin therapy in chronic hepatitis C patients of genotype 2 and 3.

Study Design: Case series.

Place and Duration of Study: The Garden Clinic, Lahore, from June 1997 to August 2007.

Methodology: All patients of both genotypes 2 and 3 receiving combination therapy were included. Standard IFN with ribavirin was started in 648 (90%) patients of genotype 2 and 3, whereas 73 (10%), all genotype 3 received pegylated IFN. Outcome parameters including End of Treatment Response (ETR) [negative PCR at the end of therapy], sustained viral response (SVR) [negative PCR both at the end of treatment and 6 months later] and relapse (PCR negative at the end of treatment but positive 6 months later) were determined. Data were analyzed using student's t-test and Chi-square.

Results: A total of 721 patients of genotype 2 and 3 were evaluated with male to female ratio of 1.78:1 and mean age 39.8 ± 9.17 years. Twenty six (3.6%) patients were of genotype 2, while 695 (96.4%) had genotype 3. Six hundred and ten patients (84.6%) completed therapy, as per protocol, whereas 58 (8.04%) had therapy beyond 6 months. SVR was 72.7% with better outcome in genotype 2 (80%) than in 3 (72%) and in those on pegylated IFN and ribavirin (85%) than patients on standard IFN-based therapy (71.1%). Relapse was seen in 116 (16.1%) and 80 (11.1%) were non-responders. Patients with baseline ALT 2-4 x UNL had better SVR than patients with ALT < 2x UNL (p-value 0.01).

Conclusion: Genotype 3 was the predominant type of virus in the studied patients. SVR patients was 72.7%. Outcome was better with high baseline ALT and pegylated interferon combination therapy.

Key words: *Genotype. Hepatitis C. Interferon.*

INTRODUCTION

Chronic hepatitis C afflicts 170 million people world-over and around 20-30% of them ends up with end stage of liver disease.[1] Current treatment option available is interferon therapy which has evolved from monotherapy to combination therapy, with addition of ribavirin. Last major step forward in antiviral therapy was introduction of pegylated interferon which not only enhanced the therapeutic outcome but also brought the convenience of weekly injection.[2]

Response to treatment is defined in terms of Sustained Viral Response (SVR), i.e. negative qualitative PCR, six months after completed therapy.[3] SVR varies for different genotypes with best response in genotype 2 and 3, ranging from 70-85%.[4] Response is better with pegylated IFN therapy as compared with standard IFN but due to marked difference in cost, standard IFN combination therapy is still the predominant form of therapy for genotype 2 and 3, especially in developing countries like Pakistan.[5] Difference in response to the two forms of treatment in our population is unknown due to paucity of published data.

Duration of therapy needed for genotype 2 and 3 is being debated these days. There are studies recommending 4 months therapy but others have questioned shorter duration of treatment.[6-8] Treatment response in genotype 3 has recently been identified to be lower than genotype 2 and continuation of therapy for genotype 3 beyond 6 months in selected patients is being suggested,[7] albeit all these guidelines are from population with lower prevalence of these genotypes. Applicability of these recommendations in the local population will depend on pattern of response in these patients which is largely unknown. More importantly, an excess of 25% patients of hepatitis C, fail to have interferon therapy due to non-affordability.[9] It is imperative to develop cost-effective approach for treating these patients, thus, needs comprehensive therapeutic outcome analysis.

The objective of this study was to determine Sustained Viral Response (SVR) to Interferon (IFN) and ribavirin therapy in chronic hepatitis C patients of genotype 2 and 3.

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METHODOLOGY

It was a case series of cohort pattern, which was based on computerized database of patients with chronic hepatitis C treated at The Garden Clinic, Lahore, from June 1997 to August 2007. Patients with genotypes 2 and 3, who received interferon therapy were included. Patients with genotype other than 2 and 3; those features of decompensated liver disease like ascites, variceal bleeding or portosystemic encephalopathy; and those with co-morbid conditions like positive hepatitis B surface antigen, positive HIV (Human Immunodeficiency virus), other chronic liver diseases i.e. alcoholic liver disease, hepatotoxic drugs, autoimmune chronic hepatitis, haemochromatosis and cirrhosis with child class C also excluded.

Variables of patients at the outset including age, gender, weight, bilirubin, baseline alanine aminotransferase (ALT), haemoglobin, platelet count and coagulation profile were noted. All patients were counseled regarding both options of interferon therapies available, i.e. standard interferon and ribavirin or pegylated interferon and ribavirin, with complete information regarding duration, results and cost of treatment. Choice of therapy was decided by patient primarily determined by their economic status. Study patients were followed fortnightly for first month and monthly thereafter. On each visit, detailed history and examination regarding possible side effects of therapy were done. Complete blood count and liver function tests were carried out on each follow-up. Duration of treatment, side effects experienced during therapy and number of injections used was recorded.

Patients who received 80% of standard duration and dose of therapy were declared to have completed treatment. Standard therapy was defined as minimum of 72, thrice weekly injections of standard interferon or 24, weekly injections of pegylated interferon along with ribavirin ≥ 800 mg/day. Patients who lost to follow-up and those in whom treatment has to be discontinued due to side effects were considered as non-responders for intention to treat analysis.

End of treatment response (ETR) and Sustained Viral Response (SVR) were determined for each patient with qualitative PCR of lower limit of detection as 50 IU/ml. PCR was carried out by Nested PCR based on five major processes, i.e. extraction of HCV RNA from serum sample, reverse transcription of target RNA to generate c DNA, two rounds of PCR amplification and detection.[10] ETR was defined as negative qualitative PCR at end of treatment, while SVR was defined as negative PCR 6 months after completion of therapy. Patients with PCR positive, at the end of treatment and also 6 months after complition of treatment were declared as non-responders, whereas those with positive PCR at the end of treatment and negative PCR, six months after completion of therapy were defined as late responders. Those with negative PCR at the end of treatment and positive PCR, 6 months after stopping treatment were labeled as relapse. These definitions of ETR, SVR, relapse and non-responders used were as per AASLD guidelines.[3] Results were analyzed using software package (SPSS 12.0.; SPSS Inc, 1989-1999 Chicago, Ill). Results were expressed as mean ± SD. Categorical variables were expressed in percentage. Patients with and without SVR were compared using student's t-test for numerical variables and Chi-square test and cross tabulation for categorical variables. Results were analyzed as per intention to treat and patients lost to follow-up or those in whom treatment was discontinued due to side effects were considered as non-responders. P-value < 0.05 was considered significant.

RESULTS

Out of 817 patients with chronic hepatitis C recorded, 721 with genotype 2 or 3 were included in final analysis. Male to female ratio was 1.78:1 (462/259), whereas mean age of 39.8±9.17 years and mean weight of 69.36±12.39 kg were noted. Baseline mean ALT was 122.56±98.8. Twenty six (3.6%) patients were of genotype 2 and 695 (96.4%) patients had genotype 3. Standard IFN with ribavirin was started in 648 (90%) patients and 73 (10%) patients, all of genotype 3, received pegylated IFN along with ribavirin.

Among 721 patients included, 610 (84.6%) completed therapy as per protocol for 6 months, whereas treatment was abandoned before completion in 32 (4.7%) patients. Treatment was discontinued due to intractable side effects in 12, while 20 patients were lost to follow-up. Extreme weakness with inability to tolerate therapy was responsible for discontinuation in 6 patients, severe depression in 2, thyroid dysfunction in 3 and recurrent leucopenia resulted in stopping injection therapy in one patient.

Combination therapy was continued for 6-9 months in 44 (6.1%) patients, 9-12 months in 30 patients, whereas 5 patients received therapy for more than one year. All patients on extended therapy were on standard interferon in combination with ribavirin. Decision to prolong therapy was based individualized in selected patients, in order to achieve sustained response, depending on stage of disease and pattern of response as is recommended in AASLD guidelines.

Biochemical ETR at the end of therapy with ALT ≤ 1x UNL was seen in 536 (74.4%) patients, whereas 185 (25.7%) patients had raised ALT at completion of therapy. Virological ETR was seen in 599 (84%) patients, whereas 122 had positive qualitative PCR on completion of treatment. Negative PCR, both at the end of therapy and 6 months after stopping treatment was seen in 483 (67%) patients, relapse in 116 (16.1%)

patients and late response was noted in 42 (5.8%) patients, 80 patients (11.1%) were non-responders. Overall SVR was 72.7%. Distribution of response in two genotypes is shown in Table I. Overall SVR was better in genotype 2 (80%) as compared with genotype 3 (72%) though number of patients with genotype 2 were too small as comparable to much larger group of genotype 3 patients. All patients of genotype 2 were treated with standard interferon with ribavirin.

SVR in patients with genotype 3 receiving pegylated IFN therapy was 85% (62/73), significantly better (p = 0.008) than those receiving standard IFN therapy, 71.1% (463/648).

Side effect profile of patients included in analysis is shown in Figure 1. Fever in 648 (89.9%) patients, hair loss in 505 (70%) patients, insomnia in 356 (49.3%), loss of libido in 258 (35.7%) and minor depression in 274 (38%) patients were commonly observed side effects.

When the variables of patients with and without SVR (Table II) were compared, patients with weight of 70 Kg or less had better but statistically not significant (p = 0.52) response than those with weight above 70 Kg (75.4% vs. 69.4% SVR). Patients with duration of therapy beyond 6 months also had better outcome as compared to patients with therapy 6 months or less (SVR 86.2% vs 72.42%), again the difference was statistically not significant (p = 0.07). It is perhaps due to difference in sample size in two groups, respectively.

Table I: Response distribution in genotype 2 and 3.

Type of response	Genotype 2 (N*-26)	Genotype 3 (N-695)	Total (N-721)
Sustained viral response	20	463	483
Relapse	3	113	116
Non-responders	2	78	80
Late response	1	41	42
Total number of patients	26	695	721

**N = Total number of patients.*

Table II: Comparison of patients with SVR and those without SVR of both genotype 2 and 3.

Variables	SVR	No SVR	p-value
Mean age (years)	39.98 ± (9.4)	39.63 ± (8.2)	0.65
Male	331	131	0.185
Female	194	65	
Mean weight (kg)	68.78 ± (13.36)	70.69 ± (11.85)	0.16
Weight ≤ 70 kg	311	101	0.52
Weight > 70 kg	214	94	
Mean haemoglobin g/dl	13.53 ± (1.75)	13.33 ± (1.77)	0.22
Mean platelet count (x10^3/µL)	231.89 ± (81.00)	241.69 ± (74.7)	0.18
Mean baseline ALT IU/L	119.95 ± (93.07)	130.09± (112.86)	0.22
ALT < 2 x UNL	145	70	0.01
ALT 2-4 x UNL	277	75	
ALT > 4 x UNL	103	51	
Baseline bilirubin (mg/dl)	1.05 ± (1.55)	1.01± (1.05)	0.72
Duration of treatment			
< 80% of treatment	22	10	0.078
Six months therapy	454	156	
More than 6 months	50	8	

**UNL = Upper normal limit*

Patients with ALT 2-4 x UNL had significantly better response as compared to those with value < 2 x UNL (p = 0.01).

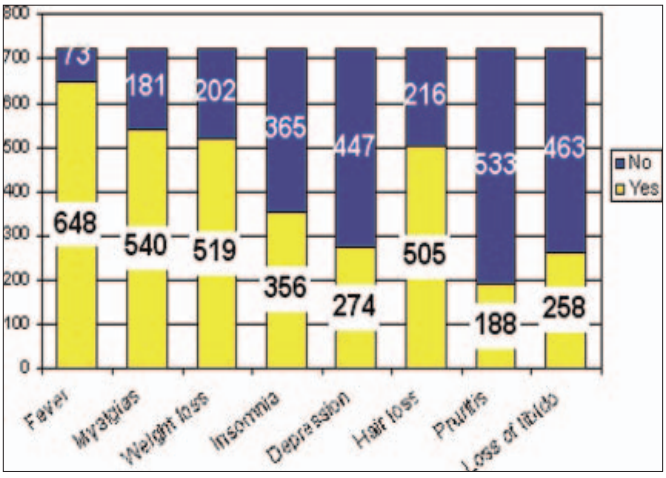

Figure 1: Major side effect profile of interferon therapy.

DISCUSSION

Hepatitis C has gained endemic proportions in our population with reported prevalence varying from 6% to 23%.[5] With improving awareness, number of patients being treated with interferon is on rise. The data on outcome of treatment is among largest of its kind from this region.

Genotype 3 was the predominant virus type (85%) in this data with only 3.1% patients of type 2 in this study. Azhar *et al.* reported 70% patients with hepatitis C of genotype 3 whereas, only 4.8% were genotype 2.[11] Another Indian study found genotype 3 in 80.2% and genotype 2 in 2.5% patients of chronic hepatitis C.[12] Khokhar *et al.* and Moatter *et al.* reported similar predominance of genotype 3 in our population.[13,14]

Both genotypes 2 and 3 are considered as good responders to therapy. Farooqi *et al.* from Peshawar have reported 82% SVR in patients treated with combination therapy.[15] In a study of 279 patients from Armed Forces Institute of Pathology, SVR was checked in only 50 patients and it was 76%.[16] Hazari *et al.* from India have noted 64.4% SVR with thrice weekly standard interferon and ribavirin treatment[17] whereas it was 78.8% in a study of 350 patients by Muhammad *et al.*[18] and 71.4% in data of 42 patients treated with combination therapy by Sheikh *et al.*[19] Batool *et al.* has documented ETR of 83.6% in a study of 161 patients while SVR was checked in 68 patients and it was 68%.[20]

Contrary to this, SVR reported in a rapid communication of 76 patients by Zuberi *et al.* was 33%, 58.8% in those with Rapid Viral Response (RVR) and 27.8% in those without RVR.[21] However, this very low SVR is unlikely to be reflective of response to therapy in our population as in this study, patients with RVR were treated for 16

weeks only, a treatment option still being tested in clinical trials and not recommended for clinical practice. Another retrospective review of data of 400 patients at molecular virology diagnostic centre reported 50.5% SVR.[22] SVR in a study of 70 patients by Sarwar *et al.* was 56.6%.[23] This diversity in reported SVR, varying from 50% to more than 80% in our population can only be reduced with the help of further clinical studies with larger number of patients spanning over many years as is our data. Response in this study was 72.7% which was better in genotype 2 as compared with type 3. Similar better response in genotype 2 was noted by Shiffman *et al.*[7]

Better response was noted in hepatitis C patients treated with pegylated interferon alpha 2a than with standard interferon in combination with ribavirin in genotype 3. It is difficult to have definite conclusion from the data due to disproportionate number of patients treated with these two drug regimens. Better response with pegylated IFN combination therapy was seen in a large multi-centre study of 1121 patients by Fried *et al.*[24] Response rate in excess of 80% was also noted with once weekly therapy by Hadziyannis *et al.*[25]

Shiffman *et al.* identified genotype 2, viral load less than 400,000 IU/ml, age 45 or less, weight ≤ 80 kg, ALT quotient (patient's ALT/ 1 x UNL) > 3 to be associated with better response in a study of genotype 2 and 3 hepatitis C patients.[7] Similarly, low viral load, age < 40 years and low body weight were predictors of better outcome in a meta-analysis.[3] Genotype 2 and ALT 2-4 x UNL were better outcome predictors in this study, whereas patients with weight < 70 kg and duration of therapy > 6 months had better SVR, but it was statistically not significant. Longer duration of therapy beyond 6 months in genotype 3 is recommended by American Gastroenterology Association for patients with high viral load or advanced fibrosis on biopsy.[4] In order to improve outcome in genotype 3 patients, Khokhar selected 100 consecutive patients of hepatitis C and treated them for 48 weeks with standard interferon in combination with ribavirin and SVR noted in this study was 79.5%, better than mostly reported with 6 months therapy.[26] Abbas *et al.* has reported SVR of 88% with daily interferon therapy in combination with ribavirin for hepatitis C in 35 treatment naïve patients.[27] Randomized prospective trials for longer duration or higher dose of treatment in genotype 3 are needed before recommending it in our population due to its financial and compliance related implications.

The present study is limited by its retrospective nature as decisions regarding type of therapy given or duration of treatment were non-randomized but it can be the strength of our data in that it brings forth real life clinical scenario where decisions of type and duration of therapy and baseline parameters checked are largely dictated by financial status of patients, clinical assessment of treating physician regarding treatment related complications, mitigating cessation of therapy at any stage of disease. These factors can not be uniform for each patient. This data will enable us to develop treatment guidelines in as much as its duration, limitations and complications for a typical Pakistani population.

CONCLUSION

Genotype 3 was the predominant type of virus in the studied patients. Sustained viral response achieved with interferon and ribavirin therapy was 72.7% with better outcome in patients with high baseline ALT and those receiving pegylated interferon-based combination therapy.

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