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End treatment response and sustained viral response in hepatitis C virus genotype 3 among Pakistani population

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BACKGROUND AND OBJECTIVES: This study aimed to determine the end treatment response (ETR) and sustained viral response (SVR) to interferon (IFN) and ribavirin in hepatitis C virus (HCV) genotype 3 in the Pakistani population.

DESIGN AND SETTINGS: This is an interventional study conducted from January 2010 to December 2012 in Lyari General Hospital and Abbasi Shaheed Hospital, Karachi, outpatients department.

METHODS: All patients with chronic hepatitis C genotype 3 infections were included. Patients with decompensated chronic liver disease, or having coexisting hepatitis B virus/human immunodeficiency virus were excluded. All patients received IFN alpha, 3 million international units (MIU), subcutaneously 3 times weekly and ribavirin >800 mg/d for a period of 6 months. Outcome parameters included ETR (negative polymerase chain reaction [PCR] at the end of therapy), 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.

RESULTS: A total of 1170 patients were included with a female to male ratio of 1.64:1 and a mean age of 31.6 (8.4) years. Among 1170 patients, 985 completed the therapy as per the protocol, 119 were defaulted (treatment abandoned before completion), and 66 had to stop treatment due to side effects. ETR was 74.1%, SVR was 98%, relapse rate was 1.5%, and 10.1% were nonresponders. SVR was seen only in patients who had achieved an ETR (n=867). SVR was achieved in 848 patients (out of 867) (98%), relapse was seen in 13 (1.5%), and 6 (0.7%) patients lost follow-up after stopping treatment. Patients achieving ETR and SVR had a mean serum alanine aminotransferase of 71.3 (57.1) and 71.0 (56.5), respectively, which is approximately twice the upper normal limit.

CONCLUSION: The conventional IFN and ribavirin therapy in genotype 3 chronic HCV-infected patients gives an ETR and SVR of 74.1% and 98%, respectively.

Chronic hepatitis C affects 170 million people worldwide, and around 20% to 30% of them end up with end stage of liver disease.[1,2] It is estimated that approximately 10 million people are infected with hepatitis C in Pakistan with an average prevalence of 6%.[3,4] Type 3 is the most prominent genotype in Pakistan with a prevalence of 75% to 90%.[5]

The current treatment option available is the interferon (IFN) therapy, which has evolved from monotherapy to combination therapy with the addition of ribavirin. The last major step forward in the antiviral therapy was the introduction of pegylated IFN, which not only enhanced the therapeutic outcome but also brought the convenience of weekly injection;[1,6] however, this is expensive.

Response to treatment is defined in terms of SVR, i.e., negative qualitative polymerase chain reaction (PCR) 6 months after the therapy completed.[1,7] SVR varies for different genotypes with best response in genotypes 2 and 3, ranging from 70% to 85%.[1,8] Response is better with the pegylated IFN therapy as compared with the conventional IFN; however, due to marked difference in the cost, the conventional IFN combination therapy is still the predominant form of the therapy for genotype 3, especially in developing countries like Pakistan.[1,9]

Treatment response in genotype 3 has recently been identified to be lower than that in genotype 2, and the continuation of therapy for genotype 3 beyond 6 months in selected patients is being suggested.[1] These guidelines are from the population with lower prevalence of these genotypes. The applicability of these recommendations in the local population will depend on the pattern of response in these patients, which is largely unknown. More importantly, an excess of 25% patients of hepatitis C fail to have the IFN therapy due to nonaffordability.[10] It is imperative to develop a cost-effective approach for treating these patients, which would need a comprehensive therapeutic outcome analysis. The objective of this study was to determine the ETR and SVR to the conventional IFN and ribavirin therapy in chronic hepatitis C patients of genotype 3.

METHODS

This is an interventional study conducted from January 2010 to December 2012 in Lyari General Hospital and Abbasi Shaheed Hospital, Karachi, outpatients department. A favorable ethical opinion was obtained from the Layari General Hospital and Abbasi Shaheed hospital ethical committee for the study. A total of 1170 patients were enrolled after informed consent. Patients with chronic infection of HCV, confirmed with RNA PCR (qualitative analysis) with a genotype 3, were included in the study. Those with the features of decompensated liver disease such as ascites, variceal bleeding, or portosystemic encephalopathy and those with comorbid conditions such as positive hepatitis B surface antigen, positive HIV (human immunodeficiency virus), other chronic liver diseases i.e., alcoholic liver disease, hepatotoxic drugs, autoimmune chronic hepatitis, and hemochromatosis were excluded.

This study was performed in two stages. In the first stage, all as HCV genotype 3 diagnosed patients, who fulfilled the inclusion criteria, were enrolled during the period of 2 years. They all received the conventional IFN therapy plus ribavirin as per the given protocol for a period of 6 months. On the completion of therapy, their HCV RNA PCR was repeated. Those who achieved an end treatment response (ETR) were then classified as patients who had an HCV RNA PCR positive and were labeled as nonresponders. PCR negative patients (achieved an ETR) defaulted the therapy due to some reason and stopped treatment due to side effects. In the second stage, only those patients who at the end of treatment had a negative PCR (i.e., who achieved an ETR) were followed up for further 6 months to see if they achieved a sustained viral response (SVR). Those who achieved an SVR were then classified as patients

who had an HCV RNA PCR positive or negative or lost to follow-up.

Primary outcome variables were ETR, SVR, nonresponders, and relapse rate. Secondary outcome variables of patients at the outset including age, gender, and baseline alanine aminotransferase (ALT) were noted. All patients were counseled about the standard IFN and ribavirin therapy with complete information regarding duration, results, and side effects of the therapy. Study patients were followed up initially fortnightly for a month and then monthly. On each visit, detailed history and examination regarding the progress of the patients and possible side effects of the therapy were done. Complete blood count and liver function tests were carried out on each follow-up. The duration of treatment, side effects experienced during the therapy, and the number of injections used were recorded. The standard therapy was defined as minimum of 72 sub-cutaneous injections, thrice weekly, of standard IFN along with ribavirin 800 mg (if weight <70 kg) in 2 divided doses and 1200 mg (if weight >70 kg) in 3 divided doses. All patients underwent HCV RNA PCR (qualitative analysis) at the end of treatment and 6 months after stopping the treatment. The 2 main reasons for not considering liver fibrosis as a major outcome measure in this study were as follows: (1) the economic/financial condition and the cost issue was one of the major barriers as this is a public sector setting and (2) patients and their families did not give consent for an invasive procedure like liver biopsy. However, decompensated chronic liver disease was excluded on the basis of clinical, hematological, biochemical, and ultrasonographic findings.

The ETR and 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 5 major processes, i.e., extraction of HCV RNA from serum sample, reverse transcription of target RNA to generate cDNA, and 2 rounds of PCR amplification and detection.[11] ETR was defined as negative qualitative PCR at the end of treatment, while SVR was defined as negative PCR 6 months after the completion of therapy. Patients with PCR positive at the end of treatment and 6 months after the completion of treatment were declared as nonresponders. 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 nonresponders used were as per American Association for the Study of Liver Diseases guidelines.[7]

Statistical analysis
Statistical analysis was performed using SPSS, ver-

sion 20.0 (IBM Corp, Armonk, NY). Frequencies and percentages computed for gender, ETR, SVR, nonresponders, and relapse rate. Age and ALT were expressed as mean, standard deviation (SD), and 95% confidence interval (CI). Chi-square test was used to compare the relative frequencies of ETR and SVR in gender; whereas, independent t test was used to compare the mean of age and ALT in the ETR and SVR groups.

RESULTS

A total of 1170 patients were included. The mean age was 31.6 (8.4) years. Overall, female predominance was noted with 727 (62.1%) females. The female-to-male ratio was 1.64:1 (727/443). The mean baseline ALT was 71.6 (56.3). Among 1170 patients, 985 (84.3%) completed the therapy, 119 (10.1%) were defaulters (treatment abandoned before the completion of therapy), and 66 (5.6%) had to leave treatment due to side effects.

The ETR was achieved in 867 (74.1%), nonresponders were 118 (10.1%), defaulters were 119 (10.1%) (treatment abandoned before the completion of therapy), and 66 (5.6%) stopped treatment due to side effects. The ETR in respect of both genders was 70.4% in males and 76.3% in females, which was statistically insignificant (Chi Sq-0.082). An independent t test was conducted to compare age of PCR positive (nonresponders) and PCR negative (achieved an ETR) participants. There was no significant difference in the age for nonresponders (M=31.58, SD=8.32) and they achieved an ETR (M=31.56, SD=8.53); P=.986 (95% CI 1.62-1.65).

SVR was observed only in patients who had achieved an ETR (n=867). SVR was achieved in 848 (98%), relapse was seen in 13 (1.5%), and 6 (0.7%) patients lost follow-up after stopping treatment. The SVR in respect of both genders was 69.7% in males and 74.1% in females, which was statistically insignificant (Chi Sq-0.337). An independent t test was conducted to compare age of patients with PCR positive and PCR negative in the second stage. There was a no significant difference in the age of patients with PCR positive (M=31.85, SD=7.2) and PCR negative (M=31.57, SD=8.5); P=.89 (95% CI 4.1-4.7).

In the patients who achieved the ETR and SVR, the mean baseline ALT was 71.3 (57.1) and 71.0 (56.5), respectively, which is approximately 1.5 to 2 times the upper normal limit; whereas, the mean baseline ALT of nonresponders was found to be 68.3 (47.2), while patients who relapsed had a mean baseline ALT of 72.3 (57.1). Independent t-test confirmed no signifi-

cant difference in the baseline ALT of both the groups of patients; P=.59, 95% CI (-13.7-7.8).

DISCUSSION

Hepatitis C has gained endemic proportions in our population. The reported prevalence of hepatitis C virus (HCV) in our population varies from 6% to 23%.[9] Genotype 3 is the commonest virus type seen in patients with hepatitis C in our population.[12,13] Being the commonest virus type, our study focused only on genotype 3. In our study, a total of 1170 patients of HCV genotype 3 were enrolled with female dominance and a mean age of 31.6 (8.4) years. On the contrary, some studies[1,14] reported male dominance in their patients. In addition, a similar mean age of 39.8 (8.1) years was reported.[3]

Our study reported an ETR of 74.1% and 10.1% were nonresponders. An ETR of 81% and 17% nonresponders has been reported by Qureshi et al.[3] Another local study reported an ETR of 83.6% with a sample size of 161 patients, while SVR was seen in only 68 patients that was reported as 68%.[15]

Our study reported an SVR in 867 patients in which 848 (98%) patients achieved an SVR, 13 (1.5%) patients relapsed, and 6 (0.69%) patients were lost to follow-up. SVR reported in all local studies have been reported to be lesser than that in our study. Qureshi et al reported SVR of 58% and 24% relapsed.[3] In one study at Peshawar, SVR of 82% has been reported.[16] In another study with a sample size of 279 patients, only 50 patients were checked for SVR and SVR was found to be 76%.[17] Zuberi et al,[18] reported an SVR of 58.8% in 76 patients. A retrospective data was analyzed of 400 patients with SVR of 50.5%.[19] Sarwar et al[20] reported in their study an SVR of 56.6%. In India SVR was reported to be 64.4% with the same treatment protocol.[21] Two local studies reported an SVR of 78.8%[22] and 71.4%.[23] We have reported the largest number of patients up till now from Pakistan; 867 patients is a large data that has reported a 98% of SVR.

To improve outcome in genotype 3 patients, Khokhar selected 100 consecutive patients of hepatitis C and treated them for 48 weeks with the conventional IFN in combination with ribavirin, and SVR noted in this study was 79.5%.[24] However, our study showed an SVR of 72.47% with the 24 weeks of therapy. Abbas et al. reported an SVR of 88% with a daily IFN therapy in combination with ribavirin for hepatitis C in 35-treatment naïve patients.[25] 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, untoward effects

and compliance related implications.

The limitation of this study was a nonrandomized trial, offering just 1 mode of treatment due to the financial constraints. However, this brings forth the real clinical scenario in which the treating physician, duration, and type of therapy is dictated by the financial status of patients, clinical assessment of treating physician regarding treatment complications, and side effects. These factors cannot be uniform in each patient, especially, in our population. This data will help develop guidelines regarding duration, limitations, mode of treatment, and their side effects in the Pakistani population.

In conclusion, the conventional IFN and ribavirin therapy in genotype 3 HCV- infected patients gives an end treatment and SVR of 74.1% and 98%, respectively.

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