Original Article

Short Duration Therapy with Standard Interferon and Ribavirin in Chronic Hepatitis-C Genotype 3a Patients. Is it too short?

*Sohail Bhutta**
*Wasim uddin***
*Muzamil Jamil****

Associate Professor of Medicine Wah Medical College, P.O.F. Hospital, Wah Cantt
Head of department of Medicine Wah Medical College, P.O.F. Hospital, Wah Cantt
Wah Medical College, P.O.F. Hospital, Wah Cantt

Objective: To determine the efficacy of 12 weeks therapy for genotype 3a chronic hepatitis C (CHC) patients, who achieve RVR after 4 weeks of start of treatment and to determine the predictors of good response among these patients.

Study Design:

Place and duration:

Materials and Methods: In this 57 treatment known CHC genotype 3a patients between 16-60 years of age fulfilling inclusion criteria were treated with standard interferon and ribavirin for 3 months, provided the patients achieved positive RVR at one month . The frequency of RVR, ETR and sustained virological response (SVR) was calculated and predictors of good response were determined.

Results: Male to female ratio was 1:1.1. Mean age of patients was 39.2± 2 years. RVR was found in 82% of patients. ETR was observed in 82% amongst those achieving RVR. SVR was 60.97% among those achieving end treatment response (ETR). Relapse rate was 31.71%. Mean age among SVR patients was 34 years. Among the patients showing SVR 56% were males. Average baseline ALT among patients with SVR was 115 I.U.

Conclusion: Short duration therapy of 12 weeks based on standard interferon and ribavirin in genotype 3 patients may not be an effective regimen. It is associated with high breakthrough and relapse rates. Simply by prolonging the duration of therapy to 24 weeks in patients who achieve RVR might be a good alternative. Raised ALT, male gender and young age are predictors of good response in our patients.

Key Words: Chronic Hepatitis C, Ribavirin

Address for Correspondence
Dr. Sohail Bhutta
Associate Professor of Medicine
Wah Medical College, POF Hospital
Wah Cantt
Email: *sibpk66@hotmail.com*

Introduction

Chronic hepatitis C (CHC) is a serious global health problem. Around 170 million people worldwide are affected and more than 20% of them require treatment[1]. Interferon, an immune modulating cytokine was introduced for the first time in 1987. As an antiviral agent for the treatment of CHC. Interferon's initial sustained virological response (SVR), following its 24 weeks treatment was less than 20%[2]only, as being the sole agent for CHC treatment at that time . Based on later studies, the treatment duration for interferon was prolonged to 48 weeks[3,4] to achieve better results. The addition of antiviral drug, ribavirin increased SVR from 20% to 40%. Studies on treatment of CHC patients, infected with genotypes 2 and 3, with standard interferon and ribavirin in combination for 24 weeks revealed SVR of 65%.[3,5] The use of Pegylated interferon in combination with ribavirin for CHC associated with genotype 2 and 3 for 24 weeks achieves SVR of 80%[6,7,8]. Both interferon and ribavirin are not only associated with many side effects but are also expensive, particularly for developing countries like Pakistan. Efforts have been made by the hepatologists to counter these problems by shortening the duration of treatment in appropriate group of patients without compromising SVR. Genotypes 2 and 3 are more responsive to Pegylated interferon and ribavirin as compared to genotype 1, where the response rate is only 42% with 48 weeks[9] treatment. According to Hadziyannis et al[7] and Zeuzem et al[10], patients with genotypes 2 and 3 can be safely treated for 24 weeks instead of 48 weeks. . More recently the concept of rapid virological response (RVR) has been used to further shorten the treatment duration in genotypes 2 & 3. A number of studies have already demonstrated a good SVR ranging between 62% - 90% in genotypes 2 & 3 patients with short duration treatment. These

patients were treated with Pegylated interferon along with ribavirin for 12-16 weeks only, provided they showed negative PCR after 4 weeks of start of treatment (RVR). These results are comparable with treatment duration of 24 weeks in the similar patient groups.[11-13] In all the above trials Peginterferon has been used for short duration therapy. Among our patients of CHC, the cost of pegylated interferon is the major issue in selecting treatment options. Genotype 3a is the most prevalent type among CHC patients in Pakistan.[14,-19]

We carried a prospective study on CHC genotype 3 patients by treating them with a combination of standard Interferon and weight based ribavirin for 12 weeks instead of 24 weeks, provided they achieve RVR after 4 weeks of start of treatment. Our objective was to find the efficacy of this 12 weeks therapy, the frequency of RVR, ETR (end treatment response) and SVR following this short therapy so that the treatment can be made more cost effective. We also wanted to determine the predictors of good response among these patients.

Materials and Methods

This study was carried out in the department of medicine at POF Hospital, Wah Medical College, Wah Cantt from June 2006 to Feb. 2009. A formal approval from hospital ethical committee was obtained. All the treatment naïve CHC patients with genotype 3 between 16-60 years of age full filling the following inclusion criteria were included in the study. An informed consent was taken.

Inclusion Criteria: Adults of either gender aged 16-60 years who were HCV positive on PCR qualitatively or quantitatively and having no evidence of cirrhosis liver on ultrasound examination.

Exclusion Criteria: Patients with serological evidence of Hepatitis B, pregnancy/ lactation, Known chronic renal failure, congestive cardiac failure, respiratory failure, and auto immune disease were all excluded.

PCR for HCV RNA was obtained from Armed Forces Institute of Pathology, Rawalpindi by using Real time PCR method at 0, 4 & 12 weeks of treatment to determine baseline status, RVR & ETR respectively. Fourth PCR was carried out after 24 weeks of end of treatment to determine SVR in patients who demonstrated ETR. All the patients who had a positive RVR received 3 million units of standard interferon thrice a week subcutaneously along with weight based ribavirin orally daily. Patients weighing less than 55 kg received 800 mg/d, those between 56-75 kg received 1000 mg/d and the ones with more than 76 kg were given 1200 mg/d of ribavirin.[11]

During the treatment period all the patients were followed up fortnightly, their complete blood counts and ALT were obtained at 4 weekly intervals. Patients were also monitored for any possible side effects. Patients with negative RVR were excluded from the study. Patients having breakthrough infection were also excluded from the study. Those who had positive ETR were declared responders after 12 weeks treatment. Responders were further followed up by getting ALT 4 weekly for 24 weeks and their PCR was repeated after 24 weeks to determine SVR.

The data were recorded on a prescribed Proforma and analyzed with SPSS version 10.

Results

Metabolic A total of 57 patients were enrolled for this study. We had 47.4% males (27 patients) and 52.6% females (30 patients). Male to female ratio was 1:1.1. The age of the patients included ranged between 16-60 years. Their mean age was 39.2 +/- 2 years.

RVR was observed in 87.7% of patients (n=50) at 4 weeks. 12.3% of patients (n=7) not achieving RVR were excluded from this study. Out of these 50 patients, 82% of patients (n=41) achieved ETR at 12 weeks and were considered responders. Only 6 patients had a breakthrough infection and 3 patients (6%) were lost to follow up. Out of the 41 patients having ETR, 60.97% patients (n=25) showed SVR. But out of 50 patients having RVR, SVR is only 50%. 13 patients (31.71 %) had relapse and 3 patients (7.32%) were further lost to follow up after having ETR. The different predictions of SVR an shown in table I.

Table-I Predictors of SVR

Variables			Good Predictors
Sex			
	Male (56%)	14	Male sex
	Female (44%)	11	
Average base line ALT in patients having SVR		115 i.u.	
Average base line ALT in Relapsers		81 i.u.	High base line ALT
Age			
	SVR years	34	Younger age
	Relapsers years	40	

Discussion

There are approximately 10 million people infected with HCV in Pakistan with an average prevalence rate of 6 %[14.] A major bulk of health resources in Pakistan has to be diverted for the treatment of CHC. Introduction of standard interferon

and subsequently the addition of ribavirin in this regimen was a great hope for CHC patients.[3] Later studies focused on duration of therapy. For genotype 3a which is most prevalent in Pakistan[14-19] as well, the duration of 24 weeks was suggested to be adequate, achieving a SVR of 65%[3,5]. With the introduction of pegylated interferon the focus of treatment of CHC has been shifted from standard interferon to pegylated interferon along with ribavirin. For genotype 3 this combination for 24 weeks has been found adequate, giving a SVR of approximately 80%.[6 - 8]

In our study, the use of standard interferon and ribavirin revealed RVR up to 87.7%, which is much higher than the results of Mangia A et al[11] and Shiffman et al.[12] They found RVR of 62% and 64% respectively with the use of pegylated interferon for 12 weeks and 16 weeks in patients of CHC with genotype 2 and 3. Saleem Qureshi et al [14] achieved RVR of 70% using standard interferon and ribavirin. The use of RVR as a rule to guide treatment duration overcomes the possible viral and host linked factors which may reduce SVR when the duration of treatment is truncated [11]. However RVR has been studied extensively with pegylated interferon and not with standard interferon. In our study, out of these 87% patients achieving RVR, 82% patients achieved ETR, which again is comparable with Mangia et al [11] (90%) and shiffman at al[12] (89%). Mangia N et al [21] however reported higher ETR up to 94%. SVR in our study was 60.97% which is very close to 62% SVR reported by Shiffman et al.[12] Though it is much lower than Mangia A et al[11] who achieved SVR of 77%. We calculated this SVR by taking in account only our 41 responders with ETR. If we base our SVR taking in consideration 50 patients with RVR, our SVR drops to 50%. In this case we are completely ignoring our 12% lost follow up's which could have made a significant influence on our SVR. One of the factors in this drop in SVR may be the effect of standard interferon used which showed good response during the short treatment duration of 12 weeks achieving an ETR of 82%.But it failed to maintain its effect after 12 weeks duration as compared to Pegylated interferon which has a longer duration of action. This needs further trials to compare 12 and 24 weeks treatments using standard & pegylated interferon in genotype 3 patients who achieve RVR.

Standard interferon has been used in genotype 3 for 24 weeks with good results in different studies. S. Qureshi et al[14] achieved SVR Of 90% by using standard interferon for 24 weeks in their CHC genotype 3 patients who achieved RVR. This reflects that simply prolonging the treatment duration to 24 weeks may be required to improve our SVR from 60.97% to that closer to what is achieved by S. Qureshi et al in this group of patients. Prolonging the treatment with standard interferon & ribavirin up to 24 weeks in genotype 3 patients who achieve RVR may be a more cost effective strategy as compared to using pegylated interferon for 12-24 weeks in poor countries like Pakistan.

Our study also showed that high ALT (> 2.5 x ULN), male gender and age younger than 35 years are good predictors of response in genotype 3 patients treated with standard interferon. This is comparable to international studies. Mangia N et al [21] in their study on treatment of CHC patients among Italians found that age more than 45 years was an independent predictor of relapse in genotype 2 and 3 patients treated with pegylated interferon & ribavirin for 12 weeks. Patel K et al [9] also mentioned age less than 40 years as a good predictor of SVR in CHC patients treated with pegylated interferon. Mangia A et al [11] showed that age less than 40 years and ALT more than 3 times upper limit of normal (ULN) was associated with better response in genotype 2 and 3.

Conclusion

Short duration therapy of 12 weeks based on standard interferon and ribavirin in genotype 3 patients may not be an effective regimen. It is associated with high breakthrough and relapse rates. Simply by prolonging the duration of therapy to 24 weeks in patients who achieve RVR might be a good alternative. Raised ALT, male gender and young age are predictors of good response in our patients.

References

1)Perz JF, ,Farringten LA, Pecoraro C, Hutin YJ, Armstong GL.Estimated global prevalence of hepatitis C virus infection. J infect dis 2004; 154:A357

2) Hoofnagle Jay H, Seef LB.Peginterferon & Ribavirin for chronic hepatitis C. N Eng. J Med2006; 355:2444-51

3) McHutchison JG, Gordon SC, Schiff ER et al. Interferon alfa - 2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Eng. J Med1998; 339:1485-92

4)Poynard T,Marcellin P,Lee SS et al. Randomized trial of interferon alfa 2b plus ribavirin for 48 weeks or for 24 weeks for treatment of chronic infection with hepatitis C virus. International hepatitis interventional therapy group (IHIT) Lancet 1998; 352:1426-32

5)Poynard T,Yuen MF,Ratziu V,Lai CL.Viral hepatitis C.Lancet 2003;362:2095-2100

6)Strader DB,Wright T,Thomas DL,Seef LB.Diagnosis, management and treatment of hepatitis C.Hepatology 2004;39:1147-71

7)Hadziyannis SJ,Sette H Jr, Morgan TR et al. Peginterferon alfa 2a and ribavirin combination therapy in chronic hepatitis C:a randomized study of treatment duration and ribavirin dose.Ann of intern Med 2004;140:346-55

8)Manns MP,McHutchison JG,Gordon SC et al. Peginterferon alfa 2b plus ribavirin compared with interferon alfa 2b plus ribavirin for initial treatment of hepatitis C:a randomized tial.Lancet 2001;358:958-65

9)Patel K, McHutchison JG.Post grad med 2003;114(1):48-62

10)Zeuzen S,Hultcrantz R,Bourliere M et al.Peginterferon alfa-2b plus ribavirin for treatment of chronic hepatitis C in previously untreated patients infected with genotype 2 or 3.J Hepatol 2004;40:993-999.

11)Mangia A,Santoro R,Mnerva N et al. Peginterferon alfa-2b and ribavirin for 12 vs 24 weeks in HCV genotype 2 or 3.N Eng J Med2005;352:2609-2617
12)Shiffman ML,Sulter F,Bacon BR et al. Peginterferon alfa-2a plus ribavirin for16 or 24 weeks in HCV genotype 2 or 3.N Eng J Med 2007;357:124-34.
13) Dalgard O,Bjoro K, Hellman KB et al. Treatment with pegylated interferon and ribavirin in HCV infection with genotype 2 or 3 for 14 weeks : a pilot study .Hepatology 2004;41:1260-63.
14) Qureshi S,Batool U,Qureshi O et al.Rapid virological response as a predictor of efficacy of treatment in patients treated with standard interferon and ribavirin in chronic HCV genotype 3 infection. The Pak J of Gastroenterology Oct 2008; 22(2):35-38
15)Azhar MA,Bukhari MH,Ghani U,Khan A,Malik JI,Shah AH. Prevalence of hepatitis C virus and its serotypes in Bahawalpur division. Biomedica Jun 2003;19:18-22
16)Ansari N,Ahmed A, Esmail I,Mujeeb A.HCV serotypes in Karachi: a Liaqat National Hospital experience.J Pak Med Assoc May 2002;52(5):219-20
17)Zuberi SJ,Arif A. Serotyping of the heaptitis C in Pakistan. J Pak Med Assoc May 2002;52(5):218-19
18)Khokhar N,Naila A,Khokhar OS.Hepatitis C serotypes in chronic liver disease.Pak J Med Sci Jun 2002;18(2):156-59
19)Nasir J,Alam B,Shafi MS.Prevalence of genotypes in HCV positive patients in Rawalpindi/Islamabad,Abstract.17th International Congress Of Gastroenterology and G.I. Endoscopy March 23-25,2006.Islamabad
20)Mumtaz K,Hamid S,Moatter T,Abid S,Shah HA,Jaffri N,Jaffri W.Distribution of Hepatitis C virus genotypes and response to treatment in Pakistani patients.JPMA2005;19(1):61
21)Mangia N,Minerva D,Bacca R et al. Factors predictive of relapse in genotype 2& 3 patients treated for 12 weeks with peginterferon alfa 2b and weight based ribavirin combination. Conference report.43rd EASLconference,April23-27,2008,Milan, Italy
22)Von Wagner M,Huber M,Beg et al. Peginterferon alfa 2a and ribavirin for 16 weeks in patients with genotypes 2 or 3 chronic hepatitis C.Gastroenterology 2005;129:522-27.
1.