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Full Length Research paper

Frequency of rapid viral response (RVR) and influence of various factors on the response rates in chronic hepatitis C infected patients treated with interferon and ribavirin combination therapy

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The aim of this study was to determine the frequency of rapid viral response (RVR) and influence of various factors on the response rates in chronic hepatitis C infected patients treated with interferon and ribavirin combination therapy. This study was conducted in Isra University Hospital, Hyderabad-Pakistan and Liaquat University of Medical and Health Sciences, Jamshoro/ Hyderabad, Pakistan, from July 2007 to December 2008. All consecutive adult patients aged between 18 and 65 years who were naïve to interferon-based therapy and fulfilled the following criteria were eligible for this study: anti-HCV antibody, HCV RNA positive, genotype 3, and with elevated ALT (alanine aminotransferase) levels. Statistical analysis was performed using the statistical program for social sciences (SPSS 16.0 for window SPSS Inc: Chicago, IL).This descriptive case series study included 195 consecutive patients of which 113 (57.9%) were male and 82 (42.1%) female. The mean age of the patients was 37.3± 9.62 years. 150 (76.9%) patients were on conventional interferon. Rapid viral response was seen in 167 (85.6%) patients. In univariate analysis, only serum glutamic pyruvic transaminase (SGPT) quotient has shown a statistically significant difference as 96/107 (89.7%) patients with quotient < 2.3 went into RVR as compared to 71/88 (80.6%) patients with >2.3 quotient (p=0.03). In multivariate analysis, SGPT quotient has shown statistical significance with SGPT quotient < 2.3; this indicates that odds ratio of 0.40 (p=0.04) RVR is rapidly becoming a new tool for predicting treatment outcomes in patients with chronic hepatitis C and represents a key opportunity to individualize therapy according to treatment-related viral kinetics

Key words: Hepatitis C, serum glutamic pyruvic transaminase (SGPT), rapid viral response (RVR).

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is estimated to affect 170 million individuals worldwide (Alter, 1997). Hepatitis C virus infection is the major cause of chronic hepatitis and eventually liver cirrhosis and hepatocellular carcinoma in Pakistan (Farooqi and Farooqi, 2000; Durrani et al., 2001). The combination treatment with interferon and ribavirin for 6 to 12 months is the current treatment of choice for chronic hepatitis C infection (Poynared et al., 1998; Mc Hutchison et al., 1998).

In the treatment of chronic hepatitis C with interferon (IFN), there have been few reliable markers of viral infection that predict response to therapy. Genotype and baseline hepatitis C virus (HCV) RNA have been associated with the likelihood of a sustained response, while demographic information such as age, sex, liver

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enzymes, and histology have also been useful (Jenkins et al., 1996).

Although it is apparent that viral clearance (that is, undetectable HCV RNA) is the most reliable initial indicator of sustained biochemical and virological response, just how early an accurate prediction for virological response can be made is still not settled. The presence of early viral response (EVR) at week 12 was considered to be an important predictive factor of sustained viral response (SVR) by the National Institutes of Health (NIH) in 2002 and was a routine part of monitoring patients (National Institutes of Health, 2002). However, recent studies suggest that in patients with chronic hepatitis C treated with interferon and ribavirin, a rapid viral response was frequently an indication of early viral response at week 12, and can predict sustained viral response (Zeuzem et al., 1998). Civeira and Prieto (1999), while reviewing 18 studies involving 988 patients, concluded that undetectable levels of HCV RNA after 4 weeks of therapy correlate with a subsequent SVR in about 50% of patients (positive predictive value), whereas the presence of HCV RNA at 4 weeks correctly predicts failure to achieve SVR (negative predictive value) in over 97% of patients. This would be helpful in limiting unsuccessful treatment for patients with chronic hepatitis C, thus reducing side effects and cost. It would also allow other therapeutic options to be pursued sooner in the course of treatment.

The aim of this study was to determine the frequency of rapid viral response (RVR) and influence of various factors on the response rates in chronic hepatitis C infected patients treated with interferon and ribavirin combination therapy.

MATERIALS AND METHODS

Ethics

The study was conducted in accordance with the principles of the declaration of Helsinki and the International Conference on Harmonization for good clinical practice. All patients provided written informed consent before enrolment.

Patients

All consecutive adult patients aged between 18 and 65 years who were naïve to interferon-based therapy and fulfilled the following criteria were eligible for this study: presence of an anti-HCV antibody (Abbot HCV EIA 2.0 Abbot Diagnostic, Chicago, IL) and HCV RNA for than 6 months, genotype 3 and with elevated ALT (alanine aminotransferase) levels.

Patients were excluded from the study if they had non genotype 3 hepatitis C, neutropenia (neutrophil count < 1500/mm^3), thrombocytopenia (platelet count <90,000/ml^3), co-infection with hepatitis B virus (HBV), chronic alcohol abuse (daily alcohol consumption > 20 g/day), autoimmune liver diseases, decompensated cirrhosis (Child Pugh class B and C), neoplastic disease, organ transplantation or immuno- suppressive therapy, evidence of drug abuse, poorly controlled autoimmune diseases, cardio pulmonary diseases, neuropsychiatric disorders and were unwilling to take contraceptive during the study.

Study design

This descriptive case series study was started in two centers (Isra University Hospital and Liaquat University of Medical and Health Sciences) in Hyderabad-Pakistan from July 2007 and till December 2008. Eligible patients were assigned to receive either once weekly subcutaneous injection of 180 µg pegylated interferon α-2a (Pegasys, F. Hoffmann, La Roche, Basel, Switzerland) or thrice weekly subcutaneous injection of 3 MIU standard interferon α-2b (Bioferon, BIOSIDUS S.A. Constitucion, 4234 (C1254ABX) BuenousAires, Argentina) for 24 weeks. All patients received dosage of ribavirin mg/day according to body weight in two or three divisions. Participants received the study drugs on out patient basis. Furthermore, they received out patient visits to assess the efficacy and safety at monthly interval until the end of therapy. Laboratory tests including blood CBC and serum ALT levels were assessed at each out patient visit. Serum HCV RNA was evaluated qualitatively at base line, and at week 4 of the study (CobasAmplicor HCV monitor V2.0 Roche Molecular Systems Pleasanton CA; with detection cut off level of 50 IU/ml). HCV genotyping was performed at base line by a reverse hybridization technique (Inno-LIPA HCV II, Innogenetics, Ghent, Belgium). The RVR was defined as undetectable HCV RNA by a sensitive qualitative assay test at week 4 of the study.

Assessment of efficacy

The primary efficacy end point was RVR, defined as undetectable HCV RNA by a sensitive qualitative test at week 4 of the study by intention to treat (ITT) analysis. The secondary efficacy end point was to delineate the positive (favorable) predictors of RVR in this population of patients. The base line predictors were: age (<40 years), sex, body weight (<66 kg) at baseline, BMI (<25) at baseline, type of interferon (whether conventional or pegylated), ALT quotient (the average of the serum ALT values before treatment, divided by the upper limit of normal) (<2.3) AST (aspartate aminotransferase) quotient (the average of the serum AST values before treatment, divided by the upper limit of normal) (<2.3), and baseline platelets level (> 150,000 ml^3). The normal value of ALT and AST were taken 33 IU/L in males and 19 IU/L in females (R)

Statistical analysis

This was performed using the statistical program for social sciences (SPSS 16.0 for window SPSS Inc: Chicago, IL). The estimated sample size of 180 patients was based on type I error rate of $\alpha = 0.05$, with the assumption of 60 to 80% RVR in genotype 3 patients treated with conventional or pegylated interferon. The independent student t test was used to compare quantitative variables, and X^2 test or Fischer's exact test was used for qualitative variable. ITT analysis for efficacy was performed on the basis of patient who received at least one dose of the study medication. The secondary efficacy end point was to analyze only in those patients who had tested for pre treatment and week 4 HCV RNA. The relatedness of pre treatment variables to RVR was examined by univariate analysis, multivariate logistic regression analysis and X^2 test. A p-value of <0.05 was considered statistically significant. All the statistical tests were two-tailed.

Table 1. Baseline characteristics of patients.

Quantitative variable	Mean	±Std. deviation
Age of patients	37.3	9.62
SGPT IU/l	74.47	59.59
SGOT IU/l	50.11	34.92
Palelet count 10^9/L	236	62.17
Qualitative variable	**Frequency**	**Percentage (%)**
Male	113	57.9
Female	82	42.1
Diabetes mellitus	19	9.7
Conventional interferon	150	76.9
Rapid viral response	167	85.6

RESULTS

This descriptive case series study included 195 consecutive patients. There were 113 (57.9%) male and 82 (42.1%) female. The mean age of the patients was 37.3± 9.62 years. The mean serum glutamic pyruvic transaminase (SGPT) was 74.47 59.59 IU/l, serum-glutamate-oxaloacetate transaminase (SGOT) levels was 50.11± 34.92, and platelet count 236±62.17× 10^3. Diabetes mellitus was present in 19 (9.7%) patients. 150 (76.9%) patients were on conventional interferon. Rapid viral response was seen in 167 (85.6%) patients (p=0.0001). Table 1 shows the baseline characteristics of the patients. In univariate analysis, only SGPT quotient has shown a statistically significant difference as 96/107 (89.7%) patients with quotient < 2.3 went into RVR as compared to 71/88 (80.6%) patients with >2.3 quotient (p=0.07). Depending on age, type of interferon, sex, and SGOT quotient, diabetes mellitus has shown nonsignificant difference as 116/134 (86.5%) patients < 40 years of age showed RVR as compared to 51/61 (83.6%) patients > 40 years of age (0.66) and 126/150 (84%) patients on conventional interferon based therapy to 41/45 (88%) RVR on peg-interferon based therapy (p=0.33). Table 2 shows univariate analysis performed by Fisher's exact test of chi square. In multivariate analysis, SGPT quotient has shown statistical significance with SGPT quotient < 2.3 showed odds ratio of 0.40 (p=0.04). Table 3 shows multivariate analysis by logistic regression of all variables.

DISCUSSION

The primary endpoint in this study was a rapid virological response (SVR), that is, absence of serum HCV RNA after 4 weeks of the treatment.

In our study, the serum HCV RNA was cleared at 4 weeks in 167 (85.6%) patients. Our study confirms the results of Zeuzem et al. (2004) who saw RVR in 85% of cases. According to them, rapid viral response (RVR: undetectable HCV-RNA at 4 weeks of therapy) emerged as a strong predictor of SVR. In a randomized trial conducted by Von Wagner et al. (2005) involving six tertiary centers, and enrolling 153 patients, RVR was achieved in 92% of the patients with HCV 3; this again shows the importance of rapid viral response as a strong predictor of sustained viral response. According to ACCEL-ERATE study, RVR emerged as the strongest predictor for SVR as patients with RVR and low viral level (LVL) achieved SVR in 94% cases, while those with RVR and high viral levels (HVL) achieved SVR in 88% cases (Shiffman et al., 2007). Only 49% of non-RVR subjects achieved an SVR. Civeira and Prieto (1999), reviewing 18 studies involving 988 patients, concluded that undetectable levels of HCV RNA after 4 weeks of standard IFN and ribavirin therapy correlate with a subsequent SVR in about 50% of patients (positive predictive value), whereas the presence of HCV RNA at 4 weeks correctly predicts failure to achieve SVR (negative predictive value) in over 97% of the patients.

No data is available for prediction of RVR in patients undergoing treatment for HCV, although some data is available for SVR. One such study has been reported that at the age of 20 years, no cirrhosis/bridging fibrosis, ALT quotient ≤ 7,body mass index ≤20 kg/m, and viral load ≤40 × 1062 IU/L was associated with a 97% probability of SVR (Foster et al., 2007).

In our study, SGPT has been found as a statistically significant factor influencing the rapid viral response as SGPT < 2.3 has shown better RVR as compared to > 2.3 in accordance to Bader et al. (2008). One of the most important finding in our study was the nonsignificant difference between standard interferon and peg interferon as far as RVR is concerned in accordance to Mann et al. (2001) who observed 80% sustained viral response with both type of treatments in genotype 2 and 3 hepatitis C. More studies are needed for this important issue because peg interferon is very costly and if there is not much difference between peg interferon and standard interferon, then it would be cost effective in this economically poor country where genotype 3 is more preponderant.

In this study, no significant difference in response was found among the gender, age, weight and the presence of diabetes mellitus. Weaker associations have been reported for gender (women responding better than men) (Poynard et al., 2000; Hayashi et al., 1998) and body weight (Camps, 1993). According to Idress and Riazuddin (2009), age has been seen as a factor for predicting the sustained viral response in patients with hepatitis C.

In this study, the multivariate analysis of the variables associated with RVR found only one significant association with SGPT (odds ratio) and three significant associations with genotype non-1 (odds ratio, 3.25),

Table 2. Univariate analysis performed by Fisher's exact test of chi square.

Parameter	RVR (n = 195)		P value
	Positive n = 167 (%)	Negative n = 28 (%)	
Age in group			0.66
< 40	116 (86.5%)	18 (13.5%)	
> 40	51 (83.6%)	10 (16.4%)	
Type of INF			0.33
CONV	126 (84%)	24 (16%)	
PEG based	41 (88%)	4 (12%)	
Body mass index (kg/m^2)			0.92
< 25	70 (41.9%)	12 (42.9%)	
> 25	97 (58.1%)	16 (57.1%)	
Gender			0.58
Male	95 (84.1%)	18 (15.9%)	
Female	72 (87.8%)	10 (12.2%)	
Weight (in kg)			0.68
< 66	86 (51.5%)	13 (46.4%)	
> 66	81 (48.5%)	15 (53.6%)	
Diabetes mellitus			0.16
Present	14 (73.6%)	5 (27.3%)	
Absent	153 (86.9%)	23 (13.1%)	
SGPT			0.03
< 2.3	96 (89.7%)	11 (10.3%)	
> 2.3	71 (80.6%)	17 (19.4%)	
SGOT			0.75
< 2.3	133 (85.2%)	23 (14.8%)	
> 2.3	34 (87.1%)	5 (12.9%)	

Table 3. Multivariate analysis by logistic regression (n = 195).

Parameter	Adjusted odds ratio	95% Confidence interval	P value
Age > 40 years	0.79	0.34 – 1.83	0.58
Type of interferon(CONV/Peg)	1.90	0.58 - 6.18	0.28
BMI < 25 (kg/m^2)	1.14	0.44 – 2.96	0.78
Gender (male/female)	1.41	0.57 – 3.51	0.54
Weight < 66 (kg)	0.85	0.33 – 2.18	0.74
Presence of diabetes mellitus	2.15	0.66 – 6.98	0.20
SGPT < 2.3	0.40	0.16 – 0.98	0.04*
SGOT < 2.3	1.76	0.48 – 6.43	0.39

age<40 years (odds ratio, 2.60) and body weight < 75 kg(odds ratio, 1.91) (Fried et al., 2002).

Conclusion

RVR is rapidly becoming a new tool for predicting, which patients with hepatitis C have a high likelihood of attaining SVR. In addition, it may identify patients for whom a truncated course of therapy is appropriate. In patients infected with HCV G2 or G3, EVR has little usefulness. In contrast, RVR is an important point at which strategies for shortened treatment regimens can be

evaluated. Additional studies are necessary to improve understanding of the relationship between baseline viral load and RVR and how these factors can be used together to define optimal treatment duration. Shortened courses of treatment may be useful if adverse effects or costs are an issue and are particularly valuable in patients who experience substantial adverse effects that may pose a health risk if treatment is continued. Thus, RVR represents a key opportunity to individualize therapy according to treatment-related viral kinetics.

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