ASSOCIATION BETWEEN BASELINE PARAMETERS AND END OF TREATMENT RESPONSE TO COMBINATION OF CONVENTIONAL INTERFERON & RIBAVIRIN IN PATIENTS WITH CHRONIC HEPATITIS C

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ABSTRACT

Objective: To study the association between baseline parameters and end of treatment response (ETR) to conventional interferon treatment in patients with chronic hepatitis C.

Methodology: This retrospective analytical study was conducted in Gastroenterology department of Lady Reading Hospital Peshawar from January 2012 to June 2012. A total of 222 patients with chronic hepatitis C, on combination of conventional interferon and ribavirin therapy were included in the study who reported with ETR. Various baseline parameters included sex (male vs. female), age (< 40years vs. >40years), weight (<70kg vs. >70kg), viral load (< 800000IU/ml vs. >800000IU/ml) and ALT quotient (<3 vs. >3). These variables were compared with ETR to see for any significant association.

Results: Two hundred and twenty two patients were included in the study out of which 94(42.3%) were male and 128(57.7%) were females. 121(54.5%) of the patient achieved ETR while 101(45.5%) failed to achieve ETR. Among various variables tested weight <70kg (59% vs. 43%) and ALT Quotient >3(70% vs. 50%) were significantly associated with ETR with a p value of 0.01 and p value of 0.013 respectively while there was no statistically significant association between other parameters and ETR.

Conclusion: High baseline ALT and baseline low body weight are significantly associated with better ETR. Among these weight is a modifiable factor and obese patients should be advised to lose weight before embarking them on anti viral therapy in order to improve their chances of viral clearance.

Key Words: Chronic hepatitis C, End of treatment response (ETR), Conventional antiviral therapy.

INTRODUCTION

HCV is a single-stranded positive-sense RNA virus that belongs to the Flaviviridae family and has been classified as the sole member of the genus Hepacivirus[1]. HCV virus is divided into 6 major genotypes (designated by numbers), with sequence similarities of 60% to 70%, and more than 70 subtypes (designated by a lower case letter) within these major genotypes, with sequence similarities of 77% to 80%[2] Furthermore, a high replication rate and the lack of proofreading activity of the viral RNA-dependent RNA polymerase generate a dynamic mosaic of closely related variants, usually referred to as quasispecies within an infected individual. This phenomenon allow chronic infection establishment and may also have important implications in pathogenicity and resistance to antiviral drugs[3].

Hepatitis C virus (HCV), with an estimated 170 million people infected worldwide, is the major causative agent of chronic liver disease, cirrhosis and hepatocellular carcinoma[4]. It is also one of the major health related problem being faced by Pakistan, with prevalence as high as 16% in certain localities[5] Chronic hepatitis C is the only chronic viral infection that can be cured by antiviral therapy. Currently, 40% to 50% of patients infected with

HCV genotype 1 who tolerate full-dose treatment with pegylated interferon and ribavirin achieve a sustained virologic response (SVR) to treatment, defined as absence of HCV RNA in serum six months after discontinuation of treatment; an SVR is almost always associated with a durable eradication of the virus[6,7]. SVR rate in genotype 2 and 3 is from 70% to 80%. Pegylated-interferon alpha (PegIFN-a) and Ribavirin (RBV) combination therapy constitutes the current standard of care for chronic hepatitis C treatment[8,9], however due to marked difference in cost conventional Interferon with Ribavirin is still the preferred 1st line therapy for CHC in Pakistan [10].

Several factors have been attributed with therapeutic response of CHC patients including host factors, viral factors, metabolic factors, histological factors, type of regimen used and duration of infection. A number of host-related factors have been associated with a lower likelihood of response to treatment, such as race, advanced liver fibrosis or cirrhosis, old age, male gender, obesity, lower transaminase levels, and host genetic polymorphisms[11,1 2]. Among the later, the RS12979860 polymorphism near the IL28B gene is the strongest predictive factor of SVR identified so far[12]. With regards to baseline virological factors, high viral loads[13],genotype, high levels of genetic variability within the E1–E2 and NS5A regions, as well as mutations in the so-called interferon sensitivity determining region (ISDR) and Core regions, have been related to therapeutic failure. Nevertheless, such findings have not been found in other studies and remain Controversial[14,15].

Similar correlations are found between other virological responses like RVR and ETR. Among these several variables we chose age, sex, weight, viral load and ALT to see their association with ETR.

This study is thus conducted to find the association between these baseline parameters and end of treatment response to combination of conventional interferon & ribavirin in patients with chronic hepatitis C.

METHODOLOGY

This retrospective analytical study was conducted in Department of Gastroenterology, Lady Reading Hospital Peshawar from January to June 2012. Two hundred and twenty two chronic hepatitis C patients, who successfully completed the conventional anti viral therapy, were included in the study. The conventional interferon was given in a dose of 3 million IU thrice weekly while the dose of ribavirin was 1200 mg in 3 divided doses. Patients were monitored monthly for side effects of treatment and dose was adjusted or additional drugs were given according to standard protocol. At the end of treatment ETR was done in all patients.

Both male and female chronic hepatitis C patients between 15 to 65 years of age with normal baseline HB, TLC, Platelets were included in the study. Patients non responder to previous conventional antiviral therapy, with decompensated cirrhosis, co infection with hepatitis B and uncontrolled diabetes were excluded from the study. Various Baseline parameters studied were sex, age (< 40years vs. >40years), weight (<70kg vs. >70kg), viral load (< 800000IU/ml vs. >800000IU/ml) and ALT quotient (<3 vs. >3). These variables were compared with ETR which is defined as undetectable HCV RNA by quantitative PCR at completion of 6 months of antiviral therapy.

Data was analyzed using SPSS version 17 and presented in the form of percentages of ETR +ve and ETR –ve patients. Logistic regression analysis was done to measure the significance of association using univariate analysis and Odd's ratio was calculated for different variables/parameters under study.

RESULTS

Two hundred and twenty two patients were included in the study out of which 94(42.3%) were male and 128(57.7%) were females. End of treatment response (ETR) was achieved in 121(54.5%) of the patient while 101(45.5%) did not achieve the ETR. Mean age of the patients was 37.95 + 11.23 year with a range of 15 to 62 while the mean weight of the patients was 63.81 + 9.73 kg with range of 40 to 86kg. Further breakup of the variables between ETR +ve and -ve patients is given in the Table 1.

Among various variables tested weight <70kg(59%) vs. >70kg(43%) and ALT quotient>3 (70%) vs. ALT quotient <3 (50%) were significantly associated with ETR with a p value of 0.01 and 0.013 respectively, while in patients with age <40years(52%) vs. >40years(58%), viral load <800000IU/ml(57%) vs. >800000IU/ml(50%) and female sex (57%) vs. male sex (51%) there was no significant difference between two groups with a p values of 0.11, 0.73 and 0.7 respectively. All these p values were calculated using univariate analysis while multiple logistic regression was used to calculate the odd's ratio (Table 2).

DISCUSSION

Our study demonstrated that among several characteristics ALT levels and weight are associated with successful achievement of ETR in patients infected with HCV which is in agreement with other studies. In several studies obesity, insulin resistance, and hepatic steatosis has been associated with decrease chances

Table 1: Patients characteristics

Characteristic	Total	ETR +ve	ETR −ve
Male	94(41.4%)	48(51.06%)	46(48.94%)
Female	128(58.6%)	73(57.03%)	55(42.97)
Age (mean in yr)	37.95	38.55	37.24
Weight (mean in kg)	63.48	62.9	64.89
Viral load (mean IU/ml)	2963369	2639350	3216789
ALT (mean IU/ml)	72	75.79	67.70

Table 2: Statistical analysis of various parameters

Variable		TOTAL	ETR +VE	P VALUE	OR
Gender	Male	94(42.3%)	48(51.06%)	0.7	1.27
	Female	128(57.7%)	73(57.03%)		
Age	<40years	118(53.2%)	61(51.69%)	0.11	0.78
	>40years	104(46.8%)	60(57.69%)		
Weight	<70kg	153(68.9%)	91(59.47%)	0.01	1.90
	>70kg	69(31.1%)	30(43.47%)		
Viral load	<800000IU/ml	139(82%)	79(56.83%)	0.73	1.28
	>800000IU/ml	83(18%)	42(50.60%)		
ALT	ALT quotient<3	178(80.2%)	90(50.6%)	0.013	2.33
	ALT quotient>3	44(19.8%)	27(70.5%)		

of ETR[16,17]. These factors appear to affect the ETR and SVR independently. In a study SVR in patients weighing less than 65 kg was 70% while SVR in patients weighing>65 was 50.46%. (OR=2.277, 95% CI=1.246-4.161, p=0.007)[18].Weight reduction leads to an improved SVR to HCV therapy. Similarly low weight and BMI are associated with better RVR (rapid virologic response) and EVR (early virologic response) as well. In a recent study BMI< 27 was associated with EVR in 59.3% of patients as opposed to 49.3% in patients with BMI>27(p value 0.0001)[19]. In the same study weight <75 was associated with EVR in 58.4% of patients as opposed to 51.5% in patients weighing more than 75 kg(p value 0.0095), however this association was not statistically significant. Similarly in another study BMI>27 was associated with failure to achieve viral clearance at 12 weeks (EVR) in both univariate and multivariate analysis[13]. In our study effect of weight was comparable to other studies.

Serum ALT levels are usually elevated in patients with chronic HCV, but more than half of patients may have a normal ALT level at some point due to its fluctuation.

Serum ALT, a surrogate marker of hepatocyte damage or death, decreases during antiviral treatment, and shows the lowest activity at the end of treatment. Theoretically, the rapid declines in ALT may reflect a rapid decrease of ongoing inflammation in the same manner as removal of the virus. In an older study ALT level (three fold higher than upper limit of the normal) is associated with favorable outcome, however in some recent studies the results of normal ALT is comparable to elevated ALT or there is no association of pretreatment ALT level.[20] In a recent study ALT quotient >3 was associated with ETR in 62.2% of the patients in comparison to 51.5% of ETR in patients with ALT quotient > 3(p value 0.004)[21]. In our study ETR in patients with ALT quotient >3 was higher and statistically significant than ALT quotient<3.

There is mixed data about female sex as a predictor of good response to interferon therapy. Female patients had been shown to achieve higher SVR rates than males in two studies using the combination of standard IFN and RBV (p < 0.004), however, in both of the pegIFN/RBV registration trials, no statistically significant cor-

relation was found between sex and SVR[22]. According to data in the Phase III clinical trials, sex has no impact on SVR response to protease inhibitors Boceprevir and Telaprevir [23,24]. In another study logistic regression identified five independent factors significantly associated with response: genotype 2 or 3, viral load less than 2 million copies/mL, age 40 years or less, minimal fibrosis stage, and female sex[25]. Our data shows a slightly increase percentage of ETR in female patients; however this is not statistically significant on univariate analysis.

Similarly pretreatment viral load predicts the treatment outcome in patients with hepatitis C. A low viral load has consistently been associated with a higher SVR, independent of HCV genotype. Studies have used different cutoff values to define a "low" viral load, with a range of <400,000 IU/ml to <800,000 IU/mL[16]. In a study conducted by Shiffman et al the sustained virological response rates in patients with a pretreatment serum HCV RNA level of 400,000 IU per milliliter was 81% with the 24-week regimen which was more as compared to patients with viral load between 400,000 and 800000(74%) and patients with viral load more than 800,000 viral load(67%) (Odds ratio for ≤400,000 IU per milliliter vs. >800,000 IU per milliliter was 3.01; 95% CI, 2.15 to 4.20; P<0.001; and odds ratio for >400,000 - 800,000 IU per milliliter vs. >800,000 IU per milliliter was1.64; 95% CI, 1.10 to 2.46; P = 0.02)[26]. In a study conducted by Mogaddam A et al SVR in patients with viral load<400,000 IU/ml was 89% while 76% in patients with viral load >400,000 IU/ml[27]. In our study the association was not statistically significant. This may be due to different cutoff value for low and high viral load.

CONCLUSION

High baseline ALT and baseline low body weight are significantly associated with better ETR. Among these weight is modifiable factor and obese patients should be advised to lose weight before embarking them on anti viral therapy in order to improve their chances of viral clearance.

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CONTRIBUTORS