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Delayed Viral Response and its Predictors in Non Responder Chronic Hepatitis C Patients to Conventional Interferon and Ribavirin Therapy

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Research Article

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ABSTRACT

Objective: To determine delayed viral response and its influencing factors in non responders patients of chronic hepatitis C who were not taking any antiviral treatment 6 months after completion of their conventional interferon therapy.
Study Design: Retrospective; Cohort Study
Place and Duration of Study: Department of Medicine, Gastroenterology and Hepatology, SIMS / Services Hospital, Lahore, from January, 2007 to December, 2010.
Methodology: The medical record of non-responder patients of chronic hepatitis C to conventional interferon and ribavirin were retrospectively analyzed as well as their viral status was checked by Real Time Amplification method during 6 months to 2 years post-treatment. Non-compliant and incomplete follow-up cases were excluded. Factors influencing the post-treatment viral response were analyzed by bivariate analysis.
Results: A total of 1175 patients received interferon therapy along with ribavirin; 700 were called, but only 314 came for follow up. Among 70 patients who were non responders to conventional interferon, 5 (7.14%) patients developed delayed response and 65 (92.86%) remained still non responders. Post-treatment delayed self clearance of virus was seen more in male gender, having age >40 years, body weight <70 Kg and normal ALT at the end of treatment. However, there was a statistically significant association between the body weight (OR=0.839, CI: 0.719-0.979, p=0.014) and delayed response of chronic hepatitis c virus. Result depicts that chance of delayed response among over weight non-responder patients decreases to 16.1%.
Conclusion: Post treatment follow up for viral status in non responders patients of

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chronic hepatitis C can be beneficial in the form of delayed response and body weight <70 Kg is its best predictor.

Keywords: Chronic hepatitis C virus; non-responder; delayed viral response; interferon therapy; chi-square; odds ratio;

1. INTRODUCTION

The hepatitis C virus (HCV) is a foremost public health issue and a principal cause of chronic liver disease(Williams, 2006). In Pakistan; about 6% people are infected with hepatitis C virus, with genotype 3 being the most prevalent (Idrees et al., 2009; Jafri and Subhan, 2010).

Chronic HCV infection is usually treated with interferon alpha 2. Pegylated interferon is much better option than conventional interferon and now considered as standard of care for these patients. For genotype 1 and 4, duration of treatment is one year and quantitative HCV-RNA estimation at 12 weeks is recommended for determining whether treatment should be continued or not. In contrast for genotype 2 and 3, the duration of therapy is 6 months and testing for HCV-RNA is considered sufficient at the end of therapy and at six months post antiviral therapy to document End Treatment Response (ETR) and Sustained Virological Response (SVR) respectively. Absence of HCV-RNA from serum by a sensitive Polymerase Chain Reaction (PCR) assay at end of antiviral therapy (i.e. end of either a 24-week or 48-weeks course of therapy) is called ETR while undetectable virus 24 weeks following discontinuation of therapy is referred to as an SVR.

Persons who fail to clear HCV-RNA after 24 weeks of therapy are Non-responders (Ghany et al., 2009). If SVR is achieved, HCV testing should be performed annually for at least 2 years after completion of therapy, and if patient relapse or is non responder to conventional interferon, then re-treatment with pegylated interferon is advised (Jacobson et al., 2005; Shiffman et al., 2004; Taliani et al., 2006).

Known factors predictive of response to treatment in chronic hepatitis C include low serum HCV-RNA level, non genotype 1, absence of cirrhosis, age younger than 40 years, lack of steatosis or obesity, mode of acquisition of infection, and white race (Alberti and Benvegnu, 2003; Strader, Wright, Thomas, & Seeff, 2004). A body mass index higher than 30 has been associated with poor response to therapy. Weight reduction, in turn leads to improved outcome (McCullough, 2003).

According to our best knowledge there is not a single study available in literature in which issue of delayed response have been raised. Keeping in view this situation we aim to determine post treatment viral status, delayed viral clearance and associated factors in non-responder patients of chronic hepatitis C who were not taking any treatment after completion of their conventional interferon therapy.

2. MATERIALS AND METHODS

A retrospective analysis of the record of patients of chronic hepatitis C, who were treated with conventional interferon and ribavirin provided by “Prime Minister Programme for

Prevention and Control of Hepatitis", from January, 2007 to December, 2009 at Department of Medicine, Gastroenterology and Hepatology, Services Hospital, Lahore, was done. A total 1175 patients were treated. Out of these, 700 patients who had completed treatment with regular visits were called for follow up during July, 2010 to December, 2010.

Only 314 patients responded, among which 70 patients of genotype 2 and 3 were included in the study on the basis of:

1. Failure to achieve ETR with conventional interferon and ribavirin
2. The time from end of treatment to their visit between 6 months to 2 years
3. Patient not taking any re-treatment

The serum of these non responders patients were tested for HCV-RNA quantitatively by Real Time Amplification method of PCR with lower limit of detection 125 IU per ml. The available data of these patients about different variables during their 6 month interferon therapy was evaluated retrospectively. The result of PCR test performed within 2 years after end of treatment, gender, fatty liver on ultrasound, history of diabetes, abnormal Alanine Aminotransferase (ALT) at start of treatment and at the end of treatment were the qualitative variables while age, weight, ALT, hemoglobin (Hb), platelet count and white blood cells (WBC) at start of treatment, and ALT at end of treatment were quantitative variables. Investigation data was interpreted in negative or positive values.

Frequencies and percentages were computed for presentation of qualitative variables and means and standard deviations were calculated for quantitative variables. Chi-square test was applied to determine any significant association between delayed response and its predictors at 5% level of significance. A p-value of equal to or less than 0.05 was assumed as significant. More over in order to find the risk, odd ratio with their 95% CI (confidence interval) was also found. All data was analyzed by SPSS version 15.

3. RESULTS AND DISCUSSION

A total of 1175 patients received interferon therapy along with ribavirin and 700 were called, but only 314 came for follow up visit. Out of these 314, only 70 patients who were non responders to conventional interferon and ribavirin were included. About 37 (52.9%) patients were males and 33 (47.1%) females. Thirty nine (55.7%) patients have weight equal or more than 70 Kg, 52 (74.3%) have fatty liver on ultrasound and 16 (22.9%) were diabetic. Only 5 (7.1%) patient have their ALT within normal limit at the start of interferon therapy while 21 (30%) patients have normal ALT at the end of interferon therapy even though they did not achieved ETR (Table 1).

The mean age of patients with Standard deviation was 40.13 ± 6.97 years and mean weight 66.96 ± 11.53 kg. The mean value of ALT was 55.19 ± 26.77 IU/L with a range of (16.0 - 10.4 IU/L). The mean value of WBC count was 7715.71 ± 1368.23/ mm^3 with a range of 5300 - 9800/ mm^3. Similarly, the mean platelets count was 228, 314 ± 31,660/mm^3 with a range of (150,000 – 291,000/mm^3) (Table 2).

Table 1. Frequency distribution of qualitative variables (n=70)

Variable	Category	Frequency	Percentage
Gender	Male	37	52.9
	Female	33	47.1
Weight	*<70Kg*	*31*	*44.3*
	>70Kg	39	55.7
Fatty Liver on ultrasound	Yes	52	74.3
	No	18	25.7
History of Diabetes	Yes	16	22.9
	No	54	77.1
HCV-PCR within 6 months to 2 years post-treatment	Detected	65	92.9
	Not-detected	5	7.1
ALT at start of treatment	Normal	5	7.1
	Abnormal	65	92.9
ALT at end of treatment	Normal	21	30
	Abnormal	49	70

ALT= Alanine Aminotransferase; HCV-PCR=Hepatitis C Virus-Polymerase Chain Reaction

Table 2. Descriptive statistics of quantitative variables (n=70)

Quantitative variables	Minimum	Maximum	Mean± SD
Age (years)	30	57	40.13±6.97
Weight (Kg)	48	89	69.96±11.53
ALT at start of treatment(U/L)	16	104	55.19±26.77
ALT at end of treatment(U/L)	19	122	38.79±26.90
Hb at start of treatment(g/dl)	10	14	12±1.07
WBCs Count at start of treatment(/mm^3)	5300	9800	7715.71±1368.23
Platelet count at start of treatment(/mm^3)	150,000	291,000	228,314.29±31660.58

ALT= Alanine Aminotransferase; Hb=Hemoglobin; WBC=White Blood Cells

Among 70 non-responders, 5 (7.14%) were delayed responders and 65 (92.86%) remained still non-responders within 6 month to 2 years after the completion of the therapy. Post treatment delayed self clearance of virus was seen 1.750 times more likely in male than female, in patients with age >40 years, having body weight <70 Kg and normal ALT at the end of treatment. However there was a statistically significant association between the body weight <70 Kg and slow response of chronic hepatitis c virus (OR=0.839, 95%CI=0.719-0.979, p=0.014) (Table 3).

Table 3. Slow Response within 6 months to 2 years post-treatment (n=70)

Predictors	Category	Persistent Non-responders	Slow responders	Odd ratio (95% Confidence interval	p-value
Gender	Male	35	2	1.750 (0.274-11.179)	0.661
	Female	30	3		
Age(years)	<40	40	1	6.400 (0.676-60.573)	0.152
	≥40	25	4		
Weight(Kg)	<70	26	5	0.839 (0.719-0.979)	0.014
	≥70	39	0		
Fatty Liver on Ultrasound	No	47	5	0.904 (0.828-0.988)	0.318
	Yes	18	0		
History of Diabetes	No	50	4	0.833 (0.086-8.034)	1
	Yes	15	1		
ALT at start of treatment	Abnormal	60	5	0.923 (0.861-0.990)	1
	Normal	5	0		
ALT at end of treatment	Abnormal	47	2	3.917 (0.604-25.409)	0.155
	Normal	18	3		
Hemoglobin (g/dl)	<12	40	3	1.067 (0.166-6.836)	1
	≥12	25	2		

In this retrospective analysis of 700 chronic hepatitis C patients receiving conventional interferon and ribavirin therapy with their record maintained at Department of Gastroenterology and Hepatology, Services Hospital Lahore, a large number of patients 386 (55%) were lost to follow-up, either due to financial problem or lack of interest and awareness about their health issues.

Among 70 non responder patients, 5 patients (7%) showed delayed virological response beyond 6 month after stopping interferon therapy. The inherently high mutational rate of Hepatitis C virus may be resulting in considerable heterogeneity in the genome, (Pawlotsky, 2003) as a consequence of the RNA-dependent RNA polymerase of HCV. Thus created a lack of 3′-to-5′-exonuclease proofreading ability to remove the mismatched nucleotides incorporated during replication with an average of one error for every 10^4 to 10^5 nucleotides copies and favoring a high viral turnover rate; 10^{10} to 10^{12} virions are produced per day (Neumann AU, 1998). Because of these functional differences in HCV proteins, genetic variation of the genome confers advantages by evading or inhibiting the host immune system, whereas other mutations may be lethal to the virus itself if they lead to defective replication machinery. Similarly interferon in these delayed responder patients might have made the replication machinery defective resulting in delayed virological response. Other possibility may be the laboratory error. However in these 5 cases, reports were from different laboratories that minimize the chance of laboratory error.

Various factors were studied to predict this delayed response, which was more in males, having age >40 years, body weight <70 Kg and normal ALT at the end of treatment. However the only statistically significant association ascertained was between the body weight <70 Kg and delayed response of chronic hepatitis c virus. Patients weighing more than 70 kg showed about 16.1% poor response compared to those weighing 70 kg or less, which is similar to the earlier studies (Qureshi et al., 2009; Rubbia-Brandt et al., 2001). This data reveals poor response in the patients with heavier weight, either due to obesity or a need for dose adjustment according to weight as suggested in an earlier study (Manns et al., 2001).

Shiffman et al. identified genotype 2, viral load less than 400,000 IU/ml, age 45 or less, weight $\leq$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 (Shiffman et al., 2007). A meta-analysis also revealed low viral load, age < 40 years and low body weight were predictors of better outcome (Strader et al., 2004) .

At this moment exact statistics about the delayed response of virus in non-responder cases of hepatitis C is not well documented. Therefore, we recommend that further studies should be conducted with sufficiently large sample size to find out an average time for which clinician should have to wait before re-treatment with new methodology in non-responders. So that the patients can be given chance of delayed self virological clearance and thus re-treatment may avoided.

4. CONCLUSION

This study concludes that post treatment follow up for viral status in non responders patients of chronic hepatitis C can be beneficial in the form of delayed response. Among the predictive factors (gender, age, weight, fatty liver, diabetes, ALT at the start of treatment, ALT at the end of treatment, Hb. Concentration) only body weight is found to be significantly associated with delayed virology response.

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