ORIGINAL ARTICLE

Gamma Glutamyl Transferase Level as A Predictor of Sustained Virologic Response in Patients Treated With Interferon and Ribavirin for Chronic Hepatitis C Infection

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ABSTRACT

Aim: To determine normal ɣ-glutamyl transferase(GGT) level at End of Treatment Response(ETR) as a predictor of sustained virological response (SVR) in patients with Hepatitis C Virus (HCV) treated with Standard interferon α2b and ribavirin therapy.
Study Design: Quasi Experimental Study
Place & duration of study: Medical Out Patient Department (OPD) and Hepatology Clinic, Mayo Hospital, Lahore from September 2015 to September, 2016.
Methods: All patients presenting in the Medical Out Patient Department and Hepatology Clinic of Mayo hospital, were inducted in the research after acquiring a written consent. Patients who had completed 24 weeks of therapy with standard interferon α2b and ribavirin were investigated for qualitative HCV RNA to see ETR and GGT at the baseline. Patients were assigned into two groups, one (Group I) having normal GGT and the other with raised GGT (Group II) which is further more categorized into 2 times the elevation from normal (Group II-A) or less than twice (Group II-B).
Results: At ETR all 128 patient's RNA level was <50 IU/ml. Among these patients GGT was normal among 80(62.5%) patients (Group I), GGT was raised but less than twice the normal value in 43(33.6%) patients (Group II-A) and in 5(3.9%) patients (Group II-B) GGT was more than 2 times normal value. At 24th week after achieving ETR, statistically noticeable relation was seen between GGT level and viral load. Normal GGT level was seen in patients having HCV RNA less than 50 IU/ml as compared to those patients having HCV RNA greater than 50 IU/ml. GGT level at ETR was compared with results of PCR at 24th week.
Conclusion: Normal gamma glutamyl transferase level at ETR was a reliable marker of sustained virologic response in patients who received standard interferon therapy along with ribavirin for chronic infection with hepatitis C.
Keywords*:* ɣ-glutamyltransferase, End of Treatment Response, Sustained virological response, Ribavirin

INTRODUCTION

Chronic hepatitis C has worldwide distribution affecting approximately 170 million population[1]. Hepatitis C virus (HCV) is very common in Pakistan and unfortunately its expected to increase in coming years due to unsafe medical practices. In their study, Umer et al showed that in Pakistan prevalence of HCV among adults is 6.8%, while the prevalence of active HCV infection is 6%[2]. Hepatitis C is a viral illness, infectious in nature, caused by HCV which affects liver[3]**.** HCV belongs to Flaviviridae of the genus Hepacivirus[4]. HCV is a RNA virus with human as the only reservoir[5]. HCV can be classified into 6 genotypes[6]. Approximately 90% of infection in United States of America is caused by genotypes 1, 2, and 3[7]**.** But genotypes 1, 3, and 6 accounts for hepatitis C infection in Asia[8].

Hepatitis C has incubation period of approximately 6-7 weeks and its symptoms are vague and mild[9]. Spontaneous resolution is seen in 15%-25% of cases, more commonly in infants and young women[10]**.**

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The diagnosis of chronic HCV infection is based on the presence of both anti-HCV antibodies and HCV RNA, detected by enzyme immunoassays and molecular assays respectively. Furthermore HCV genotype and subtype can be determined via various method including genotype specific real timepolymerase chain reaction(PCR[11].

Approximately 55-85% of acute hepatitis C infection leads to chronic infection by evading the host immune response[12]**.** As the incidence of chronic infection increases so does their dreadful complication such as cirrhosis and hepatocellular carcinoma. WHO data suggests that 700,000 people die annually from hepatitis C related disease and its complications[13]. This significant increase in morbidity and mortality leads to high economic burden for any country. Among different chronic viral infections, Chronic hepatitis C infection can be treated with therapy[14]. Therefore successful treatment can alleviate such complications.

Treatment of chronic HCV infection has two goals. The first is to achieve sustained virologicalresponse(SVR) and second is to prevent complications. Predicting SVR for chronic HCV has been difficult and challenging.

The enzyme ɣ-glutamyltransferase(GGT) accelerates the process of devolution of ɣ-glutamyl group from glutathione (GSH) and other ɣ-glutamyl compounds to animo acids and dipeptid[15]**.** It is also involved in the breakdown of the ɣ-glutamyl bond. The enzyme is found in many organs but liver is the main source[16]. Reduce levels of ɣ-glutamyltransferase before treatment has shown to be associated with higher rate of SVR in certain studies[17].

Study done by James Everhart et al showed that ɣ-glutamy ltransferase is an independent foreteller of virological response in liver disease due to HCV[18]. Hamish Innes et al also reported GGT as a valuable predictor of SVR in patients with Chronic HCV undergoing interferon and ribavirin therapy[19]**.** Study conducted by Kau, Vermehren and Sarrazin showed low GGT level was an independent predictive factor for SVR in patients with Chronic HCV and should be considered for pre-treatment screening[20].

The above mentioned research has shown that pre-treatment normal GGT was an independent predictor of SVR in HCV patients. But studies showing elevated GGT at end of treatment (ETR) for predicting SVR has yet to be seen. So, this study aims to show the relationship between GGT levels at ETR and the outcome of treatment response.

Owing to its long treatment course and serious life threatening complications, the overall economic burden of HCV is very high. If proven, this study will help us to identify the patients who will achieve SVR or not. So, patients with high GGT at end of treatment can be evaluated for further treatment and normal GGT at end of treatment can be used as an economical marker of SVR.

MATERIAL AND METHODS

All patients presenting in the Medical Out Patient Department and Hepatology Clinic who fullfil the operational definition and satisfy the inclusion criteria were registered in the research after getting a written consent. The eligible candidates i.e. who have undergone all routine baseline investigation before start of the therapy Including liver biochemistry, prothrombin time, renal function, complete blood count, TFT, blood sugar, HCV RNA , HCV genotyping, abdominal ultrasound and completed 24 weeks of therapy with standard interferon α2b and ribavirin were investigated for qualitative HCV RNA to see ETR and GGT at the baseline. While patients with Co-infection with hepatitis B,alcohol intake, decompensated liver disease, diagnosed case of hepatocellular carcinoma, patients taking anti epileptic drug (Carbamazepine, Valproic Acid, Phenytoin) Oral Contraceptive Pills, Furosemide and Methotrexate were excluded from the study. Patients were divided into two groups, one with normal GGT and the other with raised GGT which is further categorized into 2 times the elevation from normal or less than twice. Then GGT and qualitative HCV RNA was repeated 6 months after achieving ETR to look for Sustained Virological Response (SVR).

The data was analyzed in the SPSS 20. Continuous variables like age was expressed in the form of mean±SD. Categorical variables like sex was expressed in the form of frequencies (percentage). Association between normal GGT, elevated GGT and treatment response was determined using Chi Square. The inferences with p value of <0.05 was taken as significant and accordingly conclusions of the study was made.

RESULTS

In this study 42(32.8%) patients were in the age group 15-30 years, 60(46.9%) patients were in the age group 31-45 years and 26(20.3%) patients were in the age group 40-60 years.

Gender distribution of patients showed that there were 60(46.88%) male and 68(53.12%) female patients included in the study**.** At ETR all 128(100%) patient's PCR result showed undetectable HCV RNA level (<50 IU/ml). At 24th week 69(53.9%) patients RNA level was <50 IU/ml and 59(46.1%) patients RNA level was >50 IU/ml.

At ETR 80(62.5%) patients GGT level was normal, 43(33.6%) patients GGT level was less than 2 times the normal value and 5(3.95%) patients GGT level was more than 2 times.

At 24th week 79(61.7%) patients GGT level was normal, 38(29.7%) patients GGT level was less than 2 times the normal value and 11(8.6%) patients GGT level was more than 2 times. At ETR all 128 patients RNA level was <50 IU/ml. Among these patients GGT was normal among 80(62.5%) patients, GGT was less than 2 times normal value in 43(33.6%) patients and in 5(3.9%) patients GGT was more than 2 times normal value (Table1)**.** At 24th week 69 patients RNA level was <50 IU/ml and 59 patients RNA level was >50 IU/ml. Patients whose RNA level was <50 IU/ml among them GGT was normal in 61(88.4%) patients however patients whose RNA level was >50 IU/ml among them GGT was normal in only 18(30.5%) patients only. Less than 2 times normal value of GGT was seen in 7(10.1%) patients whose RNA level was <50 and patients whose RNA level was >50 among them GGT value was less than 2 times the normal value in 31(52.5%) patients. As per this trend patients with RNA level <50 IU/ml had significantly higher number of patients whose GGT level was normal as compared to those patients whose RNA level was >50 IU/ml. i.e. p-value=0.000. GGT level at ETR was compared with PCR results of 24th week. Results showed 60 patients achieved SVR who had a normal GGT levels at ETR (i.e <50 IU/L) as compared to just 20 patients who achieved SVR despite a higher GGT levels at ETR. 9 patients with GGT level between 50-100 IU/L also achieved SVR. 39 patients with GGT >50 IU/L at ETR didn't achieved SVR and among them 34 had GGT levels between 50-100 IU/L and 5had levels more than 100 IU/L. In terms of p-value, statistically significant difference was seen for normal level of GGT at ETR in patients with RNA level <50 IU/ml and with RNA level >50 IU/ml at 24th week (SVR). i.e., p-value=0.000 (Table2).

Table1: ETR in relation to ɣ-glutamyltransferase (GGT)

GGT	**PCR after 24 Weeks**		**Total**
	<50 IU/ml	**>50 IU/ml**	
Normal	80(62.5%)	0(0%)	80
Less than 2 times	43(33.6%)	0(0%)	43
More than 2 times	5(3.9%)	0(0%)	5
Total	*128*	*0*	128

Table-2: PCR results after 24 weeks after ETR in relation to ɣ-glutamyltransferase (GGT-1)

GGT at ETR	**PCR after 24 Weeks**		**Total**
	<50 IU/ml	**>50 IU/ml**	
Normal	60(87%)	20(33.9%)	80
Less than 2 times	9(13%)	34(57.6%)	43
More than 2 times	0(0%)	5(8.5%)	5
Total	*69*	59	128

Chi-Square Test= 38.99
p-value= 0.000

DISCUSSION

The advancement in the treatment of chronic hepatitis C has occurred rapidly in previous two decades. With emergence of interferon freedirect-acting antivirals(DAAs), therapy for chronic hepatitis C has become easy, patient friendly and highly effective. But the costs of these newer therapies are very high and beyond reach of common people of developing nation. So, the interferon-based regimes are still used in such under-developed countries. These old inferferon therapies have lower success rate and predicting the treatment response has been a major challenge for clinicians. Many studies have been conducted to analyze the predictors of sustained virologic response. Some are found to be quite reliable but expensive to perform requiring advance equipment and expertise and some are cheap but not that reliable. As gamma glutamyltransferase is a cheap and widely available test, proving it as a reliable predictor for SVR will be a boon for society. Therefore, it is a matter of great interest to have knowledge about gamma glutamyltransferase as the indicator of sustained virologic response in chronic hepatitis C[21].

The GGT enzyme accelerates the breakdown of extracellular glutathione (GSH) in the translocation of amino acids and peptides through cell membranes, forming a “gamma-glutamyl cycle”. GGT is found in hepatocytes, intestines, biliary tract, heart, kidney, pancreas, spleen, and brain. However, it may be raised in liver disorder, cholestasis, intake of hepatotoxic drugs, as an indicator of alcohol use in pancreatitis, and relation with coronary heart diseases risk. In spite of several studies, there is negligible data indicating the curative response of GGT in chronic hepatitis C. That is why, there is interest in knowing about the p value of GGT as a predictor of response in regards Management of chronic hepatitis C in poor countries like Pakistan is out of reach for the poor patients, as therapy comprising of newer and expensive drugs are far from reach, thus conventional interferon-based therapy is being used. Predicting treatment outcome , using cheap and easily available laboratory test like gamma-glutamyl transferase will be beneficial for the treating clinicians and for the poor patients as well. Thus, this study has shown that normal gamma glutamyltransferase level at end of the therapy is a reliable indicator of sustained virologic response in patients managed with standard interferon and ribavirin for chronic hepatitis C.

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