LETTER TO THE EDITOR

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A Low Serum γ-Glutamyltransferase Level Predicts a Sustained Virological Response in Patients with Chronic Hepatitis C Genotype 1

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Güzelbulut *et al*.[1] recently demonstrated that low γ-glutamyltransferase (GGT) level does not predict a sustained virological response (SVR), although it may be a predictor of high fibrosis scores. However, in a lot of studies, low baseline GGT level was shown to be an independent predictor of a SVR.[2-5] Thus, we planned a retrospective study to evaluate whether low GGT level is an independent predictor of a SVR in hepatitis C virus (HCV) genotype 1 patients treated with peginterferon α-2a at a dose of 180 μg per week and peginterferon α-2b at the standard dose, 1.5 μg/kg of body weight per week, both in combination with oral ribavirin (RBV) at a dose of 1,000 to 1,200 mg per day, according to body weight (<75 kg, 1,000 mg per day; ≥75 kg, 1,200 mg per day).

Medical records of patients with chronic HCV, who were treated between the years 2008 and 2012 at the Adana Numune Training and Research Hospital in Turkey, were retrospectively reviewed. Eligible patients had chronic HCV genotype 1 infection with compensated liver disease and a detectable plasma HCV-RNA level, and had not been previously treated for hepatitis C infection. Patients who were on treatment or withdrew because of adverse events or were lost during follow-up were excluded. Patients were also excluded if they had co infection with hepatitis B or human immunodeficiency virus, any other cause of liver disease such as alcohol abuse or autoimmune hepatitis, morbid obesity (body mass index, >40), poorly controlled diabetes mellitus, a severe psychiatric disorder, or active substance abuse. Finally 114 patients who are followed up for at least 6 months after completion of treatment were included in the study. Most patients had undergone liver biopsy within 6 months before screening. The liver histology was graded by the histological activity index (HAI) according to criteria of Ishak *et al*.,[6] which comprise two major components namely HAI and fibrosis.

Baseline serum alanine aminotransferase (ALT) and GGT values were recorded. HCV-RNA levels were measured with the use of the Cobas TaqMan assay (Roche Diagnostic, Milan Italy), which has a lower limit of quantitation of 20 IU per milliliter. Measurements were obtained at baseline; weeks 4, 12, 24, and 48 during the treatment period; and follow-up weeks 24. Rapid virological response (RVR) was defined as the undetectable serum HCV-RNA level at the end of 4 weeks. Patients with undetectable HCV-RNA at week 12 were said to have a complete early virological response (cEVR). End of treatment response (ETR) was defined as the undetectable serum HCV-RNA level at the end of treatment. SVR was defined as the undetectable serum HCV-RNA levels at 24 weeks after completing treatment. The study was approved by our institutional review board and was conducted in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines.

Data management and statistical analyses were performed with SPSS version 18.0.0 Release for Windows (IBM Co., Armonk, NY, USA). Student t-test was used to assess the significance of baseline characteristics and virological responses between groups. Univariate analysis and multiple logistic regression were used to identify predictive factors for sustained response and high GGT levels. A $p<0.05$ was considered as statistically significant.

We categorized 114 patients into two groups according to the initial GGT level being high (group 1) or normal (group 2). Baseline characteristics and virological responses in group 1 and 2 were summarized in Table 1. GGT levels were elevated in 43 patients (37.7%). Overall, SVR rate was 55%. Initial ALT level was higher in group 1. ALT levels were related to GGT levels ($r=0,279$, $p<0.05$).

In the multiple logistic regression for the strength of influence factors, RVR, cEVR, and low GGT were identified as independent significant predictive factors for SVR (Table 2). Presence of cirrhosis and male gender (unlike the study of Güzelbulut *et al*.[1])

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Table 1. Comparison of Baseline Characteristics and Virological Responses of Patients in Group 1 and 2

Characteristic	High GGT level (group 1, n=43)	Low GGT level (group 2, n=71)	p-value*
Age, yr	57.9±10.0	57.8±10.7	0.964
Male sex	33 (76.7)	23 (32.4)	0.000
Weight, kg	80.3±12.8	74.1±11.4	0.068
Initial GGT, IU/L	125.1±137.8	25.4±11.9	0.000
Initial ALT, IU/L	88.5±101.1	53.3±54.0	0.017
Initial HCV-RNA, $\log_{10}$ IU/mL	6.0±1.1	5.8±1.0	0.296
Steatosis	30 (69.8)	45 (63.4)	0.701
RVR	15 (34.9)	26 (36.6)	0.853
cEVR	29 (67.4)	53 (74.7)	0.411
ETR	22 (51.2)	54 (76.1)	0.006
SVR	15 (34.9)	44 (62.0)	0.005
ISHAK score			
Biopsy of receipt	29 (67.4)	48 (67.6)	0.986
Histological activity index	9.5±3.5	8.0±2.9	0.060
Fibrosis score	3.1±1.5	2.8±1.2	0.211
Cirrhosis (F5-6)	8/29 (27.6)	4/48 (8.3)	0.024

Data are presented as mean±SD or number (%).
GGT, γ-glutamyltransferase; ALT, alanine aminotransferase; HCV, hepatitis C virus; RVR, rapid virological response; cEVR, complete early virological response; ETR, end of treatment response; SVR, sustained virological response.
*Student t-test.

were significantly associated with high serum GGT levels (Table 3).

Treatment with peginterferon α-2a or peginterferon α-2b, plus RBV, for 48 weeks is the standard treatment for patients infected with HCV genotype 1. So, the rates of RVR, EVR, ETR, and SVR were similar among patients infected with HCV genotype 1 who received peginterferon α-2a or peginterferon α-2b, in combination with RBV in our previous study.[7]

There are some pretreatment factors related to SVR. The viral factors are HCV genotype and serum HCV-RNA levels at baseline, and numerous host factors include age, sex, race, weight, liver fibrosis, and insulin resistance.[8] Recently, an interleukin-28 polymorphism has been acknowledged as powerful pretreatment predictor of SVR.[9] Serum GGT levels have shown to be elevated in 32% to 63% of patients with chronic HCV infection.[2] In a lot of studies, low baseline GGT level was shown to be an independent predictor of a SVR.[2-5] Our findings were consistent with these studies in contrast to study of Güzelbulut *et al*.[1]

Once treatment is initiated, the monitoring of viral responses such RVR and EVR can further aid in predicting treatment response.[10] Also, there is a positive correlation between the magnitude of the decrease in HCV-RNA at week 4 and the probability of SVR.[11] So, we demonstrated that, patients with a ≥3 $\log_{10}$ drop in HCV-RNA at week 4 have a high probability of achieving an SVR in the patients treated with either peginterferon α-2a-RBV or peginterferon α-2b-RBV.[12] In this study, SVR and cEVR were identified as most independent significant predictive factors for SVR (Table 2).

Table 2. Multivariate Analysis of Factors Associated with Sustained Virological Response

Parameter	Odds ratio (95% CI)	p-value
Female gender	1.76 (0.92–3.36)	0.087
Low GGT level	2.79 (1.28–6.08)	0.009
RVR	7.05 (3.1–16.05)	0.000
cEVR	17.55 (6.32–48.76)	0.000

CI, confidence interval; GGT, γ-glutamyltransferase; RVR, rapid virological response; cEVR, complete early virological response.

Table 3. Multivariate Analysis of Factors Associated with High γ-Glutamyltransferase Level

Parameter	Odds ratio (95% CI)	p-value
Cirrhosis	4.19 (1.13–15.50)	0.028
Male sex	6.89 (2.90–16.35)	0.000

In conclusion low serum GGT level predicts a SVR in patients with chronic hepatitis C genotype 1. Also, presence of cirrhosis and male gender were independent predictors of high serum GGT level in our study.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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