

Rapid normalization of alanine aminotransferase predicts viral response during combined peginterferon and ribavirin treatment in chronic hepatitis C patients

Yun Jung Kim, Byoung Kuk Jang, Eun Soo Kim, Kyung Sik Park, Kwang Bum Cho, Woo Jin Chung, and Jae Seok Hwang

Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea

Background/Aims: The treatment for chronic hepatitis C (CHC) is removal of the virus in order to prevent progression to liver cirrhosis and hepatocellular carcinoma (HCC). Few data have been presented regarding the clinical significance of changes in the alanine aminotransferase (ALT) level in this context. We analyzed the patterns of changes in ALT level and investigated the relationship between the rapid normalization of ALT and sustained virologic response (SVR) after combined treatment with peginterferon and ribavirin. **Methods:** CHC patients (n=370) were classified into four groups according to the initial ALT level and subsequent changes: (1) initially abnormal ALT level and sustained abnormal ALT level during treatment, (2) initially abnormal ALT level but achievement of ALT normalization, (3) initially normal ALT level and variable ALT abnormality during treatment, and (4) initially normal ALT level and sustained normalization of ALT level during treatment. We subdivided groups 1 and 2 into those with patterns of decreased and normalization of ALT, with or without rapid normalization. We checked the end-treatment response (ETR) and SVR rates in each group and the factors associated with SVR, including patterns of changes in ALT level. **Results:** A total of 168 patients completed the therapy (age=54.34±10.64 years [mean±SD], 95 males [56.5%], genotype 1:82 [48.8%]). SVR was achieved in 115 (68.45%) of the completely treated patients. The SVR rate was significantly lower in group 1 than in group 2 (37.8 vs. 81.6%, $P<0.001$), and significantly higher in the rapid normalization group than in the group without rapid normalization (78.5% vs. 41.2%, $P<0.001$). Multiple logistic regression analysis revealed that age (odds ratio [OR]=0.94, 95% confidence interval [CI]=0.91-0.98, $P=0.005$), viral genotype (OR=2.76, 95% CI=1.20-6.38, $P=0.017$), and initial hepatitis C virus RNA titer (OR=0.28, 95% CI=0.10-0.75, $P=0.012$) were identified as independent significant predictive factors for SVR. **Conclusions:** The SVR rate is significantly associated with normalization, and especially rapid normalization of ALT. Rapid normalization of ALT by 4 weeks after treatment might be a useful response factor that is readily available in clinical practice, and especially for genotype 1 patients. (*Korean J Hepatol* 2012;18:41-47)

Keywords: Hepatitis C; Chronic; Ribavirin; Alanine transaminase; Peginterferon

See Editorial on Page 29

INTRODUCTION

Hepatitis C virus (HCV) infection is an important cause of

chronic liver disease and primary hepatocellular carcinoma (HCC) in the world.¹ The likelihood of achieving sustained virological response (SVR) could be predicted based on several factors, including virus genotype, age, sex, histological finding and initial HCV RNA titer. These factors have been reported in many previous studies,^{2,3} but

Received July 29, 2011; Revised December 5, 2011; Accepted December 19, 2011

Abbreviations: ALT, alanine aminotransferase; APRI, AST platelet ratio index; BMI, body mass index; CHC, chronic hepatitis C; ETR, end-treatment response; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; SVR, sustained virologic response

Corresponding author: Jae Seok Hwang

Department of Internal Medicine and Institute of Gastroenterology and Hepatology, Keimyung University School of Medicine, 56 Dalseong-ro, Jung-gu, Daegu 700-712, Korea

Tel. +82-53-250-7088, Fax. +82-53-250-7088, E-mail: gastro@dsmc.or.kr

Copyright © 2012 by The Korean Association for the Study of the Liver

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/3.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

the pattern of change in alanine aminotransferase (ALT) during treatment has not been completely established. In clinical practice, ALT is an important laboratory test marker, both inexpensive and readily available for monitoring HCV disease activity.

Therefore, the goal of this study was to evaluate the relationship between the patterns of change in ALT during treatment and virologic response to peg-interferon alpha and ribavirin combination treatment in chronic hepatitis C (CHC), and to establish the clinical meaning of rapid normalization of ALT.

PATIENTS AND METHODS

Patients

We retrospectively reviewed the medical records of patients diagnosed with chronic hepatitis C who underwent peg-interferon alpha and ribavirin combination treatment from May 2004 to May 2010 at Keimyung University Dong San Hospital. A total 370 consecutive patients were considered for this study. Patients who were on treatment or withdrew because of adverse events or were lost during follow-up were excluded. We also excluded patients with human immune-deficiency virus infection, hepatitis B virus co-infection, alcohol abuse, autoimmune hepatitis and other causes of liver disease. Thus, final analyses included 168 patients followed up for at least 6 months after completion of treatment.

Study design

ALT patterns were analyzed throughout the course of treatment and follow-up period. We categorized patients into four groups according to initial ALT levels and ALT variability during treatment: group 1, patients who had initial abnormal ALT levels and sustained abnormal ALT levels during treatment (Gr 1), group 2, patients who had initial abnormal ALT levels and obtained normalization of ALT (Gr 2), group 3, patients who had initial normal ALT levels and variable ALT abnormality during treatment (Gr 3) and group 4, patients who had initial normal ALT levels and sustained normal ALT levels during treatment (Gr 4) (Fig. 1). We compared the end treatment response (ETR) and SVR rates between groups, based on the eradication of virus (Table 1).

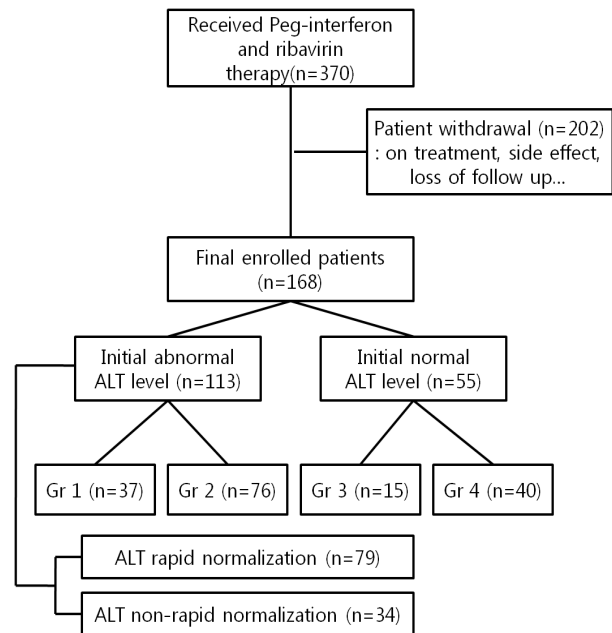


Figure 1. Schematic diagram showing patient group flow according to initial alanine aminotransferase (ALT) level and subsequent pattern of change. Group 1, initially abnormal ALT level and sustained abnormal ALT level during treatment. Group 2, initially abnormal ALT level but achievement of ALT normalization. Group 3, initially normal ALT level and variable ALT abnormality during treatment. Group 4, initially normal ALT level and sustained normalization ALT level during treatment.

Also for analysis of decreased and normalization of ALT pattern, patients who had initial abnormal ALT levels (i.e. Gr 1 and 2) were subdivided into two groups: (1) patients who had initial abnormal ALT levels with rapid normalization, i.e. within 1.5 times of normal range of ALT 4 weeks after starting treatment and (2), patients who had initial abnormal ALT levels without rapid normalization, i.e. not within 1.5 times of normal range of ALT 4 weeks after starting treatment.

Treatment with peg-interferon plus ribavirin

Patients with genotype 1 infection were subcutaneously administered 180 µg of peg-interferon alpha-2a (Pegasys[®], Roche, Seoul, Korea) or 1.5 µg/kg of peg-interferon alpha-2b (PEG-Intron[®], Schering Corp, Seoul, Korea) once a week, and orally administered 1,000 mg (for patient weighing <75 kg) or 1,200 mg of ribavirin daily (for those weighing >75 kg) for 48 weeks. Patients with genotype non-1 infections received the same dosage of peg-interferon alpha-2a or -2b and 800 mg per day of oral ribavirin for 24 weeks.

Table 1. Baseline demographic, clinical characteristics, and virologic responses in patients with different patterns of change in alanine aminotransferase (ALT) level during treatment (n=168)

Variable/group	Gr 1* (n=37)	Gr 2† (n=76)	Gr 3‡ (n=15)	Gr 4§ (n=40)	P-value
Age (years, mean±SD)	55.5±9.3	54.1±11.4	53.9±10.6	53.9±10.6	0.89 ^{**}
Gender (male, %)	21 (56.8)	48 (63.2)	7 (46.7)	19 (47.5)	0.35 ^{††}
BMI (kg/m ² , mean±SD)	24.4±3.2	23.6±2.7	24.3±2.2	23.9±2.8	0.52 ^{**}
Initial ALT (IU/L, mean±SD)	122.8±86.2	109.4±61.0	29.1±11.2 ^{‡‡}	29.7±8.4 ^{‡‡}	<0.01 ^{**}
Initial APRI score	1.8±2.2	1.0±1.1	1.7±3.4	0.7±0.9 ^{‡‡}	0.01 ^{**}
Cirrhosis confirmed by image	13 (35.1)	13 (17.1)	4 (26.7)	7 (17.5)	0.14 ^{††}
HCV genotype 1/non-1 (%)	20/17 (54.1/45.9)	36/40 (47.4/52.6)	6/9 (40/60)	20/20 (50/50)	0.81 ^{††}
HCV RNA (n, %)					0.19 ^{††}
<400000	16 (43.2)	34 (44.7)	4 (26.7)	9 (22.5)	
≥400000, <800000	10 (27.0)	16 (21.1)	3 (20.0)	10 (25.0)	
≥800000	11 (29.7)	26 (34.2)	8 (53.3)	21 (52.5)	
ETR (%)	31 (83.8)	70 (92.1)	13 (86.7)	38 (95)	0.34 ^{††}
SVR (%)	14 (37.8)	62 (81.6)	8 (53.3)	31 (77.5)	<0.01 ^{††}

*Patients who had initial abnormal ALT levels and sustained abnormal ALT levels during treatment; †Patients who had initial abnormal ALT levels and obtained normalization of ALT; ‡Patients who had initial normal ALT levels and variable ALT abnormality during treatment; §Patients who had initial normal ALT levels and sustained normal ALT levels during treatment; ††Chi-squared test; **Anova test; ||,‡‡Same symbols indicate no statistical significance based on Turkey's HSD post-hoc test.

BMI, body mass index; ALT, alanine aminotransferase; APRI, AST (aspartate amine transferase) platelet ratio index; HCV, hepatitis C virus; ETR, end treatment response; SVR, sustained virologic response.

Clinical and laboratory assessment

We followed patients by performing blood samples and measuring biochemical variables. Blood samples were tested for complete blood counts (CBC), serum ALT levels, serum aspartate amine transferase (AST), HCV genotype (baseline only) and serum HCV RNA. Serum ALT levels were obtained from all patients at baseline and at weeks 4, 12, 24 and 48 of peg-interferon alpha and ribavirin combination treatment, and 24 weeks after completing therapy. The upper normal for serum ALT was 45 IU/L. Body mass index (BMI) was calculated as weight in kilograms/height square in meters. AST platelet ratio index (APRI) score was calculated according to the formula proposed by Wai et al⁴ in 2003, namely, [(AST/upper limit of normal)/platelet count (10⁹/L)]×100. The reference value for AST was considered to be 40 IU/L, which is the upper normal limit in our laboratory.

Assessment of efficacy

The primary end point of efficacy was SVR. i.e. the undetectable serum HCV RNA levels at 24 weeks after

completing treatment. ETR was defined as the undetectable serum HCV RNA level at the end of treatment. Virologic relapse was defined as the detectable HCV RNA level during follow-up in patients with previously undetectable HCV RNA level at the end of treatment.

Statistical analysis

Data management and statistical analyses were performed with SPSS software version 15.0 (SPSS Inc., Chicago, IL). Rates and proportions were calculated for categorical data. Means were calculated for continuous variables. The chi-square and Fisher's exact tests were used to compare the distribution of categorical variables between the groups, respectively. To compare continuous variables among groups, Student's *t*-test or ANOVA test was used as appropriate. Univariate analysis and multiple logistic regression were used to identify predictive factors for sustained response. In multiple logistic regression analysis, we determined the strength of influence of possible variables (age, viral genotype, HCV RNA titer and ALT variability) for sustained response. A *P*-value of <0.05 was considered as statistically significant.

RESULTS

Patient demographics

Of the 370 patients, 202 patients withdrew because of adverse events, were lost during follow-up, or were on treatment or diagnosed with co-infection with hepatitis B or other liver disease. Total 168 patients followed up for at least 6 months after treatment ended were finally enrolled. The baseline characteristics of the patients are summarized in Table 1. The mean age of patients was 54.34±10.64 years (range, 28-76 years). The gender distribution was 95 males and 73 female and the genotype distribution was 82 of genotype 1 and 86 of non-genotype 1.

Virologic responses according to ALT variability during treatment

For analysis purposes, patients were divided into four groups based on initial ALT levels and ALT variability during treatment. Of the 168 patients treated with peg-interferon-ribavirin combination, 115 (68.45%) showed SVR and 53 (31.55%) showed non-sustained response. The ETR and SVR rates in the four groups were listed in Table 1. The ETR rates was not significantly different between the four groups. The SVR rate was significantly lower in group 1 compared with group 2 patients (37.8 vs. 81.6%, P -value <0.001), but was not different between group 3 and 4.

Virologic responses according to rapid/non-rapid normalization of ALT levels 4 weeks after treatment

For analysis purposes, the baseline characteristics of the

patients who had initial abnormal ALT levels are summarized in Table 2. Baseline clinical characteristics including age, gender, initial ALT level and genotype were not different between the two groups. However, the SVR rate was significantly higher in rapid normalization group compared to without rapid normalization group (78.5 vs. 41.2%, P <0.001).

For subanalysis of SVR rates with or without rapid normalization of an initially abnormal ALT level according to genotype are summarized in Figure 2. The SVR rate was significantly higher in rapid normalization, especially in genotype 1 group compared to genotype non 1 group (P =0.01 in genotype 1 group vs. P =0.11 in genotype non-1 group).

Analysis of factors that predicted sustained virological response to combination therapy

We performed univariate analysis using the chi-square test to investigate the association of SVR with various factors. Age, sex, viral genotype, initial RNA titer, patterns of changes in ALT and BMI were selected as possible significant factors. In the multiple logistic regression for the strength of influence factors, age (OR 0.94; 95% CI 0.91-0.98; P -value=0.005), viral genotype (OR 2.76; 95% CI 1.20-6.38; P -value=0.017), initial HCV RNA titer (OR 0.28; 95% CI 0.10-0.75; P -value=0.012) were identified as independent significant predictive factors for SVR (Table 3).

Among patients who had initial abnormal ALT levels (Gr 1-2), the SVR rate was significantly higher in group 2, compared with group 1. In the multiple logistic regression, compared to group 1, group 2 had significantly higher SVR

Table 2. Comparison of baseline clinical characteristics and virologic responses in patients with or without rapid normalization of an initially abnormal ALT level during treatment

ALT normalization	Group 1* (n=79)	Group 2† (n=34)	P-value
Age (years, mean±SD)	54.9±11.0	53.8±10.1	0.61‡
Gender (male,%)	49 (62.0)	20 (58.8)	0.75§
Initial ALT (IU/L, mean±SD)	105.3±51.7	133.3±99.1	0.05‡
Genotype I (n, %)	39 (49.4)	17 (50.0)	0.95§
ETR (n, %)	73 (92.4)	28 (82.4)	0.18§
SVR (n, %)	62 (78.5)	14 (41.2)	<0.01§

*Patients who had initial abnormal ALT levels with rapid normalization, i.e. within 1.5 times of normal range of ALT 4 weeks after starting treatment; †Patients who had initial abnormal ALT levels without rapid normalization, i.e. not within 1.5 times of normal range of ALT 4 weeks after starting treatment; ‡Student's t -test; §Chi-squared test.

ALT, alanine aminotransferase; ETR, end treatment response; SVR, sustained virologic response.

rate (OR 10.51; 95% CI 3.68-22.99; $P < 0.001$), as well as group 4 (OR 9.85; 95% CI 2.99-32.37; $P < 0.001$) (Table 3).

DISCUSSION

Chronic hepatitis C (CHC) is the third most common cause of chronic liver disease and HCC in Korea, following hepatitis B virus (HBV) infection and alcohol.⁵ The successful treatment of CHC is measured by the virological and biochemical response and by histological improvement to clearance of virus, for preventing liver cirrhosis and HCC.

There were attempts to determine non-responders as early as possible in order to avoid prolonged treatment without benefits.⁶ In an effort to determine whether patients could be preselected for treatment, many studies have attempted to identify clinical or virological features that may distinguish CHC patients who may or may not respond to interferon therapy.^{3,7} Those studies showed that pretreatment prognostic features statistically associated with favorable response included younger age, female gender and absence of cirrhosis. Low levels of pretreatment serum HCV RNA and the presence of viral genotype other than 1 were also reported to be associated with favorable response to CHC therapy.^{2,3,8} However, there were patients who had responded to combination therapy, but did not meet the specified pretreatment characteristics.⁷ Thus, the effort to identify useful predictive markers, especially during treatment is still necessary.

In the natural history of HCV infection, it is well known

that the first detectable biochemical marker is the presence of HCV RNA and elevation of ALT level may occur, within 4 to 12 weeks.⁹ Although this elevation reflected hepatocyte damage, ALT level may fluctuate sometimes, and a single value in the normal range can neither rule out active infection nor help gauge the severity of underlying liver disease.¹⁰ In general, decreased pattern of ALT level is the accepted basic indicator of interferon therapeutic effect in CHC, and several studies have shown that delayed

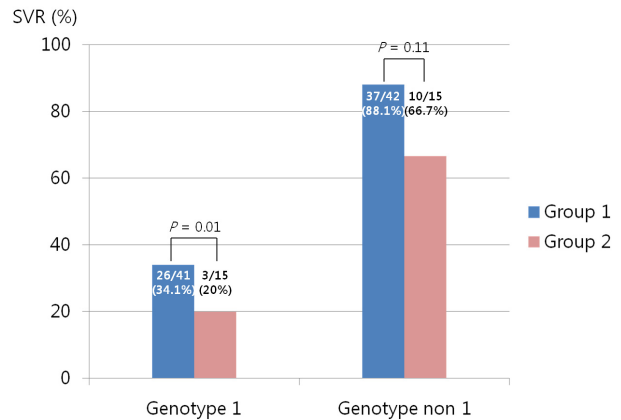


Figure 2. Comparison of virologic responses in patients with or without rapid normalization of an initially abnormal ALT level according to genotype. Group 1, initially abnormal ALT level with rapid normalization (i.e., within 1.5 times the normal range of ALT level by 4 weeks after starting treatment). Group 2, initially abnormal ALT level without rapid normalization (i.e., not within 1.5 times the normal range of ALT level by 4 weeks after starting treatment). Levels of statistical significance (i.e., P) were calculated using the chi-squared test. SVR, sustained virologic response.

Table 3. Independent factors associated with a sustained virologic response (SVR) in chronic hepatitis C (CHC) treatment: multivariate analysis

	Odds ratio	95% CI	P -value
Age (years)	0.94	0.91-0.98	0.005
Gender (male)	0.64	0.28-1.46	0.286
Genotype (non-1 type)	2.76	1.20-6.38	0.017
BMI (kg/m^2)	0.93	0.80-1.08	0.332
Initial HCV RNA (<400000)	1.00		
≥ 400000 , <800000	0.98	0.33-2.98	0.975
≥ 800000	0.28	0.10-0.75	0.012
Group 1 (Abnormal→Abnormal)	1.00		
Group 2 (Abnormal→Normal)	10.51	3.68-29.99	<0.001
Group 3 (Normal→Abnormal)	2.51	0.62-10.25	0.199
Group 4 (Normal→Normal)	9.85	2.99-32.37	<0.001

BMI, body mass index; HCV, hepatitis C virus; ALT, alanine aminotransferase.

normalization of ALT level might indicate poor response to interferon therapy,^{6,11} although the viral response was not always associated with biochemical response.^{6,12} However, Hung et al⁶ observed that 13% of CHC patients who obtained SVR to standard interferon and ribavirin treatment showed persistently elevated ALT levels during treatment; in contrast, in the study by Zeuzem et al¹³ using peg-interferon and ribavirin, 41% of patients did not achieve ALT normalization until the end of therapy. These findings seem to suggest that lack of ALT normalization is not necessarily associated with decreased efficacy of treatment. However, this phenomenon has not been systematically characterized, and little is known about its incidence and clinical characteristics in chronic hepatitis C patients treated with peg-interferon and ribavirin combination therapy.

In our study, we subdivided patients into four groups, according to initial ALT levels and ALT variability during treatment. In the analysis of virological response according to ALT variability, we found significantly different SVR rates between the four groups. In particular, compared to group 1 (initial abnormal ALT and sustained abnormal ALT levels after treatment), group 2 (initial abnormal ALT and obtained normal ALT levels after treatment) had significantly higher SVR rate, as well as group 4 (initial normal ALT and sustained normal ALT levels after treatment). In clinical practice, normalization and sustained normal ALT level after treatment could be a good predictive factor for obtaining SVR.

Rapid normalization of ALT was defined in this study as normalization within 1.5 times of normal ALT levels 4 weeks after treatment. Its concept is similar to rapid virological response (RVR), which means undetectable serum HCV RNA determined by quantitative PCR after 4 weeks of treatment, and is rapidly becoming a useful tool for predicting treatment outcomes in patients with CHC. Indeed, in our analysis, rapid normalization of ALT 4 weeks after treatment was a cost effective and useful tool that predicted obtaining of SVR as soon as possible. These results supported previous reports showing that absence of ALT level elevation during treatment was associated with SVR,¹⁴ whereas failure to return to normal ALT level was a strong predictor of combination treatment failure.¹⁵ Thus, SVR rate was significantly associated with ALT normalization during combination treatment in patients with initial abnormal ALT levels; in particular, rapid normalization of

ALT during treatment in genotype 1 group might be considered as useful response factor in clinical practice, for patients with initial abnormal ALT levels.

During the natural course of CHC treatment, some patients may continue to show abnormal ALT levels despite of virological response. As demonstrated in previous studies, these patients had persistent rises in ALT during follow-up, but they had eradicated HCV RNA from serum and were classified as sustained responders.¹⁶ The reasons for this discrepancy remain unclear, but previous studies have also indicated that some of these patients may have cirrhosis, steatosis, thyroid dysfunction or other potential causes for the persistently abnormal biochemical results.⁷ In our study, 37 patients had persistent abnormal ALT level during follow-up, but 37.8% of them had eradicated HCV RNA from serum and obtained SVR. Basso et al¹⁷ reported the incidence and clinical meaning of elevated ALT in chronic hepatitis C virus RNA-negative patients, during peg-interferon and ribavirin combination therapy. Among 173 study patients, 57 patients (33%) had elevated ALT in at least one evaluation from initial normal ALT level and the authors mentioned that this phenomenon, especially in the latter phase of therapy, was more common in relapsing patients. Moreover, peg-interferon and ribavirin treatment-induced elevations of liver enzymes have been observed, and the underlying liver disease might be exacerbated if the relationship between viral replication and the host immune response is altered. Therefore, in clinical practice, any potential cause, as well as the patterns of changes in ALT during treatment should be considered.

In our study, to further evaluate the relationship between ALT variability during treatment and virologic response to peg-interferon and ribavirin combination therapy, we stratified four groups by the patterns of change in ALT in patients with chronic hepatitis C. Also, the new concept of rapid normalization of ALT levels after 4 weeks of treatment was closely related to SVR. It is noteworthy that ALT variable pattern during peg-interferon and ribavirin combination therapy is a phenomenon that may be encountered in clinical practice, although its incidence and clinical meaning have not been fully elucidated. To the best of our knowledge, no study has been conducted to date, classifying patients according to rapid normalization of ALT during treatment and investigating the clinical meaning and association with SVR.

Results of this study are subjected to some limitations. First, the study had retrospective and observational design and was conducted in a single institution. Thus, our results may not reflect a general situation. Second, our analysis was carried out in a relatively small number of patients, and it will be interesting to determine whether this incidence and association holds true in larger groups of patients. Third, we did not investigate chronic hepatitis C patients according to disease progression, including cirrhosis and hepatocellular carcinoma, and did not include patients with liver disease of other origins. Thus, in future studies, analysis of ALT variability during treatment should be performed according to liver status. Fourth, several factors previously known as main putative causes for ALT variability, were not investigated in our study (i.e. thyroid dysfunction, lipid profile, HOMA-IR, the use of herb medication and alcohol consumption).

In conclusion, in patients with initial abnormal ALT levels, the SVR rate was significantly associated with ALT normalization during combination therapy; ALT normalization during treatment might be considered as useful predictive factor for obtaining SVR in patients with initial abnormal ALT levels. In particular, rapid normalization of ALT 4 weeks after treatment in genotype 1 group might be considered an indicator of favorable response to treatment, readily available in clinical practice.

Conflict of interest

None of the authors have any conflict of interest to disclose.

REFERENCES

1. Tong MJ, Lee SY, Hwang SJ, Co RL, Lai PP, Chien D, et al. Evidence for hepatitis C viral infection in patients with primary hepatocellular carcinoma. *West J Med* 1994;160:133-138.
2. Lee SS, Heathcote EJ, Reddy KR, Zeuzem S, Fried MW, Wright TL, et al. Prognostic factors and early predictability of sustained viral response with peginterferon alfa-2a (40KD). *J Hepatol* 2002;37:500-506.
3. Ferenci P, Fried MW, Shiffman ML, Smith CI, Marinos G, Gonçalves FL Jr, et al. Predicting sustained virological responses in chronic hepatitis C patients treated with peginterferon alfa-2a (40 KD)/ribavirin. *J Hepatol* 2005;43:425-433.
4. Wai CT, Greenon JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. *Hepatology* 2003;38:518-526.
5. Lim YS. Current status of liver disease in Korea: hepatitis C. *Korean J Hepatol* 2009;15(Suppl 6):S25-S28.
6. Hung CH, Lee CM, Lu SN, Wang JH, Tung HD, Chen TM, et al. Is delayed normalization of alanine aminotransferase a poor prognostic predictor in chronic hepatitis C patients treated with a combined interferon and ribavirin therapy? *J Gastroenterol Hepatol* 2002;17:1307-1311.
7. Tong MJ, Blatt LM, McHutchison JG, Co RL, Conrad A. Prediction of response during interferon alfa 2b therapy in chronic hepatitis C patients using viral and biochemical characteristics: a comparison. *Hepatology* 1997;26:1640-1645.
8. Yamada G, Takatani M, Kishi F, Takahashi M, Doi T, Tsuji T, et al. Efficacy of interferon alfa therapy in chronic hepatitis C patients depends primarily on hepatitis C virus RNA level. *Hepatology* 1995;22:1351-1354.
9. Hoofnagle JH. Course and outcome of hepatitis C. *Hepatology* 2002;36(Suppl 1):S21-S29.
10. Puoti C, Magrini A, Stati T, Rigato P, Montagnese F, Rossi P, et al. Clinical, histological, and virological features of hepatitis C virus carriers with persistently normal or abnormal alanine transaminase levels. *Hepatology* 1997;26:1393-1398.
11. Davis GL, Lindsay K, Albrecht J, Bodenheimer HC Jr, Balart LA, Perrillo RP, et al. Clinical predictors of response to recombinant interferon-alpha treatment in patients with chronic non-A, non-B hepatitis (hepatitis C). The Hepatitis Interventional Therapy Group. *J Viral Hepat* 1994;1:55-63.
12. Civeira MP, Prieto J. Early predictors of response to treatment in patients with chronic hepatitis C. *J Hepatol* 1999;31(Suppl 1):237-243.
13. Zeuzem S, Feinman SV, Rasenack J, Heathcote EJ, Lai MY, Gane E, et al. Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000;343:1666-1672.
14. Jeong SW, Kim JD, Woo HY, You CR, Lee SW, Song MJ, et al. Impact of adherence to peginterferon-ribavirin combination therapy in chronic hepatitis C patients on achieving a sustained virologic response. *Korean J Hepatol* 2009;15:338-349.
15. Davis GL, Lau JY. Factors predictive of a beneficial response to therapy of hepatitis C. *Hepatology* 1997;26(Suppl 1):122S-127S.
16. Blatt LM, Tong MJ, McHutchison JG, Russell J, Schmid P, Conrad A. Discordance between serum alanine aminotransferase (ALT) and virologic response to IFN-alpha2b in chronic hepatitis C patients with high and low pretreatment serum hepatitis C virus RNA titers. *J Interferon Cytokine Res* 1998;18:75-80.
17. Basso M, Giannini EG, Torre F, Bianchi S, Savarino V, Picciotto A. Elevations in alanine aminotransferase levels late in the course of antiviral therapy in hepatitis C virus RNA-negative patients are associated with virological relapse. *Hepatology* 2009;49:1442-1448.