

## Research Paper

# Alanine Aminotransferase Elevation during Peginterferon Alpha-2a or Alpha-2b plus Ribavirin Treatment

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## Abstract

Alanine aminotransferase (ALT) elevation was occasionally observed during the treatment with combination peginterferon alpha plus ribavirin. Two forms of peginterferon are currently available as a standard of care with or without direct-acting antivirals against hepatitis C virus (HCV). Until the appearance of interferon-sparing regimen, peginterferon alpha plus ribavirin will play a central role in the eradication of HCV. In the present study, we compared ALT elevations in response to peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin in HCV genotype-1-infected patients. There were no significant differences in ALT elevations between treatments with the two peginterferons, but in a comparison of the proportions of patients with transient ALT elevation from baseline between the two groups, transient ALT elevation was observed more in sustained virological response (SVR) patients treated with peginterferon alpha-2a than with peginterferon alpha-2b. However, no patients discontinued treatment due to ALT elevation. Patients with transient ALT elevation from baseline during the treatment had less favorable IL28B rs8099917 genotype in the peginterferon alpha-2b group. Patients achieving SVR tended to have lower ALT levels, although some had persistent ALT elevation during treatment. In conclusion, clinicians should pay attention to possible ALT elevation during the treatment of chronic hepatitis C patients.

Key words: ALT, HCV, IL28B, Peginterferon, Ribavirin.

## INTRODUCTION

Peginterferon alpha-2a or peginterferon alpha-2b plus ribavirin has been the current standard of care treatment for chronic hepatitis C [1-3]. Even after the appearance of the new standard of care, telaprevir- and boceprevir-including regimens, peginterferon plus ribavirin will still be needed to eradicate hepatitis C virus (HCV) until interferon-sparing regimens finally become available [4-8]. Peginterferon alpha-2a is a subcutaneous formulation of interferon alpha-2a, produced by its attachment to a 40-kDa branched

polyethylene glycol moiety by a stable amid bond [9]. A semi-synthetic form of interferon alpha-2b, by attaching to a 12-kDa mono-methoxy polyethylene glycol, has been developed as peginterferon alpha-2b, which fulfills the requirements of a long-acting interferon alpha protein while providing significant clinical benefits [10].

Elevations of alanine aminotransferase (ALT) levels were occasionally observed while interferon alpha or peginterferon alpha was administered to

HCV-infected patients [11-15]. HCV infection is persistent in the majority of instances in the face of a humoral and cellular immune response [16]. Previous studies suggested that cytotoxic T lymphocytes as well as antibodies to viral epitope, crucial in the eradication of virus-infected hepatocytes, cannot completely eliminate HCV and may contribute to chronic liver injury. It is possible that some changes in ALT levels were dependent on this HCV pathogenesis [12,14]. ALT elevation was also reported as one of the side effects of interferon alpha [18]. Chronic hepatitis C sometimes presents features such as autoimmune hepatitis [19], and there are several reports of interferon inducing autoimmune liver diseases and causing ALT elevation in chronic hepatitis C patients [11,13,15]. Thus, ALT elevation is often observed during the treatment of chronic hepatitis C and occasionally leads to life-threatening disease [20-22].

Peginterferon alpha is currently available in two forms: peginterferon alpha-2a and peginterferon alpha-2b. Thus, in the present study, we designed a retrospective study to compare ALT elevations in response to peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin in HCV genotype-1-infected patients. We also determined IL28B rs8099917 and investigated its effects on ALT eleva-

tion.

## MATERIALS AND METHODS

### Patients

Chronic hepatitis C patients with genotype 1 who visited Chiba University School of Medicine Hospital between August 2004 and June 2012 and were treated with peginterferon alpha plus ribavirin were consecutively included and analyzed in this study. Of them, 41 and 60 patients were treated with peginterferon alpha-2a and alpha-2b, respectively (Table 1). Patients were eligible if they met the following inclusion criteria: (1) infected with HCV genotype 1, (2) age  $\geq$  20 years, (3) diagnosed as chronic hepatitis C, (4) no pregnancy, (5) no severe heart disease, (6) no abnormal hemoglobinemia, (7) no chronic renal failure, (8) no mental disorder, (9) no severe hepatic failure, (10) no autoimmune disorder, (11) no drug allergy for interferon or for nucleos(t)ide analogues including ribavirin, (12) no current intravenous drug abuse, and (13) no HIV infection [23,24]. The study protocol was approved by the Ethics Committee of Chiba University School of Medicine (No.1462) and conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

**Table 1.** Baseline characteristics of patients in the present study.

	Total patients	PegIFN alpha-2a	PegIFN alpha-2b	P-values
Number of patients	101	41	60	
Age (years)	54.7 $\pm$ 11.3	52.9 $\pm$ 11.8	56.2 $\pm$ 10.8	NS
Gender (male/female)	52/49	21/20	31/29	NS
Body mass index (kg/m <sup>2</sup> )	23.0 $\pm$ 3.6	22.6 $\pm$ 3.7	23.3 $\pm$ 3.5	NS
IL28B, major/minor	67/34	30/11	37/23	NS
HCV viral load (high/low)	100/1	41/0	59/1	NS
AST (IU/L)	59.8 $\pm$ 52.8	59.4 $\pm$ 47.7	60.1 $\pm$ 56.1	NS
ALT (IU/L)	71.5 $\pm$ 67.5	71.7 $\pm$ 65.6	71.4 $\pm$ 69.1	NS
$\gamma$ -GTP (IU/L)	60.7 $\pm$ 79.3	67.9 $\pm$ 96.0	55.3 $\pm$ 65.4	NS
Hemoglobin (g/dL)	14.1 $\pm$ 1.1	14.0 $\pm$ 1.1	14.1 $\pm$ 1.1	NS
Platelet ( $\times 10^4/\mu$ L)	19.2 $\pm$ 23.3	17.5 $\pm$ 4.8	20.2 $\pm$ 30.0	NS
AFP (ng/mL)	9.2 $\pm$ 8.8	10.0 $\pm$ 11.1	8.6 $\pm$ 6.7	NS
HbA1c (%)	5.1 $\pm$ 0.54	5.2 $\pm$ 0.69	5.1 $\pm$ 0.31	NS
Total cholesterol (mg/dL)	178 $\pm$ 30.4	184 $\pm$ 26.8	174 $\pm$ 32.1	NS
Treatment-naive (%)	72 (71.2)	30 (73.1)	42 (70)	NS
Adherence, good/poor	75/26	32/9	43/17	NS
RVR (%)	12 (11.8)	9 (21.9)	3 (5)	0.023
EVR (%)	50 (49.5)	23 (56.0)	27 (45.0)	NS
SVR (%)	50 (49.5)	20 (48.7)	30 (50.0)	NS

IL28B, IL28Brs8099917; Adherence was evaluated by 80/80/80 (>80% of PegIFN dose, >80% of ribavirin dose, >80% treatment duration) [28]. Adherence good: 80/80/80 (+); adherence poor: 80/80/80 (-); RVR, rapid virological response; EVR, early virological response; SVR, sustained virological response; NS, not statistically significant difference.

## Treatment and definition of virological response

Peginterferon alpha-2b (Peg-intron; MSD, Tokyo, Japan) was administered as a once-weekly dose of 1.5 µg/kg (weight-based dosing). Peginterferon alpha-2a (Pegasys; Chugai Pharmaceutical CO., LTD, Tokyo, Japan) was used as a once-weekly dose of 180 µg. Ribavirin was administered according to weight-based dosing (600 mg for patients ≤ 60kg, 800 mg for patients weighing 60 to 80 kg, and 1,000 mg for patients > 80 kg). Patients received 48 weeks of treatment with either peginterferon alpha-2a plus ribavirin (Copegus; Chugai Pharmaceutical CO., LTD, Tokyo, Japan) or 48 weeks of treatment with peginterferon alpha-2b plus ribavirin (Rebetol; MSD, Tokyo, Japan).

Clinical and laboratory assessments were performed at 4, 12, 24 and 48 weeks after the commencement of therapy and after the 24-week follow-up period. Adverse reactions were investigated by patient interviews, physical examinations and laboratory tests. Patients with negative HCV RNA within the initial 4 weeks of treatment were considered to have had rapid virological response (RVR). Patients who had negative HCV RNA within the initial 12 weeks of treatment were considered to have had complete early virological response (cEVR) (described as EVR in this article). Sustained virological response (SVR) was defined as negative serum HCV RNA at 24 weeks after the end of treatment [6,23].

## Measurement of HCV RNA in plasma and laboratory tests

HCV RNA was measured by COBAS TaqMan HCV test (Roche Diagnostics, Tokyo, Japan) (range 1.2-7.8 log IU/mL). A qualitative result below the lower limit of quantification was also determined as being either positive or negative [23]. HCV serotype was examined by serological genotyping assay [25]. Measurement of serum HCV RNA, serum ALT levels (range 8-42 IU/L), and other biochemical tests were carried out by standard methods every 4 weeks before, during the treatment, and for at least 24 weeks after the end of treatment.

## DNA extraction and TaqMan SNP assay for IL28B rs8099917

To prepare DNA samples from blood cells, we used DNA Extract All Lysis Reagents (Applied Biosystems Inc., Foster City, CA, USA). A specific TaqMan genotyping assay was performed for rs8099917. Primers were manufactured by Applied Biosystems. Thermal cycling was performed with the ABI Step

One real-time PCR system according to the manufacturer's protocol. Activation of TaqMan GTXpress Master Mix (Applied Biosystems) and the initial denaturation cycle was at 95°C for 20 seconds, followed by 40 cycles at 95°C for 3 seconds and 60°C for 20 seconds. We analyzed IL28B rs8099917 TT as major type and TG/GG as minor type in the present study [26, 27]. The study protocol for IL28B analysis was approved the Ethics Committee of Chiba University School of Medicine (No.282/333).

## Statistical analysis

Data are expressed as mean ± standard deviation (SD). Differences were evaluated by Student's t-test or chi-square test.  $P < 0.05$  was considered statistically significant.

## RESULTS

### Baseline characteristics

One hundred one patients infected with HCV genotype 1 were enrolled in the present study. Baseline characteristics of the patients are shown in Table 1. All patients were Japanese, and had a median age of 54.7 years (range: 20 - 72); 52 (51.4%) patients were men. Patients over 64 years of age accounted for 19 of 101 (18.8%). IL28B rs8099917TT, TG and GG, respectively, were 30, 11 and 0 in the peginterferon alpha-2a group, and 37, 21 and 2 in the peginterferon alpha-2b group [*not statistically significant difference (NS)*]. There were no differences in patient characteristics between the peginterferon alpha-2a and peginterferon alpha-2b groups. Eleven and 18, respectively, were re-treated patients in the peginterferon alpha-2a and peginterferon alpha-2b groups. Of the 11 (26.8%) retreated patients in the peginterferon alpha-2a group, 7, 3 and 1 were relapse, null and unknown of previous response. Of the 18 (30.0%) retreated patients in the peginterferon alpha-2b group, 3, 10 and 5 were relapse, null and unknown of previous response. Only one patient in the peginterferon alpha-2b group had lower than 5 log IU/mL of HCV RNA at baseline (Table 1).

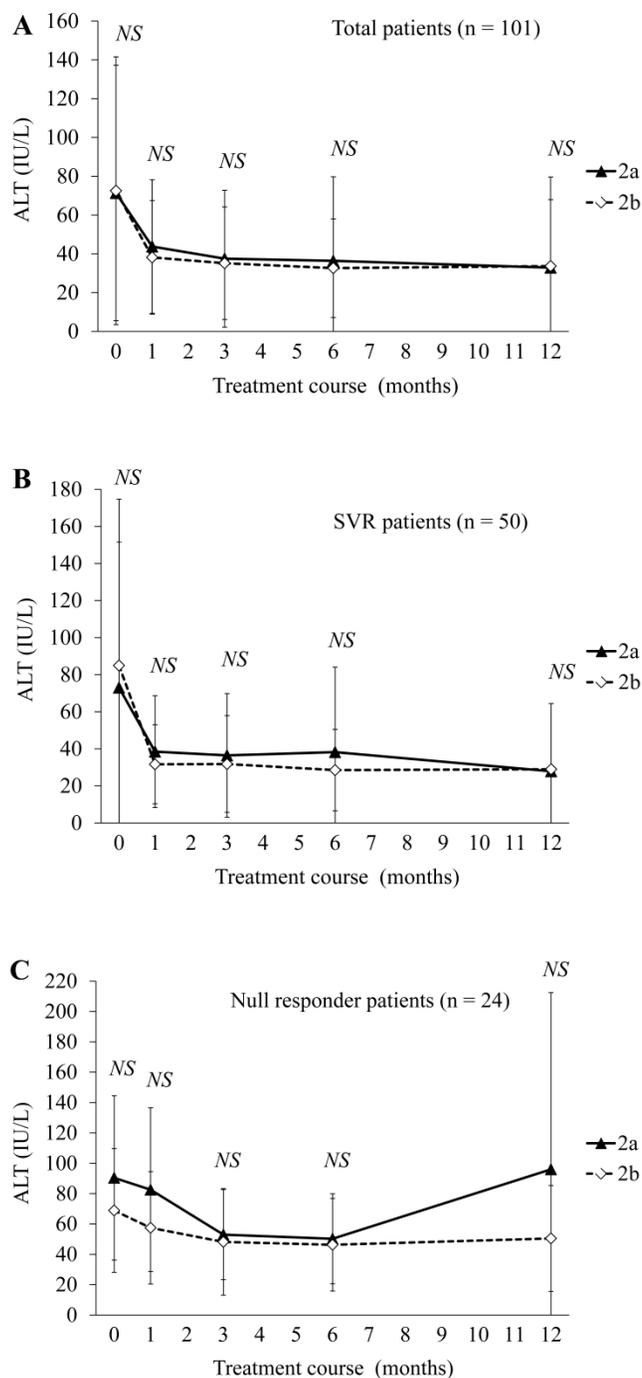
### Virological response

Adherence 80/80/80 [28], EVR, and SVR were not different between the two groups (Table 1). However, RVR was achieved in 41 patients of the peginterferon alpha-2a group (21.9%) higher than that in the 60 patients of the peginterferon alpha-2b group (5.0%) ( $P = 0.023$ ). As for these results, 20 and 30 of the patients, respectively, achieved SVR in the peginterferon alpha-2a and peginterferon alpha-2b groups; 11 and 16 were relapsers, and 5 and 19 were

null responders.

### Abnormal ALT levels during treatment

Next, we compared ALT changes between the treatments in the peginterferon alpha-2a ( $n = 41$ ) and peginterferon alpha-2b groups ( $n = 60$ ) (Figure 1). There were no differences in ALT levels between the combination treatments in the peginterferon alpha-2a and peginterferon alpha-2b groups (Figure 1A). Compared to each of the ALT levels at baseline, the proportions of patients with transient ALT elevation were 13 (31.7%) and 12 (20.0%) during treatment with peginterferon alpha-2a and peginterferon alpha-2b, respectively. No patients discontinued treatment due to ALT elevation. Concerning the distribution of ALT elevation, 10 and 9, 0 and 1, 0 and 2, 2 and 0, and 1 and 0 patients in the peginterferon alpha-2a and peginterferon alpha-2b groups, respectively, were classified into  $\leq 2$ -fold,  $2 \sim \leq 3$ -fold,  $3 \sim \leq 4$ -fold,  $4 \sim \leq 5$ -fold, and more than 5-fold of ALT at the upper limit of normal range. When severe ALT elevation was defined as more than 3-fold of the upper limit of the normal range of ALT, severe ALT elevation was observed in 3 (7.3%) and 2 (3.3%) of the peginterferon alpha-2a and peginterferon alpha-2b groups, respectively. There were no significant differences in ALT levels of SVR patients between the combination treatments in the peginterferon alpha-2a ( $n = 20$ ) and peginterferon alpha-2b groups ( $n = 30$ ) (Figure 1B). The proportions of SVR patients with transient ALT elevation were 7 (35.0%) and 2 (6.6%) during treatment with peginterferon alpha-2a and peginterferon alpha-2b, respectively ( $P = 0.029$ ). Transient ALT elevation was observed more in SVR patients treated with peginterferon alpha-2a than in those with peginterferon alpha-2b. There were no significant differences in ALT levels of null-response patients between the combination treatments in the peginterferon alpha-2a ( $n = 5$ ) and peginterferon alpha-2b groups ( $n = 19$ ) (Figure 1C). The proportions of null-response patients with transient ALT elevation were in 2 (40%) and 9 (47.3%) during treatment with peginterferon alpha-2a and peginterferon alpha-2b, respectively (NS).



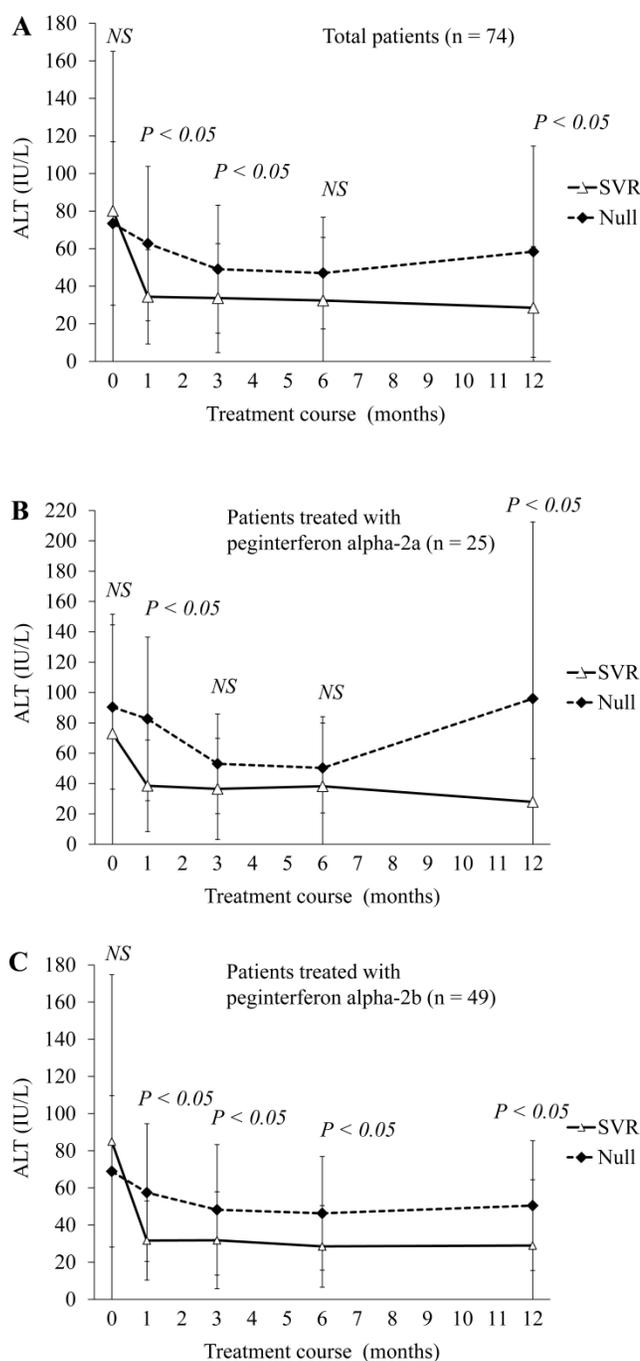
**Fig 1.** ALT changes during peginterferon alpha plus ribavirin treatment for chronic hepatitis C: comparison of patients treated with peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin. (A) Total patients ( $n = 101$ ). Black triangles and white diamonds indicate patients treated with peginterferon alpha-2a plus ribavirin ( $n = 41$ ) or peginterferon alpha-2b plus ribavirin ( $n = 60$ ). (B) SVR patients ( $n = 50$ ). Black triangles and white diamonds indicate patients treated with peginterferon alpha-2a plus ribavirin ( $n = 20$ ) or peginterferon alpha-2b plus ribavirin ( $n = 30$ ). (C) Null responder patients ( $n = 24$ ). Black triangles and white diamonds indicate patients treated with peginterferon alpha-2a plus ribavirin ( $n = 5$ ) or peginterferon alpha-2b plus ribavirin ( $n = 19$ ). NS, no significant difference between two groups by Student's *t*-test.

### The impact of IL28B rs809917 genotypes on transient ALT elevation from baseline during the treatment

There have been several reports on the association between IL28B genotypes and ALT levels in chronic hepatitis C patients [29-31]. Next, we examined whether IL28B genotypes had an impact on ALT elevation from baseline in response to peginterferon alpha-2a plus ribavirin or peginterferon alpha-2b plus ribavirin in HCV genotype-1-infected patients. In the total patients ( $n = 101$ ), those with transient ALT elevation during the treatment had less favorable IL28B rs809917 genotype (major/minor: 11/14) than those without transient ALT elevation during the treatment (major/minor: 56/20;  $P = 0.013$ ). In the peginterferon alpha-2a group ( $n = 41$ ), there were no differences in the distributions of IL28B rs809917 genotypes between patients with and without transient ALT elevation during the treatment (major/minor: 8/5 and 22/6; NS). However, in the peginterferon alpha-2b group ( $n = 60$ ), patients with transient ALT elevation during the treatment had less favorable IL28B rs809917 genotype (major/minor: 3/9) than those without transient ALT elevation (major/minor: 34/14;  $P = 0.0096$ ). Three and two patients with severe ALT elevation during the treatment had IL28B rs809917 (major/minor: 1/2 in the peginterferon alpha-2a group and 1/1 in the peginterferon alpha-2b group, respectively).

### Patients achieving SVR tended to have lower ALT levels than patients with null response

Next, we compared ALT changes between the treatments of 50 SVR patients and 24 null-response patients (Figure 2A). ALT levels were significantly lower at 4, 12 and 48 weeks in SVR patients than in the null responders. At 24 weeks, ALT levels also tended to be lower in SVR patients than in null responders. In the comparison of 20 SVR patients with 5 null-response patients treated with combination peginterferon alpha-2a plus ribavirin, ALT levels were significantly lower at 4 and 48 weeks in the SVR patients than in null responders (Figure 2B). In this treatment group, ALT levels tended to be lower at 12 and 24 weeks in the SVR patients than in null responders. In the comparison of 30 SVR patients with 19 null-response patients treated with combination peginterferon alpha-2b plus ribavirin, ALT levels were significantly lower from 4 to 48 weeks in the SVR patients than in null responders (Figure 2C). We showed that the ALT levels were significantly lower in SVR than in null-response patients, but this seems to be a natural consequence.



**Fig 2.** ALT changes during peginterferon alpha plus ribavirin treatment for chronic hepatitis C: comparison of SVR patients with null responders. (A) Total patients ( $n = 74$ ). White triangles and black diamonds indicate SVR-achieving patients ( $n = 50$ ) and null responders ( $n = 24$ ), respectively. (B) Patients treated with peginterferon alpha-2a plus ribavirin ( $n = 25$ ). White triangles and black diamonds indicate SVR-achieving patients ( $n = 20$ ) and null responders ( $n = 5$ ), respectively. (C) Patients treated with peginterferon alpha-2b plus ribavirin ( $n = 49$ ). White triangles and black diamonds indicate SVR-achieving patients ( $n = 30$ ) and null responders ( $n = 19$ ), respectively. P-value, significant difference between two groups by Student's t-test. NS, no significant difference.

### **ALT normalization was observed in 4 of 5 SVR-achieved patients with persistent ALT elevation during treatment**

In 5 of 50 SVR-achieved patients, ALT elevation was persistently observed during the treatment. Two and 3 patients with persistent ALT elevation during the treatment were observed among 20 peginterferon alpha-2a and 30 peginterferon alpha-2b-treated patients, respectively. Of interest, in 4 of these 5 patients, ALT normalization was observed, but only one peginterferon alpha-2b-treated patient had prolonged ALT elevation 12 months after stopping the treatment.

## **DISCUSSION**

This retrospective analysis indicates that there were no significant differences in ALT elevations between treatments with peginterferon alpha-2a plus ribavirin and peginterferon alpha-2b plus ribavirin. When we compared the proportions of patients with transient ALT elevation from baseline between the two groups, transient ALT elevation was observed more in SVR patients treated with peginterferon alpha-2a than in those with peginterferon alpha-2b. In spite of these ALT elevation, no patients discontinued treatment. In the peginterferon alpha-2b group, patients with transient ALT elevation from baseline during the treatment had less favorable IL28B rs8099917 genotype. Patients achieving SVR tended to have lower ALT levels than null-responding patients, which seems to be a natural consequence. We also found that 5 patients achieving SVR had ALT elevation during the treatment, and in 4 of them, ALT returned to normal limits within 12 months after stopping treatment.

There have been several reports that the two peginterferons showed comparable anti-HCV activities [32-34], although there were also several controversial reports [35-38]. There is insufficient evidence in terms of any differences regarding adverse events [38]. Although the study number was small, our results support the previous studies [32-34], and there were no differences in ALT elevation between the two peginterferons. However, we found that the proportion of RVR patients was higher in the peginterferon alpha-2a-treatment group (Table 1).

Recently, several reports on genetic variation in IL28B have predicted peginterferon alpha and ribavirin treatment-induced HCV clearance [26, 27, 39-42]. Two studies reported that IL28B rs12979860 CC genotype was associated with higher ALT [29, 31]. But Nunnari et al. [30] reported that the distribution of IL28B rs12979860 CC genotype did not differ between persistently normal ALT and hyper-ALT groups. In

the present study, we found that patients with transient ALT elevation during the treatment had less favorable IL28B rs8099917 genotype when treated with peginterferon alpha-2b.

Aoki et al. [43] reported that mean ALT values were significantly higher at certain time points during treatment with peginterferon alpha-2a plus ribavirin than those with peginterferon alpha-2b plus ribavirin. Therefore, attention should be paid to treated patients to avoid potentially severe adverse events such as acute exacerbation or liver failure [12, 22-25]. As HCV itself rarely causes severe liver injury [44, 45], peginterferon and/or ribavirin, or autoimmune mechanisms induced by such drugs, might lead to these phenomena and result in such as the reported severe liver injuries [22-25].

In conclusion, we observed no significant differences in ALT elevations between the two groups. However, comparing the proportions of patients with transient ALT elevation from baseline between the two groups, more transient ALT elevation was seen in SVR patients treated with peginterferon alpha-2a than with peginterferon alpha-2b. None discontinued treatment due to the ALT elevation. Nevertheless, some SVR patients showed persistent ALT elevation during treatment. Although ALT levels returned to normal limits after treatment completion in most cases, clinicians should be aware of possible ALT elevation during the treatment of chronic hepatitis C patients.

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## **Contributors**

MN and TK designed the study. TK, TM, and OY saw the patients. MN, TK, TM, WS, and SN analyzed the data. MN and TK drafted the paper and all authors approved the paper.

## **CONFLICT OF INTEREST**

Dr. Tatsuo Kanda reports receiving lecture fees from Chugai Pharmaceutical, MSD, Ajinomoto, and GlaxoSmithKline, and Prof. Osamu Yokosuka reports receiving grant support from Chugai Pharmaceutical,

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