Increase in albumin by daclatasvir/asunaprevir therapy is correlated with decrease in aspartate transaminase

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ABSTRACT

Objective: To elucidate the mechanism of an increase in the albumin levels by daclatasvir (DCV)/asunaprevir (ASV) therapy, we assessed the factors associated with an increase in the albumin levels. **Methods:** We retrospectively analyzed 125 patients with chronic hepatitis C virus (HCV) infection, treated with DCV/ASV from November 2014 to January 2016. **Results:** Albumin levels significantly increased from 4.0 ± 0.4 g/dL at baseline to 4.2 ± 0.4 g/dL at 24 weeks after the end of treatment (EOT) ($P < 0.0001$) in 108 patients with SVR. Patients with SVR were divided into three groups according to their baseline albumin levels: group A, ≥ 4 g/dL; group B, 3.6–3.9 g/dL; and group C, ≤ 3.5 g/dL. The increase in albumin levels from baseline to at 24 weeks after EOT was significantly larger in group C (0.5 ± 0.5 g/dL, $P < 0.0001$) and group B (0.2 ± 0.4 g/dL, $P = 0.0059$) than in group A (0.0 ± 0.3 g/dL). Multivariate analysis showed that aspartate transaminase (AST) levels was the only factor associated with ≥ 0.3 g/dL increase in albumin levels in groups B and C ($P = 0.0305$). An increase in albumin levels was significantly correlated with a decrease in AST levels ($r = 0.4729$, $P = 0.0119$). **Conclusion:** DCV/ASV therapy resulted in an increase in albumin levels in SVR patients, which was significantly correlated with a decrease in AST levels. It is probable that the reduction of inflammation, but not by reduction of fibrosis, mainly caused an increase in albumin levels.

Key words: daclatasvir, asunaprevir, hepatitis C virus, albumin, cirrhosis, aspartate transaminase, inflammation, sustained virological response

INTRODUCTION

Chronic hepatitis C virus (HCV) infection affects approximately 180 million people worldwide. HCV usually causes a chronic infection, which can result in chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma (HCC).^[1,2] In Japan, approximately 1.5 million patients with hepatitis are infected with HCV; approximately 70% of them have HCV genotype 1b, which is resistant to interferon (IFN)-based therapy.

On September 2014, Japan authorized IFN-free therapy with oral direct-acting antivirals (DAAs), daclatasvir (DCV; NS5A inhibitor) and asunaprevir (ASV; NS3/4A protease inhibitor) for patients with HCV

genotype 1b. DCV/ASV therapy increased the sustained virological response (SVR) rate to about 90% and caused less adverse effects than IFN-based therapy.^[3–7]

In Japan, DCV/ASV therapy can be administered to patients with chronic hepatitis or compensated cirrhosis with a Child-Pugh score of 6 or less, but not to those with decompensated cirrhosis with a Child-Pugh score of 7 or more. In some other countries, IFN-free therapy is authorized for patients with decompensated cirrhosis, and high SVR rates are reported with it.^[8,9]

Albumin levels are one of the factors constituting the Child-Pugh score formula; they are also one of the outcome predictors

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Access this article online

Website:
www.intern-med.com

DOI:
10.1515/jtim-2017-0028

Quick Response Code:

of compensated HCV-related cirrhosis.^[10] It has been reported that IFN-free therapies can reverse liver dysfunction in decompensated patients.^[11–14] Although IFN-free therapies reportedly increase albumin levels, the mechanism of an increase in albumin levels has not been elucidated.

Here, we retrospectively assessed whether DCV/ASV therapy improved albumin levels, and we aimed to elucidate the factors associated with an increase in albumin levels.

MATERIALS AND METHODS

DCV/ASV therapy

From November 2014 to January 2016, 125 patients with HCV genotype 1b were treated with DCV/ASV (Bristol-Myers KK, Tokyo, Japan) in our hospital (Table 1). None of the patients had previously received IFN-free DCV/ASV therapy. Thirty-six patients had liver cirrhosis and 23 had a history of HCC. When serum HCV RNA was negative at 24 weeks after EOT, the patients were considered as having achieved SVR.

Ethical statement

This study was performed in strict accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the Research Ethics Committee at our hospital, approval report 92 and HG14-002. All study participants provided written informed consent.

Detection of resistance-associated substitutions (RASs) of L31F/M/V or Y93H

RASs of L31F/M/V or Y93H were detected using a polymerase chain reaction (PCR)-invader assay with substitutions-specific probes after PCR as previously reported (BML, Tokyo, Japan).^[15] When the portions of 20% or more of RASs were detected, the presence of RASs was considered to be significant.

Acoustic radiation force impulse (ARFI) measurement

The measurement of shear wave velocity (Vs) using ARFI was performed with a Siemens ACUSON S2000 (Mochida Siemens Medical Systems Co., Ltd., Tokyo, Japan). The details of ARFI measurement procedure have been described in a previous report.^[16]

Albumin levels

To assess the factors associated with albumin elevation, the patients were divided into three groups according to their baseline albumin levels: group A, ≥ 4 g/dL; group B, 3.6–3.9 g/dL; and group C, ≤ 3.5 g/dL.

Statistical analysis

Results are expressed as mean $\pm$ standard deviation. Comparisons between the groups were performed using χ^2 test or Student's *t*-test, as appropriate. The factors associated with increased albumin levels were analyzed using multiple logistic analyses. Correlations between two factors were analyzed using linear regression analysis. Statistical analyses were performed using the StatFlex version 6.0 for Windows (StatFlex, Osaka Japan). A two-sided *P*-value of < 0.05 was considered significant.

RESULTS

Response to DCV/ASV therapy

HCV RNA became negative in 92.8% (116/125) patients at the end of treatment (EOT) or at discontinuation. Four patients experienced a relapse after EOT. Fifteen patients discontinued the treatment; five of them discontinued due to liver damage, but achieved SVR and were included in the analysis. Seven patients discontinued treatment due to a breakthrough (two patients), appetite loss (two patients), skin eruption (one patient), or their own decision (two patients). These patients did not achieve SVR, and were included in the analysis. One patient discontinued treatment due to fatigue, one developed hepatic encephalopathy, and one developed HCC and died before the SVR assessment; these and other three patients were lost to follow-up. These six patients lost to follow-up were not included in the analysis. There was only one patient with a RAS of Y93H, who achieved SVR. Thus, we analyzed 108 of 125 (86.4%) patients who achieved SVR and 11 who did not achieve SVR.

Increase in albumin levels

Albumin levels significantly increased from 4.0 ± 0.4 g/dL at baseline to 4.1 ± 0.5 g/dL at EOT ($P = 0.0152$) and to 4.2 ± 0.4 g/dL at 24 weeks after EOT ($P < 0.0001$) in patients with SVR. However, the albumin levels did not significantly increase in patients who did not achieve SVR (from 4.1 ± 0.4 g/dL at baseline to 4.2 ± 0.2 g/dL at EOT and to 4.2 ± 0.3 g/dL at 24 weeks after EOT) (Figure 1).

Baseline albumin levels were significantly higher in group A than in groups B and C ($P < 0.0001$). They were also significantly higher in group B than in group C ($P < 0.0001$). In group A, the albumin levels did not increase significantly after DCV/ASV therapy, from 4.4 ± 0.2 g/dL at baseline to 4.4 ± 0.3 g/dL at 24 weeks after EOT. In group B, the albumin levels significantly increased from 3.8 ± 0.1 g/dL at baseline to 4.0 ± 0.4 g/dL at 24 weeks after EOT ($P = 0.0039$). In group C, the albumin levels significantly increased from 3.3 ± 0.2 g/dL at baseline to 3.7 ± 0.5 g/dL at 24 weeks after EOT ($P = 0.0026$) (Figure 2a).

Table 1. Characteristics of the patients studied.

All the patients (n = 125)	SVR patients (n = 108)	non-SVR patients (n = 11)	P-Value (SVR patients vs. non-SVR patients)	Group A (n = 64)	Group B (n = 28)	Group C (n = 16)	P-Value (A vs. B)	P-Value (A vs. C)	P-Value (B vs. C)
Gender (male : female)	55 : 70	3 : 8	NS	28:36:00	9:19	11:05	NS	NS	0.019
Age (years)	68.1 ± 9.4	70.7 ± 10.8	NS	65.9 ± 9.4	68.3 ± 7.5	72.8 ± 6.8	NS	0.0081	NS
History of past IFN- based therapy (none : relapse : breakthrough : nonvirological response : discontinuation)	57 : 22 : 3 : 39 : 4 37 : 3	8 : 1 : 0 : 1 : 1	NS	24 : 17 : 0 : 22 : 1	12 : 1 : 2 : 12 : 1	9 : 2 : 1 : 3 : 1	0.0299	NS	NS
Platelets (10 ⁴ /μL)	14.5 ± 6.0	14.3 ± 5.9	NS	15.8 ± 5.9	13.2 ± 5.4	10.1 ± 4.2	0.0477	0.0005	NS
Albumin (g/dL)	4.0 ± 0.5	4.0 ± 0.5	NS	4.4 ± 0.2	3.8 ± 0.1	3.3 ± 0.2	< 0.0001	< 0.0001	< 0.0001
Total bilirubin (mg/dL)	0.9 ± 0.3	0.9 ± 0.3	0.0318	0.9 ± 0.3	0.9 ± 0.3	1.0 ± 0.4	NS	NS	NS
AST (IU/L)	49.2 ± 27.3	48.6 ± 27.6	NS	45.9 ± 26.5	47.8 ± 27.1	60.9 ± 31.3	NS	NS	NS
ALT (IU/L)	45.0 ± 32.6	44.4 ± 32.9	NS	45.1 ± 35.5	39.2 ± 26.4	50.6 ± 33.3	NS	NS	NS
Hyaluronic acid (ng/mL)	247.4 ± 270.3	267.0 ± 314.1	NS	133.7 ± 99.8	451.0 ± 380.0	390.0 ± 325.0	< 0.0001	< 0.0001	NS
α-fetoprotein (ng/mL)	15.0 ± 24.0	14.9 ± 24.7	NS	9.2 ± 12.0	25.4 ± 43.3	20.3 ± 15.6	0.0089	0.0027	NS
PIVKA-2 (mAU/mL)	21.1 ± 15.3	21.7 ± 16.9	NS	20.0 ± 8.1	17.0 ± 7.1	32.1 ± 35.8	NS	0.0198	0.0498
Vs by ARFI (m/s)	1.85 ± 0.73	1.86 ± 0.73	NS	1.60 ± 0.57	2.20 ± 0.78	2.46 ± 0.79	0.0001	0.0001	NS
HCV RNA (Log IU/mL)	6.1 ± 0.7	6.1 ± 0.8	NS	6.1 ± 0.7	6.2 ± 0.5	5.9 ± 1.2	NS	NS	NS
Presence of liver cirrhosis (positive : negative)	36 : 89	32 : 76	NS	10:54	12:16	10:06	0.0048	0.0001	NS
History of hepatocellular carcinoma (positive : negative)	23:102	20:88	NS	8:56	5:23	7:09	NS	0.0042	NS
RAS of Y93 (positive : negative)	1:124	1:107	NS	0:64	0:28	1:15	NS	NS	NS

Data are expressed as mean ± SD. NS: not significant. SVR: sustained virological response. AST: aspartate aminotransferase. ALT: alanine aminotransferase. PIVKA-2: protein induced by vitamin K absence or antagonist-2. Vs: velocity of shear wave. ARFI: acoustic radiation force impulse. RAS: resistance associated substitutions.

Figure 1: (a) Albumin levels significantly increased from 4.0 ± 0.4 g/dL at baseline to 4.1 ± 0.5 g/dL at the end of treatment (EOT) ($P = 0.0152$) and to 4.2 ± 0.4 g/dL at 24 weeks after EOT ($P < 0.0001$) in patients who achieved sustained virological response (SVR). (b) Albumin levels did not significantly increase in patients who did not achieve SVR (from 4.1 ± 0.4 g/dL at baseline to 4.2 ± 0.2 g/dL at EOT and to 4.2 ± 0.3 g/dL at 24 weeks after EOT).

Figure 2: (a) Baseline albumin levels were significantly higher in group A than in group B ($P < 0.0001$) and in group C ($P < 0.0001$). Baseline albumin levels were significantly higher in group B than in group C ($P < 0.0001$). In group A, albumin levels did not increase significantly after daclatasvir/asunaprevir treatment, from 4.4 ± 0.2 g/dL at baseline to 4.4 ± 0.3 g/dL at 24 weeks after the end of treatment (EOT). In group B, albumin levels significantly increased from 3.8 ± 0.1 g/dL at baseline to 4.0 ± 0.4 g/dL at 24 weeks after EOT ($P = 0.0039$). In group C, albumin levels significantly increased from 3.3 ± 0.2 g/dL at baseline to 3.7 ± 0.5 g/dL at 24 weeks after EOT ($P = 0.0026$). At 24 weeks after EOT, albumin levels in group A (4.4 ± 0.3 g/dL) were significantly higher than those in group B (4.0 ± 0.4 g/dL; $P < 0.0001$) and in group C (3.7 ± 0.5 g/dL; $P < 0.0001$). They were significantly higher in group B than in group C ($P = 0.0293$). (b) The increase in albumin levels from baseline to at 24 weeks after EOT was significantly greater in group C (0.5 ± 0.5 g/dL; $P < 0.0001$) and group B (0.2 ± 0.4 g/dL; $P = 0.0059$) than in group A (0.0 ± 0.3 g/dL).

Twenty-four weeks after EOT, the albumin levels in group A (4.4 ± 0.3 g/dL) remained significantly higher than those in groups B (4.0 ± 0.4 g/dL; $P < 0.0001$) and C (3.7 ± 0.5 g/dL; $P < 0.0001$) (Figure 2a). The levels were significantly higher in group B than in group C ($P = 0.0293$). The increase in albumin levels from baseline to at 24 weeks after EOT was significantly greater in groups C (0.5 ± 0.5 g/dL; $P < 0.0001$) and B (0.2 ± 0.4 g/dL; $P = 0.0059$) than in group A (0.0 ± 0.3 g/dL) (Figure 2b).

The factors associated with ≥ 0.3 g/dL increase in albumin levels were assessed in groups B and C using univariate analysis. Higher aspartate transaminase (AST) levels ($P = 0.0140$), alanine transaminase levels ($P = 0.0301$), and Vs values measured using ARFI ($P = 0.0423$) were significantly associated with ≥ 0.3 g/dL increase in albumin levels. Multivariate analysis showed that AST levels were the only significant factor associated with albumin elevation ($\beta = 0.03546$, SE = 0.01649, $P = 0.0305$) (Table 2).

A decrease in AST levels was significantly associated with an increase in albumin levels ($r = 0.4729$, $P = 0.0119$) (Figure 3).

DISCUSSION

The present study confirmed that DCV/ASV therapy yielded a high SVR rate (86.4%) as previously reported.^[3-7]

It has been reported that IFN-free therapy significantly increases albumin levels^[11-14]. One study reported that albumin levels significantly increased only in patients with SVR, while there was no change in patients who did not achieve SVR.^[13] The present study also showed that albumin levels significantly increased in patients with SVR, but not in patients who did not achieve SVR.

Although albumin levels at 24 weeks after EOT were significantly higher in group A than in groups B and C,

Table 2. Univariate analysis and multivariate analysis for factors associated with albumin elevation of 0.3 g/dl or more in group B and C.

	Univariate analysis			Multivariate analysis		
	Patients with albumin elevation of 0.3 g/dL or more ($n = 24$)	Patients without albumin elevation of 0.3 g/dL or more ($n = 20$)	<i>P</i> -Value	β	SE (β)	<i>P</i> -Value
Gender (male : female)	11:13	9:11	NS			
Age (years)	70.0 $\pm$ 4.9	69.8 $\pm$ 9.9	NS			
History of past IFN-based therapy (none : relapse : breakthrough : nonvirological response : discontinuation)	12 : 2 : 2 : 7 : 1	9 : 1 : 1 : 8 : 1	NS			
Platelets ($10^4/\mu$ L)	11.0 $\pm$ 4.3	13.3 $\pm$ 5.9	NS			
Albumin (g/dL)	3.6 $\pm$ 0.3	3.6 $\pm$ 0.3	NS			
Total bilirubin (mg/dL)	1.0 $\pm$ 0.3	0.9 $\pm$ 0.4	NS			
AST (IU/L)	62.2 $\pm$ 33.2	41.0 $\pm$ 17.6	0.014	0.03546	0.01649	0.0305
ALT (IU/L)	52.0 $\pm$ 33.3	33.1 $\pm$ 19.6	0.0301	-	-	-
Hyaluronic acid (ng/mL)	471.9 $\pm$ 346.6	381.3 $\pm$ 375.8	NS			
α -fetoprotein (ng/mL)	27.2 $\pm$ 35.7	19.5 $\pm$ 35.0	NS			
PIVKA-2 (mAU/mL)	18.0 $\pm$ 6.8	28.4 $\pm$ 33.7	NS			
Vs by ARFI (m/s)	2.55 $\pm$ 0.65	2.04 $\pm$ 0.82	0.0423	0.84931	0.51791	0.101
HCV RNA (Log IU/mL)	6.2 $\pm$ 0.5	5.9 $\pm$ 1.1	NS			
Presence of liver cirrhosis (positive : negative)	12:12	10:10	NS			
History of hepatocellular carcinoma (positive : negative)	7:17	5:15	NS			
RAS of Y93 (positive : negative)	0:24	1:19	NS			

Data are expressed as mean $\pm$ SD. NS: not significant. SE: standard error. AST: aspartate aminotransferase. ALT: alanine aminotransferase. PIVKA-2: protein induced by vitamin K absence or antagonist-2. Vs: velocity of shear wave. ARFI: acoustic radiation force impulse. RAS: resistance associated substitutions.

the increase in albumin levels from baseline to at 24 weeks after EOT was significantly greater in groups B and C than in group A. In group A, the baseline albumin levels were within normal range and the levels remained unchanged after achieving SVR, probably due to homeostasis, which maintains normal albumin levels. In contrast, the baseline albumin levels were lower than the normal limit in groups B and C, and after achieving SVR, the levels increased, approaching the normal levels. Deterding *et al.* also observed that after achieving SVR, there was a marked increase in the albumin levels in patients with albumin levels below 3.5 g/dL.^[12]

Deterding *et al.* showed that mean albumin levels increased by 0.3 g/dL, from 3.0 g/dL at baseline to 3.3 g/dL at 12 weeks after EOT, in the patients with baseline albumin levels of below 3.5 g/dL.^[12] In the present study, mean increases of albumin levels were 0.2 g/dL in group B and 0.5 g/dL in group C. Thus, we assessed the factors associated with ≥ 0.3 g/dL increase in albumin levels in groups B and C. The only factor associated with ≥ 0.3 g/dL increase in albumin levels was the baseline AST level. We also showed that a decrease in AST levels was significantly associated with an increase in albumin levels.

In healthy subjects, the albumin turnover time is approximately 25 days, and it reflects a liver albumin synthesis rate of approximately 10.5 g/day, balanced by renal (6%), gastrointestinal (10%), and catabolic (84%) clearances.^[17] Since only 20-30% of hepatocytes are committed to the production of albumin in healthy subjects, liver has a large functional reserve to increase the synthesis of albumin by 3–4 times. In cirrhosis, liver has lost this capacity. The production of albumin is mainly regulated by the osmolality and oncotic pressure, induced by hormonal factors (insulin, cortisol and growth hormone) and inhibited by acute phase cytokines, such as interleukin 6 and tumor necrosis factor α .^[18] Inflammation increases catabolic rate and results in hypoalbuminemia.^[19]

Hypoalbuminemia in cirrhosis can be attributed mainly to the dysfunction of hepatocytes caused by fibrosis and partially to the suppression of albumin synthesis by inflammatory cytokines and increase in the catabolic rate of albumin caused by liver inflammation, which was reflected as increased AST levels. The amelioration of inflammation that suppresses albumin synthesis and increases catabolism of albumin is a reason for the association between a decrease in AST levels and an increase in the albumin levels after SVR. In groups B and C, the albumin levels at 24 weeks after EOT were still lower than those in group A. This indicates that the recovery of liver function depressed by fibrosis and destruction of functional structure may take

Figure 3: The decrease in aspartate transaminase (AST) levels is significantly associated with the increase in albumin levels ($r = 0.4729$, $P = 0.0119$).

a longer period after achieving SVR.

In conclusion, DCV/ASV therapy yielded a high SVR rate and increased albumin levels in patients with SVR. An increase in albumin levels was significantly associated with a decrease in AST levels. Thus, an increase in the albumin levels can be attributed to amelioration of inflammation that suppresses liver albumin synthesis and increases the catabolic rate of albumin. However, albumin levels did not recover to within the normal range, probably because liver function is largely suppressed by fibrosis and destruction of functional structure. Recovery of albumin levels to within the normal range may take a longer period, which enables the reduction of fibrosis and recovery of functional structure.

Conflicts of Interest

The authors declare no conflict of interest.

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How to cite this article: Kan T, Hashimoto S, Kawabe N, Nakano T, Nakaoka K, Yoshioka K. Increase in albumin by daclatasvir/asunaprevir therapy is correlated with decrease in aspartate transaminase. *J Transl Intern Med* 2017; 5: 148-54.