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【 CASE REPORT 】

Improvement of Skeletal Muscle Mass after Ledipasvir and Sofosbuvir Treatment for Hepatitis C Virus in Decompensated Liver Cirrhosis

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Abstract:
Hepatitis C virus (HCV) can be eliminated by direct-acting antivirals in patients with decompensated liver cirrhosis. Although viral clearance in decompensated liver cirrhosis leads to improvement of the liver function and quality of life, changes in the skeletal muscle mass after sustained virologic response (SVR) in patients with decompensated liver cirrhosis have not been reported. We present the first report of skeletal muscle mass improvement with the achievement of SVR for HCV in a 76-year-old woman with decompensated liver cirrhosis. After achieving SVR through ledipasvir/sofosbuvir treatment, the patient showed an improvement in her liver function and an increase in her skeletal muscle mass.

Key words: ledipasvir, sofosbuvir, decompensated liver cirrhosis, skeletal muscle index (SMI), sarcopenia, direct-acting antiviral (DAA)

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Introduction

Hepatitis C virus (HCV) in patients with decompensated liver cirrhosis can be eliminated by direct-acting antivirals (DAAs) (1). An improvement in not only the liver function but also the quality of life was observed as an effect of sustained virologic response (SVR) in chronic liver disease patients with HCV infection (2). Furthermore, it was reported that skeletal muscle mass increased in chronic hepatitis or compensated liver cirrhosis patients upon HCV eradication by DAAs (3). However, there have been no reports on the change in skeletal muscle mass in decompensated liver cirrhosis patients after SVR.

We herein report the first case of a Japanese patient with decompensated cirrhosis who achieved an improvement in the liver function and an increase in the skeletal muscle mass over a long period after HCV elimination by ledipasvir (LDV)/sofosbuvir (SOF) treatment.

Case Report

The patient was a 76-year-old woman. At 73 years of age, she was diagnosed with decompensated liver cirrhosis with HCV infection when she was hospitalized for rupture of esophageal varices (EVs). Afterward, she developed recurrent pleural effusion and needed drainage and pleurodesis. Therefore, she was referred to our hospital for further treatment at the 75 years of age.

In May 2017, she visited our hospital using a wheelchair and presented with breathlessness due to right pleural effusion. She had a history of partial gastrectomy for gastric cancer, stent placement for a thoracic aortic aneurysm and replacement of an abdominal aortic aneurysm with a synthetic graft. Her complications were a history of myocardial infarction, thoracoabdominal aortic aneurysm, valvular dis-

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Table. Laboratory Data before the Start of Ledipasvir/sofosbuvir Therapy.

WBC	3,390 /μL	Na	138 mEq/L	Zn	57 μg/dL
RBC	3.90×10^6 /μL	K	3.9 mEq/L	AFP	4 ng/mL
Hb	11.7 g/dL	Cl	103 mEq/L	DCP	393 mAU/mL
Ht	34.5 %	BUN	14 mg/dL	ANA	40
Plt	11.7×10^4 /μL	Cr	0.64 mg/dL	BTR	3.62
PT	74 %	eGFR	67.4 mL/min/1.73 m^2	BCAA	235 μmol/L
PT-INR	1.17	TP	7.5 g/dL	TYR	65 μmol/L
AST	24 U/L	Alb	3.1 g/dL	HBsAg	N.D.
ALT	10 U/L	NH_3	11 μg/dL	Anti-HBs	N.D.
γ-GTP	20 U/L	T-Cho	212 mg/dL	Anti-HBc	N.D.
ALP	244 U/L	Glucose	82 mg/dL	Anti-HCV	Positive
LDH	168 U/L	HbA1c	5.3 %	HCV genotype	1b
T-Bil	1.4 mg/dL	Type 4 collagen 7s	11.0 ng/mL	HCV RNA	6.1 LogIU/mL
D-Bil	0.5 mg/dL	hyaluronic acid	456.0 ng/mL	FIB4-index	4.93
CRP	0.51 mg/dL	M2BPGi	9.01	ALBI score	-1.72

WBC: white blood cell, RBC: red blood cell, Hb: hemoglobin, Ht: hematocrit, Plt: platelet, PT: prothrombin time, PT-INR: prothrombin time international normalized ratio, AST: aspartate aminotransferase, ALT: alanine aminotransferase, γ-GTP: γ-glutamyl transpeptidase, ALP: alkaline phosphatase, LDH: lactic acid dehydrogenase, T-Bil: total bilirubin, D-Bil: direct bilirubin, CRP: C-reactive protein, BUN: blood urea nitrogen, Cr: creatinine, eGFR: estimated glemerular filtration rate, TP: total protein, Alb: albumin, T-Cho: total cholesterol, M2BPGi: mac-2-binding protein glycosylation isomer, AFP: α-fetoprotein, DCP: des-γ-carboxy prothrombin, ANA: antinuclear antibody, BTR: ratio of total branched-chain amino acid, BCAA: branched chain amino acid, TYR: tyrosine, HBsAg: hepatitis B surface antigen, Anti-HBs: antibody to hepatitis B surface antigen, Anti-HBc: antibody to hepatitis B core antigen, Anti-HCV: antibodies against hepatitis C virus, ALBI: albumin bilirubin, N.D.: not detected

ease of the heart, hyperuricemia, anemia, ascites and gastric antral vascular ectasia (GAVE) of the gastric remnant. Laboratory tests showed a deteriorated liver function (Table). High serum HCV RNA levels were detected, and the genotype of her HCV was 1b. Abdominal computed tomography (CT) revealed irregularities of the liver surface, a small amount of ascites (Fig. 1A) and splenomegaly, but no HCC or extrahepatic portosystemic shunts other than EVs were detected.

DAA treatment for patients with decompensated cirrhosis in Japan was not covered by public health insurance at that time, but LDV/SOF plus ribavirin (RBV) was approved for decompensated cirrhosis in the United States by the Food and Drug Administration (FDA) in February 2016. Since she wanted to undergo DAA treatment at her own expense because she had refractory ascites (Fig. 1B), we decided to treat her with LDV/SOF for 12 weeks without RBV because of a history of cardiovascular disease and anemia at the patient's proposed medical system, which was started in April 2016 in Japan.

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki. The Institutional Review Board of Osaka University Hospital approved this prospective study in June 2018. The committee of the Ministry of Health, Labor and Welfare approved this study in September 2018. Written informed consent was obtained from the patient. The expenses associated with the medicines, hospitalization and clinical trial were borne by the patient.

In September 2018, at 76 years old, the patient was hospitalized to receive antiviral treatment, and at that time, she was confined to a wheelchair because of significant pleural effusion. Pleural effusion was reduced by inserting a chest drainage tube for one month and adjusting the doses of the diuretics. The patient's chest drainage tube was removed after the reduction of pleural effusion, and then she started a 12-week course of a daily fixed-dose LDV (90 mg/day)/SOF (400 mg/day) combination in October 2018. Her body mass index (BMI) was 18.7, and no encephalopathy was observed. At the start of treatment, the patient's Child-Pugh score was 7 points, her Model for End-Stage Liver Disease (MELD) score was 5 points, and her albumin bilirubin (ALBI) score was -1.72 (Table, Fig. 1C, 2). The day before the start of LDV/SOF, abdominal CT revealed a portal thrombus, which had not been detected by abdominal CT performed two weeks earlier. Concentrated human antithrombin III was started on day 3 after the start of LDV/SOF and continued for 15 days. One month later, the portal thrombus had disappeared. Because no particular adverse events were observed, she was discharged walking on a walker on day 26.

Treatment was continued on an outpatient basis until the final administration of LDV/SOF, and no particular adverse events occurred during the treatment. HCV RNA was undetectable on day 42, and SVR subsequently persisted for more than one year (Fig. 2). The patient's liver function was improved at the end of treatment (EOT) (Child-Pugh class, B; Child-Pugh score, 7 points; MELD score, 4 points; ALBI score, -2.19) (Fig. 2). Four months after the EOT, hospitalization was required due to urinary tract infection and heart failure with atrial fibrillation (AF). The heart failure was considered to be due to mitral incompetence and required dose adjustment of diuretics (Fig. 2). No ascites or pleural

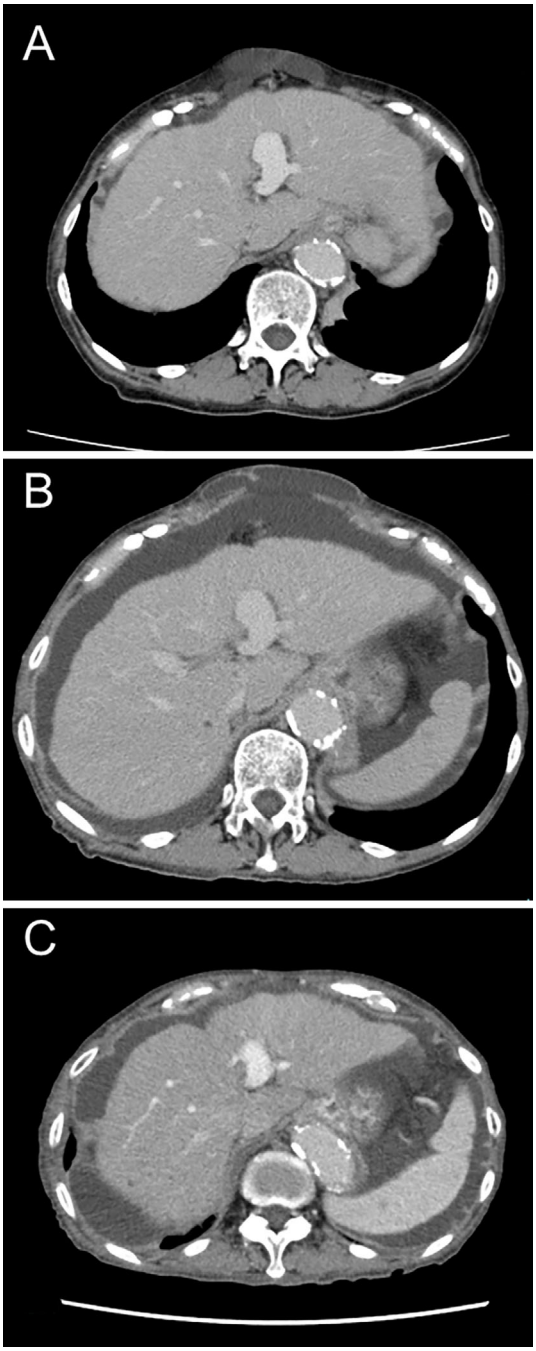


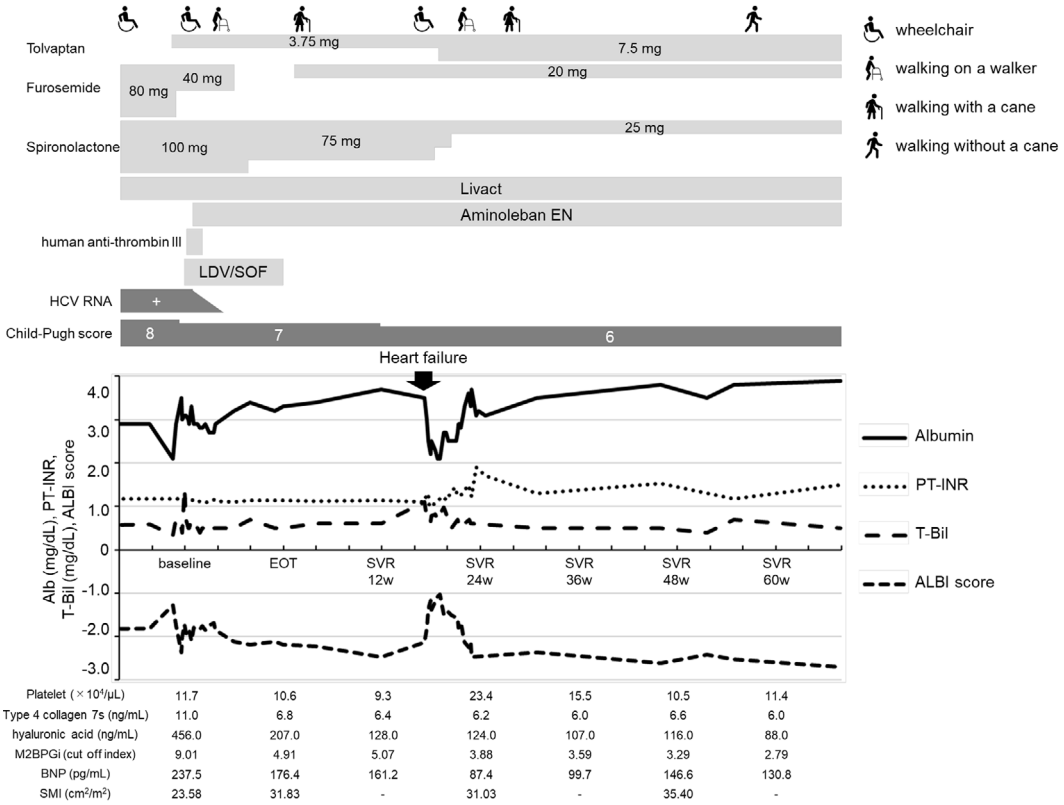
Figure 1. Computed tomography (CT) images obtained when the patient was referred to our hospital (A), 1 year before the start of DAA treatment (B), and at the start of DAA treatment (C). DAA: direct-acting antiviral

effusion were observed during hospitalization. Verapamil hydrochloride and edoxaban tosylate hydrate were started for AF. The prothrombin time international normalized ratio (PT-INR) was increased due to the use of edoxaban tosylate hydrate. The MELD score was unevaluable because the value of PT-INR was unstable after the use of edoxaban tosylate hydrate. The serum albumin level and ALBI score improved throughout the entire course after DAA treatment except during the period of heart failure (Fig. 2). No hepatocellular carcinoma (HCC) and no decompensated events, such as pleural effusion or ascites, occurred for more than one year after the EOT.

The body composition, including skeletal muscle, subcutaneous adipose tissue areas, visceral adipose tissue areas and intramuscular adipose tissue areas, was assessed by cross-sectional CT at the third lumbar vertebra (L3) level using Slice-O-Matic (Tomovision, Magog, Canada), version 5.0. They were automatically segmented based on the radiodensity specific to these tissues. The obviously inappropriate parts were manually corrected. The skeletal muscle index (SMI), which was defined as the measured skeletal muscle area divided by the square of the height, at 3 years before the start of DAA treatment, 1 year before the start of DAA treatment, the start of DAA treatment, EOT, 24 weeks after EOT and 48 weeks after EOT was 33.61 cm^2/m^2, 27.42 cm^2/m^2, 23.58 cm^2/m^2, 31.83 cm^2/m^2, 31.03 cm^2/m^2, 35.40 cm^2/m^2, respectively (Fig. 3). The SMI was decreased from 3 years before the start of DAA treatment to the start of DAA treatment and increased from the start of DAA treatment to 48 weeks after the EOT (Fig. 2, 3). Initially, the patient used a wheelchair before DAA treatment; she did not need a wheelchair and used a walker during DAA treatment (Fig. 2). After the EOT, the patient walked with a cane until heart failure occurred. Although she temporarily needed a wheelchair or a walker during heart failure treatment, she started walking with a cane again after discharge from hospitalization for heart failure. She did not require a crutch for daily life 1.5 years after treatment. The trend in brain natriuretic peptide (BNP) values was not correlated with the changes in walking or the SMI (Fig. 2).

Discussion

Skeletal muscle loss in cirrhosis advances as liver disease worsens and affects the prognosis of liver cirrhotic patients (4). In particular, the SMI at the L3 level is associated with a poor prognosis of liver cirrhotic patients (5). Furthermore, a decline in the SMI at the L3 level is correlated with increases in the Child-Pugh score and MELD score (6). The SMI is an essential factor among the sarcopenia assessment criteria according to the Japan Society of Hepatology guidelines for sarcopenia in liver disease (7). However, SVR induced by DAAs reduces the MELD score and HCC incidence and improves the quality of life and patient-reported outcomes (8). SVR induced by DAAs was reported to suppress skeletal muscle loss (9), and the SMI indirectly estimated using the bioimpedance analysis was increased in patients who had had their HCV eradicated by DAAs (3, 10). However, these studies excluded patients with decompensated cirrhosis. Regarding the effect of viral eradication in decompensated liver cirrhosis patients, the further progression of EVs among cirrhotic patients with existing EVs did not differ markedly between SVR and non-SVR patients (11). Thus, there might be a point of no return in cases of decompensated liver cirrhosis. Thus far, there have been no reports of SMI evaluations in decompensated liver cirrhotic patients who achieved SVR.



	baseline	EOT	SVR 12w	SVR 24w	SVR 36w	SVR 48w	SVR 60w
Platelet ($\times 10^4/\mu L$)	11.7	10.6	9.3	23.4	15.5	10.5	11.4
Type 4 collagen 7s (ng/mL)	11.0	6.8	6.4	6.2	6.0	6.6	6.0
hyaluronic acid (ng/mL)	456.0	207.0	128.0	124.0	107.0	116.0	88.0
M2BPGi (cut off index)	9.01	4.91	5.07	3.88	3.59	3.29	2.79
BNP (pg/mL)	237.5	176.4	161.2	87.4	99.7	146.6	130.8
SMI (cm^2/m^2)	23.58	31.83	-	31.03	-	35.40	-

Figure 2. Clinical course of a 76-year-old Japanese woman treated with LDV/SOF. LDV: ledipasvir, SOF: sofosbuvir, Alb: albumin, PT-INR: prothrombin time international normalized ratio, T-Bil: total bilirubin, ALBI: albumin bilirubin, EOT: end of treatment, SVR: sustained virologic response, M2BPGi: mac-2-binding protein glycosylation isomer, BNP: brain natriuretic peptide, SMI: skeletal muscle index

This is the first report of a decompensated liver cirrhosis patient with HCV who achieved muscle mass gain after SVR. The skeletal muscle mass was increased over time after the treatment, and the patient's performance in activities of daily living, such as walking, was also improved. The serum albumin level and ALBI score were improved after recovery from heart failure compared with baseline and EOT. Our patient continued supplementation with one packet of branched-chain amino acid (BCAA) granules three times daily after meals and Aminoleban EN powder mix (Otsuka Pharmaceutical, Tokushima, Japan) as a late-evening snack. Although BCAA supplementation prevents sarcopenia in patients with liver cirrhosis (12), no effect of muscle gain has been reported in cases of liver cirrhosis. Pleural effusion, which occurred repeatedly before LDV/SOF treatment, did not occur after LDV/SOF treatment. The clinical outcome of the liver function due to the eradication of HCV might indicate a reduction in the incidence of decompensated events, as in a previous report (13).

LDV/SOF treatment for decompensated liver cirrhosis with HCV infection is not approved in Japan (14), whereas LDV/SOF plus RBV treatment is recommended for decompensated liver cirrhosis with HCV infection by the American Association for the Study of Liver Disease (AALSD) (15) and European Association for the Study of the Liver (EASL) (16). While a clinical trial of velpatasvir (VEL)/SOF with or without RBV for HCV patients with decompensated liver cirrhosis recruited participants in Japan (17), some patients were excluded through the exclusion criteria. Since the survival period of decompensated cirrhotic patients was limited, the excluded patients might have missed treatment opportunities while waiting for the approval of DAA therapy for decompensated liver cirrhosis. Only one case was reported with the use of LDV/SOF plus RBV for decompensated liver cirrhosis in Japan (18), but RBV is intolerable to patients with anemia. Our patient agreed to the self-proposed clinical trial of LDV/SOF without RBV for decompensated liver cirrhosis according to the patient's proposed medical system started in April 2016 in Japan and completed the treatment without severe adverse events before VEL/SOF therapy was approved in Japan.

In conclusion, our case demonstrated that LDV/SOF combination therapy for decompensated liver cirrhosis with HCV infection led to an improvement in the liver function and skeletal muscle mass after SVR. This case is the first report wherein persistent improvement of skeletal muscle was observed in a decompensated liver cirrhotic patient after SVR.

Author's disclosure of potential Conflicts of Interest (COI).

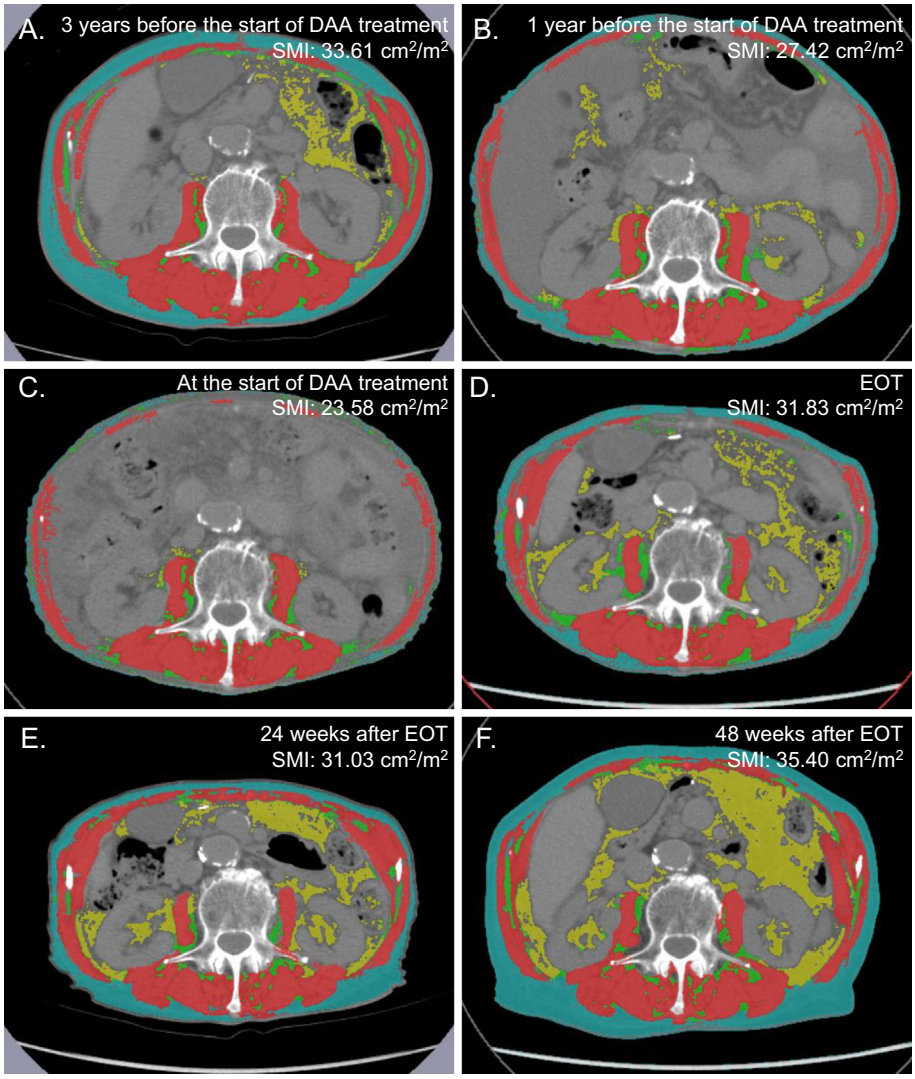


Figure 3. **The assessment of the total L3 cross-sectional area at the third lumbar vertebra using the Slice-O-Matic research software program. Areas of skeletal muscle, subcutaneous adipose tissue areas, visceral adipose tissue areas and intramuscular adipose tissue were automatically segmented based on the radiodensity specific to these tissues. The obviously inappropriate parts were manually corrected. CT images taken 3 years before the start of DAA treatment (A), 1 year before the start of DAA treatment (B), the start of DAA treatment (C), the EOT (D), 24 weeks after EOT (E) and 48 weeks after EOT (F). Red, blue, yellow and green shading indicate skeletal muscle, subcutaneous adipose tissue areas, visceral adipose tissue areas and intramuscular adipose tissue areas, respectively. The SMI, defined as the measured skeletal muscle area divided by the square of the height, at each time point from A to F was 33.61 cm^2/m^2 (A), 27.42 cm^2/m^2 (B), 23.58 cm^2/m^2 (C), 31.83 cm^2/m^2 (D), 31.03 cm^2/m^2 (E) and 35.40 cm^2/m^2 (F). The subcutaneous adipose tissue areas at each time point were 41.88 cm^2 (A), 17.08 cm^2 (B), 6.09 cm^2 (C), 26.02 cm^2 (D), 34.17 cm^2 (E), 73.42 cm^2 (F), respectively. Visceral adipose tissue areas at each time point were 12.93 cm^2 (A), 8.20 cm^2 (B), 0.71 cm^2 (C), 18.90 cm^2 (D), 25.47 cm^2 (E) and 52.60 cm^2 (F). The intramuscular adipose tissue areas at each time point were 8.72 cm^2 (A), 7.97 cm^2 (B), 7.60 cm^2 (C), 8.96 cm^2 (D), 7.80 cm^2 (E) and 12.44 cm^2 (F). CT: computed tomography, DAA: direct-acting antiviral, EOT: end of treatment, SMI: skeletal muscle index**

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