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Efficacy and safety of daclatasvir and asunaprevir combination therapy in chronic hemodialysis patients with chronic hepatitis C

Goki Suda 1
Mineo Kudo 2
Atsushi Nagasaka 3
Ken Furuya 4
Yoshiya Yamamoto 5
Tomoe Kobayashi 6
Keisuke Shinada 7
Miki Tateyama 8
Jun Konno 9
Yoko Tsukuda 1,3
Kazushi Yamasaki 1
Megumi Kimura 1
Machiko Umemura 1
Takaaki Izumi 1
Seiji Tsunematsu 1
Fumiyuki Sato 1
KatsumiTerashita1
Masato Nakai 1
Hiromasa Horimoto 1,5
Takuya Sho 1
MitsuteruNatsuizaka1
Kenichi Morikawa 1
Koji Ogawa 1
Naoya Sakamoto 1,* Phone+81 11-716-1161 Emailsakamoto@med.hokudai.ac.jp
1Department of Gastroenterology and HepatologyGraduate School of Medicine, Hokkaido UniversityNorth 15, West 7, Kita-kuSapporoHokkaido060-8638Japan
2Sapporo Hokuyu HospitalHokkaidoJapan
3Sapporo City General HospitalHokkaidoJapan
4JCHO Hokkaido HospitalHokkaidoJapan
5Hakodate City HospitalHokkaidoJapan
6Tomakomai City HospitalHokkaidoJapan
7Keiwakai Ebetsu HospitalHokkaidoJapan
8Tomakomai Nissho HospitalHokkaidoJapan
9Hakodate Central General HospitalHokkaidoJapan

Abstract

Background

HCV infection in chronic hemodialysis patients is high, has a poor prognosis and high risk of renal graft failure, and requires nosocomial infection control measures. However, options of anti-HCV therapy in such patients are limited and unsatisfactory. In this study, we report effectiveness and safety of HCV-NS5A-inhibitor daclatasvir (DCV) and protease-inhibitor asunaprevir (ASV) combination therapy for hemodialysis patients with HCV infection.

Methods

This study was registered at the UMIN Clinical Trials Registry as UMIN000016355. Thirty-four dialysis patients were treated with DCV/ASV combination therapy between January 2015 and November 2015. Of those, 21 patients who were followed more than 12 weeks after treatment ended were included. We evaluated the 12-week sustained virologic response (SVR12) and adverse events during treatment.

Results

Of the 21 patients, four had compensated liver cirrhosis and three had resistance-associated variant of NS5A (NS5A RAVs)-Y93H at baseline. Overall, total of 95.5 % (20/21) of the patients achieved SVR12. Of note, all patients with cirrhosis or NS5A RAVs achieved SVR12. One relapser patient at 4 weeks post-treatment had NS3 D168E RAVs at baseline. A total of 20 patients (95.5 %) completed the 24-week therapy. One patient discontinued treatment at week 12 due to ALT elevations and achieved SVR12.

Conclusions

DAV and ASV combination therapy for chronic hemodialysis patients with HCV infection was highly effective and well tolerated, even in elderly patients and patients with liver cirrhosis and NS5A-RAVs.

Keywords
HCV
Hemodialysis
Daclatasvir
Asunaprevir

Abbreviations

DAAs	Direct-acting antivirals
HCV	Hepatitis C virus
CHC	Chronic hepatitis C
HD	Hemodialysis
RBV	Ribavirin
SVR	Sustained virological response
DCV	Daclatasvir
ASV	Asunaprevir
DM	Diabetes mellitus
RAVs	Resistance-associated variants

For the NORTE Study Group.
The members of NORTE Study Group are listed in the Acknowledgments.

Introduction

Hepatitis C virus (HCV) infects more than 170 million people worldwide and causes liver cirrhosis and hepatocellular carcinoma. Thus, HCV infection is an important health concern [1, 2]. The prevalence of HCV infection is high in patients with end-stage renal dysfunction, especially in hemodialysis (HD) patients (7.3–16.8 %) [3, 4]. Recent studies have clearly revealed that the prognosis of HD patients with an HCV infection is significantly worse compared with dialysis patients not infected with HCV [5–7]. Fabrizi et al. [8] showed that HCV infection was an independent risk factor for death in HD patients, and the adjusted relative risk of all-cause mortality was 1.34 from a meta-analysis of seven studies involving 11,589 HD patients. Thus, HCV infection is an important issue in HD patients. Recently, the Kidney Disease Improvement Global Outcome (KIDIGO) and Japanese Society for Dialysis Therapy (JSDT) established the Guideline of Treatment of Hepatitis C Virus Infection in Dialysis Patients [9, 10]. In these guidelines, if life prognosis is favorable, anti-HCV therapy for dialysis patients with an HCV infection is highly recommended.

Until recently, PEGylated interferon (PEG-IFN) with or without ribavirin (RBV) was the standard therapy for chronic HCV. However, these therapies could only achieve a sustained virological response (SVR) rate of approximately 50 % [11]. Quite recently, novel, direct-acting antivirals (DAAs) that specifically target viral proteins, including HCV NS3, NS5A, and NS5B, were developed. Several phase 3

studies have revealed that these DAA-based therapies have led to significant improvements in the SVR rates and safety [12–14]. However, there is no established DAA therapy for dialysis patients with an HCV infection.

Currently, the standard therapy for dialysis patients with an HCV infection is IFN-monotherapy, because ribavirin cannot be used for patients with severe renal dysfunction, including HD patients. This is due to the fact that RBV is eliminated through the kidney, and cannot be eliminated by dialysis. In addition, it was reported that the HCV protease inhibitor telaprevir and INF-based therapy without ribavirin resulted in a low SVR rate [15]. Moreover, recently approved novel DAAs, such as the NS5B inhibitor sofosbuvir (SOF), cannot be used for patients with severe renal dysfunction, including HD patients, because SOF is eliminated through the kidney.

The Peg-IFN therapy for dialysis patients with an HCV infection can only achieve SVR rates of 37–50 % [16–18]. Additionally, the rates of adverse events and treatment discontinuation are relatively high compared to patients with normal renal function. Therefore, safe and effective anti-HCV therapies for dialysis patients with HCV infection are needed.

Recently, combination therapy of the protease inhibitor asunaprevir (ASV) and the NS5A inhibitor daclatasvir (DCV) was approved in Japan. A phase 3 study in Japan showed that this combination therapy could achieve a high SVR rate up to 85 % [19]. Importantly, these two DAAs are mainly eliminated through liver. Therefore, this combination therapy is not contraindicated in patients with severe renal dysfunction, including HD patients. However, the effectiveness and safety of DCV and ASV combination therapy for HD patients with an HCV infection remains unclear. Therefore, in this study, we aimed to evaluate the effectiveness and safety of DCV/ASV combination therapy for HD patients with an HCV infection.

Methods

Patients and study design

In this prospective, observational, multicenter study at Hokkaido University Hospital and associated hospitals in the NORTE STUDY group, between January 2015 and November 2015, a total of 34 HD patients with an HCV infection received DCV and ASV combination therapy. In this study, eligible patients were under HD due to renal dysfunction with chronic hepatitis C or compensated cirrhosis, and were 20 years of age or older at the time of informed consent. Patients were excluded if they had decompensated liver cirrhosis, poorly controlled cardiac disease, co-infection with HIV, administration of prohibited concomitant

medications for DCV or ASV, or malignancy. The presence of liver cirrhosis was diagnosed by either a FibroScan score of more than 12.5 kPa (n = 3) or, if FibroScan or liver biopsy could not be conducted, cirrhotic change by imaging modalities plus a Fib4 index of more than 3.25 [20] (n = 1).

The study protocol conformed to the ethical guidelines of the Declaration of Helsinki and was approved by the ethics committee of each participating hospital. Written informed consent to participate in this study was obtained from each patient.

This study was registered at the UMIN Clinical Trials Registry as UMIN000016355.

Treatment regimen and follow-up

Both DCV (60 mg, once daily) and ASV (100 mg, twice daily) were orally administered for 24 weeks. During treatment, patients were assessed as outpatients on weeks 2, 4, 6, and 8 at minimum, and then every 4 weeks thereafter for the duration of treatment. Physical examinations and blood tests were performed at all time points before HD. Patients were followed for an additional 12 weeks after treatment, and physical examinations and blood tests were performed.

Analysis of resistant-associated variants (RAVs)

At pre-treatment points, the RAVs in NS5A (aa31 and aa93) were investigated by a direct sequencing method (n = 2) or PCR-invader assay (n = 19). PCR-invader assays were conducted by BML Inc. (Saitama, Japan), and weakly positive and negative samples were defined as substitution-negative. In direct sequencing analysis, a minor sequence was regarded as substitution-positive when its strength was more than 20 % than that of a major sequence. One patient with virological relapse was investigated for RAVs in the NS3 region by a PCR invader-assay.

Outcomes

The primary endpoints of this study were SVR, which was defined as undetectable serum HCV RNA 12 weeks after the end of treatment, and safety during the combination therapy. Additionally, we analyzed changes in blood parameters, including liver fibrosis markers, alanine transaminase (ALT), alpha-fetoprotein (AFP), and albumin at pre-, during, and post-treatment points.

Safety evaluation

Safety evaluations were conducted at weeks 2, 4, 6, and 8 at a minimum, and then every 4 weeks thereafter for the duration of treatment by clinical laboratory tests and physical examinations. ALT elevation was defined as an ALT level greater than the upper limit of normal.

Statistical analysis

Continuous variables were analyzed with the paired Mann–Whitney *U* test. All *p* values were two-tailed, and the level of significance was set at $p < 0.05$. All statistical analyses were performed using SPSS version 21.0 (IBM Japan, Tokyo, Japan).

Results

Patients

We included 34 dialysis patients who received DCV and ASV combination therapy between January and November 2015. Of these, 21 patients who finished this therapy and were followed for more than 12 weeks after treatment completion were included. The baseline characteristics of patients are shown in Table 1.

Table 1

Baseline characteristics of the participating patients

Total number	**21**
HCV genotype (1b/1a/ND)	19/1/1
Age (years)[a]	63.0 (50–79)
Sex (male/female)	15/6
Etiology of renal dysfunction (DM/glomerulonephritis/others)	8/7/6
HD duration (years)	7 (1.5–33)
Baseline hemoglobin level (g/dl)[a]	11.1 (8.6–17.7)
Baseline platelet count ($\times 10^4/\mu$l)[a]	14.2 (4.6–26.2)
Baseline ALT level (IU/L)[a]	18 (9–55)
Baseline HCV RNA level ($\log_{10}$ IU/ml)[a]	5.7 (2.9–6.8)
IL28 B gene (rs8099917) (TT/non-TT/ND)	15/4/2
Liver cirrhosis (yes/no)	4/17
Previous treatment (naive/relapse/NVR)	15/2/4
NS5A inhibitor RAVs (yes/no)	3/18

HCV hepatitis C virus, *IL28B* interleukin 28B, *Peg-IFN* PEGylated interferon, *RBV* ribavirin, *ALT* alanine transaminase, *DM* diabetes mellitus, *RAVs* resistance-associated variants

[a]Data are shown as median (range) values

All patients had a chronic serotype 1 HCV infection (genotype 1b, 1a and unknown: 19, 1 and 1 case). The patients were aged 50–79 years (median, 63 years), and approximately 71.4 % (15/21) were male. Four patients had compensated liver cirrhosis and the others had chronic hepatitis. Three patients had NS5A RAVs of Y93H at baseline. The duration of hemodialysis was 1.5–33 years (median, 7 years) and the common causes of renal dysfunction were diabetes mellitus (DM, 38 %, 8/21) and glomerulonephritis (33 %, 7/21). Seven patients had previously received IFN-based therapies, and others were naive to HCV treatments. The baseline laboratory findings (albumin, hemoglobin, platelet, ALT, AFP, and HCV RNA levels) and interleukin 28B (IL28B) single nucleotide polymorphisms (SNPs) are shown in Table 1. As previously reported [21], serum ALT levels were low compared to patients with normal renal function who were infected with the HCV (data not shown), and were almost within normal range.

Treatment outcomes

After initiation of the combination therapy, serum HCV RNA decreased rapidly, even in patients with the NS5A RAV or liver cirrhosis (Fig. 1). A total of 85.7 % (18/21) of patients achieved a rapid viral response (RVR), and at 6 weeks after the initiation of treatment, all patients had an undetectable HCV RNA level. Overall, a total of 95.5 % (20/21) of patients could achieve an SVR12 (Table 2). Of note, even in patients with cirrhosis, serum HCV RNA decreased rapidly and 100 % (4/4) of patients with liver cirrhosis could achieve an SVR12. Additionally, 100 % (3/3) of patients with RAVs in the NS5A region could achieve an SVR12. Also, four patients with a non-TT IL28B genotype could achieve an SVR12.

Fig. 1

Mean changes in hepatitis C virus (HCV) RNA during treatment in all patients, patients with resistance-associated variants (RAVs) in NS5A, or patients with liver cirrhosis

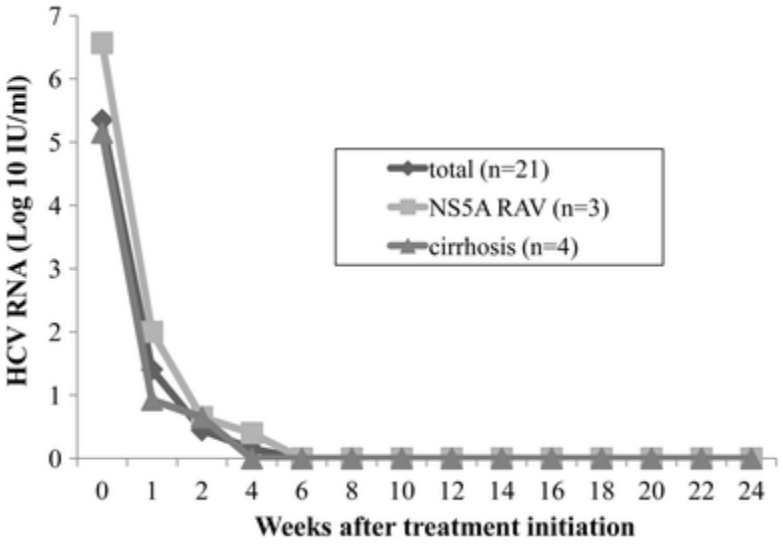


Table 2

Response during and after treatment

Virologic response	***n* (%)**
Week 4	18 (85.7 %) of 21
Week 6	21 (100 %) of 21
Week 12	21 (100 %) of 21
End of treatment	21 (100 %) of 21
SVR 4	20 (95.5 %) of 21
SVR12	20 (95.5 %) of 21
Relapse	1 (4.5 %) of 21
Viral breakthrough	0 (0 %) of 21
SVR12 by subpopulations	
NS5A RAVs	3 (100 %) of 3
Liver cirrhosis	4 (100 %) of 4
Elderly age (>65)	8 (100 %) of 8
IL28B genotype (non-TT)	4 (100 %) of 4

HCV hepatitis C virus, *IL28B* interleukin 28B, *SVR* sustained viral response, *RAVs* resistance-associated variants

Of the 21 dialysis patients treated with DCV/ASV, one had virological failure. This patient was a 62-year-old man without cirrhosis, and his IL28B SNP was the TT

genotype. His serum HCV RNA level became undetectable 6 weeks after the initiation of the combination therapy, and was sustained as undetectable until the end of the treatment. However, HCV RNA relapsed at post-treatment week 4. At baseline, this patient did not have RAVs in the NS5A region. However, they did have RAVs in the NS3 D168E region by PCR-invader assay.

Safety analysis

A total of 20 patients (95.5 %) completed 24 weeks of therapy. No patients had any lethal adverse events during the study period. One patient (4.5 %) discontinued at 12 weeks after treatment initiation due to an elevated ALT of nearly ten times the upper limit of the normal value and a decreased platelet count of 7.5– to 4.4 ($\times 10^4/\mu l$). However, the ALT and platelet count improved rapidly after discontinuing treatment, and this patient achieved an SVR12. A serious adverse event was observed in one case. Hepatocellular carcinoma (HCC) was detected at the end of therapy in one patient who had a past history of HCC.

Adverse events were observed in 67 % (14/21) of the patients. The most common adverse events were anemia, nasopharyngitis, and an increased ALT (Table 3). ALT elevations were observed in 14.3 % (3/21) of patients and elevations above twofold of the upper limit of normal were observed in 9.5 % (2/21); this result is consistent with a phase 3 study in Japan [19]. Anemia in patients was mild and speculated to be partially due to renal anemia.

Table 3

Summary of AE and grade 3–4 laboratory abnormalities during the treatment period

Adverse event and laboratory abnormality	***n*** **= 21**
Any adverse event	14 (67 %)
Serious adverse event	1 (4.5 %)
Adverse event	
Nasopharyngitis	6 (28.6 %)
Pyrexia	2 (9.5 %)
Loss of appetite	1 (4.5 %)
Increased ALT	3 (14.3 %)
Decreased platelets	2 (9.5 %)
Anemia	6 (28.6 %)

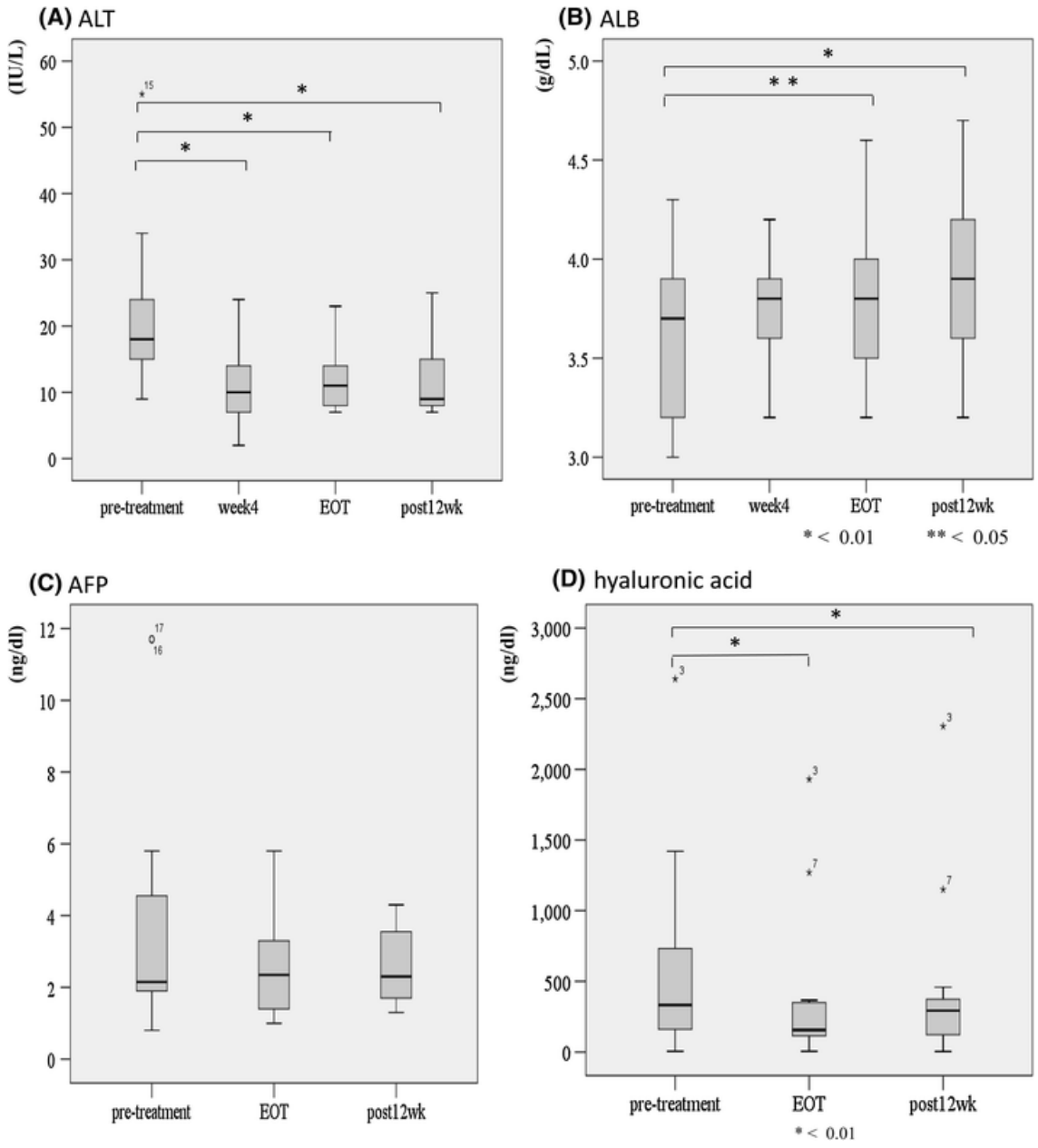
Grade 3–4 laboratory abnormality	
ALT	1 (4.5 %)
Platelets	1 (4.5 %)
ALT alanine transaminase, *AE* adverse event	

Changes in biochemistry, tumor, and fibrosis markers

We examined the effect of treatment on changes in biochemical, tumor, and fibrosis markers. As shown in Fig. 2a, serum ALT levels were significantly decreased 4 weeks after the initiation of treatment (median, 10; range 5–26 IU/l) compared with pre-treatment values (median, 18; range, 9–55 IU/l) and lasted for 12 weeks after treatment completion (median, 9; range 7–25 IU/l). Serum albumin was increased 4 weeks after the initiation of treatment (pretreatment median, 3.7 and range 3–4.3 g/dl; 4-week median, 3.8 and range 3.2–4.2 g/dl), and was significantly increased at the end of treatment (EOT) (median, 3.8; range 3.2–4.6 g/dl). The increase was sustained for 12 weeks after treatment completion (median, 3.9; range, 3.2-4.7 g/dl) (Fig. 2b). One of the tumor markers, AFP, did not change between pretreatment, EOT, and 12 weeks after treatment completion (Fig. 2c). However, in patients with an AFP value more than 4 ng/ml at pretreatment (n = 6), the AFP value was significantly decreased 12 weeks after treatment completion (pretreatment median, 5.8 and range 4.3–11.7 ng/ml; 12 weeks post-treatment median, 3.8 and range, 3.4–4.3 ng/ml, p = 0.026). Finally, we evaluated changes in the fibrosis marker hyaluronic acid (n = 14). As shown in Fig. 2d, hyaluronic acid was significantly decreased at the EOT compared with pretreatment values (pretreatment median, 380 and range 48–2640 ng/ml; EOT median, 157 and range 21–1930 ng/ml). This decrease was sustained 12 weeks after treatment completion (median, 324; range 64–2305 ng/ml).

Fig. 2

Changes in biochemistry, tumor, and fibrosis markers during and after daclatasvir and asunaprevir combination therapy; **a** alanine transaminase (n = 21), **b** serum albumin (n = 21), **c** alpha-fetoprotein (n = 20), **d** hyaluronic acid (n = 16). *EOT* end of treatment, *post. 12 wk* 12 weeks post-treatment completion, *ALT* alanine transaminase, *AFP* alpha-fetoprotein. Paired Mann–Whitney *U* test, $^{**}p < 0.05$, $^{*}p < 0.01$



Discussion

In this study, to our knowledge, we are the first to report the effectiveness and safety of DAV/ASV combination therapy in dialysis patients with an HCV infection. DCV and ASV combination therapy was highly effective in dialysis patients with serotype 1 HCV infection; even in elderly patients and in the presence of NS5A RAVs and liver cirrhosis, nearly 95 % of patients (20/21) achieved an SVR12. Additionally, DCV and ASV combination therapy for dialysis patients with an HCV infection was well tolerated compared with past-IFN-based therapies [16],

and as safe as in patients without HD [19]. Finally, treatment with DCV/ASV combination therapy significantly improved serum ALT, albumin, and hyaluronic acid values. Although the number of enrolled patients was limited, these study results clearly indicate the possibility that DCV and ASV combination therapy could be a standard therapy for dialysis patients with a serotype 1 HCV infection.
Treatment for HCV infection is thought to be crucial for dialysis patients with an HCV infection because the prognosis of HD patients with this infection is significantly worse than dialysis patients without an HCV infection [5–7]. In addition, the prevalence of HCV is high in dialysis patients. Especially, candidates for kidney transplantation should be treated because the outcome of kidney transplantation in HCV-positive patients is worse than that of HCV-negative patients [22]. However, treatment options for dialysis patients with an HCV infection have been limited to Peg-IFN monotherapy [9, 10]. In addition, the SVR rate of Peg-IFN monotherapy is not high and significant rates of adverse events have been observed [16–18].
DCV is the first approved NS5A inhibitor in Japan and has potent pan-genotypic and strong anti-HCV activity. ASV is a potent HCV NS3/4 protease inhibitor. In a phase III trial of DCV and ASV combination therapy in Japan, a total of 84.7 % of patients achieved an SVR. Importantly, DCV is metabolized through liver cytochrome P450 (CYP) 3A4 [23], and ASV is metabolized by CYP3A and eliminated mostly in the feces (84 %) [24]. Therefore, even in dialysis patients, this combination therapy can be used.
In this study, all dialysis patients with liver cirrhosis, IL28 non-TT genotype, or elderly age achieved an SVR12. In the end, more than 95 % of the dialysis patients could achieve an SVR12. These results were comparable to the outcome of the phase 3 study of DCV/ASV combination therapy in Japan. One patient who could not achieve an SVR12 had the RAVs D168E in the NS3 region at baseline. However, Suzuki et al. reported that the prevalence of naturally occurring NS3 RAVs was not high [25]. Therefore, apart from RAVs in the NS5A region, the impact of NS3 RAVs might be not significant.
In a phase 3 study of DCV and ASV combination therapy in Japan, the existence of RAVs in the NS5A region at baseline was a significant predictive factor of a non-SVR [19]. Specifically, if patients had RAVs in NS5A, the SVR rate was less than 50 % (15/37). In this study, 100 % (3/3) of patients with NS5A RAVs achieved an SVR12. The reason for this discrepancy could not be elucidated, and further analysis is therefore required.

In this study, more than 95 % of patients (20/21) could complete the treatment. One patient who discontinued treatment due to an elevation in ALT after 12 weeks rapidly improved their ALT level within a week of discontinuing treatment. Additionally, the rate of serious adverse events was low. This result clearly indicates that DCV and ASV therapy is well tolerated, even in dialysis patients. Serum ALT levels were within the normal limit in 95 % (20/21) of the patients at pretreatment. This result is consistent with previous studies [6]. The reasons for the lower serum ALT levels in dialysis patients are not fully understood. However, there are some hypotheses. Ono et al. reported that the level of pyridoxal-5′-phosphate (PLP), which is a co-enzyme for aminotransferases, is significantly decreased in hemodialysis patients; this could partly explain the low ALT values in dialysis patients [26].

As shown in Fig. 2a, even though the median ALT levels were within the normal limit at baseline, serum ALT levels were significantly decreased at the end of treatment and 12 weeks after treatment. This may indicate that even though the serum ALT was within the normal limit, there was active hepatitis. In DCV/ASV therapy, elevation of ALT is one of common adverse event, and can sometimes develop to grade 3 or 4 adverse events, resulting in discontinuation of treatment [19]. Because basal ALT levels are lower in dialysis patients, attention should be paid to changes in ALT. The ALT levels in dialysis patients were reported to be 20–30 % lower than those in non-dialysis patients. Guh et al. reported that the mean ALT level was 20.3 IU/l in dialysis patients and 16.3 IU/l in non-dialysis patients [21]. Espinosa et al. reported that the mean ALT level was 15.6 IU/l in dialysis patients and 22.7 IU/l in non-dialysis patients, in addition, the upper limit of the normal range of ALT in dialysis patients was estimated to be 27 IU/ml [27]. Moreover, Nakayama et al. reported that the mean ALT level was 22.8 IU/l in dialysis patients with HCV infection and 16.1 IU/l in dialysis patients without HCV infection, respectively [6]. Taking together these previous reports and our observation, the normal range of ALT in dialysis patients might be 20–30 % lower than that in non-dialysis patients. In addition, the criteria for discontinuation due to elevation in ALT should be strict in dialysis patients and might be 20–30 % lower than that of non-dialysis patients.

So far, DAA therapy for dialysis patients has not been established. Therefore, the effect of DAA therapy on biochemistry, tumor, and fibrosis marker changes were unknown in dialysis patients. Our results clearly show that DCV/ASV therapy improved ALT, albumin, and fibrosis markers, including hyaluronic acid. However,

the AFP values did not change significantly. In patients with a relatively high AFP value (>4 ng/ml), AFP values were significantly decreased post-treatment compared with pretreatment. Asahina et al. reported that high ALT and AFP values post-treatment are associated with hepatocarcinogenesis, even if an SVR was achieved [28]. In our study about DCV/ASV combination therapy, ALT and AFP values were significantly decreased. Further investigations are required to clarify whether this decreased ALT and AFP is associated with suppression of hepatocarcinogenesis or not in dialysis patients.

The primary limitation of this study was that the number of patients was relatively limited. Therefore, larger studies are required to validate these results.

In conclusion, we were the first to reveal that DAV and ASV combination therapy for dialysis patients with an HCV infection was highly effective and well tolerated, even in the elderly and patients with liver cirrhosis and NS5A RAVs. These study results suggest that DCV and ASV combination therapy could be the standard therapy for dialysis patients with a serotype 1 HCV infection.

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Compliance with ethical standards

Conflict of interest

Professor Naoya Sakamoto received lecture fees from Bristol Myers Squibb and Pharmaceutical K.K, grants and endowments from MSD K. K and Chugai Pharmaceutical Co., Ltd, and research grant from Gilead Sciences. Inc. Dr Goki Suda received research grants from Bristol Myers Squibb. The other authors have nothing to disclose.

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