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Virological response to daclatasvir and asunaprevir combination therapy for chronic hepatitis C virus genotype 1b infection in dialysis patients: a prospective, multicenter study

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Abstract

Background: The introduction of direct-acting antiviral agents (DAAs) for the treatment of chronic hepatitis C virus (HCV) infection in patients undergoing hemodialysis (HD) has improved sustained virological response (SVR) rates. Our aim was to assess the characteristics of the virological response to daclatasvir (DCV) and asunaprevir (ASV) combination therapy for HCV in HD patients.

Methods: A multicenter prospective study was conducted at eight centers in Japan. Patients on HD with chronic genotype 1b HCV infections were orally administered DCV and ASV for 24 weeks at doses of a 60-mg capsule once daily and a 100-mg tablet twice daily, respectively. The primary endpoint of this trial was the proportion of patients with a sustained virological response at 24 weeks after the treatment ended (SVR24). We also investigated the characteristics associated with the virological response to combination therapy.

Results: Thirty patients were enrolled in this study, and the proportion that achieved an SVR24 after treatment was 83.3% (25/30). Virological failure was observed in 4 patients (13.3%). Two exhibited virological breakthrough at weeks 16 and 20 of drug administration, and viral relapse occurred in 2 patients at weeks 4 and 8 after the end of treatment. Virological failure was defined as HCV-RNA levels exceeding 5.5 $\log_{10}$ IU/mL, and resistance-associated variants (RAVs) NS5A-L31M/V and Y93H were not exhibited at baseline.

Conclusions: DCV and ASV therapy for chronic HCV on HD was significantly effective. Most importantly, patients with the low viral loads undergoing HD demonstrated a higher response to combination therapy regardless of RAV.

Trial registration: UMIN Clinical Trials Registry UMIN000016181

Keywords: Daclatasvir, Asunaprevir, Chronic kidney disease, Hepatitis C virus

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Background

Hepatitis C virus (HCV) has been recognized as the most important causative agent of liver disease in patients receiving long-term hemodialysis (HD) in both developed and less-developed countries [1]. There are six distinguishable HCV genotypes, and the use of conventional interferon (IFN), pegylated IFN-α, or a combination of IFN with ribavirin for treatment depends on the genotype of the HCV virus [2]. Although treatment options for patients on HD are the same as for the general population, it is important to consider that treatment-related toxicity with IFN and ribavirin occurs frequently in patients on HD [3, 4]. According to the KDIGO (Kidney Disease Improving Global Outcome) guidelines, monotherapy with standard IFN is the therapy of choice for HCV-infected patients on maintenance HD [5]. Although IFN-related therapy achieves a sustained virological response (SVR) in 33–45% of HD patients with genotype 1, alternative therapies are required [4].

Presently, direct-acting antiviral agents (DAAs) have assumed a more prominent role in the treatment of patients with HCV [6–10]. The introduction of DAAs has improved SVR rates and shortened treatment durations. DAAs also enabled successful treatment without IFN therapy [7]. In Japan, a phase III study demonstrated that a 24-week combined regimen of daclatasvir (DCV) and asunaprevir (ASV) was highly effective in patients with HCV genotype 1b infections [10]. DCV was the first nonstructural protein 5A (NS5A) replication complex inhibitor to show potential efficacy against all HCV genotypes [11–14]. ASV is a second-generation NS3 (nonstructural protein 3) protease inhibitor that exhibited strong antiviral activity against HCV genotypes 1 and 4. It has been shown to act by inhibiting the viral nonstructural 3/4A serine protease required for viral replication [15, 16]. The pharmacokinetics of DCV and ASV, which are eliminated primarily by hepatic metabolism, have been assessed in patients with end-stage renal disease, which indicated that dose adjustments of either drug were unnecessary in cases of severe renal dysfunction. Recently, two prospective studies reported the efficacy of DCV and ASV combination therapy for the treatment of chronic HCV in patients undergoing HD, showing dramatically improved rates of sustained virological response at 12 weeks after treatment (SVR12) compared with monotherapy with standard IFN [17, 18]. However, it remains unclear whether end-stage renal disease, including those in patients on HD, affects the viral response to DAA-based antiviral therapy for HCV. Therefore, we studied the characteristics associated with the virological response to DCV and ASV combination therapy for HCV on HD patients.

Methods

Study design and patients

A multicenter prospective study was conducted at eight centers in Japan. The enrollment commenced in February 2015, and the study was completed in August 2016. Patients with chronic genotype 1b HCV infection undergoing HD received DCV and ASV for 24 weeks. DCV and ASV were administered orally at doses of a 60-mg capsule once daily and a 100-mg tablet twice daily, respectively, according to the manufacturer's prescribing information for both medications. The discontinuance criteria for the enrolled patients included (1) viral breakthrough occurrence (increase in plasma HCV-RNA levels exceeding 1 $\log_{10}$ IU/mL compared with the lowest recorded on-treatment value), (2) a lower than 2 $\log_{10}$ IU/mL decrease in HCV-RNA levels compared with those at the baseline and at week 8, (3) occurrence of severe adverse events (≥grade 3) according the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0, and (4) the patient's desire to terminate.

Eligibility criteria

This study enrolled patients with chronic HCV genotype 1b infection for at least 6 months and plasma HCV-RNA levels exceeding 2 $\log_{10}$ IU/mL. Eligible patients consisted of men and women who were treatment-naïve or treatment-experienced (previously treated with an IFN-based therapy), over 20 years of age, and currently undergoing HD.

The main exclusion criteria included the presence of (1) decompensated liver cirrhosis (Child-pugh B and C), (2) hepatocellular carcinoma, (3) infection/co-infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV), (4) previous exposure to IFN-based therapy within 1 month before drug administration, (5) previous exposure to DAA inhibitors, and (6) defined laboratory abnormalities during screening. Furthermore, patients with alanine aminotransferase (ALT) levels greater than five times the upper limit of the normal range, platelet, and white blood cell (WBC) counts lower than 50,000 and 4000/mm^3, respectively, and hemoglobin levels less than 8.5 g/dL, were also excluded.

Clinical parameters

The clinical characteristics evaluated were the demographic information, plasma HCV-RNA levels, and baseline laboratory data before and after the study drug administration. Blood samples were collected at each study visit before a dialysis, and the plasma HCV-RNA levels were quantified using the Cobas TaqMan version 2.0 assay (Roche Diagnostics, Tokyo, Japan); the lower limits of quantification were 1.2 $\log_{10}$ IU/mL. The HCV-RNA levels were measured at baseline and at weeks 0, 2,

4, 8, 12, 16, 20, and 24, as well as at posttreatment weeks 4, 8, 12, and 24. The resistance-associated variants (RAVs) of NS5A-Y93H and L31M/V were identified using direct sequencing [19], which was conducted on all enrolled patients. The laboratory tests performed were the analysis of hemoglobin, WBC count, neutrophils, platelets, serum albumin, blood urea nitrogen (BUN), creatinine, total bilirubin, aspartate aminotransferase (AST), ALT, and α-fetoprotein levels.

Efficacy

The primary endpoint of this trial was the proportion of patients with a sustained virological response 24 weeks after the treatment ended (SVR24) as determined by using intention-to-treat analysis. The secondary endpoints were the proportion of patients with undetectable HCV-RNA levels at weeks 4, 8, 12, 16, 20, and 24, at the end of the treatment, and at weeks 4, 8, and 12 after the treatment ended. We also investigated the characteristics associated with the virological response to the combination therapy. To study the pharmacological effects of combination therapy, laboratory data on blood biomarkers were assessed.

Safety assessment

To evaluate drug safety during the trial period, we assessed the adverse events that occurred after the commencement of trial drug administration at each study visit. The data on all adverse events were collected from the start of study drug administration to up to 30 days after the last study drug dosing. The severity of any serious or nonserious adverse events was graded using CTCAE, version 4.0.

Statistical evaluation

Our estimation of the SVR24 rates in patients undergoing HD was 85% based on previous studies [10]. With an alpha of 0.05 and power of 80%, 30 patients were required for this trial. Under the principles of intent to treat, the population analyzed consisted of all patients who signed informed consent forms. The data were analyzed using the statistical software JMP 11.0.1 (Statistical Analysis Software, SAS Institute). All the data were expressed as mean ± standard deviation, and the Wilcoxon signed-rank test was used for the analysis of the paired data. All differences with a P value <0.05 were considered significant.

Results

Characteristics of patients

A total of 33 patients were assessed in February 2015, and the study was completed in August 2016 (Fig. 1). Of these 33 patients, 3 patients dropped out during the run-in period due to failure to meet the criteria to commence treatment. The remaining 30 patients received the combination therapy, and of these, only 1 patient did not complete the study due to nontreatment-related death (sudden death at week 13 of drug administration). The enrolled patients' demographics and other baseline clinical characteristics are summarized in Table 1. All patients who were enrolled in the trial were included in the analyses. The patients' mean age was 65.5 ± 7.7 years

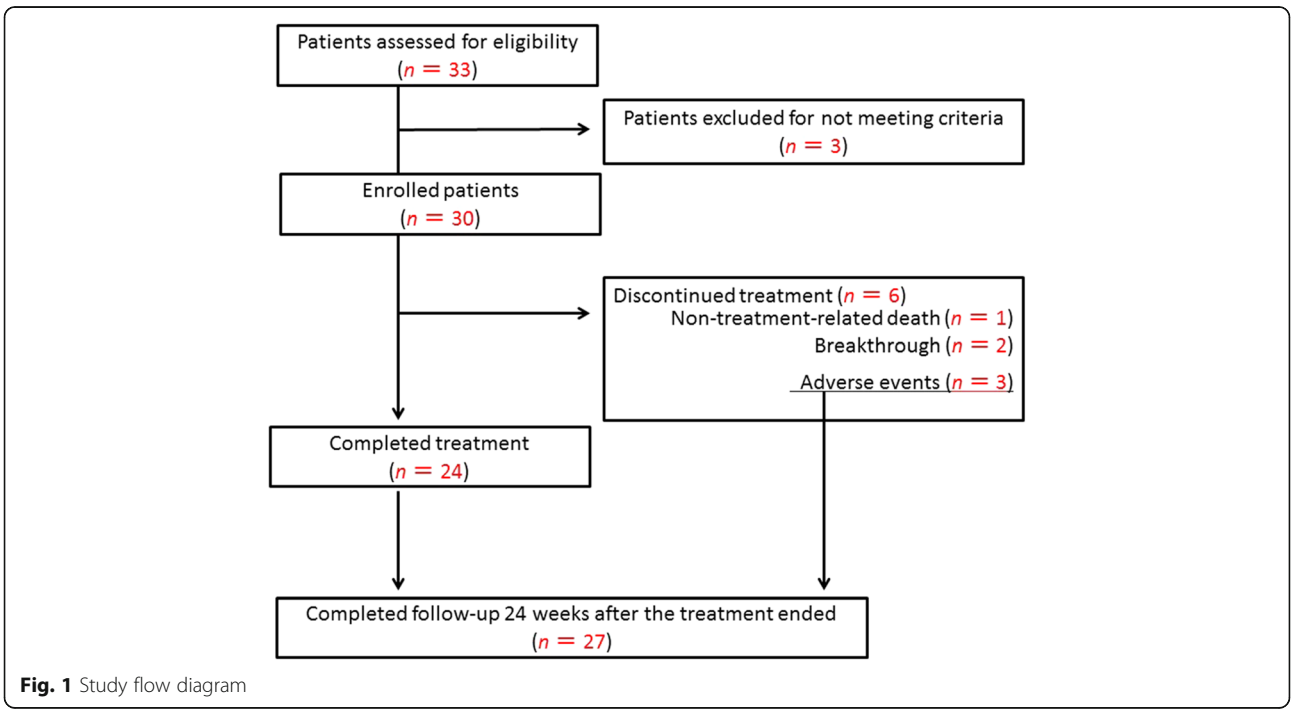

Fig. 1 Study flow diagram

Table 1 Patient baseline clinical characteristics

Characteristics		All patients
N		30
Age, years		65.5 ± 7.7
Sex, male	*n* (%)	23 (76.7)
Duration of hemodialysis	years	15.4 ± 10.5
Etiology of end-stage renal disease	*n* (%)	
Diabetic nephropathy		13 (43.3)
Polycystic kidney disease		2 (6.7)
Interstitial nephritis		3 (10.0)
Glomerulonephritis		7 (23.3)
Others		5 (16.7)
Weight	kg	51.2 ± 10.1
Previous treatment	*n* (%)	
Naïve		21 (70.0)
Relapse		5 (16.6)
Non-viral response		4 (13.3)
Liver cirrhosis	*n* (%)	9 (30.0)
Serum HCV-RNA levels	$\log_{10}$IU/mL	5.15 ± 0.95
NS5A inhibitor RAVs	*n* (%)	2 (6.7)
Laboratory data		
Hemoglobin	g/dL	10.6 ± 1.50
WBC	/μL	5484 ± 1760
Neutrophils	/μL	3718 ± 1381
Platelets	$\times 10^4$/μL	16.5 ± 6.38
Serum AST	IU/L	20.1 ± 13.1
Serum ALT	IU/L	16.1 ± 8.21
Serum albumin	g/dL	3.40 ± 0.35
BUN	mg/dL	51.9 ± 16.5
Serum creatinine	mg/dL	9.31 ± 2.39
Serum total bilirubin	mg/dL	0.36 ± 0.16
Alpha-fetoprotein	ng/mL	2.39 ± 0.98

Data are expressed as median, number (%), or mean ± standard deviation
RAVs resistance-associated variants, *BUN* blood urea nitrogen, *PT-INR* international normalized ratio of prothrombin time

(range 53–82 years), and 23 patients (76.7%) were male. Furthermore, 9 patients (30%) had liver cirrhosis and received previous treatment. The duration of HD was 15.4 ± 10.5 years (range 0.5–35 years), and the cause of end-stage renal dysfunction was diabetic nephropathy in 13 patients, polycystic kidney disease in 2 patients, and glomerulonephritis in 7 patients. The mean HCV level was 5.15 ± 0.95 $\log_{10}$ IU/mL (range, 3.2–6.9 $\log_{10}$ IU/mL). The mean serum albumin, creatinine, and ALT levels were 3.40 ± 0.35 g/dL, 9.31 ± 2.39 mg/dL, and 16.1 ± 8.21 IU/L, respectively (ranges 2.5–4.0 g/dL, 7.9–15.1 mg/dL, and 4–44 IU/L, respectively). Furthermore, the RAV NS5A-Y93H was detected in 2 patients (6.9%) while L31M/V was not detected at baseline.

Virological response

The patient plasma HCV-RNA levels declined following administration of the combination therapy (Fig. 2), and the mean decrease from baseline was 4.4 $\log_{10}$ IU/mL at week 4. The results of the primary endpoint determination revealed an SVR24 rate of 83.3% (25/30). The proportions of patients with undetectable HCV-RNA levels at treatment weeks 4, 8, and 12, and at the treatment end were 26/30, 30/30, 30/30, and 27/30 (86.7, 100, 100, and 90.0%), respectively, while at weeks 4, 8, and 12 after the treatment ended, the proportions were all 25/30 (83.3%). Furthermore, the 3 patients who were followed up to the discontinuation of the combination therapy, due to adverse events and laboratory abnormalities, achieved SVR24.

Virological failure

The demographics of the patients with virological failure and other baseline clinical characteristics are summarized in Table 2. Virological failure was observed in 4 patients (13.3%), 2 patients exhibiting virological breakthrough, one of those at week 16 and the other at week 20 of drug administration, respectively, and viral relapse occurred in 2 patients, one at week 4 and the other at week 8 after the treatment ended.

Virological failure had HCV-RNA levels exceeding 5.5 $\log_{10}$ IU/mL, although there were no significant differences with the virological response and failure group in the mean viral load. There were no significant differences with the virological response or failure group in age, sex, duration of hemodialysis, liver cirrhosis, or previous treatment.

We also investigated the influence of pretreatment RAVs of NS5A-L31M/V and Y93H. We discovered that the patients who showed virological failure did not exhibit RAVs at baseline, while NS5A-L31M/V and Y93H were observed at the time of failure.

Pharmacological effects

Following drug administration, a decrease in the mean ALT level from 16.1 ± 8.21 to 10.2 ± 10.6 IU/IU was observed at the end of the treatment ($P = 0.0475$). The baseline and posttreatment serum creatinine levels were indistinguishable (9.31 ± 2.39 vs. 9.31 ± 3.82 mg/dL, $P = 0.481$). The baseline and posttreatment hemoglobin levels were indistinguishable (10.6 ± 1.50 vs. 10.5 ± 1.82, $P = 0.736$). There were no significant differences in the levels of WBC counts, neutrophils, platelets, serum albumin, BUN, total bilirubin, or α-fetoprotein.

Safety assessment

The observed adverse events are summarized in Table 3. Adverse events were observed in 10 patients (33.3%) receiving treatment, and there were no treatment-related

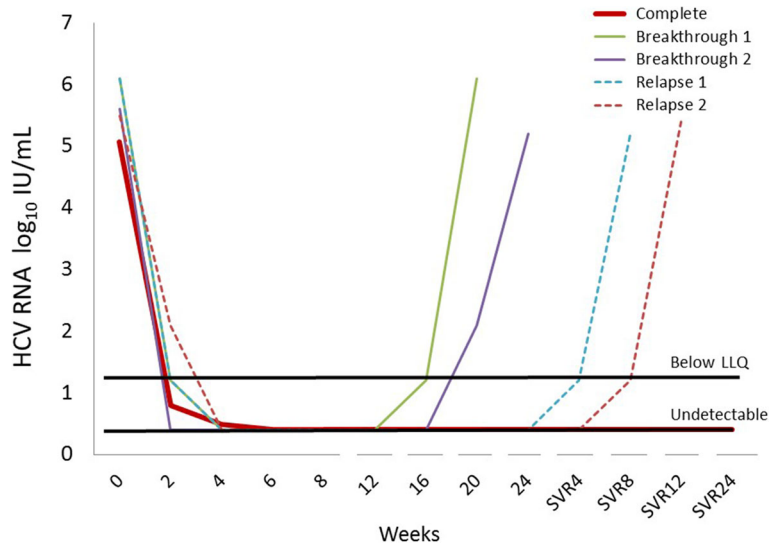

Fig. 2 Change in HCV-RNA levels during treatment with daclatasvir and asunaprevir in complete, relapse, and breakthrough patients. HCV-RNA levels at baseline, at weeks 0, 2, 4, 8, 12, 16, 20, and 24, and posttreatment at weeks 4, 8, 12, and 24. *LLQ* lower limit of quantification (IU/mL). Complete indicates patients with a mean sustained virological response at 24 weeks after the treatment ended

deaths. Incidences of headache, diarrhea, and fatigue were reported in 9 patients (30.0%) during the treatment. Although serious adverse events (≥grade 3) were not reported, there were three adverse events that led to the discontinuation of the combination therapy. Two patients, who discontinued therapy, exhibited fatigue at week 14 and had diarrhea at week 20. Another patient showed increased ALT levels (grade 2), leading to the discontinuation of the combination therapy at week 13 due to the physician's decision (Fig. 3).

Discussion

We evaluated the DCV and ASV combination therapy for the treatment of chronic HCV genotype 1b infection in patients undergoing HD. In this multiple prospective study, we demonstrated that the achievement of an SVR24 in HCV genotype 1b infection in patients on HD was significantly higher following combination therapy, and there were a number of virological failures in patients who had HCV-RNA levels exceeding 5.5 $\log_{10}$ IU/mL without the RAVs NS5A-L31M/V and Y93H. It is commonly known that the most important factor related to the viral response to DAAs is the presence of RAVs [20]. In a phase III study of a 24-week regimen of DCV plus ASV, multivariate analysis confirmed that the RAVs, NS5A-Y93H, and L31M/V were independent of the factors affecting the response to this combination therapy (overall response (OR) 17.81; 95% confidence interval (CI) 7.17–44.25; and OR 26.81; 95% CI 4.61–155.7, respectively). Therefore, the high SVR rate of 83.3% achieved in this study was assumed to be attributable to the lower proportion of RAVs, where NS5A-Y93H was detected in only two cases and L31M/V was not detected at the baseline. The patients with the RAV NS5A-Y93H fortunately also achieved SVR12.

Table 2 Virological failure baseline clinical characteristics

Characteristics	Complete ($n = 25$)	Failure ($n = 4$)	*P* value
Age, years	64.9 ± 8.19	69.5 ± 2.69	0.182
Sex, male (*n*) [%]	21/25 (80.7)	2/4 (50.0)	0.180†
Duration of hemodialysis (years)	16.1 ± 9.5	15.3 ± 10.4	0.393*
Previous treatment (*n*) [%]			
Naïve	19/25 (76.0)	1/4 (25.0)	0.076†
Relapse and non-viral response	6/25 (24.0)	3/4 (75.0)	
Liver cirrhosis (*n*) [%]	6/25 (24.0)	3/4 (75.0)	0.076†
Serum HCV-RNA levels ($\log_{10}$ IU/mL)	5.06 ± 0.99	5.88 ± 0.28	0.158*
≥5.0 $\log_{10}$ IU/mL (*n*) [%]	16/25 (64.0)	4/4 (100)	0.280†
≥5.5 $\log_{10}$ IU/mL (*n*) [%]	9/25 (36)	4/4 (100)	0.030†
NS5A inhibitor RAVs (*n*) [%]	2/25 (8)	0/4 (0)	1.000†

Data are expressed as median, number (%), or mean ± standard deviation
*Mann-Whitney *U* test, †Fisher's exact test

Table 3 Adverse events and laboratory abnormality during the treatment period

Adverse events	Clinical events ($n = 10$)	[*n* (%)]
	Any grade	≥Grade 3
Diarrhea	4 (13.3)	0
Headache	2 (6.7)	0
Bloating	2 (6.7)	0
Fatigue	1 (3.3)	0
ALT increased	1 (3.3)	0

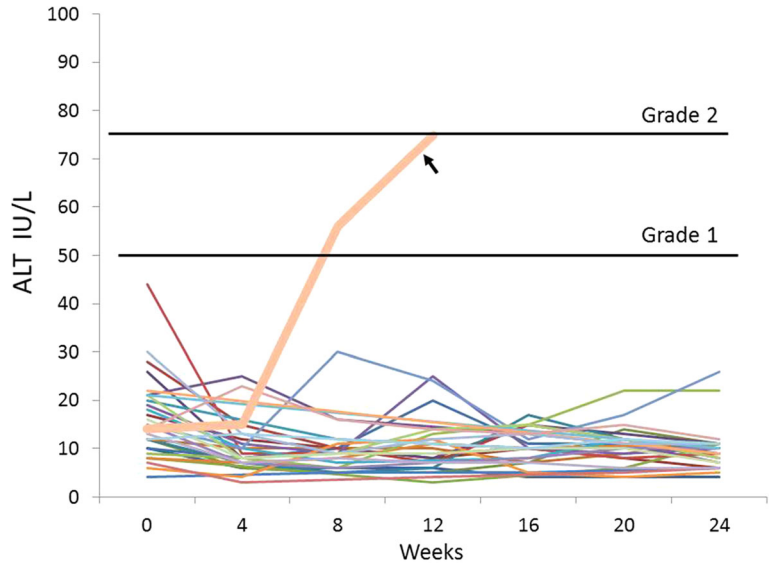

Fig. 3 Individual patient serum ALT levels at weeks 0, 4, 8, 12, 16, 20, and 24 after the administration of daclatasvir and asunaprevir. Only 1 patient discontinued treatment 12 weeks after commencing therapy due to elevation of serum ALT to 75 IU/l (*black arrow*). All the other patients continued through week 24

On the other hand, the present study demonstrated a number of characteristics of treatment failure in patients undergoing HD. All of the virological failures occurred in patients without the RAVs NS5A-Y93H and L31 M/V, and all patients had HCV-RNA levels exceeding 5.5 $\log_{10}$ IU/mL even though the HCV-RNA quantity was not correlated with the response to the combination therapy in patients without renal dysfunction [10]. We suggested that high viral loads on HD affected the viral response to direct-acting antiviral agents regardless of RAVs. According to a recent study, maintenance HD decreased the HCV-RNA levels in HD patients with chronic HCV infections [21, 22]. The influence of high viral loads in patients on HD might be significantly higher than that on non-uremic patients. Consequently, hemodialysis, which decreased the HCV-RNA levels, may affect the viral response of direct antiviral agents.

Furthermore, the SVR rate in the present study was considerably lower than those in other articles [17, 18]. Another factor that differs from other studies was that the present study was conducted under the principles of intent to treat and did not elucidate RAVs NS3 D168. We also consider that serum concentrations and drug activity of DCV and ASV combination therapy on hemodialysis may affect the viral response. Although DCV and ASV undergo hepatic biotransformation to more polar but less pharmacologically active compounds that require intact renal function for their efficient elimination [23], it has been reported that renal impairment affects the non-renal clearance of many drugs through mechanisms that appear to include downregulation/inhibition of cytochrome P450 activity by blood uremic components [23–26]. However, this mechanism is not clear because there is little data presented to support this conclusion.

The administration of the combination therapy was well tolerated in patients with chronic kidney disease (CKD) undergoing HD, relative to IFN- or ribavirin-related therapies. It is noteworthy that hemoglobin declines were not frequent because this regimen was managed without interruption of ribavirin. The study of DAAs with ribavirin in stages 4 or 5 CKD including those in patients on HD demonstrated that declines in hemoglobin levels were frequent [27]. The absence of ribavirin could be an advantage in avoiding severe side effects. However, in the present study, four clinical events that led to the discontinuation of the combination therapy must not be ignored. In particular, 1 patient died of unknown causes during the study period. This patient had an ischemic heart disease, and he was found dead at his home. We determined that the sudden death had been probably due to shock and sudden failure of the heart's action, and this clinical event was a nontreatment-related death. It is well known that the predominant cause of death in patients on regular dialysis is cardiovascular, and sudden cardiac death frequently occurs in CKD patients [28]. HCV infection in patients undergoing HD was also reported as a cardiovascular risk factor [29, 30]. We need to consider that HCV patients on dialysis have a high risk of sudden death due to cardiac disease during combination therapy.

This study has four limitations. First, it was conducted with a relatively small number of patients and a selection bias. Second, we postulated that the achievement of a high SVR rate following treatment with the DCV and ASV combination therapy was likely due to effects of the RAVs in the patients on HD. However, the evidence to support the involvement of the RAVs was insufficient, and further research is warranted to elucidate the other predictors in combination with RAVs, including NS3 D168. Third, although our results suggested that the elimination of HCV in patients undergoing HD may decrease cardiovascular mortality risk, it is not clear whether or not the DAAs improved the long-term prognosis of these patients. Finally, more detailed in vivo pharmacokinetic studies of DCV and ASV combination therapy should be performed and subsequently used to predict serum concentrations and drug activity.

Conclusions

We demonstrated that DCV and ASV combination DAA therapy for chronic HCV genotype 1b infection in patients undergoing HD was significantly effective. Higher responses to the combination therapy in patients with low viral loads can be expected. Therefore, hemodialysis, by decreasing the HCV-RNA levels, could likely affect the viral response of direct antiviral agents.

Additional file

Additional file 1: Supporting information files. (XLSX 19 kb)

Abbreviations

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ASV: Asunaprevir; BUN: Blood urea nitrogen; CKD: Chronic kidney disease; CTCAE: Common Terminology Criteria for Adverse Events; DAA: Direct-acting antiviral agent; DCV: Daclatasvir; HCV: Hepatitis C virus; HD: Hemodialysis; IFN: Interferon; KDIGO: Kidney Disease Improving Global Outcome; LLQ: Lower limit of quantification; NS3: Nonstructural protein 3; NS5A: Nonstructural protein 5A; RAVs: Resistance-associated variants; SVR: Sustained virological response; SVR24: Sustained virological response 24 weeks after the treatment ended; WBC: White blood cells

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Availability of data and materials

Data are uploaded as Additional file 1.

Authors' contributions

HU and TK contributed equally to this work. HU, SK, TO, and TK designed the research. SM, MO, YY, TK, HY, TK, KT, TF, JHS, and MK performed the research. HU analyzed the data. HU and HH wrote the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Ethics approval and consent to participate

This study was approved by the Institutional Review Board Ethics Committee of the Tokushukai Medical Group (license number: TGE00508-059). Informed consent was obtained from patients and their families before study participation commenced.

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