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ORIGINAL ARTICLE

Retrospective Study

Direct-acting antivirals for hepatitis C virus-infected patients with hepatocellular carcinoma

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Abstract

BACKGROUND

Hepatocellular carcinoma (HCC) in hepatitis C virus (HCV)-infected patients has a high risk of recurrence. Although eradication of HCV is expected to reduce this risk, the risk in patients with a history of HCC may be high after treatment with direct-acting antivirals (DAAs).

AIM

To determine the risk factors for HCC recurrence in patients with HCV and a history of HCC.

METHODS

The risk of HCC recurrence in patients with a history of HCC and/or of HCC occurrence in patients without a history of HCC after DAA therapy was retrospectively analyzed in 311 HCV patients treated at our institution and several neighboring hospitals. The frequency and predictors of HCC recurrence/ occurrence after DAA treatment were included in these analyses. The clinical course of HCC before and after DAA treatment was also evaluated.

RESULTS

HCV patients with a history of HCC were older and had greater progression of

liver fibrosis and diabetes than patients without a history of HCC. Median recurrence-free survival (RFS) was 1092 d in patients with a history of HCC, and post-DAA HCC recurrence/occurrence was observed in 29 patients (53.7%) with and 5 (1.9%) without a history of HCC over 6 years ($P < 0.001$). RFS in patients with a history of HCC did not differ significantly before and after DAA treatment. The frequency of HCC recurrence/occurrence in patients with a history of HCC was lower after than before DAA treatment. Multivariate analysis showed that the incidence rate of HCC recurrence/occurrence before DAA treatment was the only independent predictor of HCC recurrence/occurrence after DAA treatment. Liver function was well preserved and clinical course was good in patients with HCC recurrence/occurrence after DAA therapy.

CONCLUSION

DAA therapy in patients infected with HCV is also effective in patients with a history of HCC. Curative treatment for HCC is desirable before DAA therapy. The frequency of HCC recurrence/occurrence before DAA therapy was associated with a significantly increased risk of HCC recurrence after DAA therapy. Careful observation after DAA therapy is required in patients with a history of HCC.

Key Words: Direct-acting antivirals; Hepatitis C virus; Hepatocellular carcinoma; Recurrence; Liver fibrosis; Curative treatment

Core Tip: To estimate the therapeutic value of direct-acting antivirals (DAAs) in hepatitis C virus (HCV)-infected patients with a history of hepatocellular carcinoma (HCC), the clinical course of HCV patients with or without a history of HCC after DAA therapy was retrospectively analyzed. DAA treatment did not increase the incidence rate of HCC recurrence/occurrence or enhance malignant transformation of HCC in patients with a history of HCC. The risk of HCC recurrence after DAA therapy was significantly associated with the frequency of HCC recurrence/occurrence before DAA therapy.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is one of the most frequent malignancies and a major cause of cancer-related deaths worldwide. Although HCC detected at an early stage can often be cured by surgical resection or local ablative therapy, HCC is often diagnosed at an advanced stage, precluding curative treatment and resulting in a high mortality rate[1]. Viral hepatitis is associated with the development of HCC, with hepatitis C virus (HCV) and hepatitis B virus (HBV) infections being major causes of HCC, along with nonviral etiologies such as alcoholic liver disease and nonalcoholic fatty liver disease[2]. HCV-related HCC often recurs after curative therapies for HCC, such as surgical resection or ablative therapies, with 5-year recurrence rates ranging from 60%-80%[3].

Interferon-based HCV eradication reduces the incidence rates of HCC[4]. The anti-HCV and anti-carcinogenic effects of interferon reduce liver inflammation, contributing to reductions in the rate of HCC recurrence/occurrence. It is unclear, however, whether HCV eradication with direct-acting antivirals (DAAs) increase the risk of HCC, as DAA treatment disrupts immune surveillance during rapid elimination of HCV[5]. Large-scale studies, however, have shown that DAA eradication of HCV increases the risk of HCC, whereas basal liver fibrosis is associated with the risk of HCC[6-8]. Because other studies have reported that DAA eradication results in malignant transformation, suggesting that DAA had adverse carcinogenic effects[5,9], these carcinogenic risks should be especially considered in patients with a history of HCC. The effects of DAA therapy have therefore been assessed in patients with a history of HCC. Studies have suggested that factors associated with pre-existing malignant potential, such as advanced liver fibrosis, high serum alpha-fetoprotein (AFP) concentration, and the presence of precancerous nodules, might lead to HCC recurrence in patients with a history of HCC[10-14].

This study retrospectively evaluated the risks of HCC recurrence/occurrence, defined as HCC recurrence in patients with a history of HCC and/or of HCC occurrence in those without a history of HCC, and the clinical course of HCC in HCV patients treated with DAA. The results of this study suggest that a history of HCC prior to DAA treatment is a major factor contributing to HCC recurrence/occurrence after DAA treatment.

MATERIALS AND METHODS

Patients

This study enrolled HCV patients treated with DAA at Toyama University Hospital, Takaoka Municipal Hospital, Nanto Municipal Hospital, and Saiseikai Toyama Hospital (all in Toyama, Japan) between November 2014 and July 2020. HCV infection was confirmed by HCV-RNA quantification and the genotype of HCV was determined in all patients. The fibrosis-4 (Fib-4) index, a useful noninvasive method of assessing liver fibrosis[15], was also evaluated in all patients. Liver cirrhosis was diagnosed by hepatologists, each with over 20 years' of experience, based on the results of imaging modalities such as ultrasonography (US), computed tomography (CT), and elastography, and the titers of fibrosis markers such as platelet count and Fib-4 index. HCC was diagnosed based on histological and/or imaging data such as contrast-enhanced CT or magnetic resonance imaging (MRI), according to the diagnostic criteria of the American Association for the Study of Liver Diseases[16]. Before DAA therapy, all patients were screened using US, CT, or MRI to rule out the presence of viable HCC. This multicenter study was performed in accordance with the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Toyama University (Approval No. R2019-131).

Treatment with DAAs

Before the start of DAA therapy, patients with viable HCC were treated with surgery, radiofrequency ablation (RFA), or transarterial chemoembolization (TACE). Patients who did not show viable HCC lesions on contrast-enhanced CT or MRI performed 1 to 3 mo after HCC treatment were considered eligible for DAA therapy. Treatment regimens were determined by hepatologists according to HCV treatment guidelines[17,18]. Treatment regimens included daclatasvir plus asunaprevir (DCV + ASV) in patients with HCV genotype 1b from 2014 to 2016; sofosbuvir plus ledipasvir (SOF + LDV) for patients with HCV genotypes 1b and 2a/2b from 2015 to 2020; SOF plus ribavirin (SOF + Rib) for patients with HCV genotypes 2a/2b from 2015 to 2017; and glecaprevir and pibrentasvir (GLE + PIB) for patients with any HCV genotype from 2017 to 2020. Other regimens considered included ombitasvir, paritaprevir, and ritonavir from 2016 to 2017; elbasvir plus grazoprevir in 2017; and SOF plus velpatasvir from 2019 to 2020 depending on the patient's condition and the timing of treatment. Patients were monitored every 4 wk during DAA treatment, and every 12 wk thereafter, with HCC evaluated by imaging modalities. A sustained viral response (SVR) was defined as complete clearance of HCV-RNA clearance 12 wk after the end of DAA treatment. The flow chart of this study is shown in Supplementary Figure 1. Patients were monitored for a median 1311 d (range: 28 d to 2231 d) after the end of DAA therapy.

HCC Treatment

HCC treatment in each patient was determined by discussions among surgeons, hepatologists, and radiologists at each institution and was based on Japanese practice guidelines for HCC[19]. Treatments of patients with early-stage HCC included surgical resection or RFA. Treatments of patients with multiple HCCs included TACE or systemic chemotherapy such as sorafenib, according to liver function and tumor progression and following treatment guidelines.

Statistical analyses

Variable distributions were reported as mean ± SD. Categorical variables were compared by the Fisher's exact test. Continuous variables were compared by the Student's *t*-test or the Mann-Whitney U test. Survival was evaluated using the Kaplan-Meier method, with differences in survival curve compared by log-rank tests. The incidence rates of HCC recurrence/occurrence were reported as person-years. All statistical analyses were performed using SPSS software, version 19.0 (IBM Corp., Armonk, NY, United States), with $P < 0.05$ considered statistically significant.

RESULTS

Patients and recurrence/occurrence of HCC

A total of 311 patients, 143 (46.0%) men and 168 (54.0%) women, were included in this study (Table 1). Of these 311 patients, 87 (28.0%) had cirrhosis, 229 (73.6%) were infected with HCV genotype 1b, and 53 (17.0%) had a previous history of HCC. Their mean Fib-4 index was 3.87 ± 3.24 and their mean AFP concentration was 12.0 ± 35.2 ng/mL. The 53 patients with a history of HCC were significantly older

Table 1 Characteristics of patients

	Overall	With HCC	Without HCC	*P* value[1]
Case	311	53	258	
Age in yr	68.1 ± 13.5	75.8 ± 6.7	66.5 ± 14.1	< 0.01
Male/Female	143/168	27/26	116/142	0.45
Diabetes, yes/no	47/264	19/34	28/230	< 0.01
Habitual alcohol use[2], yes/no	56/255	12/41	44/214	0.33
Liver cirrhosis, yes/no	224/87	18/35	52/206	< 0.01
Genotype, 1b/2a, 2b/others	229/73/10	45/7/1	183/66/9	0.04
Alb in g/dL	3.9 ± 0.4	3.5 ± 0.4	4.0 ± 0.4	< 0.01
ALT in U/L	44.3 ± 45.0	40.3 ± 22.0	45.1 ± 48.3	0.48
Plt as × 10^4/μL	16.0 ± 5.9	12.9 ± 5.6	16.7 ± 5.8	< 0.01
Fib-4 index	3.87 ± 3.24	6.27 ± 4.64	3.37 ± 2.60	< 0.01
AFP in ng/mL	12.0 ± 35.2	23.7 ± 52.4	9.4 ± 29.6	0.047

[1]Statistical significance set up as $P < 0.05$ as compared between with HCC *vs* without HCC.
[2]Habitual alcohol use is defined as daily alcohol consumption of > 20 g a woman or > 30 g for a man.
Alb: Albumin; AFP: Alpha fetoprotein; ALT: Alanine aminotransferase; Fib-4: Fibrosis-4; HCC: Hepatocellular carcinoma; Plt: Platelet.

(75.6 years *vs* 66.5 years; $P < 0.01$) than the 258 patients with no history of HCC. The rates of diabetes, a risk factor for HCC after DAA treatment[20] (35.8% *vs* 3.1%; $P < 0.01$) and liver cirrhosis (34.0% *vs* 20.2%; $P < 0.01$) were significantly higher, whereas the rates of HCV genotype 2 (13.2% *vs* 25.6%; $P = 0.04$) were significantly lower, in patients with than without a history of HCC. In addition, serum albumin concentrations (3.5 g/dL *vs* 4.0 g/dL; $P < 0.01$) and platelet counts (12.9 × 10^4/mL *vs* 16.7 × 10^4/mL; $P < 0.01$) were significantly lower, whereas Fib-4 index (6.27 *vs* 3.37; $P < 0.01$) and AFP concentrations (23.7 ng/mL *vs* 9.4 ng/mL; $P = 0.047$) were significantly higher in patients who had a previous history of HCC. Of the 311 patients, 56 (21.9%) had a history of habitual alcohol use, but these rates did not differ significantly in patients with and without a history of HCC. Thus patients with a history of HCC were older and had more advanced liver fibrosis progression and diabetes than patients without a history of HCC.

Treatment with DAA

Patients infected with HCV genotype 1b were administered DCV + ASV, SOF + LDV, GLE + PIB, or other regimens in accordance with contemporary guidelines. Similarly patients infected with HCV genotypes 2a/2b were administered SOF + Rib, SOF + LDV, GLE + PIB, or other regimens; and patients with other genotypes such as genotypes 3a/3b/4s were administered GLE + PIB. SVR was achieved by 52 (98.1%) of the 53 patients with and by 250 (96.9%) of the 258 patients without a history of HCC ($P = 1.00$). Several patients who did not initially achieve SVR were switched to another DAA regimen, with SVR achieved in all treated patients. Post-DAA treatment AFP levels were higher in patients with, than without, a history of HCC history, both at end of treatment and SVR, but these concentrations were lower than those before DAA therapy (Table 2).

HCC after DAA-therapy

Following DAA therapy, HCC recurrence/occurrence was found in 29 patients (53.7%) with and 5 (1.9%) without a history of HCC, with 3-year incidence rates of 50.9% (27/53) and 1.2% (3/258), respectively. Median recurrence-free survival (RFS) in patients with a history of HCC was 1092 d, whereas none of those without a history of HCC died during the 6-year study period ($P < 0.001$; Figure 1A).

HCC before and after DAA treatment

HCC recurrence and other parameters before and after DAA therapy were compared in patients with a history of HCC. Median RFS did not differ significantly in patients with HCC recurrence before and after DAA therapy [1293 d (range 554-2032 d) *vs* 1053 d (range 741-1443 d); $P = 0.884$) (Figure 2A), with incidence rates of HCC recurrence of 1/1.25 and 1/2.99 person-years, respectively (Figure 2B). HCV clearance induced by DAA treatment did not increase HCC recurrence rate. Univariate analysis showed that AFP concentration at SVR and frequency of HCC recurrence before DAA treatment were risk factors for HCC recurrence after DAA treatment, whereas multivariate analysis showed that only the

Table 2 Treatment with direct-acting antivirals

Regimens	With HCC	Without HCC
DCV + ASV/SOF + LDV/SOF + Rib/GLE + PIB/others	13/24/6/6/4	45/103/35/58/20
SVR at 12 wk post-treatment, yes/no	52/1	250/8
AFP at EOT in ng/mL	7.64 ± 6.81[a]	3.93 ± 3.99
AFP at SVR in ng/mL	6.60 ± 6.27[a]	3.68 ± 2.64

[a]$P < 0.05$ as compared between with HCC *vs* without HCC.

AFP: Alpha fetoprotein; ASV: Asunaprevir; EOT: End of treatment; DCV: Daclatasvir; GLE: Glecaprevir; HCC: Hepatocellular carcinoma; LDV: Ledipasvir; PIB: Pibrentasvir; Rib: Ribavirin; SOF: Sofosbuvir; SVR: Sustained viral response.

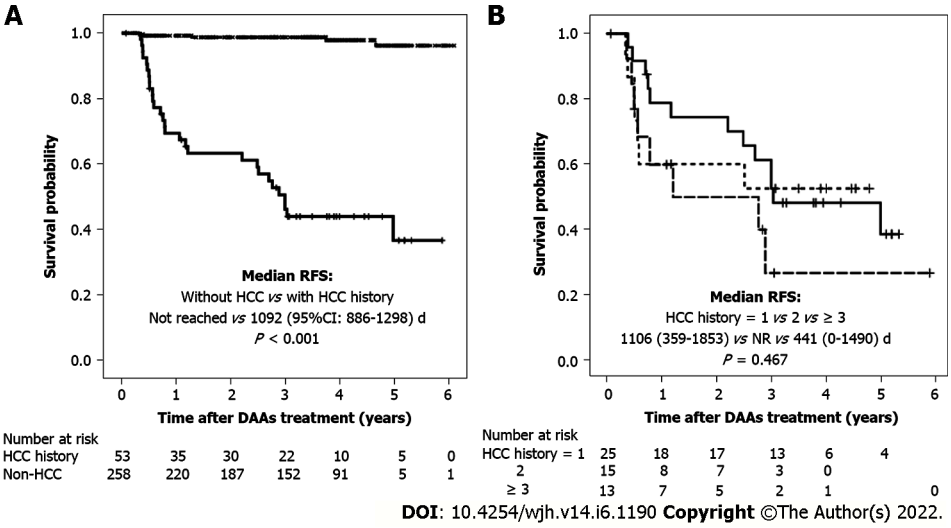

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Figure 1 Kaplan-Meier analysis. A: Hepatocellular carcinoma (HCC) recurrence/occurrence after direct-acting antiviral (DAA) treatment of patients with (solid line) and without (dotted line) a history of HCC; B: Kaplan-Meier analysis of HCC events after DAA treatment in patients with 1 (solid line), 2 (dotted line), and ≥ 3 (dashed line) HCC events before DAA treatment. Numbers in parenthesis = 95% confidence interval. NR: Not reached; RFS: Recurrence-free survival; CI: Confidence interval; HCC: Hepatocellular carcinoma.

frequency of HCC recurrence before DAA treatment was an independent predictor of HCC recurrence after DAA treatment (Table 3). Only a history of HCC before DAA treatment contributed to the risk of HCC recurrence after DAA treatment, whereas HCV clearance by DAA alone did not. The 1-year rates of HCC recurrence after DAA treatment in patients with 1, 2, and ≥ 3 HCC events before DAA treatment were 28%, 40% and 38.5%, respectively (Figure 1B).

Clinical course after HCC recurrence

All 29 patients with a history of HCC who experienced HCC recurrence after DAA therapy had been treated according to HCC treatment guidelines[19]. Six and seventeen of these patients underwent surgical resection and RFA, respectively. Multiple recurrences were observed in 6 patients, including one with portal invasion. These 6 patients were subsequently treated with TACE, hepatic artery infusion chemotherapy, or sorafenib. Two died due to advanced HCC, with survival times following DAA therapy completion of 49.7 and 52.6 mo, respectively.

DISCUSSION

This study found that DAA-induced eradication of HCV did not increase the risk of HCC recurrence, with multivariate analysis showing that a prior history of HCC was the only independent factor predicting the risk of HCC recurrence after DAA therapy. DAA treatment, however, did not worsen the clinical course of subsequent HCC events. Rather, liver reserve function was preserved following DAA treatment, allowing curative and continuous treatment of HCC. Although malignant transformation after DAA treatment has been reported[5,9], this study found that DAA therapy itself was not the causal agent.

Table 3 Univariate and multivariate analyses for hepatocellular carcinoma recurrence after direct-acting antiviral treatment

Factors	Univariate			Multivariate		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Age	0.98	0.92-1.04	0.52			
CH or LC	0.50	0.21-1.21	0.12			
Diabetes	1.12	0.79-1.59	0.53			
Habitual alcohol use	1.08	0.68-1.51	0.51			
Fib-4	1.01	0.93-1.09	0.86			
AFP at baseline	1.01	1.00-1.01	0.22			
AFP at EOT	1.09	1.00-1.19	0.05	1.10	1.00-1.01	0.05
AFP at SVR	1.01	1.00-1.01	0.04	1.01	1.00-1.01	0.08
Duration between first HCC and DAAs treatment	1.00	1.00-1.00	0.18			
Number of HCC occurrence	1.32	1.06-1.64	0.02	1.61	1.18-2.19	< 0.01

AFP: Alpha fetoprotein; CH: Chronic hepatitis; CI: Confidence interval; DAAs: Direct-acting antivirals; EOT: End of treatment; HCC: Hepatocellular carcinoma; HR: Hazard ratio; LC: Liver cirrhosis; SVR: Sustained viral response.

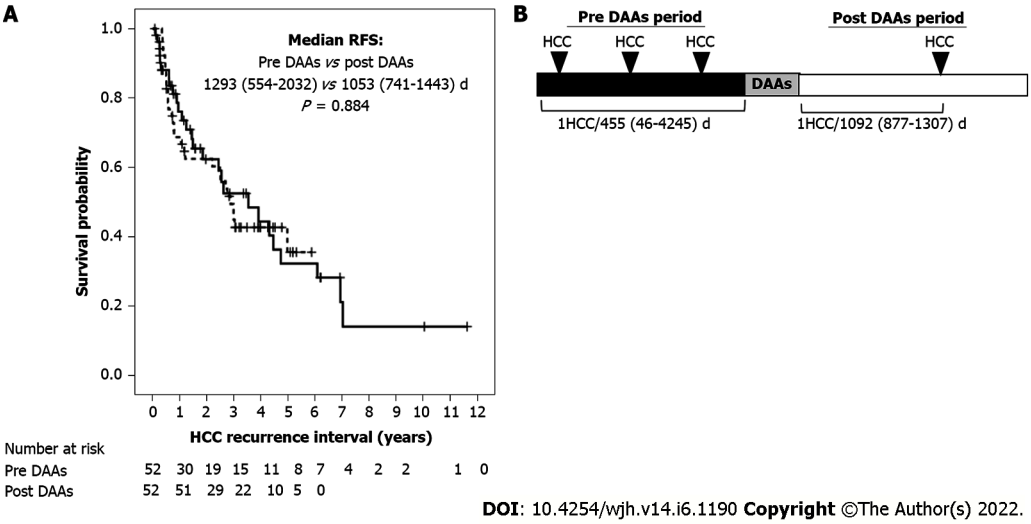

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Figure 2 Median recurrence-free survival in patients with hepatocellular carcinoma recurrence before and after direct-acting antivirals treatment. A: Kaplan-Meier analysis of hepatocellular carcinoma (HCC) recurrence before (solid line) and after (dotted line) direct-acting antiviral (DAA) treatment in patients with a history of HCC; B: Schema of HCC events. Solid triangle = one event. Black bar = period in days. Numbers in parenthesis = 95% confidence interval. RFS: Recurrence-free survival; HCC: Hepatocellular carcinoma; DAA: Direct-acting antiviral.

In this study, SVR rates in DAA-treated patients were similar in those with (98.1%) and without (96.9%), a previous history of HCC. Systematic reviews, however, have reported lower SVR rates in patients with a history of HCC[21]. This study found that treatment with DAAs was highly effective in eradicating HCV in patients with a history of HCC, despite their being older and more likely to have liver fibrosis and diabetes mellitus than patients without a history of HCC. DAAs are also effective in patients with advanced HCC[22-24]. HCV eradication by DAAs ameliorates liver inflammation and suppresses liver fibrosis progression, preserving or improving liver function. Since the introduction of DAAs as treatment for HCV, mortality rates in patients with HCV-associated HCC have improved compared with mortality rates in patients with HBV-related and nonviral HCC[25]. These findings suggest that HCV eradication might prolong overall survival in patients with HCV-related HCC.

Although HCV eradication by DAAs has been suggested to increase the subsequent risk of HCC, most studies have found that preexisting risk factors for HCC development were present at the time of DAA initiation. The progression of liver fibrosis and the presence of cirrhosis have been shown to be associated with HCC development[6-8]. Chronic HCV infection leads to the progression of liver fibrosis,

the factor that contributes most to HCC development through various epigenetic changes and the creation of a microenvironment favorable to carcinogenesis[26]. The risk of HCC recurrence/occurrence after DAA treatment was shown to be higher in patients with than without advanced liver fibrosis[27], suggesting that earlier achievement of SVR before the development of fibrosis may reduce the likelihood of HCC recurrence/occurrence.

Serum AFP concentration has also been found to predict HCC development[10,13]. Higher AFP concentration is a major biomarker for HCC occurrence after SVR[28,29], as well as being associated with liver inflammation, making AFP concentration at the end of treatment very important[30]. AFP concentrations before and after DAA treatment should therefore be measured to estimate the risk of HCC recurrence/occurrence. Another factor associated with HCC development is the presence of preexisting hepatic nodules[14]. Although all patients in the present study who were treated with DAAs were evaluated by imaging modalities, some did not undergo enhanced CT or MRI. Thus, the exact proportion of patients with dysplastic nodules was unclear. For example, a patient found to have a 1.5 cm dysplastic nodule in the liver on ethoxybenzyl-diethylenetriamine pentaacetic acid enhanced (EOB)-MRI developed HCC from the dysplastic nodule 3-years after DAA completion, akin to hypervascular transformation of 9 mm hypovascular nodules with a 3-year incidence rate of 30%[31]. Certain types of DAAs, such as SOF and DCV, were found to have greater oncogenic potential through off-target DAA effects[32]. In the present study, HCC recurrence/occurrence was not frequent in patients treated with SOF or DCV (data not shown).

Collectively, DAA treatment was effective in patients with a history of HCC, as shown by their high SVR rates. DAAs eliminated hepatic inflammation and suppressed the progression of hepatic fibrosis, leading to preserved liver function. Improvement or preservation of liver function provides benefits in the management of HCC. Further prospective studies are required to evaluate the risk of DAA-associated transformation of precancerous lesions to HCC and the effects of specific DAAs on the risks of HCC recurrence/occurrence.

Multivariate analysis of patients in the present study also found that liver fibrosis, diabetes mellitus, and serum AFP concentration before DAA treatment were unassociated with HCC recurrence/occurrence after DAA treatment. Rather, the only factor significantly associated with HCC recurrence/occurrence after DAA treatment was history of prior HCC events. DAA treatment has been reported effective in patients with multiple prior courses of HCC recurrence[33], suggesting the need for careful screening for HCC before DAA treatment of patients with a history of HCC, as well as diligent follow-up of these patients after DAA therapy. Estimating the risk of HCC after DAA treatment is important, with the degree of liver fibrosis predicting the risk HCC recurrence[34,35]. A previous history of HCC and stratification by the Fib-4 index can be used to construct a novel predictive model for HCC development after DAA treatment[36]. The need for careful screening and follow-up in patients with a history of HCC increases with the number of times patients have experienced HCC recurrence.

This study had several limitations. First, its retrospective design precluded accurate determination of the effects of DAA treatment on the risks of HCC recurrence/occurrence. Second, the number of patients included in the present study, especially of those with a history of multiple HCC events, was relatively small. Third, not all patients underwent EOB-MRI, preventing actual determination of their HCC or non-HCC status. Although all underwent enhanced CT or US performed by experienced hepatologists rather than EOB-MRI, further studies are required to evaluate precancerous lesions and HCC more precisely. In addition, other risk factors for HCC, including tobacco use, obesity, and metabolic diseases, were not analyzed.

CONCLUSION

DAA treatment of HCV-infected patients can also preserve liver function in patients with HCC. Curative treatment of HCC is desirable before DAA therapy. A history of multiple courses of HCC events before DAA treatment significantly increases the risk of HCC recurrence. Careful HCC screening prior to DAA treatment and thorough follow-up observation after DAA treatment is recommended in such patients.

ARTICLE HIGHLIGHTS

Research background

Treatment with direct-acting antivirals (DAAs) has provided many benefits to hepatitis C virus (HCV)-infected patients. Hepatocellular carcinoma (HCC) development after treatment with DAAs remains a serious issue.

Research motivation

The effect of DAA treatment on the risk of HCC development is an important clinical question.

Research objectives
To clarify the risk of HCC development after DAA treatment in patients HCV-infected patients at high risk for HCC development.

Research methods
HCC occurrence after DAA treatment was retrospectively evaluated in patients with and without a history of HCC.

Research results
The frequency of HCC recurrence/occurrence was similar before and after treatment with DAAs. The number of HCC occurrences before DAA treatment was an independent risk factor for HCC recurrence/occurrence.

Research conclusions
HCV-infected patients with a history of multiple HCCs should be monitored carefully for HCC recurrence.

Research perspectives
An effective screening method should be established for patients at high risk of HCC recurrence/occurrence.

FOOTNOTES

Author contributions: Tajiri K designed and performed the research and wrote the paper; Ito H, Kawai K, Murayama A, Hayashi Y, Minemura M, Takahara T, and Shimizu Y contributed to the management of patients; Shimizu Y and Yasuda I supervised the work.

Institutional review board statement: This study was reviewed and approved by the ETHICs Committee of Toyama University.

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