EFFICACY AND SAFETY OF TREATMENT WITH DACLATASVIR AND ASUNAPREVIR FOR HEPATITIS C VIRUS GENOTYPE 1

Takuma Ajimine[1)], Shigetoshi Ohshima[2)], Takashi Goto[2)], Masafumi Komatsu[3)], Kunio Nakane[3)], Hitoshi Yagisawa[4)], Mitsuo Goto[5)], Kou Nakajima[6)], Masato Miura[7)], Masato Funaoka[8)], Takao Hoshino[9)], Tomoyuki Kuramitsu[10)], Yuukou Fujishima[11)], Daisuke Watanabe[12)], Daisuke Segawa[13)], Masaaki Inomata[14)] and Katsunori Iijima[2)]

[1)]Kitaakita Munincipal Hospital
[2)]Department of Gastroenterology and Neurology, Akita University Graduate School of Medicine
[3)]Department of Gastroenterology, Akita City Hospital
[4)]Department of Gastroenterology Akita Red Cross Hospital
[5)]Goto Clinic
[6)]Nakajima Doctor's Office
[7)]Department of Gastroenterology, Ohmagari Kousei Medical Center
[8)]Department of Gastroenterology, Yokote Munincipal Hocpital
[9)]Department of Gastroenterology, Akita Kousei Medical Center
[10)]Kuramitsu Clinic
[11)]Department of Gastroenterology, Noshiro Kousei Medical Center
[12)]Noshiro Yamamoto Medical Association Hospital
[13)]Segawa Clinic
[14)]Inomata Clinic

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Abstract :
AIM : To assesse the efficacy and safety of therapy with daclatasvir (DCV) and asunaprevir (ASV) for HCV genotype 1.
METHOD : The study population was 253 patients who were enrolled in the Akita hepatitis C study group from 2015 to 2016. We followed them until 24 weeks after the end of treatment.
RESULT : The sustained virological response (SVR) at 24 weeks after the end of treatment rates were 84.2%. In univariate analyses, the Y93 mutation and a history of triple therapy with protease inhibitor reduced the SVR 24 rate. In multivariate analyses, the Y93H mutation, a history of triple therapy with protease inhibitor, and LC status reduced the SVR 24 rate. The most frequently reported adverse event was ALT elevation, noted in 25.7% of patients. 10.7% of patients had T-Bil elevation, 7.1% experienced drug rush, 11.5% experienced respiratory symptoms, 10.3% developed a fever, and 7.1% experienced digestive symptom. Only 9 (3.6%) patients stopped taking the drugs due to drug-related severe adverse events.
CONCLUSION : DCV and ASV therapy showed a high efficacy and low rate of adverse events.

Key words : hepatitis C virus, interferon free, daclatasvir, asunaprevir, α fetoprotein

Corresponding author : Shigetoshi Ohshima
Department of Gastroenterology and Neurology, Akita University Graduate School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan
Tel : 81-18-884-6104
Fax : 81-18-836-2611
E-mail : ohshima@doc.med.akita-u.ac.jp

Introduction

Nearly, 185 million people worldwide (3% of the world's population) are infected with the hepatitis C virus (HCV)[1]. The HCV prevalence and genotype distribution vary by region. Among the six identified HCV genotypes, genotype 1 is the most prevalent worldwide. In Japan, there are approximately 1.5–2 million people infected with HCV, with genotype 1b being the dominant genotype, thereby infecting about 70% of such people[2].

Approximately 75% of acute infections with HCV fail to clear spontaneously and progress to a state of chronic infection with serious long-term effects[3]. HCV infection causes liver cirrhosis and leads to hepatocellular carcinoma (HCC). In addition, advanced fibrosis and cirrhosis are known to be significantly associated with an increased HCC risk[4]. As such, an antiviral treatment to reduce the risk of liver cirrhosis and HCC is urgently needed[5].

For years, peginterferon alpha associated with ribavirin was the first-line therapy for chronic hepatitis (CH) C patients. However, this combination provided a sustained virological response (SVR) of only 42% to 52% in genotype 1 patients and had an unfavorable adverse effects profile[6,7]. In 2011, several direct-acting antivirals (DAAs) were approved for treatment. The HCV genome encodes 9 proteins — 2 structural and 7 nonstructural (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). These proteins provide targets for DAAs, as they are largely essential to the virus cycle of replication.

In Japan, the first-generation NS3/4A protease inhibitors telaprevir (TPV) became available for treatment of genotype 1 infection in 2011. It brought about SVR rates ranging from 34.4% to 88.1%[8]. However, despite relatively high SVR rates, patients were faced with severe adverse events (anemia, rash, depression, etc.). Thus, safer therapeutic strategies were strongly desired[8].

The second-generation NS3/4A protease inhibitors simeprevir (SMV) and vaniprevir (VPV) were approved in 2013 and 2014, respectively. These agents were also combined with peginterferon alpha and ribavirin. Their combination therapy demonstrated high SVR rates similar to that of TPV therapy, with lower adverse event rates[9]. No response to prior treatment, the existence of liver cirrhosis (LC), and IL28B polymorphism status were shown to be associated with a response to these therapies[10–12]. In addition, several host factors, including depression and pancytopenia, were also shown to be important for determining the adoption of interferon-containing regimens[13].

The HCV NS5A inhibitor daclatasvir (DCV) and the NS3/4A protease inhibitor asunaprevir (ASV) were approved in Japan in 2014 for the treatment of genotype 1 CH or compensated LC patients who were null-responders to prior treatment and intolerant or ineligible for interferon-containing therapy. This therapy was then expanded to patients who were treatment-naïve and experienced recurrence with an interferon regimen in 2015.

NS5A variants, such as Y93H/L31, are presumed to exist before treatment as naturally occurring and the presence of such variants is closely linked to the effectiveness of antiviral treatment. We should assess the presence of NS3/4A and NS5A variants in patients to predict the response to this therapy in advance.

In this paper, we assessed the efficacy and safety of therapy with DCV and ASV for HCV genotype 1.

Materials and Methods

Patients

The study population was 253 patients who were enrolled in the Akita hepatitis C study group (AHC) from 2015 to 2016. The AHC consists of Akita University, nine affiliated hospitals, and five clinics in Akita prefecture, Japan. In this multicenter retrospective study, 253 patients were treated with DCV and ASV. All of the patients were infected with HCV genotype 1, had an HCV RNA level of ≥5.0 log10 IU/ml, and were diagnosed with CH or compensated LC (Child-Pugh grade A). LC was diagnosed by the pathognomonic findings of laboratory data and/or abdominal ultrasound. The patients were 36–89 years of age (mean age : 69 years), and 111 of the patients were male. We excluded patients with HBV, autoimmune hepatitis, primary biliary cholangitis, or metabolic liver disease (such as hemochromatosis or Wilson's disease).

All of the patients gave their informed consent to participate in this study, which was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Akita University. The data of 253 patients were eligible for the analysis.

Study design

All of the patients received 24 weeks of treatment with DCV (Daklinza®, 60 mg/day ; Bristol-Myers Squibb, NY, USA) and ASV (Sunvepra®, 100 mg twice per day ; Bristol-Myers Squibb, NY, USA).

We followed all of the patients until 24 weeks after the end of treatment and measured their plasma levels of HCV RNA to assess the efficacy of the treatment at 4 weeks (RVR), at the end of treatment (EOTR), at 12 weeks after the end of treatment (SVR12), and at 24 weeks after the end of treatment (SVR24).

Study assessments

The screening assessments included the serum HCV RNA levels, standard laboratory, pretreatment NS5A variants, AFP, renal function, clinical tests, vital signs, and physical examinations. Serum HCV RNA was measured with a COBAS Taqman HCV assay (Roche Molecular Diagnostics, Tokyo, Japan). Liver fibrosis was assessed according to the Aspartate Aminotransferase to Platelet Ratio Index (APRI) and FIB4 index. The APRI relies on the aspartate aminotransferase (IU/l) to platelet count ($\times 10^4$/μl) ratio. FIB4 index relies on the age, aspartate, and aminotransferase levels and the platelet count. Pretreatment NS5A variants were examined by a PCR Invader Assay (BML, Tokyo, Japan), deep sequencing, or direct sequencing. The sequencing approach was decided by the treating physician.

Adverse events (anemia, rash, renal dysfunction) were graded according to the WHO toxicity grades. Headache, a fever, and other symptoms were sometimes observed during an interview which was conducted by the treating physician.

Statistical analyses

The baseline continuous data were expressed as the median (interquartile ranges), and categorical variables were expressed as frequencies or percentages. The chi-squared test and the independent *t*-test were used for the univariate and multivariable analyses as appropriate. $P<0.05$ was considered statistically significant. Statistical analyses were performed with the SPSS ver. 20 and Windows Excel 2010 software programs.

Results

Baseline characteristics

Among our patients, 67.2% (170/253) had CH, and 32.8% (83/253) had LC. The male : female ratio was 43.9% (111/253) to 56.1% (142/253). The average age was 69.3±0.6 years, and the average HCV-RNA was 6.0±0.04 logIU/mL, with no significant differences between the CH and LC patients in these factors. However the AST, ALT, APRI, FIB4 index, and AFP levels were significantly higher in LC patients than in CH patients, and the albumin and platelet levels were significantly lower in LC patients than in CH patients.

Patients with NS5A variants, especially the Y93H mutation, accounted for 11.1% (28/253) of the total population. The rate of an L31 mutation was significantly higher in the LC patients than in the CH patients. In past treatment, 121 patients were naïve, 109 patients had a history of treatment with interferon or peginterferon therapy (including combination with RBV), 21 patients had been previously treated with a protease inhibitor, peginterferon alpha, and ribavirin, the treatment status was unknown in 2 patients. There were no significant differences in the treatment history between CH and LC patients (Table 1).

Therapeutic outcomes and details

A total of 253 patients were enrolled in this study, and 218 finished the protocol and were followed for 24 weeks after its completion. Among them, 203 patients achieved SVR24, and 15 had virological failure. Thirty-five patients did not fully complete the therapy. Among them, 30 patients discontinued this protocol : 6 achieved SVR24, and 24 had virological failure. Five patients required a dose reduction of ASV to 100 mg/day. Among them, 80% (4/5) achieved SVR24, and 20% (1/5) had virological failure. Overall, 213 patients achieved SVR24,

Table 1. Baseline characteristics of the patients

	Total (n=253)	CH (n=170)	LC (n=83)	P value
Sex (male/female)	111/142	79/91	32/51	0.23
Age (years)	69.3±0.6	68.7±0.8	70.5±0.9	0.31
HCV-RNA (log IU/mL)	6.0±0.04	6.0±0.1	6.1±0.1	0.67
AST (IU/L)	49.8±1.8	45.6±2.1	58.7±3.3	<0.05
ALT (IU/L)	47.5±2.3	45.8±3.0	51.4±3.3	<0.05
Alb (g/dL)	4.1±0.03	4.2±0.03	3.7±0.2	<0.05
Plt ($\times 10^4/\mu$L)	14.7±0.5	17.2±0.6	9.5±0.4	<0.05
APRI	1.5±0.1	1.1±0.1	2.3±0.2	<0.05
FIB4 index	4.6±0.2	3.3±0.2	7.2±0.5	<0.05
AFP (ng/mL)	10.2±1.4	5.1±0.4	20.5±3.9	<0.05
Y93H mutation (wild/mutant/unknown)	(202/28/23)	(133/22/15)	(69/6/8)	0.4
L31 mutation (wild/mutant/unknown)	(193/5/55)	(138/3/29)	(55/2/26)	<0.05
Past treatment (naïve/IFN/PI+IFN+RBV/unknown)	(121/109/21/2)	(86/69/14/1)	(35/40/7/1)	0.48

The date are presented as numbers, average or medians with interquartile ranges. The P values were calculated using the χ^2 test or the independent t-test for continuous variables.
CH, Chronic Hepatitis ; LC, Liver cirrhosis ; APRI, Aspartate Aminotransferase to Platelet Ratio Index ; FIB4 index, fibrosis-4 index ; AFP, αfetoprotein ; PI, Protease inhivitor ; IFN, Interferon ; RBV, ribavirin.

and 40 had virological failure. Of these 40 patients, 15 had virological breakthrough (Fig. 1), 3 were non-responders, 13 developed recurrence, and 9 discontinued this protocol for various reasons (1 : cerebral vascular disease, 1 : pneumonia, 1 : meningioma, 2 : ALT elevation, 1 : skin rash, 1 : a fever, 1 : dropped out 1 : unknown) (data not shown).

Efficacy of antiviral therapy

The rates of RVR, EOTR, SVR12, and SVR24 were 84.2%, 89.3%, 84.6%, and 84.2%, respectively. Overall, 213 patients achieved SVR24, and 40 had virological failure.

The rates of RVR, EOTR, SVR12, and SVR24 in CH patients were 88.2%, 90.6%, 86.5%, and 86.5%, respectively, while those in LC patients were 76.0%, 86.7%, 80.7%, and 79.5%, respectively. The rate of RVR was significant higher in the CH patients than in the LC patients (P=0.02), but there were no significant differences in the rates of EOTR, SVR12, or SVR24 between the CH and LC patients (P=0.38, 0.26, 0.09, respectively) (Fig. 2).

Assessment of the factors associated with SVR

Univariate and multivariable analyses were performed to detect the factors associated with SVR. Two parameters reduced the SVR 24 rate in univariate analyses : the Y93 mutation (P=0.01) and a history of triple therapy with TPV or SMV (P=0.0004). Multivariate analyses revealed 3 significant independent factors which reduced the SVR 24 rate : the Y93H mutation (odds ratio [OR] 4.78 ; 95% confidence interval [CI] 1.89-12.11 ; P = 0.001), a history of triple therapy with TPV or SMV (OR 4.49 ; 95% CI 1.63-12.37 ; P = 0.004), and LC status (OR 2.70 ; 95% CI 1.19-6.10 ; P = 0.017) (Table 2).

Safety analyses

The most frequently reported adverse event was ALT elevation, noted in 25.7% (65/253) of patients. Regarding the degree of the ALT elevation, 15.8% (40/253) of patients had Grade 1, 5.1% (13/253) Grade 2, 3.2% (8/253) Grade 3, and 1.6% (4/253) Grade 4 elevation. A total of 10.7% (27/253) of patients had T-Bil elevation : 7.5% (19/253) had Grade 1, and 3.2% (8/253) had Grade 2. A total of 7.1% (18/253) had experienced drug rush (exanthema, itching sensation), 11.5% (29/253) of

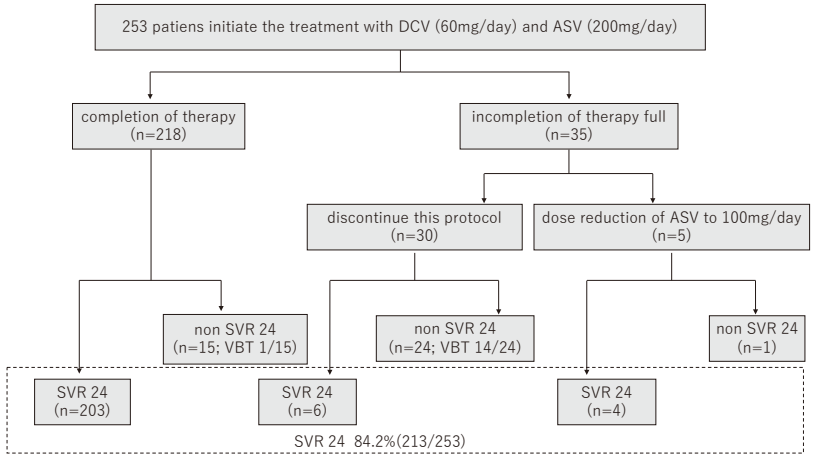

Fig. 1. Flow chart of treatment outcomes.
A total of 253 patients who enrolled in this study were followed 48 weeks. Overall, 213 patients achieved SVR24, and 40 had virological failure. Of these 40 patients, 15 had virological breakthrough. DCV, daclatasvir ; ASV, asunaprevir ; SVR, sustained virological response ; VBT, Viral Break Through

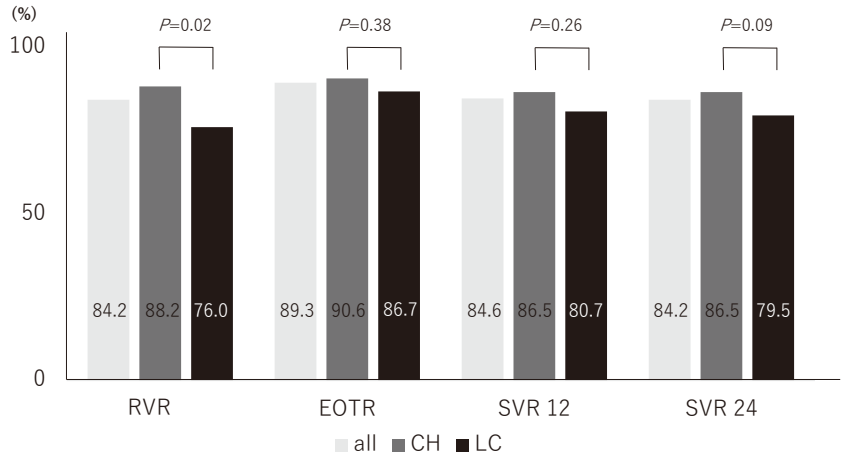

Fig. 2. HCV-RNA endetectable rates CH and LC patients.
The *P* values were calculated using independent t-test. Light grey bars indicate the SVR rates among all, grey bars indicate the SVR rates among CH patients, and black bars indicate the SVR rates among LC patients.
CH, Chronic Hepatitis ; LC, Liver cirrhosis ; RVR, Rapid virological response ; EOTR, End of treatment response

patients experienced respiratory symptoms (sore throat, rhinitis), 10.3% (26/253) developed a fever, 7.1% (18/253) experienced digestive symptom (diarrhea, appetite loss). 11 patients stopped taking the drugs due to severe adverse events (liver dysfunction in 6, a fever in 2, drug rash in 1, and drug-unrelated events in 2 [1 meningioma, 1 case of traumatic subarachnoid hemorrhaging] ; data not shown). No significant differences were noted between the CH and LC patients in the rates of ALT elevation, skin, respiratory symptoms, a fever, headache, or digestive symptoms. However, the T-Bil level in LC patients was significantly higher than that in CH patients, although no patients had severely elevated levels in either group (Table 3).

Table 2. Univariate and multivariable analyses

	Univariate analysis			Multivariable analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Sex (male/female)	1.07	0.54–2.12	0.85	1.11	0.53–2.34	0.79
Age (years)			0.26	0.99	0.95–1.02	0.41
Pre treatment HCV RNA (log IU/mL)			0.19	1.22	0.74–2.01	0.43
LC status (CH/LC)	1.65	0.84–3.34	0.14	2.7	1.19–6.10	0.017
Pretreatment Y93H (wild/mutant)	3.37	1.26–9.02	0.01	4.78	1.89–12.11	0.001
Pretreatment L31 (wild/mutant)	1.54	0.17–14.28	0.7	1.17	0.12–11.95	0.89
Previous treple therapy with protease inhibitor (Absent/Present)	4.81	1.87–12.37	0.0004	4.49	1.63–12.37	0.004
Pretreatment AFP (ng/mL)			0.73	0.98	0.94–1.01	0.2

The *P* values were calculated using χ^2 test or independent t-test and logistic regression analysis.
CH, Chronic Hepatitis ; LC, Liver cirrhosis ; AFP, α fetoprotein ; OR, Odd's ratio ; CI, Confidence Interval

Table 3. The frequency of adverse event

	Overall (*N*=253)		CH (*N*=170)		LC (*N*=83)		*P*
ALT elevation	65	25.70%	42	24.70%	23	27.70%	0.61
Grade 1	40	15.80%	24	14.10%	16	19.30%	0.29
Grade 2	13	5.10%	9	5.30%	4	4.80%	0.95
Grade 3	8	3.20%	6	3.50%	2	2.40%	0.63
Grade 4	4	1.60%	3	1.80%	1	1.20%	0.75
T-Bil elevation	27	10.70%	10	5.90%	17	20.50%	0.0004
Grade 1	19	7.50%	9	5.30%	10	12.00%	0.06
Grade 2	8	3.20%	1	0.60%	7	8.40%	0.0008
Skin	18	7.10%	14	8.20%	4	4.80%	0.32
Grade 1	15	5.90%	11	6.50%	4	4.80%	0.6
Grade 2	3	1.20%	3	1.80%	0	0%	0.55
Respiratory symptom	29	11.50%	19	11.20%	10	12.00%	0.84
Fever	26	10.30%	18	10.60%	8	9.60%	0.81
Headache	22	8.70%	15	8.80%	7	8.40%	0.89
Digestive symptom (diarrhea, appetite loss)	18	7.10%	10	5.90%	8	9.60%	0.28

The *P* values were calculated using independent t-test.
CH, Chronic Hepatitis ; LC, Liver cirrhosis

AFP and ALT levels according to the response to treatment

We measured the AFP and ALT levels of 135 patients at baseline and 24 and 48 weeks after starting treatment. In the 121 patients who achieved SVR, the AFP levels were significantly lower than those at baseline (24 weeks : $P < 0.01$, 48 weeks : $P < 0.01$) (Fig. 3A), as were the ALT levels (24 weeks : $P < 0.01$, 48 weeks : $P < 0.01$) (Fig. 3B). In the 14 patients who did not achieve SVR, the AFP levels were significantly lower than those at baseline (24 weeks : $P < 0.01$, 48 weeks : $P < 0.01$) (Fig. 3C), while the ALT levels were not significantly different (24 weeks : $P = 0.07$, 48 weeks : $P = 0.11$) (Fig. 3D).

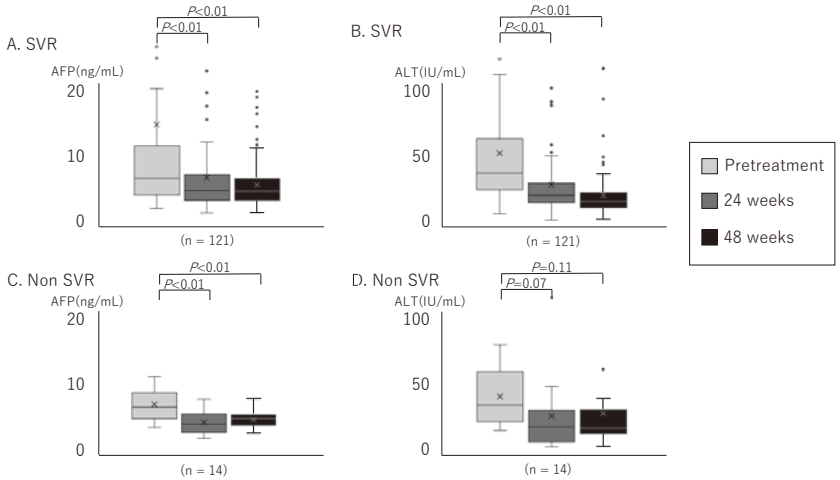

Fig. 3. AFP and ALT levels of patients who achieved SVR at baseline, 24 and 48 weeks.
A. AFP levels of patients who achieved SVR. B. ALT levels of patients who achieved SVR. C. AFP levels of patients who did not achieved SVR. D. ALT levels of patients who did not achieved SVR. Bars within the boxes indicated the median value. The box denote the 25-75th percentiles, the lower and upper bars the 10th and 90th percentiles, respectively. The cross mark indicates the each average.
AFP, α fetoprotein ; ALT, alanine aminotransferase ; SVR, sustained virological response.

Discussion

In this paper, we assessed the efficacy and safety of therapy with DCV and ASV for HCV genotype 1. We found that the treatment with DCV and ASV resulted in an overall SVR rate of 84.2%, which seems to be very high ; however, we previously reported that the SVR rates of the latest two IFN regimens were also quite high ; that of IFN plus ribavirin plus TPV was 81.1%, and that of IFN plus ribavirin plus SMV was 76.8% in Akita, Japan[9]. There were no significant differences in the SVR rates between these three therapies. However, to achieve high SVR24 rates, the latest IFN regimen needs ribavirin and protease inhibitor (TPV or SMV). This regimen causes a lot of adverse events, for example the appearance of flu-like symptoms in almost 100% of the cases, while blood disorders (leukopenia, anemia, thrombocytopenia) occur in almost 80% and skin rash sometimes causes serious problems, especially in patients undergoing TPV therapy. As a result, many patients were forced to discontinue the therapy or undergo a dose reduction. In our study with DCV and ASV, 11.9% (30/253) of patients discontinued the therapy, although only 9 of these patients did so due to drug-related adverse events.

Regarding adverse events, the most frequently reported was ALT elevation in 25.7% of patients, 4.7% of which were Grade 3 or 4 events. T-Bil elevation was noted in approximately 10.7% of patients, as were flu-like symptoms, and other blood disorders (leukopenia, anemia, thrombocytopenia) were rare enough to be ignored. The incidence of renal dysfunction is also very low, so some papers have reported that even hemodialysis patients can receive this therapy safely[14]. The average age of the total population receiving this therapy was 69.3±0.6 years, which is about 8 years older than that with IFN-based TPV or SMV therapy. These results also suggest the safety of this therapy.

This therapy can only be orally administered. Given its great efficacy, safety, and convenience, we feel confident that this therapy represents the dawn of a new era of anti-HCV therapy.

We also considered the factors contributing to the SVR24 rate. In the univariate analysis concerning the SVR24 rate, we first selected the factors associated with the response to interferon-containing regimens and additionally selected NS5A variants (Y93H/L31) and a history of protease inhibitor treatment, as NS5A and NS3/4A

variants may be involved in the response to this therapy. Our study showed that a Y93 mutation was extracted as negative factors related to the SVR24 rate as expected based on previous studies[15]. However, the L31 mutation did not affect the SVR24 rate. In addition, it was also reported that a mutation in the NS3/4 region, such as D168, would deteriorate the SVR24 rate. Our data actually showed that the SVR24 rates were significantly lower in patients with a history of IFN-based TPV or SMV therapy than in those without such a history. We investigated the D168 status in four patients, and three had a D168 mutation. The D168 mutation is reported to disappear over time[16].

In the multivariate analysis, three parameters were extracted as significant independent factors : a Y93H mutation, a history of triple therapy with TPV or SMV, and LC status. Y93H mutations and a history of triple therapy with TPV or SMV reduce the rate of SVR24. In addition, LC status of the liver worsens the SVR24 rate, even though there were no significant differences in the SVR24 rate between CH and LC patients in the univariate analysis. In IFN therapy, the progression of fibrosis in the liver is a negative factor influencing the SVR24 rate, however in our study, the APRI, FIB4 index, and albumin value did not affect the SVR24 rate (data not shown). We therefore cannot determine which factors in LC patients affect the SVR24 rate.

We also examined the time-dependent changes in the AFP value, a tumor marker of HCC. Among the patients who achieved SVR24, the AFP value was significantly lower at both 24 weeks after starting treatment (endpoint of treatment) and 48 weeks after starting treatment (24 weeks after the end of treatment) than at the baseline. This tendency was also confirmed in the ALT value. Thus, in this group, improvement in the AFP value was not only related to a reduction in the risk of HCC but also to a reduction of hepatic inflammation[17]. Furthermore, among the virological failure patients, the AFP value as also significantly lower at both 24 and 48 weeks from starting treatment than at the baseline, although there was no significant difference in the ALT value at 24 or 48 weeks from starting treatment and at the baseline. These data may suggest that DAAs reduce the HCC risk regardless of virological response. The long-term follow-up of both groups will be needed to clarify this point.

In our study IFN-free DAAs therapy with DCV and ASV showed a low rate of adverse events but high efficacy. However, we must consider patients' drug resistance and LC status when starting this therapy. New IFN-free DAAs therapies are steadily being developed, and this therapy has now become the main therapy for HCV. As such, we must take care to choose the best therapy for each patient, striving for tailor-made, individualized therapy. Furthermore, our data showed that this therapy can reduce the levels of AFP, so we will conduct a long-term follow-up of these patients with the goal of ultimately eradicating HCC.

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