Antiviral Therapy for Patients Chronically Infected with Hepatis C Virus at Tokai University Hospital

Shunji HIROSE[*1], Kota TSURUYA[*2], Yoshimasa SHIMMA[*3], Yoshitaka ARASE[*3], Shinji TAKASHIMIZU[*4], Yasuhiro NISHIZAKI[*4], Koichi SHIRAISHI[*5], Norihito WATANABE[*1], Shohei MATSUZAKI[*5], Satsuki IEDA[*3] and Tatehiro KAGAWA[*3]

[*1]*Department of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University Hachioji Hospital*
[*2]*Department of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University Oiso Hospital*
[*3]*Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine*
[*4]*Department of Clinical Health Science, Tokai University School of Medicine*
[*5]*Department of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University Tokyo Hospital*

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Objective: Hepatitis C virus (HCV) was identified in 1989. In 2020, three decades after HCV identification, three researchers won the Nobel Prize in Physiology or Medicine for the discovery of this virus. In 1992, three years after the discovery, interferon (IFN) was launched as the first anti-HCV therapy in Japan; however, the efficacy of IFN therapy was far from acceptable due to severe adverse effects. The advent of IFN-free direct-acting antivirals (DAAs) in 2014 dramatically improved the outcomes of antiviral treatment without serious adverse effects. In this study, we aimed to summarize anti-HCV therapy at the Tokai University Hospital.

Methods: We identified patients who underwent anti-HCV therapy by searching medical records from January 1992 to December 2020, analyzed their background, and compared safety and efficacy among treatments.

Results: A total of 1777 treatments were given to 1299 patients. The sustained virologic response rate has dramatically increased over the past 30 years, with only 7% for IFN monotherapy and 95% or higher for recent IFN-free DAA therapies.

Conclusions: We documented the results of anti-HCV therapy at the Tokai University Hospital. In the 30 years since the discovery of HCV, surprisingly successful progress has been accomplished in the anti-HCV treatment.

Key words: hepatitis C virus, chronic hepatitis C, direct-acting antivirals, interferon, treatment

INTRODUCTION

Hepatitis C virus (HCV) was first identified in 1989. In 2020, three decades after the HCV identification, three researchers, Harvey J. Alter, Michael Houghton, and Charles M. Rice, won the Nobel Prize in Physiology or Medicine for the discovery of this virus [1]. In 1992, three years after its discovery, interferon (IFN)-α was launched as the first anti-HCV therapy in Japan (Table 1). This drug evoked severe adverse effects such as fever, headache, myalgia, and depression; and the antiviral effects were far from sufficient. The reported sustained virologic response (SVR) rate was not as high as 10% in patients infected with genotype 1 HCV, which is known to be more resistant to IFN than genotype 2. Ribavirin (RBV) was approved in 2001 as a combination therapy with IFN. Although the mechanism of the antiviral effect of RBV is still unclear, it enhances the anti-HCV effects of IFN and other antiviral drugs [2]. In 2003, pegylated (peg)-IFN was launched. This type of IFN has a longer half-life than usual IFN, and once weekly injection became feasible.

In 2011, telaprevir (TVR) was developed as the first direct-acting antiviral (DAA) [3]. DAA represents a drug that specifically inhibits HCV proliferation. Three classes of DAAs are available at present: NS3 protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors. TVR, a protease inhibitor, was co-administered with peg-IFN α-2b and RBV. This combination therapy increased the SVR rate; however, it caused severe adverse effects, including serious skin reactions such as Stevens-Johnson syndrome. Finally, an IFN-free DAA treatment, a combination of an NS5A inhibitor, daclatasvir (DCV), and an NS3 protease inhibitor, asunaprevir (ASV), was approved in 2014. This therapy improved the SVR rate to approximately 80% in patients infected with genotype 1 HCV. However, resistance-associated substitutions (RAS) in the HCV genome have emerged in patients who failed to achieve SVR [4]. These RAS-harboring viruses that likely exist prior to antiviral therapy replicate more efficiently

Tatehiro KAGAWA, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan Tel: +81-463-93-1121 Fax: +81-463-93-7134 E-mail: kagawa@tokai.ac.jp

Table 1 History of anti-HCV therapy

Therapy	Brand name	Company	Launch year
IFN			
IFN α-2b, recombinant	Intron A	Schering-Plough, Merck/Yamanouchi	1992
IFN α	Sumiferon	Sumitomo	1992
IFN β	Feron	Toray/Dai-ichi	1992
IFN α-2a, recombinant	Roferon A, Canferon A	Roche, Takeda	1992
IFN α	OIF	Otsuka	1993
IFN α	IFN α mochida	Mochida	1993
IFN β	IFN β mochida	Mochida	1994
IFN alfacon-1, recombinant	Advaferon	Yamanouchi	2001
peg-IFN α-2a	Pegasys	Chugai	2003
IFN/RBV			
IFN α-2b, recombinant/RBV	Intron A/Rebetol	Schering-Plough, Merck	2001
peg-IFN α-2b/RBV	Pegintron/Rebetol	Schering-Plough, Merck	2004
peg-IFN α-2a/RBV	Pegasys/Copegus	Chugai	2007
IFN/RBV/DAA			
telaprevir (TVR)/peg-IFN α-2b/RBV	Telavic/Pegintron/Rebetol	Mitsubishi Tanabe	2011
simeprevir (SMV)/peg-IFN α-2a or 2b/RBV	Sovriad/Pegintron or Pegasys/ Rebetol or Copegus	Janssen	2013
vaniprevir (VPV)/peg-IFN α-2b/RBV	Vanihep/Pegintron/Rebetol	MSD	2014
IFN-free DAA			
daclatasvir (DCV)/asunaprevir (ASV)	Daklinza/Sunvepra	Bristol Myers Squibb	2014
sofosbuvir (SOF)/RBV	Sovaldi/Rebetol	Gilead	2015
sofosbuvir (SOF)/ledipasvir (LDV)	Harvoni	Gilead	2015
ombitasvir (OBV)/paritaprevir (PTV)/ritonavir (r)	Viekirax	AbbVie	2015
elbasvir (EBR)/grazoprevir (GZR)	Erelsa/Grazyna	MSD	2016
daclatasvir (DCV)/asunaprevir (ASV)/beclabuvir (BCV)	Ximency	Bristol Myers Squibb	2017
glecaprevir (GLE)/pibrentasvir (PIB)	Maviret	AbbVie	2017
sofosbuvir (SOF)/velpatasvir (VEL)	Epclusa	Gilead	2019
sofosbuvir (SOF)/velpatasvir (VEL)/RBV	Epclusa/Rebetol	Gilead	2019

with a selective growth advantage in the presence of antiviral therapy and become the dominant species. The RAS in the NS3 and NS5A regions are frequently selected in patients with failure of NS3 and NS5A inhibitor-containing regimens, respectively. Subsequently, many DAAs with higher antiviral efficacy against RAS-harboring HCV have been developed. Currently, anti-HCV regimens consist of a combination of two or three classes of DAAs [5]. In 2017, glecaprevir (GLE)/pibrentasvir (PIB) was launched. This regimen was the first and only therapy approved for treating patients infected with any genotype. Decompensated cirrhosis was the last hurdle to overcome in anti-HCV therapies. In 2019, sofosbuvir (SOF)/velpatasvir (VEL) was finally approved for the treatment of patients with this intractable disease.

Thirty years after the discovery of HCV, surprisingly rapid and successful progress has been accomplished in the treatment of patients infected with HCV. These progresses have provided tremendous benefits to patients; in a large prospective cohort study, DAA treatment decreased all-cause mortality (hazard ratio [HR] 0.48, 95% confidence interval [CI] 0.33–0.70; P = 0.0001), liver-related death (HR 0·39, 95% CI 0.21–0.71; P = 0.0020), non-liver-related death (HR 0.60, 95% CI 0.36–1.00; P = 0.048), and occurrence of hepatocellular carcinoma (HCC) (HR 0.66, 95% CI 0.46–0.93; P = 0.018) [6].

At Tokai University Hospital, we provided anti-HCV treatment to many patients for three decades since 1992. Although the efficacy of these antiviral therapies has been reported in numerous studies, we thought that our results should be documented. In this study, we searched for patients who underwent anti-HCV therapy at our hospital, analyzed their background, and compared the safety and efficacy among treatments.

PATIENTS AND METHODS

Patients

We identified patients chronically infected with HCV who received antiviral therapy at Tokai University Hospital by searching medical records from January 1992 to December 2020. We analyzed the demograph-

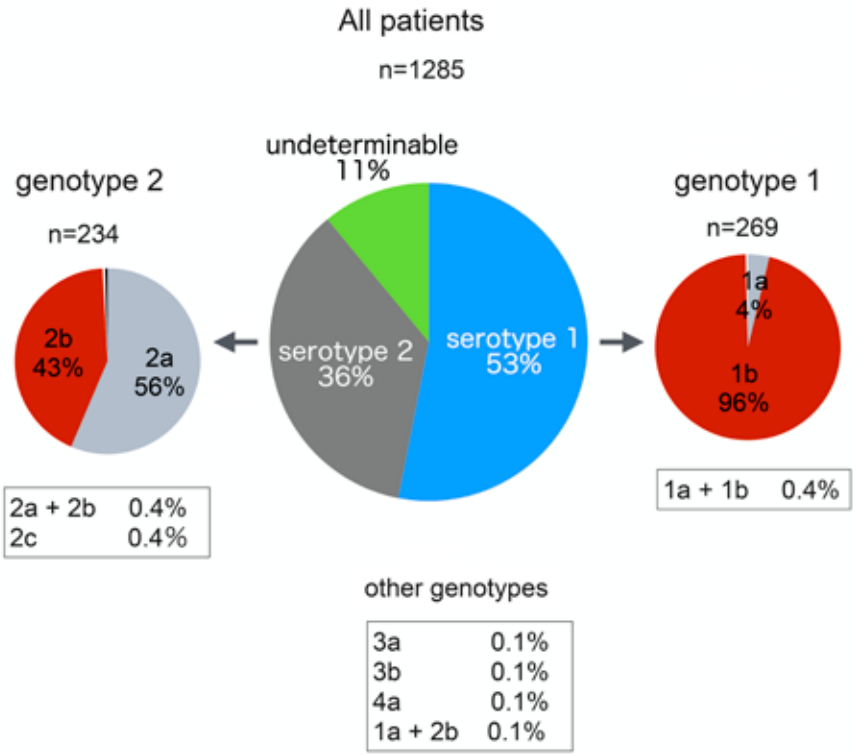

Fig. 1 Distribution of HCV serotypes and genotypes.

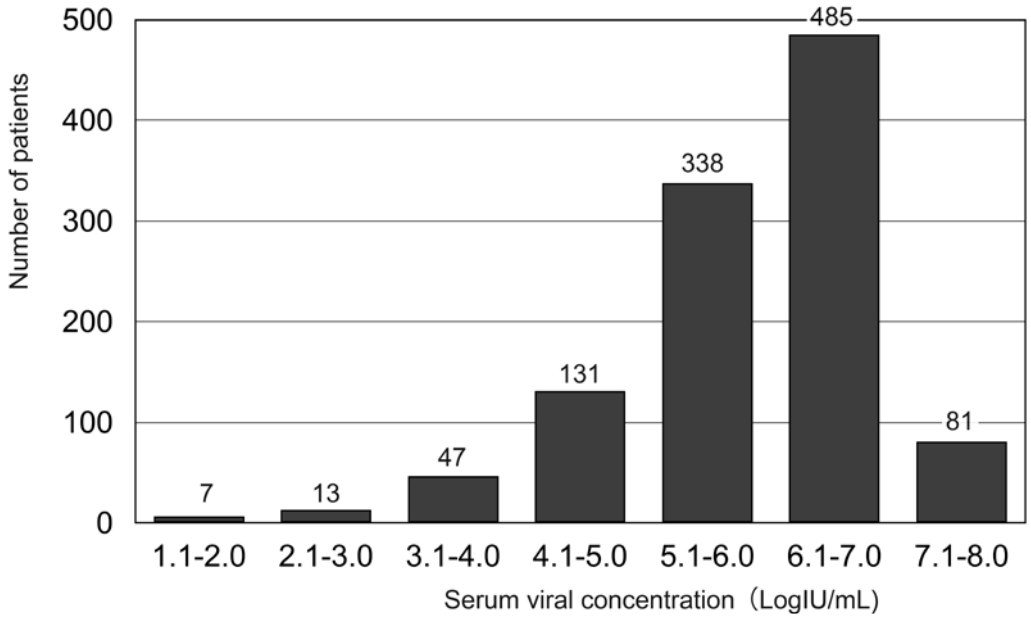

Fig. 2 Distribution of serum HCV concentration.

ic characteristics, efficacy, and adverse effects of the antiviral therapy. This study was approved by the Institutional Review Board for Clinical Research, Tokai University (21R-017).

RAS analysis

RAS was analyzed in a nationwide study conducted by Drs. Izumi and Kurosaki [7].

Statistical analysis

Numerous and dichotomous variables were evaluated using Student's t-test and Chi-square test, respectively. Statistical significance was set at $p < 0.05$.

RESULTS

Patient characteristics

We identified 1299 patients chronically infected with HCV who received antiviral therapy at least once. HCV serotypes were determined in 1285 patients (98.9%). Serotype 1 was dominant (53%), and 36% of the patients were infected with genotype 2 (Fig. 1). Serotypes were undeterminable in the remaining patients (11%). HCV genotyping was performed in 507 patients. In genotype 1, the majority was genotype 1b (96%), while 1a was observed in a small proportion of patients (4%). A mixture of 1a and 1b was detected

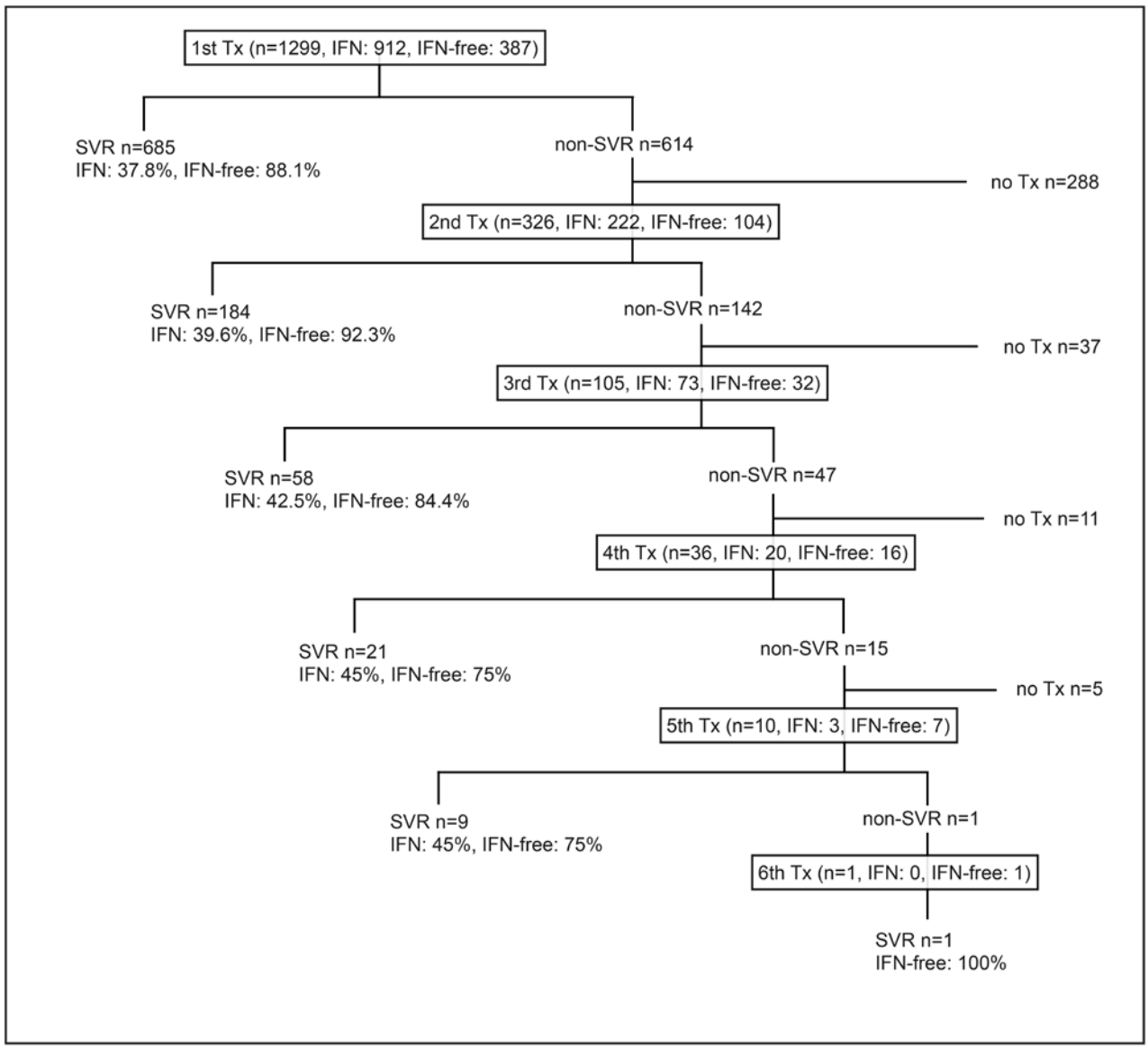

Fig. 3 Results of antiviral therapies.

in one patient. In genotype 2, 56% and 43% of the patients were infected with 2a and 2b, respectively. A mixture of 2a + 2b and 2c was found in one patient each. The other genotypes detected were 3a, 3b, 4a, and a mixture of 1b + 2b.

Although the serotype was coincident with the genotype in most patients, few cases (0.4%) revealed discordant results; Two and two serotype 1 patients turned out to be infected with genotype 2a and 2b, respectively, and a serotype 2 patient was genotype 1b positive.

Serum HCV RNA levels were determined in 1102 patients (84.8%) of the 1299 patients (Fig. 2). The median (min-max) value was 6.1 (1.6−8.0) LogIU/mL. Most patients (82.1%) had a high viral load (> 5.0 LogIU/mL). When analysis was performed according to genotype, the serum viral load was similarly high in patients with genotype 1a (6.2 ± 0.7 [mean ± standard deviation] LogIU/mL), 1b (6.1 ± 1.0), and 2b (6.2 ± 1.0), whereas it was significantly lower in those with genotype 2a (5.8 ± 1.2, $P < 0.001$).

Next, we analyzed the source of HCV infection. The distinct infection source was unclear in most cases; however, 65 patients (5.1%) had a history of post-transfusion hepatitis. A substantial proportion of patients with genotype 2a (6.8%) and 2b (9%) had a history of illicit drug use, and the percentages were significantly higher than those with genotype 1a (0%) and 1b (2.3%). In 10 patients infected with genotype 1a, four (40%) suffered from hemophilia A and one (10%) was an HIV-co-infected men who have sex with men (MSM).

A total of 912 of 1299 patients underwent IFN-based therapy as the first antiviral therapy, of which 37.8% achieved SVR (Fig. 3). The remaining 387 patients received IFN-free DAA therapy as the first antiviral therapy, and 88.1% achieved SVR. Of the 614 patients who did not achieve SVR after the first antiviral therapy, 326 patients received a second therapy; IFN-based and IFN-free DAA therapy for 222 and 104 patients, respectively. Of these, 184 patients attained SVR; the SVR rates were 39.6% and 92.3% for IFN-based and IFN-free DAA therapy, respectively. As such, 105 patients underwent a third therapy with an SVR rate of 42.5% and 84.4% for IFN-based and IFN-free DAA therapy, respectively. A fourth and fifth therapy was administered to 36 and 10 patients,

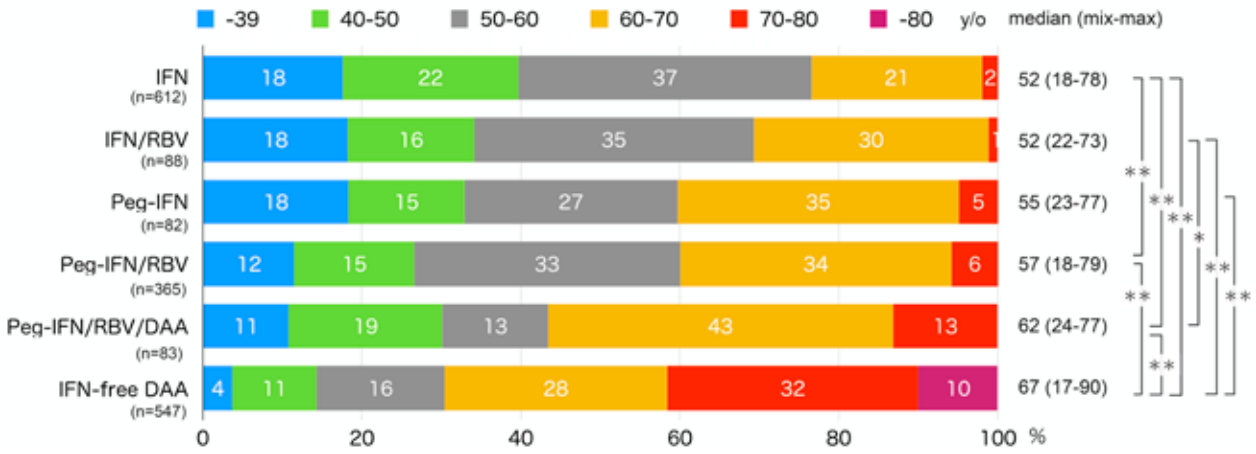

Fig. 4 Age distribution of the patients.
* P < 0.05, ** P < 0.01

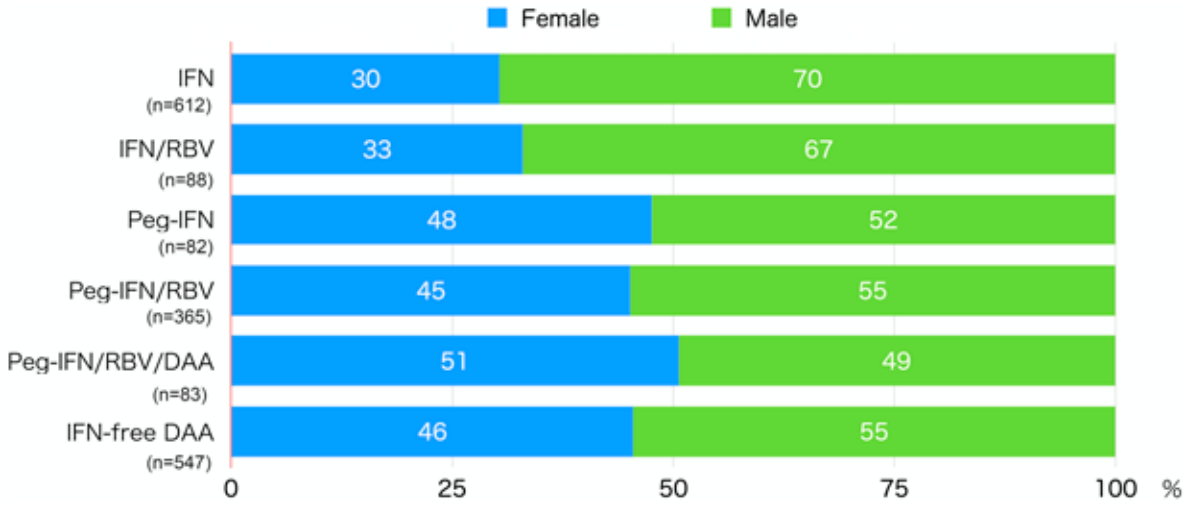

Fig. 5 Sex distribution of the patients.

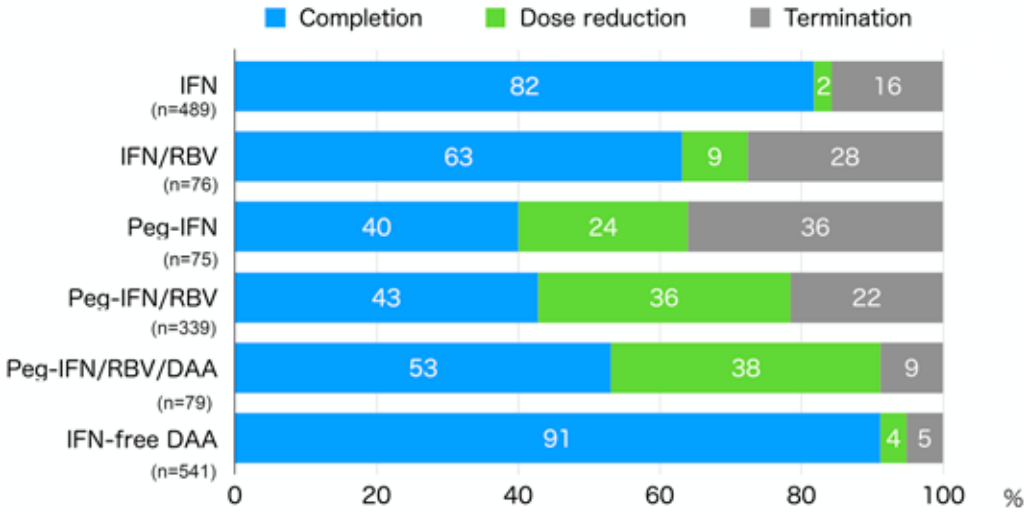

Fig. 6 Distribution of the patients who required dose reduction and termination of the treatment.

respectively. One patient received a total of six antiviral treatments, including four IFN-based and two IFN-free DAA regimens. Finally, a total of 1777 treatments were performed, and all patients who sought anti-HCV therapy achieved SVR.

Age distribution was analyzed according to the antiviral regimens (Fig. 4). The number of patients who received an IFN regimen was highest among those in their 50s, whereas it was highest among those in their 60s and 70s for Peg-IFN/RBV/DAA and IFN-free DAA regimens, respectively. The median age was highest in the IFN-free DAA regimen group. In terms of sex, males were dominant in IFN-and IFN/RBV regimens, while sex distribution was almost equal for other treatment regimens (Fig. 5). A substantial proportion of patients who received IFN-based regimens

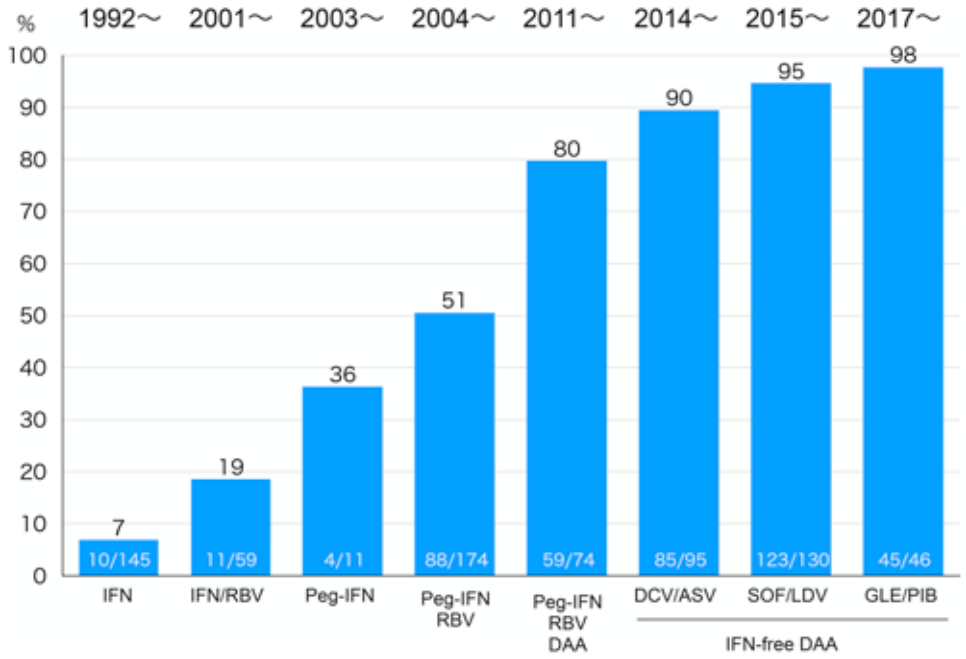

Fig. 7 SVR rates in various treatment regimens for the patients infected with genotype 1 HCV. The number in the upper portion of the graph represents the year when the relevant treatment was approved.

required dose reduction or immature termination of treatment (Fig. 6). In contrast, dose reduction and immature termination were necessary only in 4% and 5% of patients receiving IFN-free DAA regimens, respectively.

Efficacy of various anti-HCV treatment regimens in patients infected with genotype 1 HCV

The efficacy of IFN-based regimens varies according to HCV genotype; genotype 1 is resistant to IFN-based regimens, whereas genotype 2 is sensitive to them. We investigated the efficacy of various regimens in patients infected with genotype 1 HCV (Fig. 7). Only 7% of patients achieved SVR by IFN regimens, which were introduced in 1992. The SVR rate increased stepwise by the launch of new regimens: 19%, 36%, and 51% by the IFN/RBV, Peg-IFN, and Peg-IFN/RBV regimens, respectively. In 2011, Peg-IFN/RBV/DAA triple therapy emerged and achieved an 80% SVR rate. IFN-free DAA therapy was introduced in 2014. The first regimen, DCV/ASV, resulted in an SVR rate of 90%. Finally, SOF/RBV and GLE/PIB regimens achieved SVR rates of 95% or higher.

RAS

RAS was analyzed in 14 patients who failed to achieve SVR after DAA therapy. Most patients had RAS in the L31 and Y93 positions in the NS5A region (Table 2), which are well known to appear after DAA therapy failure [7]. Thirteen of 14 patients (92.9%) achieved SVR with GLE/PIB therapy. One patient had a P32 deletion variant after she failed to achieve SVR by two DAA regimens (DCV/ASV and SOF/LDV). She underwent GLE/PIB therapy but did not achieve SVR. Thereafter, she received SOF/VEL/RBV therapy for 24 weeks and finally attained SVR.

DISCUSSION

We identified 1299 patients chronically infected with HCV who received antiviral treatment at least once, and a total of 1777 treatments were administered to these patients.

To date, eight genotypes and 86 subtypes have been reported [8]. Genotype 1 infections are the most common: 44% worldwide and 60% in high-income and middle-income countries. Genotypes 3 and 4 infections ranked second (25%) and third (15%), respectively. In Japan, the majority of patients are infected with genotype 1b (60%–70%), followed by genotype 2a (15%–30%) and 2b (5%–15%) [9]. The genotype distribution in our cohort was similar to that in other areas of Japan. Notably, the serotype and genotype results were discordant in five patients (0.4%). A previous study reported that discordant cases occurred in 1.4% of cases [10]. Misrecognition of the genotype may have led to treatment failure by choosing an incorrect regimen. However, the launch of a pan-genotypic regimen, GLE/PIB, will reduce treatment failure due to genotype misrecognition.

The serum viral load was significantly lower in individuals infected with genotype 2a than in those infected with genotypes 1b and 2b. These results were concordant with those of previous studies [11, 12]; however, the reason for this difference remains unclear. Hemophilia A was frequently observed (40%) in patients with genotype 1a, as previously reported [13]. This is likely attributable to the repeated use of imported factor VIII contaminated with HCV. The genotype 2 infection was more commonly associated with a history of illicit drug use than genotype 1, in accordance with a previous study [14].

Genotype 1 infections are known to be resistant to IFN-based therapies. The IFN monotherapy that was launched in 1992 exhibited an SVR rate of only 7%.

Table 2 Resistance-associated substitutions in the NS5A region detected in patients who failed to achieve SVR after previous IFN-free DAA therapies and underwent glecaprevir/pibrentasvir therapy

Patient No.	Previous therapy	AA position											Outcome
		Q24	L2	R30	L31	P32	F37	Q54	P58	Q62	A92	Y93	
1	DCV/ASV				M		L					H	SVR
2	DCV/ASV				L/V		L	H				H	SVR
3	DCV/ASV						L		S			C	SVR
4	DCV/ASV				V		L	H		E		H	SVR
5	DCV/ASV				V		I	H				H	SVR
6	DCV/ASV			R/H/Q	M		L	H			S	H	SVR
7	DCV/ASV	K	M	Q	I/V			Q/H				Y/H	SVR
8	DCV/ASV						L	H			T		SVR
9	SOF/LDV			Q				Y	S			H	SVR
10	SOF/LDV				M		L					H	SVR
11	SOF/LDV				M		I					H	SVR
12	SOF/LDV				M			C/Y				H	SVR
13	DCV/ASV SOF/LDV		M				L	Y		E		H	SVR
14	DCV/ASV SOF/LDV				L/F	del	F/L						Non-SVR

DCV/ASV: daclatasvir + asunaprevir, SOF/LDV: sofosbuvir + ledipasvir.

As new regimens appeared, the SVR rate for genotype 1 infections increased gradually and steadily. At present, SOF/LDV, GLE/PIB, and EBR/GZR regimens are recommended for the treatment of genotype 1 infections [5]. Moreover, SVR rates higher than 95% were achieved with these regimens in our cohort.

Most patients who underwent IFN or IFN/RBV regimens were males, and they were younger than those with other regimens. On the other hand, those who received DAA regimens were significantly older. Elderly people, especially females, might have avoided IFN-based therapies because of their severe adverse effects and waited for DAA with milder adverse effects. In addition, the accumulation of patients who failed to antiviral therapies appears to have pushed up their age.

Failure of DAA therapies generates RAS. L31 and Y93 are popular AA positions where RAS occurs. In our cohort, such RAS was observed in 13 (92.9%) of 14 patients who failed to achieve SVR by DCV/ASV and/or SOF/LDV regimens. Fortunately, most of these patients achieved SVR by GLE/PIB therapy, whereas one patient who had P32del RAS did not attain SVR by GLE/PIB therapy. This patient achieved SVR after 24 weeks of SOF/VEL/RBV therapy. HCV with the P32del RAS is reported to be resistant to GLE/PIB therapy [7, 15]. The most recently approved regimen, SOF/VEL/RBV, showed considerable efficacy in this type of RAS; 4 of 5 (80%) patients achieved SVR [16]. Finally, all patients who sought antiviral therapy achieved SVR in our cohort.

The overall mortality rate and occurrence of HCC will decrease with the achievement of SVR. However, the risk of HCC still remains. Therefore, careful monitoring is required in these patients.

This study has limitations. First, the analysis was performed retrospectively in a single institution. Therefore, our results might be unable to be generalized. Second, although HCV serotype was determined in most patients, genotyping was performed in less than 40% of patients. Lack of genotype data could lead to HCV misclassification and induction of wrong treatment regimens, although the cases with inconsistent results were rare (0.4%).

We have documented the results of anti-HCV therapy at our hospital over 30 years. In the early stages of anti-HCV therapy, we struggled to treat patients. The efficacy of antiviral therapies was far from sufficient despite the unavoidable severe adverse effects, and many patients who waited for more effective treatments with milder adverse effects died of liver cirrhosis or HCC. However, the advent of DAA has completely changed the landscape of anti-HCV therapy. Nowadays, almost every patient who seeks therapy is able to eliminate the virus from the body by taking DAA pills for 8 or 12 weeks.

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CONFLICT OF INTEREST

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