Outcomes of Interferon-free Treatment of Hepatitis C Virus Infection Seven Years after Approval and Problems with Drop out during and after Treatment: A Retrospective, Single-center Study

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Abstract:

Objective This retrospective, single-center study assessed the effects of interferon (IFN)-free treatment of hepatitis C virus (HCV) infection, which has been approved for seven years; calculated the incidence of hepatocellular carcinoma (HCC) after achieving a sustained virologic response (SVR); and elucidated problems with follow-up for surveillance of post-SVR HCC, particularly the impact of the coronavirus disease 2019 (COVID-19) pandemic.

Methods We summarized the SVR achievement rate of 286 HCV-infected patients who received 301 IFN-free treatments and analyzed the cumulative incidence of initial HCC and the cumulative continuation rate of follow-up after SVR in the 253 patients who achieved SVR and did not have a history of HCC.

Results Among 286 patients who received IFN-free treatments, 14 dropped out, and the 272 remaining patients achieved an SVR after receiving up to third-line treatment. Post-SVR HCC occurred in 18 (7.1%) of the 253 patients without a history of HCC, with a cumulative incidence at 3 and 5 years after SVR of 6.6% and 10.0%, respectively; the incidence of cirrhosis at those time points was 18.2% and 24.6%, respectively. Of the 253 patients analyzed, 58 (22.9%) discontinued follow-up after SVR. Patients who had no experience with IFN-based therapy tended to drop out after SVR. Notably, the number of dropouts per month has increased since the start of the pandemic.

Conclusion Currently, IFN-free treatment is showing great efficacy. However, the incidence of HCC after SVR should continue to be monitored. In this study, the COVID-19 pandemic did not affect treatment outcomes, but it may affect surveillance for post-SVR HCC.

Key words: interferon-free treatment, hepatitis C virus, sustained virologic response, hepatocellular carcinoma, COVID-19 pandemic, dropout

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Introduction

Hepatocellular carcinoma (HCC) is the sixth-most common cancer and fourth leading cause of cancer-related mortality worldwide. In particular, Eastern Asia, including Japan, has a high prevalence of HCC (1). Although non-viral causes of HCC, such as alcoholic-related liver disease and non-alcoholic fatty liver disease, are increasing in prevalence, chronic hepatitis C virus (HCV) infection is still the most common risk factor for HCC development in Japan (2). Guidelines for surveillance and early detection of HCC are well established, especially in patients with high-risk factors (3).

In Japan, interferon (IFN)-free treatment of HCV infection with a combination of daclatasvir and asunaprevir
Patients analyzed to determine the cumulative incidence of HCC and follow-up continuation rate after achieving an SVR. HCC: hepatocellular carcinoma, SVR: sustained virologic response

(DCV+ASV) as the first direct-acting antiviral agents (DAAs) regimen, was initiated in 2014 (4). Since then, due to the discovery and development of new DAAs, such as protease inhibitor (PI)-free agents, as well as the combination of NS3/4A and NS5A/B inhibitors, most patients with any stage of liver damage associated with HCV infection, from asymptomatic carriers to those with decompensated cirrhosis, can achieve a sustained virologic response (SVR) safely, regardless of viral genotype (GT), age, and systemic complications (5). Over the last seven years, a few of the first DAAs have been replaced by more successful and safer new-generation DAAs (6), and the efficacy of IFN-free treatment is even described as “almost ultimate” (7).

The current theme of IFN-free treatments is not only their efficacy, but also post-SVR management aimed at surveillance of HCC in patients who have achieved SVR. Various findings regarding IFN-free treatment have been provided by high-volume centers and multi-institutional research efforts in Japan and overseas. The impact of successful IFN-free treatment on suppressing the incidence of HCC is now considered to be equivalent to that of IFN-based therapy (8). However, the history of IFN-free treatment is short compared with IFN-based therapy. In Japan, as of February 2022, the longest observation period of IFN-free treatment after SVR was seven years. Furthermore, during this period, an unexpected global problem in the coronavirus disease 2019 (COVID-19) pandemic occurred. There are concerns that the COVID-19 pandemic may have delayed treatment for patients with HCV infection (9-11), but few reports have described its impact on follow-up after SVR.

This retrospective, single-center study summarized the effects of the latest IFN-free treatments, showed the incidence of HCC after SVR (post-SVR HCC), and demonstrated the follow-up retention rate after SVR and the impact of the COVID-19 pandemic.

Materials and Methods

Between October 1, 2014, and April 30, 2021, we retrospectively examined 301 IFN-free treatments for 286 patients at the Kitasato University Medical Center. Data collection was closed on February 9, 2022.

We analyzed the following: i) the results of 301 IFN-free treatments for 286 patients, ii) the cumulative incidence of HCC after SVR, and iii) the follow-up continuation rate after SVR. SVR was defined as a negative HCV RNA test 24 weeks after the end of treatment (EOT) for DCV+ASV and 12 weeks after EOT for other regimens. Of the 272 patients who achieved an SVR, we determined the cumulative incidence of HCC after SVR in the 253 who did not have a history of HCC before SVR (Fig. 1). The diagnosis of HCC was determined with diagnostic imaging using abdominal ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) performed to screen for HCC after SVR. The cumulative incidence of HCC after SVR was analyzed with the Kaplan-Meier method, for which the observation period started from the confirmed SVR date to the date of the HCC diagnosis as the incidence of an ‘event’. In addition, the overall survival after the diagnosis of HCC was determined with the Kaplan-Meier method.

Risk factors for HCC after SVR were identified by comparing patients with and without HCC after SVR. Risk factors for post-SVR HCC before treatment and at EOT were assessed by a univariate analysis. In addition, the characteristics of patients at risk of post-SVR HCC were determined based on the odds ratio calculated by Fisher’s exact test for qualitative variables and the cut-off value from the receiver operating characteristic (ROC) curve for quantitative variables.

Cirrhosis was determined by two hepatologists. Liver pathology findings were given the highest priority. As other surrogate diagnostic methods, any liver morphology suggesting cirrhosis by abdominal ultrasound, computed tomography (CT), and/or magnetic resonance imaging (MRI); platelet count (<120×10^3/μL); FIB-4 index (>3.25) (12); and clinical symptoms, such as hepatic encephalopathy and ascites, or the presence of esophageal varices by esophagogastroduodenoscopy were comprehensively used for the diagnosis of cirrhosis. Hyaluronic acid, Mac-2 binding protein glycan isomer (M2BPGi), and transient elasto-
Table 1. Patient Background Characteristics.

| Characteristic                                      | Value                        |
|-----------------------------------------------------|------------------------------|
| Number of patients                                 | 286                          |
| Male/female, n                                      | 120/166                      |
| Age at SVR, years                                   | 71 (19-93)                   |
| HCV RNA level, Log IU/mL                            | 6.2 (3.4-7.6)                |
| Serogroup of HCV, n (%)                             | Serogroup 1: 208 (72.7%)     |
| Serogroup 2                                         | 76 (26.6%)                   |
| Genotype 3                                          | 1 (0.3%)                     |
| Genotype 6                                          | 1 (0.3%)                     |
| Patients who did not achieve an SVR with IFN-free treatments, n (%) | 14 (4.9%)                   |
| Patients with a history of IFN-based therapy (IFN-based therapy failures), n (%) | 82 (28.7%)                  |
| Patients with a history of HCC before IFN-free treatment, n (%) | 19 (6.6%)                   |
| Year IFN-free treatments were performed, n (% of 301 total treatments) |                      |
| 2014                                                | 14 (4.7%)                   |
| 2015                                                | 52 (17.3%)                  |
| 2016                                                | 124 (41.2%)                 |
| 2017                                                | 27 (9.0%)                   |
| 2018                                                | 50 (16.6%)                  |
| 2019                                                | 17 (5.6%)                   |
| 2020                                                | 14 (4.7%)                   |
| 2021 (through 30 April)                            | 3 (1.0%)                    |
| Patients with a history of alcohol use, n (%)       | 39 (13.6%)                  |
| Patients with liver cirrhosis, n (%)                | 69 (24.1%)                  |
| Patients with diabetes, n (%)                       | 43 (15.0%)                  |
| Patients with hepatic steatosis, n (%)              | 60 (21.0%)                  |
| Platelet count, ×10^9/L                             | 151 (48-413)                |
| Prothrombin time, LLN ≥70 %                         | 97 (27-100)                 |
| Total bilirubin, ULN ≤1.0 mg/dL                     | 0.8 (0.3-2.6)               |
| Aspartate transaminase, ULN ≤35 U/L                 | 38 (15-271)                 |
| Alanine aminotransferase, ULN ≤40 U/L               | 34 (9-340)                  |
| Alkaline phosphatase, ULN ≤55 U/L                   | 273 (110-1,065)             |
| gamma-glutamyl transpeptidase, ULN ≤80 U/L          | 30 (8-454)                  |
| Albumin, LLN ≥3.8 g/dL                              | 4.1 (2.7-5.0)               |
| alpha-fetoprotein, ULN ≤10 ng/mL                    | 5.2 (1.0-516.9)             |
| FIB-4 index                                         | 3.25 (0.27-18.2)            |
| M2BP-Gi, ULN<1.00, (n=178)                          | 2.06 (0.19-12.9)            |
| Hyaluronic acid, ULN ≤50 ng/mL, (n=173)             | 100 (10.3-1,830)            |
| Transient elastography, kPa, (n=236)                | 7.7 (2.8-48.0)              |

HCV: hepatitis C virus, IFN: interferon, SVR: sustained virologic response, HCC: hepatocellular carcinoma, M2BP-Gi: Mac-2 binding protein glycan isomer, LLN: lower limit of normal, ULN: upper limit of normal

‘n’ indicates number, and values are expressed as median (minimum - maximum), unless otherwise indicated.

Graphy (FibroScan®; Echosens, Paris, France) ≥12.5 kPa (13) were also used to diagnose cirrhosis but were not used in the risk analysis in order to avoid uncertainties due to missing data.

In addition, the 253 patients without a history of HCC who achieved an SVR were analyzed to determine the follow-up continuation rate after SVR. The definition of follow-up after SVR was that patients underwent regular visits at least once a year and were screened for HCC with diagnostic imaging, mainly abdominal ultrasound but also CT or MRI if necessary. All patients had appointments for hospital visit dates and times scheduled in advance by the hospital ordering system. The definition of drop out was a patient who withdrew from follow-up for no apparent reason.

The follow-up continuation rate after SVR was also analyzed with the Kaplan-Meier method, for which the observation period started from the confirmed SVR date to the date of withdrawal of follow-up after SVR to detect HCC as the incidence of an event. An occurrence of HCC; discontinuation of follow-up due to an obvious reason, such as death; transfer to another hospital to continue follow-up; and deterioration of physical ability were regarded as causes for ‘censoring’ in the analysis.
Table 2. Results of IFN-free Treatment of 286 Patients.

| Regimen* | Number of patients who received treatment | Number of patients who achieved SVR | Number of patients who did not achieve SVR | Number of patients who dropped out during treatment or before SVR determination | SVR Rate† |
|----------|----------------------------------------|-----------------------------------|------------------------------------------|---------------------------------------------------------------------------------|----------|
| Daclatasvir+asunaprevir | 48                                      | 40                                | 7                                        | 1                                                                                | 85%      |
| Sofosbuvir/ledipasvir  | 75                                      | 69                                | 4 (1; diarrhea)                          | 2                                                                                | 95%      |
| Sofosbuvir+ribavirin   | 41                                      | 37                                | 1                                        | 3                                                                                | 97%      |
| Ombitasvir/paritaprevir/ritonavir/ribavirin | 66                                      | 58                                | 6 (1; anasarca)                          | 2                                                                                | 90%      |
| Elbasvir+grazoprevir   | 5                                       | 5                                 | 0                                        | 0                                                                                | 100%     |
| Glecaprevir/pibrentasvir | 63                                      | 60                                | 0                                        | 3                                                                                | 100%     |
| Sofosbuvir/velpatasvir | 3                                       | 3                                 | 0                                        | 0                                                                                | 100%     |
| Total                 | 301                                     | 272                               | 18 (2)                                   | 11                                                                               | 94%      |

*Regimens consisting of individual administration of two direct acting antivirals (DAAs) are indicated by ‘+,’ and regimens consisting of compounds containing two or three DAAs are indicated by ‘/’.

†Parentheses indicate the number of patients who discontinued the treatment due to side effects.

‡Rates of SVR=number of patients who achieved SVR/(number of patients who received treatment - number of patients who dropped out during treatment or before the SVR determination).

SVR: sustained virologic response

Figure 2. Disposition of the 286 patients who received 301 IFN-free treatments. Among 275 cases, excluding 11 dropouts, 259 achieved an SVR on initial IFN-free treatment. All patients who received IFN-free treatment from the initial to third-line treatments achieved an SVR. IFN: interferon, SVR: sustained virologic response

These statistical analyses were performed with the Bell Curve for Excel software program, version 2.15 (Social Survey Research Information, Tokyo, Japan). When the p value was smaller than 0.05, we deemed the difference statistically significant.

Results

The background characteristics of the 286 patients are shown in Table 1.

i) Results of the 301 IFN-free treatments for 286 patients

The number of patients and the SVR rate for each of the IFN-free treatments are shown in Table 2. The SVR rate was calculated by dividing the number of patients who achieved SVR by the number of patients, which was calculated by subtracting the number of patients who dropped out during treatment or before the SVR determination from the number of treatments. The SVR rate was 85% for DCV+ASV, the early IFN-free treatment. Subsequent IFN-free treatments had an SVR achievement rate of ≥90%. In particular, gle-
Table 3. Clinical Course of 16 Patients for Whom Initial IFN-free Treatment Failed.

| No. | Age | Sex | History of IFN-based therapy | Liver cirrhosis | History of HCC before IFN-free treatment | Serogroup | Initial treatment | 2nd treatment | Result of the 2nd treatment | 3rd treatment | Result of the 3rd treatment |
|-----|-----|-----|------------------------------|-----------------|----------------------------------------|-----------|------------------|-------------|------------------------|--------------|-----------------------------|
| 1   | 78  | M   | Yes                          | No              | No                                     | 1         | OBV/PTV/r        | GLE/PIB     | SVR                    |              |                             |
| 2   | 78  | F   | Yes                          | No              | No                                     | 1         | OBV/PTV/r        | GLE/PIB     | SVR                    |              |                             |
| 3   | 60  | F   | No                           | No              | No                                     | 2         | OBV/PTV/r+RBV    | GLE/PIB     | SVR                    |              |                             |
| 4   | 45  | M   | No                           | No              | No                                     | 2         | OBV/PTV/r+RBV    | GLE/PIB     | SVR                    |              |                             |
| 5   | 70  | M   | No                           | No              | No                                     | 2         | SOF+RBV          | OBV/PTV/r+RBV| SVR                    |              |                             |
| 6   | 61  | F   | No                           | No              | No                                     | 1         | DCV+ASV          | GLE/PIB     | SVR                    |              |                             |
| 7   | 68  | M   | No                           | Yes             | No                                     | 1         | DCF+ASV          | SOF/LDV     | SVR                    |              |                             |
| 8   | 81  | F   | No                           | Yes             | Yes                                    | 1         | DCV+ASV          | SOF/LDV     | Non-SVR                | GLE/PIB      | SVR                        |
| 9   | 77  | M   | Yes                          | Yes             | No                                     | 1         | DCV+ASV          | OBV/PTV/r   | Non-SVR                | GLE/PIB      | SVR                        |
| 10  | 80  | F   | No                           | No              | No                                     | 1         | DCV+ASV          | SOF/LDV     | SVR                    |              |                             |
| 11  | 81  | M   | No                           | No              | Yes                                    | 1         | DCV+ASV          | SOF+RBV     | SVR                    |              |                             |
| 12  | 69  | F   | Yes                          | Yes             | No                                     | 1         | SOF/LDV          | GLE/PIB     | SVR                    |              |                             |
| 13  | 79  | F   | No                           | No              | No                                     | 1         | SOF/LDV          | GLE/PIB     | SVR                    |              |                             |
| 14  | 79  | F   | Yes                          | No              | No                                     | 1         | DCV+ASV          | Not performed due to dropout |              |                             |
| 15  | 84  | F   | No                           | Yes             | Yes                                    | 1         | DCV+ASV          | Not performed due to recurrence of HCC |              |                             |
| 16  | 81  | F   | No                           | No              | No                                     | 1         | SOF/LDV          | Not performed due to drowning at home |              |                             |

†This patient’s HCV serogroup was thought to be 1 at the time of initial treatment, but was 2 on retest.

IFN: interferon, M: male, F: female, HCC: hepatocellular carcinoma, SVR: sustained virologic response, OBV/PTV/r: ombitasvir/paritaprevir/ritonavir, RBV: ribavirin, DCV+ASV: daclatasvir+asunaprevir, SOF/LDV: sofosbuvir/ledipasvir, GLE/PIB: glecaprevir/pibrentasvir

caprevir and pibrentasvir combination therapy (GLE/PIB) was completely successful. Few patients were treated with sofosbuvir and velpatasvir combination therapies (SOF/VEL), the latest treatment and only intended for patients with decompensated cirrhosis, but they achieved an SVR rate of 100%. As a result, the SVR rate for the 301 treatments administrated to 286 patients was 94%. Only 2 patients did not achieve an SVR due to side-effect-related discontinuation, and 11 were not evaluated for efficacy due to drop out.

Results for the 286 patients who received IFN-free treatments are shown in Fig. 2. Of the 286 patients, 11 (4%) dropped out, and 16 (5%) did not achieve an SVR with the initial IFN-free treatments. Of the 16 failures, 11 patients achieved an SVR, but 2 failed again with second-line alternative IFN-free treatments. Three patients did not receive second-line alternative IFN-free treatments. The two failures of the second treatment achieved an SVR with GLE/PIB as a third-line IFN-free treatment (Table 3). As a result, all 272 patients who received up to 3 IFN-free treatments achieved an SVR, except for dropouts and failures who did not receive retreatment. There were no IFN-free treatment dropouts or failures during the COVID-19 pandemic.

**ii) Cumulative incidence of HCC after SVR**

In the 253 patients without a history of HCC, the median observation period was 39 (minimum 0, maximum 74) months, and 18 patients (7.1%) developed HCC after achieving an SVR. According to a univariate analysis, being elderly, having liver cirrhosis, a low platelet count, prolonged prothrombin time, high alkaline phosphatase, low albumin, high α-fetoprotein, high FIB-4 index before treatment and at the EOT, and high total bilirubin and aspartate transaminase (AST) levels before treatment were candidate risk factors for post-SVR HCC (Table 4).

The cumulative incidence of HCC was 2.7%, 4.8%, 6.6%, 9.0%, and 10.0% at 1, 2, 3, 4, and 5 years after SVR, respectively. A plateau in the incidence of HCC was observed after 62 months in this population (Fig. 3A). The incidence of HCC at 3 and 5 years after SVR was 18.2% [95% confidence interval (CI), 6.6-29.8%] and 24.6% (95% CI, 11.0-38.3%) in the cirrhosis subgroup and 3.4% (95% CI, 0.5-6.3%) and 5.8% (95% CI, 1.4-10.1%) in the non-cirrhosis subgroup, respectively (p<0.001; Fig. 3B).

Details of the post-SVR HCC that developed in 18 patients are shown in Table 5. Patients were generally elderly. The most definitive diagnostic method was CT. The liver function was well preserved. Most lesions had a maximum diameter of <2 cm, but some patients had lesions of ≥2 cm and multiple lesions. Although worse than stage I by the TNM classification, many patients were classified as in the very early or early stage by the Barcelona Clinic Liver Cancer (BCLC) staging system. Most patients received treatment with selective transcatheter arterial chemoembolization (TACE), but no treatment was also an option, selected at the patient’s will. Three patients died; the cause of death in two was not related to the liver (advanced gastric cancer and chronic heart failure).

The overall survival rate of the 18 patients with HCC after SVR was 83.3% and 66.7% at 2 and 4 years, respectively (Fig. 4).
### Table 4. Risk Factors for Hepatocellular Carcinoma after SVR (n=253).

|                            | Pre IFN-free treatment | End of treatment |
|---------------------------|------------------------|------------------|
|                           | Occurrence of post SVR-HCC | No occurrence of post SVR-HCC | Occurrence of post SVR-HCC | No occurrence of post SVR-HCC |
|                           | p value | Odds ratio (95% CI) | p value | Odds ratio (95% CI) |
| Number of patients        | 18 | 235 | <0.001 | 12.5 | 16.4 | 0.034 | 138 |
| Age at SVR, years         | 76 | (64-86) | 70 | (19-93) | 0.005 | 72 | 77 | (64-86) | 0.005 | 72 |
| Male/female, n            | 9/9 | 96/139 | 0.466 | 1.448 | (0.570-3.678) |
| Serogroup of HCV          | 15/3 | 168/67 | 0.413 | 1.994 | (0.596-6.627) |
| HCV RNA levels, Log IU/mL | 6.0 | 6.0 | 0.591 | 6.4 | Same as the left |
| Alcohol use history (yes/no), n | 3/15 | 31/204 | 0.718 | 1.316 | (0.387-4.524) |
| Liver cirrhosis (yes/no), n | 10/8 | 42/193 | <0.001 | 5.744 | (2.197-15.01) |
| Diabetes (yes/no), n      | 3/15 | 31/204 | 0.718 | 1.316 | (0.387-4.524) |
| Hepatic steatosis (yes/no), n | 3/15 | 55/180 | 0.771 | 0.655 | (0.196-2.201) |
| Platelet count, x10^9/L   | 11.2 | (5.8-21.8) | 15.3 | (4.9-41.3) | 12.5 | 16.4 | 0.034 | 138 |
| Prothrombin time, %       | 79 | (46-100) | 98 | (27-100) | <0.001 | 93 | 87 | (43-100) | 0.004 | 95 |
| Total bilirubin, mg/dL    | 1.0 | (0.6-1.6) | 0.8 | (0.3-2.6) | 0.033 | 1.0 | 1.0 | (0.5-1.9) | 0.285 | 0.9 |
| AST, U/L                  | 58 | (20-157) | 37 | (15-271) | 0.031 | 58 | 23 | (13-85) | 0.219 | 23 |
| ALT, U/L                  | 44 | (11-122) | 32 | (9-340) | 0.183 | 12 | 15 | (9-66) | 0.895 | 12 |
| ALP, U/L                  | 345 | (155-841) | 261 | (110-1065) | 0.006 | 315 | 344 | (191-1,414) | 0.013 | 318 |
| GGT, U/L                  | 30 | (15-116) | 30 | (8-454) | 0.812 | 41 | 21 | (12-79) | 0.339 | 19 |
| Albumin, g/dL             | 3.7 | (2.9-4.3) | 4.1 | (2.7-5.0) | <0.001 | 3.8 | 3.8 | (3.1-4.5) | 0.004 | 4.0 |
| α-fetoprotein, ng/mL      | 9.3 | (2.7-21.2) | 4.9 | (1.0-516.9) | 0.022 | 5.8 | 4.9 | (2.6-4.9) | 0.027 | 4.7 |
| FIB-4 index               | 5.45 | (2.00-12.4) | 3.05 | (0.27-18.2) | <0.001 | 5.45 | 3.95 | (1.78-9.25) | 0.003 | 3.49 |

IFN: interferon, CI: confidence interval, SVR: sustained virologic response, HCC: hepatocellular carcinoma, AST: aspartate transaminase, ALT: alanine aminotransferase, GGT: γ-glutamyl transpeptidase, ALP: alkaline phosphatase

'n' indicates number, and values are expressed as median (minimum - maximum), unless otherwise indicated. Odds ratio and 95% CI for qualitative variables were analyzed using Fisher’s exact test, and the cut-off value for quantitative variable was analyzed using the receiver operating characteristic (ROC) curve.

SVR are shown in Table 6. Except for 5 patients within 1 month of SVR determination, 248 patients received surveillance with diagnostic imaging at least semi-annually. Abdominal ultrasound, a non-invasive test, was mainly used, and CT and MRI were performed on patients who were at high risk of HCC or had poor visualization of the liver at abdominal ultrasound.

### iii) Follow-up continuation rate after SVR

Of the 253 patients without a history of HCC who achieved an SVR, 58 (22.9%) dropped out of routine follow-up after SVR. Cumulative follow-up rates after SVR for 1, 2, 3, 4, 5, and 6 years were 90%, 86%, 80%, 73%, 70%, and 70%, respectively (Fig. 5). Thirty-eight patients (66%) dropped out of follow-up after SVR between January 2016 and March 2020 (4 years and 2 months).

An emergency declaration was issued in April 2020 due to the expansion of COVID-19 in Japan, and by February 2022 (1 year and 10 months later), 20 patients (34%) had discontinued follow-up after SVR. Since the pandemic, the number of dropouts per month has increased. The median (range) length of hospital visit was 17 (0-40) months for the 38 patients who dropped out before the pandemic and 37 (0-53) months for the 20 patients who dropped out after the
Figure 3. Cumulative incidence of HCC after SVR with IFN-free treatment. A: Total population (n=253). B: Comparison of the cirrhosis subgroup (n=52) and the non-cirrhosis subgroup (n=201). HCC: hepatocellular carcinoma, SVR: sustained virologic response, IFN: interferon

Discussion

The small sample size is an important limitation of this study. However, new research on post-SVR HCC is needed, as IFN-free treatment has a short history; thus, one benefit of this study is that it can provide new information to demonstrate problems that may occur after SVR with IFN-free treatment in a timely manner. Furthermore, despite the success of IFN-free treatment, it is necessary to verify the impact of the COVID-19 pandemic, an unexpected disaster involving all humankind, on the management of individuals infected with HCV.

i) Results of the 301 IFN-free treatments for 286 patients

The treatment results of IFN-free treatment do not differ markedly among facilities in Japan, remaining excellent all around, so it is difficult to find notable considerations regarding the results of IFN-free treatment. This means that IFN-free treatment is “ultimate”. DCV+ASV was the world’s first IFN-free treatment for patients with chronic HCV genotype (GT)1 infection, with an SVR rate of 85% (4), far surpassing that of conventional IFN-based therapy. DAAs are undergoing significant new developments, and regimens that are inferior in efficacy and safety are often discontinued (5). As of June 2022, only sofosbuvir and ledipasvir (SOF/LDV), GLE/PIB, and SOF/VEL are available. SOF/LDV and GLE/PIB have excellent SVR rates (≥ 95%) in patients with chronic HCV infection classified as GT1 or GT2 (14-17), which are overwhelmingly predominant in Japan. GLE/PIB requires different durations of treatment for patients with hepatitis or cirrhosis (8 weeks for non-cirrhosis and 12 weeks for cirrhosis). Therefore, if it is difficult to distinguish between hepatitis and cirrhosis, it may be better to use SOF/LDV, which has a unified treatment period of 12 weeks for both. The advantage of GLE/PIB is that it can also be used in children (≥ 12 years old in Japan) (18) as well as in patients with renal failure (estimated glomerular filtration rate <30 mL/min/1.73 m²) (19).

In our experience, all patients who received GLE/PIB achieved an SVR. In addition, GLE/PIB was able to salvage all initial and second-line treatment failures with other regimens. In 2019, it became possible to treat patients with decompensated cirrhosis with SOF/VEL in Japan (20). SOF/VEL is contraindicated in patients with renal failure. Therefore, as of June 2022, the only special population that cannot be treated with DAAs is patients with decompensated cirrhosis with renal failure.

According to the above findings, the correct administration of recent DAAs provides near 100% SVR rates, and there are few failures due to discontinuation related to side effects. Instead, it is important to avoid drop out (21), as many failures due to discontinuation do not capture the patient’s reason for discontinuing. Losses from drop out may affect not only the efficacy of DAAs, but also the extremely high public medical expense spent on valuable DAAs.

Why the number of patients who received IFN-free treatment declined after the start of the COVID-19 pandemic in this study is unclear. The COVID-19 pandemic might have caused patients with chronic HCV infection to avoid visiting the doctor (9-11), or the decline might have been due to a natural decrease in demand as a result of treatment progress before the pandemic. This issue is likely to be clarified by the fluctuation in the number of patients who receive IFN-free treatment after the pandemic has subsided.
### Table 5. Details of Hepatocellular Carcinoma after SVR of the 18 Patients.

| At HCC diagnosis |   |
|------------------|--|
| **Age, years**    | 79 (66-88) |
| **Diagnostic imaging modality, n** |   |
| Abdominal ultrasound | 7 |
| Computed tomography | 9 |
| Magnetic resonance imaging | 2 |
| **Child-Pugh grade, n** |   |
| A | 18 |
| B | 0 |
| C | 0 |
| **Maximum diameter, cm** | 1.9 (1.0-4.3) |
| <2 cm | 10 |
| 2-2.9 cm | 7 |
| ≥3 cm | 1 |
| **Number of nodules** |   |
| Single | 11 |
| 2 | 3 |
| ≥3 | 4 |
| **Vessel invasion, n** | 0 |
| **Extrahepatic spread, n** | 0 |
| **TNM Classification, n** |   |
| I | 7 |
| II | 8 |
| III | 3 |
| IV | 0 |
| **Barcelona Clinic Liver Cancer (BCLC) staging, n** |   |
| 0 | 7 |
| A | 9 |
| B | 2 |
| C, D | 0 |
| **Up to seven criteria (in/out), n** | 17/1 |
| **Treatment and outcome** |   |
| **Initial treatment, n** |   |
| Resection | 3 |
| Radiofrequency ablation | 1 |
| Transcatheter arterial chemoembolization | 11 |
| No treatment or transferred | 3 |
| **Number of deaths, n** | 3 |
| **Cause of death, n** |   |
| Liver-related death | 1 |
| Other | 2 (advanced gastric cancer, chronic heart failure) |

SVR: sustained virologic response

‘n’ indicates number, and values are expressed as median (minimum - maximum)

### ii) Cumulative incidence of HCC after SVR

Since the start-up phase of research on the incidence of HCC after SVR with IFN-based therapy and IFN-free treatments, fibrosis before SVR has been well recognized as a strong risk factor (22). In recent years, as the observation period and number of patients have increased, reports on the occurrence of post-SVR HCC with IFN-free treatment have also increased. An older age (23), male sex (24), alcohol consumption (23), liver fibrosis (25, 26), cirrhosis (25-28),
Figure 4. Cumulative survival rate of patients with occurrence of HCC after SVR with IFN-free treatment. The prognosis of patients diagnosed with initial HCC after achieving an SVR with IFN-free treatment seems to be better than that previously reported for HCC. HCC: hepatocellular carcinoma, IFN: interferon, SVR: sustained virologic response

Table 6. Methods and Frequency of Surveillance for Hepatocellular Carcinoma after SVR (n=253).

|                     | Abdominal ultrasound | Computed tomography | Magnetic resonance imaging | One or more of the diagnostic imaging methods on the left |
|---------------------|----------------------|----------------------|---------------------------|----------------------------------------------------------|
| Number of patients who received surveillance | 238 (94.1%) | 173 (68.4%) | 59 (23.3%) | 248 (98.0%)† |
| Number of examinations performed | 4 (0-14) | 2 (0-12) | 0 (0-6) | 7 (0-19) |
| Examination interval (months) | 8.7 (0-32.5) | 12.3 (1.0-74.0) | 12.3 (0-68.0) | 5.0 (0-14.0) |

†The observation period for all five patients who did not receive any imaging was less than 1 month after SVR at the observation deadline of this study.

SVR: sustained virological response

Values are expressed as median (minimum - maximum).

high pre- or post-treatment serum α-fetoprotein levels (23), low serum albumin levels (23), high serum hyaluronic acid levels, and high FIB-4 index (25) have been suggested as risk factors for HCC after SVR with IFN-free treatments. Recently, a Japanese research group stratified the incidence of HCC by combining these risk factors (24). However, these risk factors and their cut-off values do not always match, depending on the analysis method used in a given study. In the present study, since we were concerned about obtaining unreliable results should we forcibly perform a multivariate analysis with a small sample size, we dared to show candidate risk factors for post-SVR HCC simply by a univariate analysis. Many corresponded to previously reported risk factors, but it should be noted that these factors are often confounded. For example, the age, platelet count, AST, and alanine aminotransferase are factors that directly constitute the FIB-4 index, and the FIB-4 index correlates with cirrhosis (12).

The cumulative incidence of HCC after SVR observed in this study was not significantly different from that reported in other studies (22, 29, 30). HCC occurred sporadically for at least 5 years after SVR with IFN-free treatments in this study involving a population with a mix of patients at high and low risk for HCC. For the first year after SVR, we should be particularly alert for the occurrence of HCC. However, the observation period with IFN-free treatment is not as long as with IFN-based therapy, so it remains difficult to determine when to end post-SVR surveillance.

iii) Follow-up continuation rate after SVR

There is some concern that initial or recurrent HCC may have occurred in some patients who dropped out of follow-up after SVR. Although the importance of post-SVR follow-up is well acknowledged (22), few studies have addressed
Follow-up continuation rate after SVR. The follow-up continuation rate for surveying for monitoring post-SVR hepatocellular carcinoma decreased to 70%. Dropouts tended to be more frequent during the 22 months after the start of the coronavirus disease 2019 pandemic than during the 50 months before it. SVR: sustained virologic response

the issue of drop out from post-SVR follow-up. Tamori et al. suggested that a history of injection drug use was a risk factor for drop out from post-SVR follow-up (31). Toyoda et al. reported that patients receiving IFN-free treatment were more likely to drop out after SVR than those receiving IFN-based therapy (32). The results of our study support this finding. We hypothesize that patients who have experience with IFN-based therapy may have long struggled before they were able to benefit from IFN-free treatment and may therefore be more educated about and aware of the risks of HCC.

The purpose of post-SVR follow-up is the early detection of the development of HCC after SVR. It has been shown that elimination of HCV with IFN-free treatment contributes to a reduction in the incidence of initial and recurrent HCC, as well as IFN-based therapy (22). The present findings suggest that the post-SVR HCC prognosis is better than that reported in our previous regional studies (33) and nationwide multi-institutional research projects, such as the Survival Statistics of the Japanese Association of Clinical Cancer Centers (34), which found overall survival rates of all stages of HCC in Japan of 73.8% for 1 year, 59.8% for 2 years, and 44.3% for 4 years. In the present study, three patients died during the observation period, and two of the deaths were due to other diseases.

However, despite regular surveillance after SVR, some patients had HCC tumors larger than 2 cm. This implies that there is yet room to consider more appropriate techniques, modalities, and intervals of follow-up after SVR, especially in patients with a high risk of occurrence of post-SVR HCC.

It is difficult to predict and prevent simultaneous and multiple occurrences of HCC. As a result, the TNM classification of patients with post-SVR HCC in this study was often worse than stage I. However, none of the cases was untreatable. The BCLC staging was good, and patients who fulfilled 7 or more of the up-to-seven criteria were rare. Re-

Table 7. Risk of Dropout after Achieving SVR with IFN-free Treatment (n=253).

| Time at dropout                  | Number of dropouts | number of dropouts per month |
|----------------------------------|--------------------|------------------------------|
| January 2016-March 2020 (50 months) | 38 (66%)           | 0.76                         |
| April 2020-February 2022 (22 months) | 20 (34%)           | 0.91                         |

IFN: interferon, SVR: sustained virologic response, CI: confidence interval
gardless of the fact that many patients were classified as being in the early stage according to BCLC staging, we often performed TACE rather than resection or radiofrequency ablation (RFA), as many of the patients were elderly and/or had multiple lesions, and our hospital is experienced with performing balloon-occluded selective TACE (35), especially for small lesions.

There is some concern regarding potential delays or avoidance of hepatitis C testing and treatment during the COVID-19 pandemic (9-11). However, the impact on post-SVR follow-up has not yet been clarified. In this study, fortunately, there were no cases of failure to receive IFN-free treatment associated with the COVID-19 pandemic.

Even after the start of the pandemic, our facility maintained its daily practice. However, since the pandemic, the number of dropouts per month has increased. The cause of withdrawal from follow-up after SVR may be anxiety about COVID-19 infection in addition to fatigue from long-term hospital visits, but it is difficult to statistically explain whether or not COVID-19 affected follow-up after achievement of an SVR. Nevertheless, it has been suggested that COVID-19 has a negative impact on other areas of consultation and cancer screening, so some concern may also apply to post-SVR surveillance of HCC. Therefore, it is necessary to continue to monitor future trends.

**Conclusion**

Recently, chronic HCV infections have been controlled almost completely and safely, thanks to the development of IFN-free treatments, and their efficacy is expected to reduce mortality associated with HCC in the future. Various reports have verified the risk factors for HCC after SVR with IFN-free treatment, and the characteristics of the high- and low-risk groups are also being identified. However, it may be premature to dictate the methods and endpoints of follow-up after SVR. Therefore, interruption of surveillance after SVR may be an issue in the management of HCV infection. In particular, the COVID-19 pandemic was thought to have caused a delay in the detection of malignant neoplasms in various areas, so a similar delay may have also occurred in post-SVR HCC.

In the future, attention should be paid to the increasing number of patients with advanced HCC despite the elimination of HCV.

**The authors state that they have no Conflict of Interest (COI).**

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