No Regional Disparities in Sofosbuvir Plus Ribavirin Therapy for HCV Genotype 2 Infection in Tochigi Prefecture and Its Vicinity

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Abstract:
Objective Regional disparities were observed in the outcomes of interferon (IFN)-based therapy for chronic hepatitis C virus (HCV) infection in a Japanese nationwide study. However, whether or not these regional disparities are observed in the outcomes of direct-acting antiviral drugs, including sofosbuvir (SOF) plus ribavirin (RBV) therapy, remains unclear.

Methods We conducted a multicenter study to assess the efficacy of SOF plus RBV therapy for HCV genotype 2 infection in Tochigi Prefecture and its vicinity, in which IFN-based therapy yielded a low sustained virologic response (SVR) rate. In addition, we divided Tochigi Prefecture into six regions to examine regional disparities in the SVR.

Patients We enrolled patients with chronic HCV genotype 2 infection.

Results Of the 583 patients enrolled, 569 (97.6%) completed the treatment, and 566 (97.1%) also complied with post-treatment follow-up for 12 weeks. The overall SVR12 rate was 96.1% by per protocol and 93.7% by intention-to-treat analyses. No marked differences were observed in the SVR12 between subjects ≥65 and <65 years of age. Although large gaps were observed in the characteristics of patients and accessibility to medical resources, there was no significant difference in the SVR12 rate among the six regions in Tochigi Prefecture.

Conclusion SOF plus RBV therapy was effective for HCV genotype 2 infection in an area where IFN-based therapy had previously shown unsatisfactory results. In addition, no regional disparities in the SVR12 were observed in Tochigi Prefecture.

Key words: chronic hepatitis C infection, genotype 2, regional disparities, ribavirin, sofosbuvir
Introduction

Hepatitis C virus (HCV) infection can cause chronic hepatitis, liver cirrhosis and subsequent hepatocellular carcinoma (HCC). At present, there are 1-1.5 million patients with HCV infection in Japan (1). Of the 6 HCV genotypes, 1 and 2 are the major genotypes observed in Japan, accounting for roughly 70% and 30% of cases, respectively. The standard treatment for chronic hepatitis C was interferon (IFN)-based therapy until 2014. The rate of a sustained virological response (SVR) at 24 weeks after pegylated-IFN (peg-IFN) with ribavirin (RBV) therapy was 78.4-82.6% for genotype 2 chronic HCV infection (2, 3). However, IFN-based therapy induced a number of adverse effects during the treatment, resulting in poor tolerability. As a result, a substantial number of patients dropped out from treatment regimens. In addition, elderly patients hesitated to receive the IFN-based therapy due to its adverse effects as well as poor access to medical resources (4). In fact, the SVR24 in elderly patients was lower than that in patients under 65 years of age due to the discontinuation of the therapy (5).

In 2014, the IFN-free treatment daclatasvir combined with asunaprevir was approved for the first time in Japan for patients with chronic HCV genotype 1 infection. Sofosbuvir (SOF) plus RBV was then approved for chronic HCV genotype 2 infection in May 2015. SOF is a nucleotide analog inhibitor of the HCV 5B polymerase, exerting anti-viral effects on HCV genotypes 1 to 6. A Japanese phase III trial showed that the rate of SVR at 12 weeks after therapy (SVR 12) of SOF plus RBV therapy for genotype 2 was 97% (6), which was almost the same as in previous studies performed in other countries (7, 8). In addition, the adverse effects observed in SOF plus RBV therapy were milder than those of IFN-based therapy. Real-world data in Japan also reproduced this high SVR rate without serious adverse events (9, 10, 11). Thus, SOF plus RBV therapy is currently one of the standard treatments for patients with chronic HCV genotype 2 infection.

However, the published data on SOF plus RBV therapy were collected from patients residing in metropolitan areas and their vicinity. When patients with chronic HCV infection were treated with IFN-based therapy, regional disparities were observed in a Japanese nationwide study (12). Access to medical resources was one of the reasons suspected to underlie the poor SVR rate in low-population-density regions, including the Tohoku/Hokkaido and Shikoku areas. Indeed, access to medical care in rural areas does influence the HCV management (13, 14). Furthermore, the rate of people ≥65 years of age in low-population-density regions is higher than those in high-population-density regions in Japan (https://www.mhlw.go.jp/wp/hakusyo/kousei/16/).

From 2004 to 2006, we performed a multicenter study for the treatment of HCV infection using peg-IFN plus RBV in Tochigi Prefecture, which is adjacent to the Tohoku area. The SVR24 was 66% in the 24-week-treatment group, which included HCV serogroup 2 and serogroup 1 with a low titer (<100 KIU/mL). Patients with serogroup 2 HCV infection accounted for 95.2% (120/126) of the 24-week-treatment group (15). Because the reasons for the low SVR rate were unclear, we were concerned about the efficacy and safety of SOF plus RBV therapy in Tochigi Prefecture. In addition, the reproducibility of SOF plus RBV therapy in these “developing areas in HCV treatment” and “rural areas” was unclear.

We therefore performed a multicenter study to evaluate the efficacy of SOF plus RBV therapy for patients with HCV genotype 2 infection in Tochigi Prefecture and its vicinity. The first aim of the present study was to evaluate the efficacy of SOF plus RBV therapy in Tochigi Prefecture and its vicinity compared with the outcomes of previous studies performed in metropolitan areas, in which a high SVR had already obtained. The second aim was to investigate the SVR in low-population areas in Tochigi Prefecture, where the rate of people ≥65 years of age is higher than those in high-population-density regions.

Materials and Methods

Patients

Patients chronically infected with HCV genotype 2 were enrolled in this retrospective study at 13 institutions in Tochigi Prefecture and its vicinity between May 2015 and March 2017. The leading exclusion criteria were (1) advanced liver cirrhosis (Child-Pugh grade B or C), (2) renal dysfunction [estimated glomerular filtration rate (eGFR) <50 mL/min], (3) the presence of HCC and (4) other contraindications for treatment. There were no upper limits on body weight.

All patients were scheduled to receive 12 weeks of treatment with 400 mg of SOF (Sovaldi®; Gilead Sciences, Tokyo, Japan), administered orally once daily, and RBV (Rebetol®; MSD, Tokyo, Japan, or Copegus®, Chugai, Tokyo, Japan), administered orally twice daily, with the dose adjusted according to the body weight (600-1,000 mg/day). The dosage of RBV was reduced according to the drug information provided by each company when anemia developed.

This multicenter retrospective study consisted of 583 consecutive Japanese patients. Fourteen patients discontinued the treatment within 12 weeks from the entry. Three patients stopped visiting the hospital for unknown reasons after the end of treatment. Thus, intention-to-treat (ITT) and per protocol (PP) analyses were performed in 583 and 566 patients, respectively. We recorded the age, gender, history of HCC treatment and IFN treatment, genotype (2a/2b), and status of the liver (chronic hepatitis or liver cirrhosis). The diagnosis of liver cirrhosis was made based on the following findings: aspartate aminotransferase (AST)/platelet ration index >1.5, and morphologic changes in the liver as determined by ultrasonography, computed tomography and/or magnetic reso-
nance imaging. The FIB-4 index, HCV-RNA (log IU/mL), hemoglobin (Hb) (g/dL), platelet count (×10⁴/μL), HbA1c (%) and alpha fetoprotein (AFP) (ng/mL) were also examined at the entry of the study. We also calculated the dosage of RBV [mg/body weight (kg)]. The FIB-4 index, a marker for liver fibrosis, was determined using the following formula: [age×AST(U/L)] / [platelet (Plt) (×10⁴/μL)×ALT(U/L)]². The serum HCV-RNA was measured using quantitative real-time polymerase chain reaction (COBAS® TaqMan® HCV Test, version 2.0; Roche Diagnostics, Tokyo, Japan, or AccuGENE® m-HCV RNA quantitative assay; Abbott Japan, Tokyo, Japan). The rapid virological response (RVR) and end of treatment response (ETR) were defined as undetectable HCV-RNA at four weeks and at the end of treatment, respectively. The SVR12 was also used for the evaluation of the virological response. Adverse events were recorded according to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

The institutions participated in this study are follows: for low-population-density areas (<500 people/km²), Nasu Red Cross Hospital, Nasu Minami Hospital, and Haga Red Cross Hospital, and for high-population-density areas (>500 people/km²), Jichi Medical University, Shin-Oyama City Hospital, Koga Red Cross Hospital, Tochigi Medical Center Shimotsuga, Dokkyo Medical University, Saiseikai Utsunomiya Hospital, Sano Kousei General Hospital, Tochigi Medical Center, Tochigi Cancer Center and Kamitsuga General Hospital. Data on the population and land were obtained from prefectural information (http://www.pref.tochigi.lg.jp). The distance between a patient’s home address and their visiting hospital was calculated using a free software program on the Internet (http://r1web.realwork.jp/index_ex.html).

This study was approved by the institutional review board or independent ethics committees at all participating sites and was conducted in accordance with the Declaration of Helsinki.

### Statistical analyses

Statistical analyses were performed using the Stata15 software program (STATA Corporation, College Station, USA). Continuous variables were expressed as the median (first-third quartiles or range). Chi-squared, Mann-Whitney U and Student’s t-tests as well as the Kruskal-Wallis method were used to compare the proportions of categorical variables between the groups. p<0.05 was considered statistically significant. Univariate and multivariate logistic analyses were performed after the cut-off values of continuous variables were determined by the Youden index. The cut-off values were age 65 (years), Hb 13.9 (g/dL), platelet count 23.0 (×10⁴/μL), FIB-4 index 3.3, HbA1c 5.9 (%), AFP 10.9 (ng/mL), HCV-RNA 5.15 (log IU/mL) and RBV dosage 11.9 [mg/body weight (kg)]. Variables with p<0.05 in the univariate analysis were evaluated by a multivariate logistic analysis to determine non-SVR factors. Odds ratios (ORs) and their 95% confidence intervals (CIs) are shown. p<0.05 was considered statistically significant.

### Results

#### Characteristics of patients

First, we evaluated the characteristics of the 566 patients who completed the treatment and subsequent 12 weeks’ follow-up (Table 1). The median age was 64 years (range 26-88 years), with 273 (48.2%) patients ≥65 years of age. Of the 566 patients, the numbers of men, IFN-experienced patients and patients with a history of HCC treatment were 342 (60.4%), 113 (20.0%) and 33 (5.8%), respectively. We also evaluated the features of patients ≥65 years of age and found them to be characterized by a high frequency of HCC.

### Table 1. Characteristics of 566 Patients who Completed Treatment and 12 Weeks Follow Up.

| Characteristic | Overall (n=566) | Age<65 (n=273) | Age≥65 (n=293) | p value |
|---------------|-----------------|----------------|----------------|---------|
| Age (years)   | 64 (55-71)      | 72 (67-76)     | 55 (48-60)     | <0.0001 |
| Male (%)/Female (%) | 342 (60.4)/224 (39.6) | 145 (53.1)/128 (46.9) | 197 (67.2)/96 (32.8) | 0.001  |
| History of HCC treatment +/− | 33/533 | 25/248 | 8/285 | 0.001 |
| IFN (naïve/experienced) | 453/113 | 208/65 | 245/48 | 0.027 |
| Genotype 2a/2b | 183/182 | 94/80 | 89/102 | 0.156 |
| CH/LC | 443/123 | 199/74 | 244/49 | 0.003 |
| FIB-4 index | 2.68 (1.58-4.62) | 3.6 (2.3-6.1) | 1.9 (1.1-3.6) | <0.0001 |
| HCV-RNA (LogIU/mL) | 6.1 (5.3-6.5) | 6.1 (5.3-6.5) | 6.2 (5.3-6.6) | 0.21 |
| Hemoglobin (g/dL) | 13.8 (12.9-15) | 13.3 (12.4-14.4) | 14.4 (13.5-15.3) | <0.0001 |
| Platelet count (×10⁴/μL) | 15.4 (11-20.7) | 13.8 (10.3-18.6) | 17.4 (12.7-22) | <0.0001 |
| AST (U/L) | 40.0 (26-66) | 40.0 (26-65) | 39.5 (25-73) | 0.89 |
| ALT (U/L) | 41.5 (24-74) | 37.0 (22-69) | 47.0 (26-91) | 0.0006 |
| HbA1c (%) | 5.7 (5.4-6.3) | 5.9 (5.5-6.4) | 5.6 (5.3-6.1) | 0.01 |
| AFP | 4.1 (2.7-7) | 4.0 (2.8-7) | 4.1 (2.6-7) | 0.83 |

Data are indicated median (interquartile) or number (%). p<0.05 is statistically significant between aged ≥65 and<65. HCC: hepatocellular carcinoma, IFN: interferon, CH: chronic hepatitis, LC: liver cirrhosis, AST: aspartate aminotransferase; ALT: alanine aminotransferase, HbA1c: hemoglobin A1c, AFP: alpha fetoprotein.
rates in patients and 92.9% (261/281) and 94.4% (285/302) on an ITT analysis, respectively, 96.9% (284/293) on a PP analysis (p=0.30), respectively, 3.3% (OR=2.53) and “AFP <12 were “a history of HCC treatment” (OR=9.29), “FIB-4 index ≤0.50). The SVR rates were not significantly different from those in patients <75 years of age. There was also no significant difference in the SVR12 rate between genotype 2a and 2b (p=0.73). Of the 566 patients, 22 did not obtain an SVR by treatment. The reasons for discontinuation are listed in Table 4. Six of seven patients showed symptomatic anemia (Hb <8.5 g/dL), 2 resumed the therapy after recovering from anemia and achieved an SVR12. Fourteen patients discontinued RBV . More patients and dosage. In contrast, 84% of patients completed scheduled RBV therapy. Of the 583 patients initially enrolled, 569 (97.6%) received SOF for the scheduled duration and dosage. In contrast, 84% of patients completed scheduled RBV. More patients ≥65 years of age had the dosage of RBV reduced than did those <65 years of age (Table 4). Although 3 patients temporarily discontinued RBV due to anemia (Hb <8.5 g/dL), 2 resumed the therapy after recovering from anemia and achieved an SVR12. Fourteen patients discontinued SOF plus RBV therapy during the treatment period. Of these 14 patients, 7 were ≥65 years of age (2.5% of total patients enrolled). The reasons for discontinuation are listed in Table 4. Six of seven patients showed symptomatic adverse events of Grade 1 or 2 and expressed a strong de-

**Virological responses and non-SVR factors**

We next evaluated the virological responses. The overall SVR12 was 96.1% (544/566) and 93.7% (546/583) on PP and ITT analyses, respectively (Fig. 1a). The SVR12 rate of patients ≥65 and <65 years of age was 98.2% (260/273) and 96.9% (284/293) on a PP analysis (p=0.30), respectively, and 92.9% (261/281) and 94.4% (285/302) on an ITT analysis (p=0.46), respectively (Fig. 1b). In addition, the SVR12 rates in patients ≥75 years of age on PP and ITT analyses were 93.3% (83/89) and 93.3% (84/90), respectively. These SVR rates were not significantly different from those in patients <75 years of age. There was also no significant difference in the SVR12 rate between genotype 2a and 2b (p=0.50).

Of the 566 patients, 22 did not obtain an SVR by treatment. In a univariate analysis, the risk factors for non-SVR 12 were “a history of HCC treatment” (OR=9.29), “FIB-4 ≥ 3.3” (OR=2.53) and “AFP ≥10.9 ng/mL” (OR=3.73) (Table 2). In a multivariate analysis, “a history of HCC treatment” was statistically significant for non-SVR (OR 8.05) (Table 2). The SVR12 rate was significantly lower in patients with a history of HCC treatment than in those without such a history (Fig. 2). Of the 33 patients with a history of HCC treatment, 26 (78.8%) achieved an SVR12. We further examined the characteristics of patients with non-SVR in the group with a history of HCC. The patients were significantly older in the non-SVR group than in the SVR group, although no significant differences were observed in the gender, IFN-experienced, HCV-RNA load, FIB-4 index, Hb levels, platelet count or AFP levels between these two groups. In addition, the dosage of RBV was not a risk factor for non-SVR (Table 3).

**Treatment adherence and safety**

We next evaluated the treatment adherence and safety of SOF plus RBV therapy. Of the 583 patients initially enrolled, 569 (97.6%) received SOF for the scheduled duration and dosage. In contrast, 84% of patients completed scheduled RBV. More patients ≥65 years of age had the dosage of RBV reduced than did those <65 years of age (Table 4). Although 3 patients temporarily discontinued RBV due to anemia (Hb <8.5 g/dL), 2 resumed the therapy after recovering from anemia and achieved an SVR12. Fourteen patients discontinued SOF plus RBV therapy during the treatment period. Of these 14 patients, 7 were ≥65 years of age (2.5% of total patients enrolled). The reasons for discontinuation are listed in Table 4. Six of seven patients showed symptomatic adverse events of Grade 1 or 2 and expressed a strong de-
Table 2. Univariate and Multivariate Logistic Analyses of Factors for Non SVR.

| Parameters                        | Univariate analysis | Multivariate analysis |
|-----------------------------------|---------------------|-----------------------|
|                                   | OR (95% CI) | p value | OR (95% CI) | p value |
| Age≥65                            | 0.63 (0.26-1.5)   | 0.3      |             |         |
| Gender Female                     | 0.83 (0.35-1.97)  | 0.36     |             |         |
| History of HCC treatment          | 9.29 (3.49-24.7)  | 0.0001   | 8.05 (2.61-24.8) | <0.001 |
| IFN : experienced                 | 2.38 (0.97-5.84)  | 0.056    |             |         |
| Genotype 2a                       | 1.78 (0.59-5.32)  | 0.3      |             |         |
| FIB-4 index ≥ 3.3                 | 2.53 (1.04-6.15)  | 0.039    | 0.93 (0.31-2.79) | 0.9    |
| HCV-RNA (Log IU/mL) ≥ 5.15        | 5.64 (0.75-42.3)  | 0.093    |             |         |
| Hemoglobin (g/dL) < 13.9          | 1.45 (0.60-3.44)  | 0.4      |             |         |
| Platelet count (x10^9/μL) < 23    | 0.70 (0.23-2.15)  | 0.54     |             |         |
| HbA1c (%) ≥ 5.9                   | 2.88 (0.84-9.85)  | 0.09     |             |         |
| AFP ≥ 10.9                        | 3.73 (1.45-9.59)  | 0.006    | 2.34 (0.77-7.03) | 0.12 |
| Initial RBV dose (mg/kg/day) ≥ 12 | 1.01 (0.43-2.42) | 0.97     |             |         |
| Average RBV dose (mg/kg/day) < 11.9| 1.05 (0.43-2.55) | 0.47     |             |         |
| RBV reduction (-)                 | 1.65 (0.59-4.59)  | 0.34     |             |         |
| RBV adherence<80%                 | 1.53 (0.44-5.33)  | 0.51     |             |         |

SVR: sustained virological response, RBV: ribavirin, OR: odds ratio, CI: confidence interval

Discussion

In the present study, the SVR12 rate was 96.1% by PP and 93.7% by ITT, although previous IFN-based therapy resulted in a lower SVR rate in Tochigi Prefecture. In addition, no regional disparities were observed in the SVR12 among the six regions in Tochigi Prefecture, although large gaps were observed in the characteristics of patients and the accessibility of medical resources. Thus, SOF plus RBV therapy was deemed effective, even in areas with difficulty receiving medical services.

Our study showed that SOF plus RBV therapy yielded a high SVR12 rate despite the inclusion of many patients with non-SVR factors, including those with a high FIB-4 index, platelet count and ALT levels (Table 5). However, the SVR12 rate in each region was roughly equivalent on PP (92.7-100%) and ITT (91.9-100%) analyses (Fig. 3c). We also examined the correlation between patients’ access to hospitals and the SVR. However, the distance between patients’ homes and hospitals had little effects on the SVR12 (Fig. 3d).

SVR rate in six regions of Tochigi Prefecture

The overall data in Tochigi Prefecture and its vicinity showed a high SVR rate. Because the population density is related to the accessibility of medical care (13, 14), we divided Tochigi Prefecture into six regions to evaluate the presence of regional disparities (Fig. 3a). The Nasu/Shiobara and Haga areas have a low population density, while the Usunomiya/Kanuma and Oyama areas have a high population density (Fig. 3b). In these six regions, there were several differences in the characteristics of patients, including age, genotypes, the prevalence of patients with liver cirrhosis, FIB-4 index, platelet count and ALT levels (Table 5). However, the SVR12 rate in each region was roughly equivalent on PP (92.7-100%) and ITT (91.9-100%) analyses (Fig. 3c). We also examined the correlation between patients’ access to hospitals and the SVR. However, the distance between patients’ homes and hospitals had little effects on the SVR12 (Fig. 3d).

Our study showed that SOF plus RBV therapy yielded a high SVR12 rate despite the inclusion of many patients with non-SVR factors, including those with a high FIB-4 index (12) and liver cirrhosis (9). In addition, the SVR12 rate in the patients ≥65 years of age was 95.2% and 92.9% by PP and ITT analyses, respectively, despite the present study including a relatively large number of patients ≥65 years of age who had low Hb levels, a potential cause of discontinuation of the therapy. Even with these unfavorable factors, the SVR12 rate in the present study was nearly the same as in other studies in Japan (9-11). Furthermore, SOF plus RBV therapy is safe with a high adherence. Although several adverse effects were observed during the treatment, the majorities were CTCAE Grade 2 or less severe. Even in the 14 patients who discontinued the therapy due to adverse and un-
expected events, most events were Grade 2 or less severe except for 1 patient with gastrointestinal bleeding (Grade 3). In fact, the primary reasons for discontinuation were due to patients’ strong desire to quit rather than the severity of adverse effects. Other Japanese studies have also demonstrated that SOF plus RBV therapy is safe with high adherence (9-11).

We identified “a history of HCC treatment” as a non-SVR factor. In a study of DAA treatment for genotype 1 performed in other areas, “a history of HCC treatment” was reported as a non-SVR factor (16), indicating that “a history of HCC treatment” is not specific for Tochigi Prefecture. In general, patients with advanced liver cirrhosis are prone to HCC development. The present study included a relatively larger number of men, patients >65 years of age and patients with a high FIB-4 index, all of which are risk factors for HCC (17, 18). A previous report showed that liver cirrhosis was a non-SVR factors in SOF plus RBV therapy (9). In the present study, the FIB-4 index in patients with a history of HCC was higher than that in the total enrolled patients (Table 1, Table 3). Thus, the FIB-4 index might be a confounding factor in a multivariate analysis. Further investigations are required to clarify the reasons. A history of DAA treatment failure is a non-SVR factor in the second line of DAA treatment for HCV genotype 1 infection, as multiple resistance-associated variants have developed (16). However, the present study did not include patients with a history of DAA treatment.

In 2004-2006, a multicenter study in Tochigi Prefecture showed that the SVR24 rate was 66% in a group that included HCV serogroup 2 (120/126 patients) and serogroup 1 with a low titer of HCV (<100 KIU/mL; 6/126 patients). This SVR rate was worse than that of other clinical trials (2, 3). A previously study showed that discontinuation of IFN-based therapy resulted in low SVR, particular in patients <65 years of age (5). In the present study, 97.6% (569/583) of patients completed the treatment. The treatment duration of SOF plus RBV therapy was shorter than that of IFN-based therapy (12 vs. 24 weeks). In addition, the frequency of visiting the hospital among patients receiving SOF plus RBV was lower than that among those receiving IFN-based therapy (once vs. twice in two weeks). Furthermore, the adverse events with SOF plus RBV were milder than with those with IFN-based therapy. These favorable

| Table 3. Characteristics of Patients with History of HCC Treatment. |
|-------------------|-------------------|-------------------|-------------------|-------------------|
|                   | overall           | SVR               | Non-SVR           | p value           |
|                   | n=33              | n=26              | n=7               |                   |
| Age (years)       | 72 (65-76)        | 71 (65-75)        | 73 (55-78)        | 0.04              |
| Male / Female     | 23/10             | 17/9              | 6/1               | 0.3               |
| IFN (naïve/experienced) | 25/8             | 19/7              | 6/1               | 0.49              |
| FIB-4 index       | 5.4 (3.6-7.1)     | 4.8 (3.6-7.9)     | 6.2 (2.2-7.1)     | 0.79              |
| HCV-RNA (Log IU/mL) | 5.8 (5.4-6.3)    | 5.9 (5.3-6.5)     | 5.6 (5.4-5.8)     | 0.18              |
| Hemoglobin (g/dL) | 13.1 (12.5-14.8)  | 13.0 (12.3-14.8)  | 14.2 (12.5-15.4)  | 0.49              |
| Platelet count (×10^4/μL) | 10.6 (7.8-14.9)  | 10.6 (7.8-14.9)  | 9.8 (6.1-14.9)    | 0.7               |
| HCVRNA-RNA (Long IU/mL) | 5.8 (5.4-6.3)    | 5.9 (5.3-6.5)     | 5.6 (5.4-5.8)     | 0.18              |
| Hemoglobin (g/dL) | 13.1 (12.5-14.8)  | 13.0 (12.3-14.8)  | 14.2 (12.5-15.4)  | 0.49              |
| Platelet count (×10^4/μL) | 10.6 (7.8-14.9)  | 10.6 (7.8-14.9)  | 9.8 (6.1-14.9)    | 0.7               |
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| Hemoglobin (g/dL) | 13.1 (12.5-14.8)  | 13.0 (12.3-14.8)  | 14.2 (12.5-15.4)  | 0.49              |
| Platelet count (×10^4/μL) | 10.6 (7.8-14.9)  | 10.6 (7.8-14.9)  | 9.8 (6.1-14.9)    | 0.7               |
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| Hemoglobin (g/dL) | 13.1 (12.5-14.8)  | 13.0 (12.3-14.8)  | 14.2 (12.5-15.4)  | 0.49              |
| Platelet count (×10^4/μL) | 10.6 (7.8-14.9)  | 10.6 (7.8-14.9)  | 9.8 (6.1-14.9)    | 0.7               |
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| Hemoglobin (g/dL) | 13.1 (12.5-14.8)  | 13.0 (12.3-14.8)  | 14.2 (12.5-15.4)  | 0.49              |
| Platelet count (×10^4/μL) | 10.6 (7.8-14.9)  | 10.6 (7.8-14.9)  | 9.8 (6.1-14.9)    | 0.7               |
| HCV-RNA (Log IU/mL) | 5.8 (5.4-6.3)    | 5.9 (5.3-6.5)     | 5.6 (5.4-5.8)     | 0.18              |
| Hemoglobin (g/dL) | 13.1 (12.5-14.8)  | 13.0 (12.3-14.8)  | 14.2 (12.5-15.4)  | 0.49              |
| Platelet count (×10^4/μL) | 10.6 (7.8-14.9)  | 10.6 (7.8-14.9)  | 9.8 (6.1-14.9)    | 0.7               |
| HCV-RNA (Log IU/mL) | 5.8 (5.4-6.3)    | 5.9 (5.3-6.5)     | 5.6 (5.4-5.8)     | 0.18              |
| Hemoglobin (g/dL) | 13.1 (12.5-14.8)  | 13.0 (12.3-14.8)  | 14.2 (12.5-15.4)  | 0.49              |
| Platelet count (×10^4/μL) | 10.6 (7.8-14.9)  | 10.6 (7.8-14.9)  | 9.8 (6.1-14.9)    | 0.7               |
| HCV-RNA (Log IU/mL) | 5.8 (5.4-6.3)    | 5.9 (5.3-6.5)     | 5.6 (5.4-5.8)     | 0.18              |
| Hemoglobin (g/dL) | 13.1 (12.5-14.8)  | 13.0 (12.3-14.8)  | 14.2 (12.5-15.4)  | 0.49              |
| Platelet count (×10^4/μL) | 10.6 (7.8-14.9)  | 10.6 (7.8-14.9)  | 9.8 (6.1-14.9)    | 0.7               |
| HCV-RNA (Log IU/mL) | 5.8 (5.4-6.3)    | 5.9 (5.3-6.5)     | 5.6 (5.4-5.8)     | 0.18              |

Data are indicated median (interquartile) or n/number.
factors of SOF plus RBV therapy resulted in a high treatment adherence and a subsequent high SVR.

We demonstrated for the first time that no regional disparities in SVR among patients receiving SOF plus RBV therapy exist at the prefectural and county levels. In the era of IFN-based therapy for chronic HCV infection, regional disparities have been observed in Japan. Access to medical resources is one of the reasons suspected to underlie the poor SVR in low-population-density regions (12). Because Tochigi Prefecture includes both low- and high-population-density areas, it is suitable for the investigation of regional disparities. We therefore compared the SVR between rural and urban areas as well as between patients living close to a hospital and those living far from a hospital. However, there was no significant difference in the SVR rate between these groups. In addition, we temporally evaluated the SVR rate of SOF/ledipasvir therapy to investigate the regional disparities in genotype 1. In Tochigi Prefecture, the SVR12 rates of the overall, high- and low-population-density areas were 95.6% (239/250), 96.5% (190/197) and 92.5% (49/53), respectively, on an ITT analysis. The SVR rate was not significantly different between the high- and low-population-density areas (p=0.208) (Takaoka et al., unpublished data).

These data suggest that IFN-free oral DAA treatment is extremely effective anywhere provided patients complete the treatment. There are several limitations associated with the present study. There are a substantial number of areas in Japan with poor access to medical resources. Thus, nationwide studies are required to confirm the findings that the SVR is not associated with accessibility. In addition, we did not examine resistance-associated variants for the HCV nonstructural 5B genome or the inosine triphosphatase genotype. A previous study showed that resistance-associated variants, including HCV nonstructural 5B genome or the inosine triphosphatase genotype. A previous study showed that resistance-associated variants, including HCV nonstructural 5B genome, were not detected in patients treated with SOF plus RBV therapy (11). Although the presence of the inosine triphosphatase CC genotype is a good marker for predicting RBV-induced anemia, the reduction was not a risk factor for non-SVR in the present study. Other studies also revealed that RBV reduction did not affect the non-SVR (9, 10). Because the duration of SOF plus RBV therapy (12 weeks) is shorter than that of IFN-based therapy (24 weeks), the adequate reduction of RBV may have little effect on the SVR in SOF plus RBV therapy.

SOF plus RBV and ombitasvir/paritaprevir/ritonavir plus RBV therapies have been used to treat HCV genotype 2 in-
fection in Japan. In addition, both IFN- and RBV-free treatments, including glecaprevir/pibrentasvir and SOF/ledipasvir therapies, have been available in Japan. Other treatment regimens have been under trial for HCV genotype 2 infection in Japan. In addition, both IFN- and RBV-free treatments, including SOF plus velpatasvir therapy (19). Although these IFN- and RBV-free treatments may provide further benefits for patients with HCV genotype 2 infection, real-world data are not yet available. Thus, it is important to obtain real-world data on SOF plus RBV therapy for patients with HCV genotype 2 infection from areas where IFN-based therapy resulted in a lower SVR.

In conclusion, SOF plus RBV therapy for patients with HCV genotype 2 infection overcame the low SVR of IFN-based therapy in Tochigi Prefecture and its vicinity. In addition, no regional disparities were observed in the SVR rate between high- and low-population-density areas, which was a problem in the era of IFN-based therapy.

**Table 5. Characteristics of 543 Patients Enrolled in Tochigi Prefecture.**

|                  | Overall | Nasu/Shiobara | Haga | Ryomo |
|------------------|---------|---------------|------|-------|
| Age (years)      | 63 (54-71) | 67 (57-73) | 66 (60-72) | 65 (55-73) |
| Male (%) / Female (%) | 329 (60.6) / 214 (39.4) | 39 (49.4) / 40 (60.6) | 24 (75)/ 8 (25) | 42 (65.6)/ 22 (34.4) |
| History of HCC treatment +/- | 30 (5.5) / 513 (94.5) | 2 (2.5) / 77 (97.5) | 1(3.1) / 31 (96.9) | 5 (7.8)/ 59 (92.2) |
| IFN (naive/experienced) | 435 (80.1) / 108 (19.9) | 62 (78.5)/ 17 (21.5) | 26 (81.25)/6 (18.75) | 50 (78.1)/41 (21.9) |
| Genotype2a/2b | 182 (50.1) / 181 (49.9) | 10 (62.5)/ 6 (37.5) | 0 (0)/ 3 (100) | 31 (60.8)/ 20 (39.2) |
| CH/LC | 424 (78.1)% / 119 (21.9) | 60 (75.9)/ 19 (24.1) | 26 (81.25)/ 6 (18.75) | 42 (65.6)/ 22 (34.4) |
| FIB-4 index | 2.7 (1.6-4.6) | 2.8 (1.7-4.3) | 3 (1.7-4.8) | 2.3 (1.4-4.2) |
| HCV-RNA (LogIU/mL) | 6.2 (5.3-6.5) | 6.3 (5.5-6.6) | 6.15 (5.45-6.5) | 6.3 (5.4-6.7) |
| Hemoglobin (g/dL) | 13.8 (12-15) | 13.8 (13-14.9) | 14.4 (13-15.5) | 13.5 (12-14.7) |
| Platelet count (×10^12/μL) | 15.6 (11-20.8) | 15.1 (11.4-19.3) | 15.1 (10.7-18.8) | 17.2 (12-14.2) |
| AST (U/L) | 40 (26-66) | 38 (29-56) | 55 (28-69) | 30 (22-47) |
| ALT (U/L) | 42 (24-74) | 38 (24-72) | 60 (26-107) | 27 (17-60) |
| HbA1c (%) | 5.7 (5.4-6.4) | 5.9 (5.5-6.4) | 5.9 (5.4-6.4) | 5.7 (5.4-6.1) |
| AFP | 4.1 (2.6-7) | 3.6 (2.4-5.5) | 4.6 (2.1-8.9) | 3.5 (2.4-5.7) |

|                  | Tochigi | Utsunomiya/Kanuma | Oyama | p value |
|------------------|---------|-------------------|-------|---------|
| Age (years)      | 61 (49-68) | 64 (54-73) | 62 (55-68) | 0.018 |
| Male (%) / Female (%) | 66 (61.7)/ 41 (38.3) | 90 (59.2)/ 62 (40.8) | 68 (62.4)/ 41 (37.6) | 0.166 |
| History of HCC treatment +/- | 5 (4.7) / 102 (95.3) | 7 (4.6)/ 145 (95.4) | 10 (9.2)/ 99 (90.8) | 0.401 |
| IFN (naive/experienced) | 83 (77.6)/ 24 (24.2) | 129 (84.9)/ 23 (15.1) | 85 (78)/ 24 (22) | 0.633 |
| Genotype2a/2b | 36 (42.9) / 48 (57.1) | 69 (55.2)/ 56 (44.8) | 36 (42.9)/ 48 (57.1) | 0.048 |
| CH/LC | 92 (86)/ 15 (14) | 126 (82.9)/ 26 (17.1) | 78 (71.6)/ 31 (28.4) | 0.012 |
| FIB-4 index | 2 (1.2-4) | 2.8 (1.7-5.4) | 3.2 (1.9-4.9) | 0.029 |
| HCV-RNA (LogIU/mL) | 6.1 (5.2-6.5) | 6.1 (5.2-6.5) | 6.2 (5.4-6.5) | 0.765 |
| Hemoglobin (g/dL) | 14.6 (13.3-15.6) | 13.9 (13-14.9) | 13.8 (12.7-15) | 0.135 |
| Platelet count (×10^12/μL) | 18.5 (13.6-22.3) | 15.0 (10.3-20.4) | 13.9 (9.6-18.7) | 0.0005 |
| AST (U/L) | 39 (27-68) | 42 (26-73) | 45 (26-73) | 0.078 |
| ALT (U/L) | 47 (27-84) | 41 (24-87) | 46 (24-74) | 0.004 |
| HbA1c (%) | 5.6 (5.4-6.3) | 5.6 (5.3-6.1) | 5.9 (5.4-6.7) | 0.537 |
| AFP | 4 (3-7.5) | 5 (2.8-7.7) | 4 (2.8-9) | 0.208 |

Data are indicated median (interquartile) or number (%). p<0.05 is statistically significant between six districts. HCC: hepatocellular carcinoma, IFN: interferon, CH: chronic hepatitis, LC: liver cirrhosis, AST: aspartate aminotransferase, ALT: alanine aminotransferase, HbA1c: hemoglobin A1c, AFP: alpha fetoprotein

Author’s disclosure of potential Conflicts of Interest (COI).
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