

## A COMPARISON OF THE EFFICACY AND SAFETY OF TREATMENT WITH SIMEPREVIR AGAINST TELAPREVIR

Suguru Arata<sup>1)</sup>, Shigetoshi Ohshima<sup>1)</sup>, Takashi Goto<sup>1)</sup>, Kouichi Miura<sup>1)</sup>, Masafumi Komatsu<sup>2)</sup>, Kunio Nakane<sup>2)</sup>, Hitoshi Yagisawa<sup>3)</sup>, Hironobu Tawarayama<sup>4)</sup>, Kou Nakajima<sup>5)6)</sup>, Masato Funaoka<sup>7)</sup>, Takao Hoshino<sup>8)</sup>, Tomoyuki Kuramitsu<sup>9)</sup>, Yuukou Fujishima<sup>10)</sup>, Daisuke Watanabe<sup>11)</sup>, Takuma Ajimine<sup>12)</sup> and Hirohide Ohnishi<sup>1)</sup>

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<sup>1)</sup>*Department of Gastroenterology and Hepatology, Akita University Graduate School of Medicine*

<sup>2)</sup>*Department of Gastroenterology, Akita City Hospital*

<sup>3)</sup>*Department of Gastroenterology Akita Red Cross Hospital*

<sup>4)</sup>*Yabase Medical Clinic*

<sup>5)</sup>*Nakajima Doctor's Office*

<sup>6)</sup>*Department of Gastroenterology, Ohmagari Kousei Medical Center*

<sup>7)</sup>*Department of Gastroenterology, Yokote Municipal Hospital*

<sup>8)</sup>*Department of Gastroenterology, Akita Kousei Medical Center*

<sup>9)</sup>*Kuramitsu Clinic*

<sup>10)</sup>*Department of Gastroenterology, Noshiro Kousei Medical Center*

<sup>11)</sup>*Noshiro Yamamoto Medical Association Hospital*

<sup>12)</sup>*Department of Gastroenterology, Omori Municipal Hospital*

### Abstract

**AIM :** To compare the efficacy and safety of triple therapy with simeprevir (SMV) against triple therapy with telaprevir (TPV) while treating chronic hepatitis C (CHC).

**METHOD :** A total of 230 CHC patients were enrolled in the present study. One hundred forty-three patients were treated with TPV, and 87 patients were treated with SMV. Univariate analyses were performed to evaluate the pretreatment factors contributing to a sustained virological response at 24 weeks after the end of treatment (SVR24) and adverse events in the TPV and SMV groups.

**RESULT :** The SVR24 rates in the TPV and SMV groups were 81.1% and 76.8%, respectively. The difference was not statistically significant. In the TPV group, the rates of anemia, nausea and renal dysfunction were significantly higher than those in the SMV group.

**CONCLUSION :** In the present study, the SVR24 rates achieved by the two therapies did not differ to a statistically significant extent. However, the rates of some adverse events in the TPV group were significantly higher than those in the SMV group. SMV was associated with low risk and a high SVR24 rate in patients with HCV.

**Key words :** hepatitis C virus, interferon, ribavirin, telaprevir, simeprevir

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Corresponding Author : Shigetoshi Ohshima  
Department of Gastroenterology and Hepatology, Akita  
University Graduate School of Medicine, 1-1-1 Hondo,  
Akita 010-8543, Japan  
Tel : 81-18-884-6104  
Fax : 81-18-836-2611  
E-mail : arts1122@med.akita-u.ac.jp

## Introduction

Infection with hepatitis C virus (HCV) is a major cause of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). 1.5-2 million Japanese people are infected with HCV; most are infected with genotype 1b<sup>1)</sup>. Combination therapy with pegylated (Peg)-IFN/ribavirin (RBV) has been the standard treatment for patients with HCV genotype 1b<sup>2-4)</sup>. Recently NS3/4A protease inhibitors (PI), telaprevir (TPV), has been shown to improve the SVR rate in HCV patients when it is combined with Peg-IFN/RBV<sup>5-10)</sup>. However, TPV is associated with some adverse events, and a relatively rapid emergence of resistance in patients who do not achieve a SVR<sup>11)</sup>. Then, a second-generation PI, simeprevir (SMV), was approved for use in Japan. SMV is a HCV NS3/4A PI, with potent antiviral activity against HCV genotype 1b<sup>12)</sup>. The combination of SMV and Peg-IFN/RBV has demonstrated good tolerability and high SVR rates are achieved<sup>13)</sup>. Since then many therapies including IFN-free therapy<sup>14)</sup> have been approved for HCV. However, few studies have reported the efficacy of a newer PI, SMV, in Japan. In the present study, we compared the efficacy and safety of treatment with SMV against treatment with TPV. We hope that the information provided by the present study will help in selecting the most suitable treatment for patients with HCV.

## Materials and Methods

### Patients

The study population included 230 patients who were enrolled in the Akita hepatitis C study group (AHC) from 2011 to 2014. The AHC consists of Akita University, 6 affiliated hospitals and 3 clinics in Akita prefecture, Japan. In this multicenter retrospective study, 143 patients were assigned to the TPV group and were treated with a triple therapy that consisted of TPV, Peg-IFN $\alpha$ 2b and ribavirin, and 87 patients were assigned to the SMV group and were treated with a triple therapy that consisted of SMV, Peg-IFN $\alpha$ 2a or 2b/RBV. All of the patients were infected with HCV genotype 1, had an HCV RNA level of  $\geq 5.0$  log<sub>10</sub> IU/ml and were diagnosed with chronic hepatitis. The patients were 23-81 years of age (median age : 63

years) and 118 of the patients were male. Patients with chronic hepatitis B, autoimmune hepatitis, primary biliary cirrhosis, and metabolic liver disease (such as hemochromatosis or Wilson's disease) were excluded from this study.

All of the patients gave informed consent to participate in this study, which was performed in accordance with the principles of the Declaration of Helsinki. This study was approved by the Ethics Committee of Akita University. The data of 143 patients in the TPV group and 87 patients in the SMV group were available for an analysis.

### Study design

One hundred forty-three patients (median age : 62 years ; male,  $n=76$ ) received treatment with a triple therapy containing TPV (TELAVIC<sup>®</sup> ; Mitsubishi Tanabe Pharma, Osaka, Japan) (2,250 mg or 1,500 mg per day) ; Peg-IFN $\alpha$ 2b (Peg-Intron<sup>®</sup> ; MSD, Tokyo, Japan) (1.5  $\mu$ g/kg per week, s.c.) ; and RBV (Rebetol<sup>®</sup> ; MSD, Tokyo, Japan) (bodyweight :  $\leq 60$  kg [600 mg/day] ; body weight : 61-80 kg [800 mg/day] ; body weight :  $>80$  kg [1,000 mg/day]). The patients were treated with TPV and Peg-IFN $\alpha$ 2b/RBV for 12 weeks, followed by Peg-IFN $\alpha$ 2a/RBV for 12 weeks. In the present study, the initial amount of TPV and the decrease in the dose of each drug were determined by the treating physician. Eighty-seven patients (median age : 64 years ; male,  $n=42$ ) received treatment with a triple therapy that contained SMV (Sovriad<sup>®</sup> ; Janssen Pharmaceutical K.K., Tokyo, Japan) (100 mg per day), Peg-IFN $\alpha$ 2a (Pegasys<sup>®</sup> ; Chugai Pharmaceutical Co, LTD., Tokyo, Japan) or Peg-IFN $\alpha$ 2b (Peg-Intron<sup>®</sup> ; MSD, Tokyo, Japan) (1.5  $\mu$ g/kg per week, s.c.) and RBV (for Peg-IFN $\alpha$ 2a : Copegus<sup>®</sup> ; Chugai Pharmaceutical Co, LTD, Tokyo, Japan ; for Peg-IFN $\alpha$ 2b : Rebetol<sup>®</sup> ; MSD, Tokyo, Japan) (bodyweight :  $\leq 60$  kg [600 mg/day] ; body weight : 61-80 kg [800 mg/day] ; body weight :  $>80$  kg [1,000 mg/day]). The choice of IFN also depended on the treating physician. The patients were treated with SMV, Peg-IFN/RBV for 12 weeks, followed by Peg-IFN/RBV for 12 weeks. We followed all of the patients after the end of treatment for 24 weeks and measured their plasma levels of HCV RNA to assess the endpoints of both treatments ; these included : undetectable plasma at week 4 (rapid vi-

rological response [RVR], week 12 (early virological response [EVR]), at the end of treatment (EOTR), at 12 weeks after the end of treatment (SVR12), and at 24 weeks after the end of treatment (SVR24).

### Study assessments

The screening assessments included serum HCV RNA levels, IL28B, genotyping, standard laboratory and clinical tests, vital signs and physical examinations. We measured the aspartate aminotransferase (IU/l) to platelet count ( $\times 10^4/\mu\text{l}$ ) ratio index (APRI) to assess liver fibrosis. Serum HCV RNA was measured with a COBAS Taqman HCV assay (Roche Molecular Diagnostics, Tokyo, Japan). The HCV genotype and subtype, interleukin 28B (IL28B); gene region (rs8099917) were determined according to the instructions of the manufacturer using a previously described method<sup>15,16</sup>.

Regarding adherence to TPV, the continuous use of 2,250 mg per day for 12 weeks was regarded as 100% adherence. Adherence to RBV was regarded as 100% if the patient received the prescribed amount (prescribed according to body weight) each day for 24 weeks. Adherence to IFN was regarded as 100%, if IFN (1.5  $\mu\text{g}/\text{kg}$  per week) was continuously administered for 24 weeks. Adverse events (anemia, rash, renal dysfunction) were graded according to the WHO toxicity grades. Subjective symptoms were observed during an interview which was conducted by the treating physician.

### Statistical analysis

The baseline continuous data are expressed as the median (interquartile ranges), and categorical variables were expressed as frequencies or percentages. The chi-squared test and the independent *t*-test were used for the univariate analyses as appropriate.

## Results

### Baseline characteristics

The characteristics of the patients in the TPV ( $n=143$ ) and SMV groups ( $n=87$ ) are shown in Table 1. SMV group was significantly older than TPV group. Non-TT alleles were significantly more frequently observed in the SMV group than in the TPV group. APRI in the SMV group was significantly higher than that in the TPV

group. There were no differences in the level of viremia, leukocyte count, hemoglobin level, platelet count, or the number of patients who did not respond to a previous treatment or naïve.

### The response to therapy and the reduction in the HCV RNA level

In the TPV group, the overall rate of the SVR24 was 81.1%, and the rates of RVR, EVR, EOTR and SVR12 were 80.9%, 93.0%, 90.2%, and 84.6%, respectively. In the SMV group, the SVR24 rate was 76.8%, and the rates of RVR, EVR, EOTR and SVR12 were 71.2%, 93.1%, 88.5%, and 77.0%, respectively. There was no significant difference in the response of the patients in the TPV and SMV groups to therapy (Fig. 1).

### Adherence to each of the medicines

The rate of adherence to SMV (99.6%) was significantly higher than that to TPV (66.8%). The rate of adherence to IFN in the TPV group (90.3%) was significantly higher than that in the SMV group (84.5%). There was no significant difference in the rate of RBV adherence in the two groups (Fig. 2). There were no significant differences in the rates of adherence to PI, IFN and RBV between the patients who achieved a SVR24 and the patients who did not. This result was the same in both of the groups (data not shown).

### The pretreatment factors contributing to the SVR24 in the TPV and SMV groups

Univariate analyses were performed to evaluate the pretreatment factors in the TPV and SMV groups. The following variables were included in the univariate analyses: the IL28B (rs8099917) allele type, prior treatment response, age and APRI. In the both groups, the SVR24 rate of the patients with a TT IL28B allele was significantly higher than that with a non-TT allele (Fig. 3A). The SVR24 rate of the patients with no response to a prior treatment was significantly lower than that of the patients who showed a response to a previous treatment or naïve (Fig. 3B). The SVR24 rate in the TPV group was relatively higher among the older patients (age:  $\geq 65$  years) than among the younger patients (age:  $< 65$  years). This tendency was not ob-

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Table 1. The baseline characteristics of the patients who received triple therapy with protease inhibitors, pegylated interferon and ribavirin

	Telaprevir	Simeprevir	<i>P</i> value
No. of patients	143	87	
Age (yr)	62 (55.7-67)	64 (57.5-69)	<i>P</i> <0.05
Gender (male/female)	76/67	42/45	NS
Laboratory data			
Level of viremia	6.7 (6.2-7.0)	6.5 (5.9-6.9)	NS
Leukocyte count (/mm <sup>3</sup> )	4,585 (3,780-5,850)	4,600 (3,860-5,645)	NS
Hemoglobin (g/dL)	14.0 (13.0-14.9)	14.0 (12.8-14.9)	NS
Platelet count (×10 <sup>4</sup> /mm <sup>3</sup> )	16.0 (13.0-18.5)	15.5 (12.0-19.1)	NS
SNP of IL28B (TT/non-TT/unknown)	77/45/21	35/38/14	<i>P</i> <0.05
Prior treatment response (naïve or relapse/null/other) APRI	95/44/4	55/23/9	NS
APRI	0.7197 (0.4937-1.0936)	1.0468 (0.5859-2.1531)	<i>P</i> <0.01

The data are presented as numbers or medians with interquartile ranges. The *P* values were calculated using the  $\chi^2$  test or the independent *t*-test for continuous variables.

SNP, single-nucleotide polymorphism ; IL28B, Interleukin 28B ; NS, not significant.

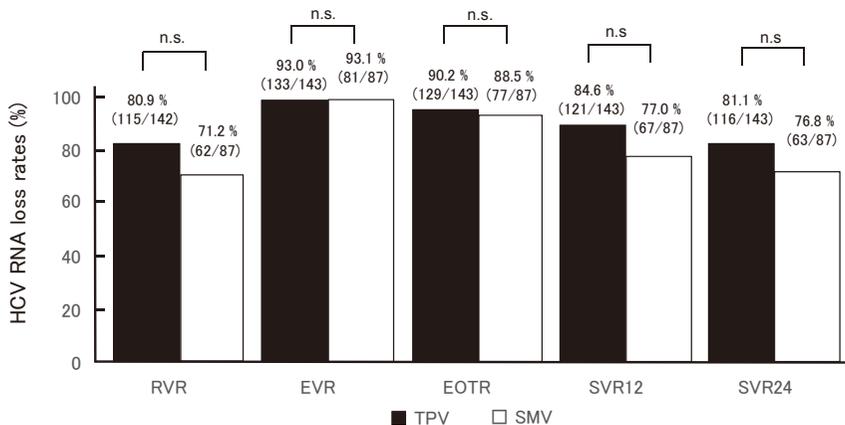


Fig. 1. The virological response rates according to the serum hepatitis C virus RNA levels in patients who received triple therapy with protease inhibitors, pegylated interferon and ribavirin

Percentages represent the proportion of patients with undetectable serum hepatitis C virus RNA levels. The numbers of the patients are shown in parentheses. *P* values were calculated using the  $\chi^2$  test. NS, not significant. Black bar : TPV group. White bar : SMV group.

served in the SMV group (Fig. 3C). Regarding APRI, there was no significant difference in the SVR24 rate of low-APRI and that of high-APRI patients in either of the groups (cut-off value : 1.50<sup>17</sup>) (Fig. 3D).

### Safety

Treatment was discontinued by 8 patients (5.5%) in the TPV group and 5 patients (5.7%) in the SMV group. There was no significant difference in the rate of treatment discontinuation. The reasons for treatment dis-

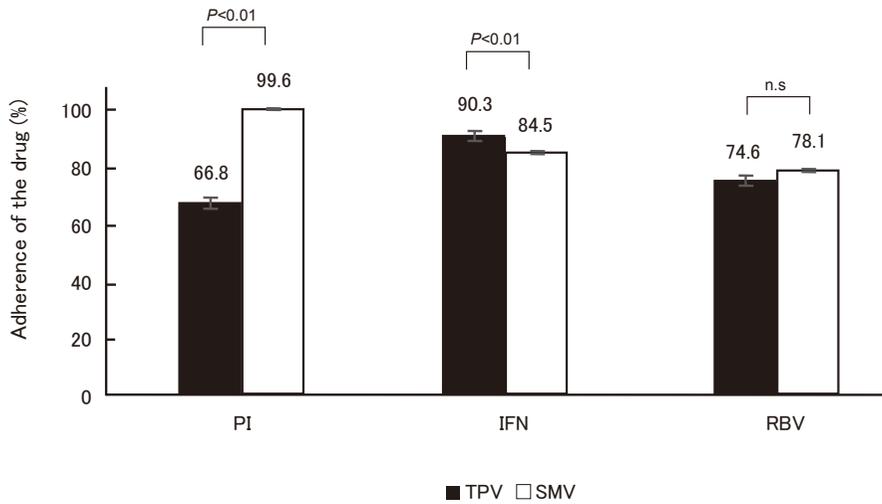


Fig. 2. Adherence to each of medicines in the TPV and SMV groups

The rate of adherence in each drug are shown in the both groups. The *P* values were calculated using the independent *t*-test. Black bar : TPV group. White bar : SMV group.

continuation in the TPV group were rash ( $n=2$ ), nausea ( $n=1$ ), anorexia ( $n=1$ ), icterus ( $n=1$ ), non-response (HCV RNA decrease  $<2$ -log during treatment) ( $n=1$ ), and unknown ( $n=1$ ). The reasons for treatment discontinuation in the SMV group were rash ( $n=1$ ), anorexia ( $n=1$ ), anemia ( $n=1$ ), and the appearance of HCC ( $n=1$ ) (data not shown). Anemia, rash, nausea and renal dysfunction were the most common adverse events in the TPV and SMV groups. We therefore compared the frequency of these events in the two groups (Fig. 4). The rate of anemia in the TPV group (74.1%) was significantly higher than that in the SMV group (58.6%). The rate of rash in the TPV group (46.1%) did not differ to a statistically significant extent from that in the SMV group (42.5%). The rate of nausea in the TPV group (37.7%) was significantly higher than that in the SMV group (16.0%). The rate of renal dysfunction in the TPV group (30.0%) was significantly higher than that in the SMV group (16.0%). We also compared the grade of the adverse events in the two groups (Fig. 5). The rate of grade 1 rash in the SMV group was significantly higher than that in the TPV group. The rate grade 3 and 4 anemia in the TPV group (19.8%) was significantly higher than that in the SMV group (8.1%). There was no sig-

nificant difference in the grade of renal dysfunction in the two groups.

## Discussion

In the present study we compared the efficacy and safety of the combination therapy of SMV with Peg-IFN/RBV against the TPV therapy with Peg-IFN/RBV. The present study was retrospective in nature. TPV therapy was approved two years before SMV. Because severe rash was reported in the clinical trial of TPV<sup>11)</sup>, patients with unfavorable characteristics might consider foregoing TPV therapy in favor of a safe future therapy. For this reason, patients with characteristics that were unfavorable for IFN-based therapy were more commonly observed in the SMV group than in the TPV (Table 1).

Until recently, the SVR24 rate for PEG-IFN/RBV has typically been 40-50%<sup>2-4)</sup>. In this context, both TPV and SMV therapy achieved a high SVR24 rate (Fig. 1). In our comparison of the adherence to the each medicine, the SMV group showed significantly better adherence to PI treatment, while the TPV group showed better adherence to IFN treatment. In the SMV group, the frequency of adverse events such as anemia, nausea and renal

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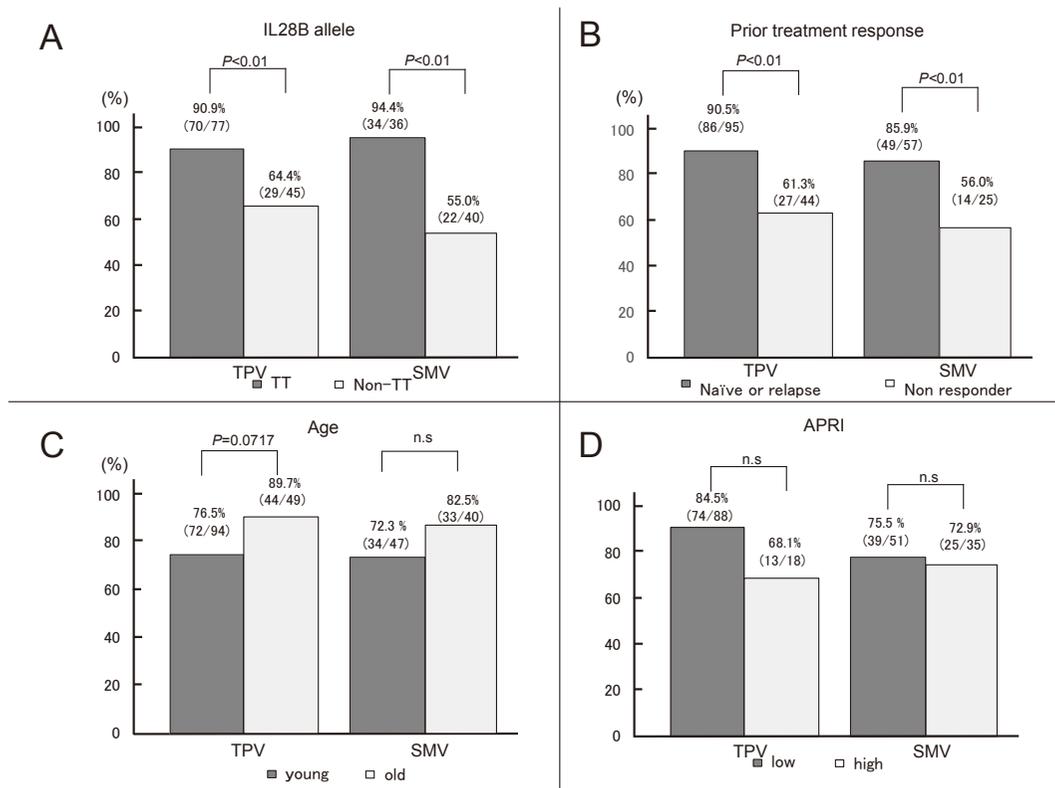


Fig. 3. The pretreatment factors contributing to a SVR24 in the TPV and SMV groups. The percentages represent the proportion of patients with a SVR24. The numbers of patients are shown in parentheses.  $P$  values were calculated using the  $\chi^2$  test. IL28B, Interleukin 28B. NS, not significant. A. Thick gray bar : TT group. Thin gray bar : non TT group. B. thick gray bar : naïve or relapse group. Thin gray bar : non-responder group. C. Thick gray bar : young group (age <65). Thin gray bar : old group (age  $\geq$ 65). D. Thick gray bar : low APRI group. Thin gray bar : high APRI group. Average of APRI : 1.304.

dysfunction was low. Almost all of the patients in the SMV group could complete the treatment without a reduction in the dose of SMV. In contrast, it was necessary to reduce the dose of TPV in a large number of cases due to adverse events. Furthermore, in the TPV group, the initial dose of TPV was 1,500 mg/day for older patients and patients who were deemed to be at high risk of adverse events. These would be reasons for the higher PI adherence in the SMV group. With regard to the IFN adherence in the SMV group, more patients had progressive liver fibrosis. This meant that the IFN dose had to be reduced in large number of patients in order for them to continue to receive SMV therapy. However there was no significant difference in PI, IFN or RBV adher-

ence in the patients of the TPV and SMV groups who achieved a SVR24 (data not shown). When the factors contributing to a SVR24 are considered, the SVR24 rate of the TT IL28B allele patients was significantly higher than that of the non-TT allele patients (Fig. 3A). Furthermore, the SVR24 rate among the patients who did not respond to a previous treatment was significantly lower than that of the treatment responders and naïve (Fig. 3B). These two factors seemed to contribute to the SVR24 rate in the both groups. Interestingly our present results show that the SVR24 rate of the older patients in the TPV group was significantly higher than of the younger patients. We could not elucidate the reason for this difference ; however, in older patients, many pa-

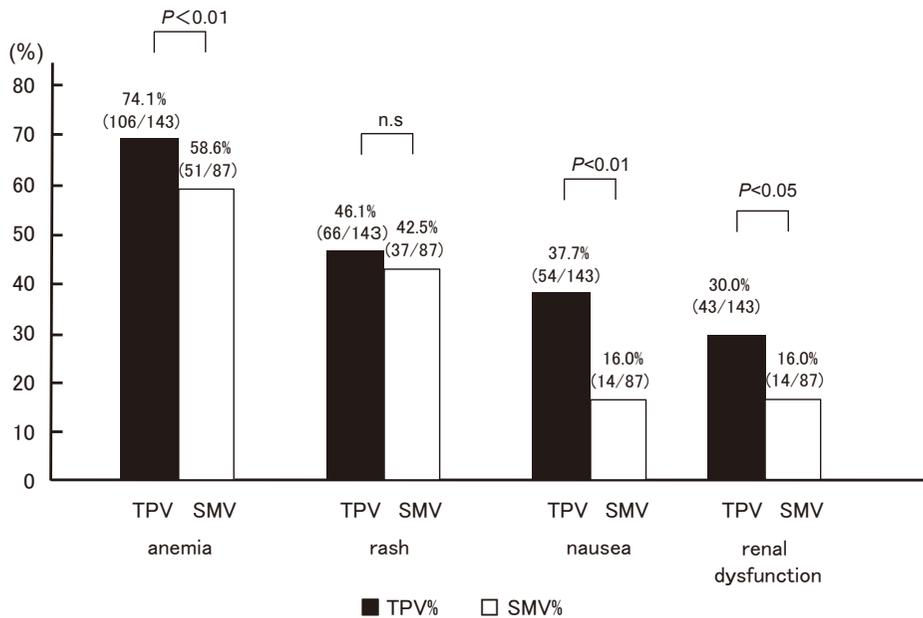


Fig. 4. The rates of adverse events and laboratory abnormalities in the TPV and SMV groups. The percentages represent the proportion of patients with adverse events and laboratory abnormalities in the both groups. The numbers of patients are shown in parentheses. The  $P$  values were calculated using the  $\chi^2$  test. NS, not significant. Black bar : TPV group. White bar : SMV group.

tients started TPV at the dose of 1,500 mg/day or when adverse events appear, reduce the dose of TPV without hesitation to continue the therapy. However there was no significant difference in the TPV adherence of the patients who achieved a SVR24 and that of the patients who did not. Thus, when TPV is used in the future, we may select 1,500 mg/day as the initial dose.

With regard to safety, the incidence of adverse events that are commonly seen in both TPV and SMV therapy (anemia, skin rash, nausea and renal dysfunction) were investigated. The frequency of these adverse events was significantly higher in the TPV group. Although there was no significant difference between two groups in total frequency of skin rash, the rate of grade 1 rash was significantly higher in the SMV group. In previous studies on IFN/RBV therapy, the incidence of anemia, nausea and rash was reported to be 54%<sup>4)</sup>, 35-43%<sup>3)</sup>, and 20-24%<sup>3)</sup>, respectively. The frequency of anemia in SMV therapy was thought to be the same level as that in IFN/RBV therapy (Fig. 4). SMV therapy is thought to be a safer treatment.

The rate of patients with a non-TT IL28B allele in the SMV group was significantly higher than that in the TPV group (Table 1); furthermore in the both groups, the SVR24 rate among the patients with a TT IL28B allele was significantly higher than that with a non-TT IL28B allele (Fig. 3A). However, there was no significant difference in the SVR24 rates of the both groups (Fig. 1). If the present study was a randomized control study, the SVR24 rate in the SMV group might be higher than that in the TPV group. From the viewpoint of the incidence of adverse events, SMV treatment was safer than TPV treatment. In conclusion, SMV is a lower risk treatment that achieved a high SVR24 rate in patients with HCV. In the present study, we investigated the efficacy and safety of TPV and SMV therapy. During the last few years, HCV treatment has progressed rapidly. It seems to be TPV and SMV therapy represent the dawn of a new era. Since their introduction, new IFN-free therapies have been continuously developed. It is therefore necessary for us to understand the properties of each therapy, and to select the best therapy for each

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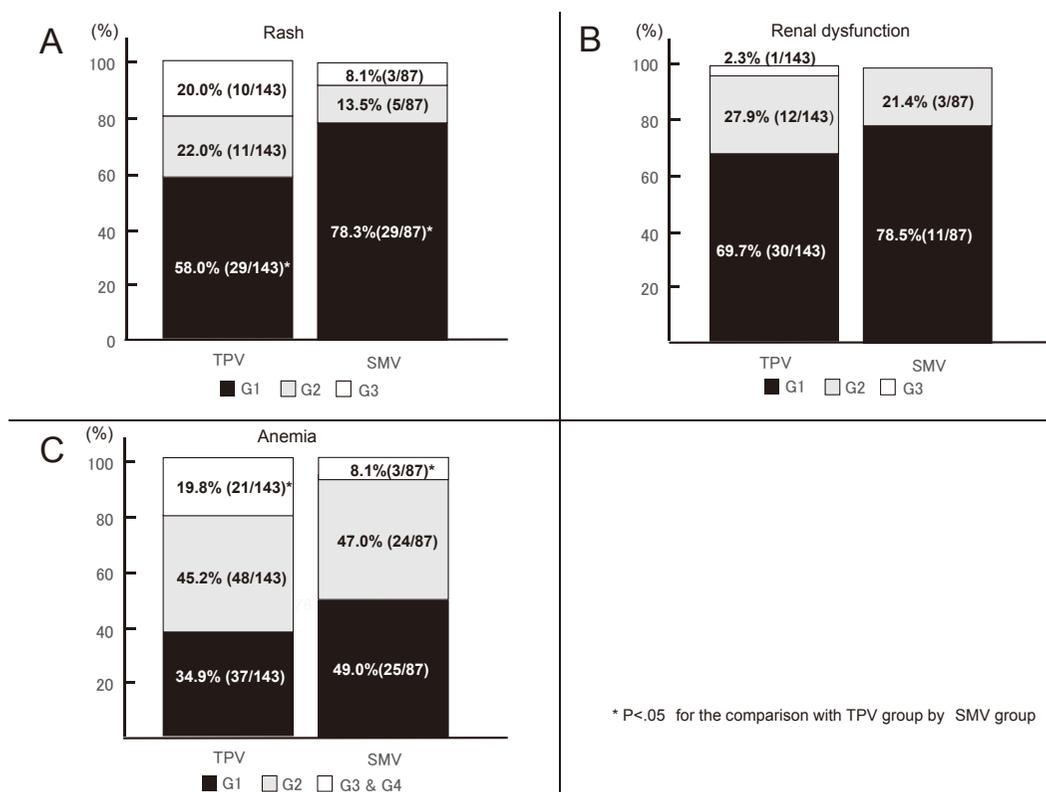


Fig. 5. The grade of each adverse event and laboratory abnormality in the SMV and TPV groups. The percentages represent the proportion of patients with each grade of rash (A), renal dysfunction (B), and anemia (C) in the both groups. Numbers of the patients are shown in parentheses. The  $P$  values were calculated using the  $\chi^2$  test. NS, not significant. Black bar : grade 1. Gray bar : grade 2. White bar : grade 3 and grade 4.

patient ; this is referred to as tailor-made treatment. Although there are great expectations for IFN-free therapies because of their high efficacy and low risk of adverse events, we have to pay attention to the problems of drug resistance and cost-effectiveness. IFN-based TPV or SMV combination therapy should still be considered in patients with drug resistance and in patients TT allele in IL28B.

### Conflicts of Interest

The authors declare no conflicts of interest.

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