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*Original Article*

# Effectiveness of Extending Treatment Duration in Therapy with Pegylated Interferon and Ribavirin for Genotype 2 Hepatitis C Virus Infection

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**The effectiveness of extending treatment duration as response guided therapy was previously reported for chronic hepatitis C (CHC) genotype 1, but is still controversial for genotype 2. The present study is a retrospective cohort study to investigate the effectiveness of extending treatment duration in therapy with pegylated interferon and ribavirin for patients with CHC genotype 2 by focusing on the timing at which patients obtained undetectable HCV RNA. A total of 306 patients who obtained undetectable HCV RNA by week 24 of treatment and completed 24 weeks of treatment were enrolled. Rapid virological response (RVR) to standard therapy was achieved by 122 patients (51%), and 89% of them obtained sustained virological response (SVR), while 69% of non-RVR patients achieved SVR. Non-RVR patients with undetectable HCV RNA at week 8, and insufficient adherence < 80% pegylated interferon and ribavirin during the first 24 weeks, significantly improved their SVR rate by extended therapy. Among patients receiving extended therapy, drug adherences did not differ between SVR and non-SVR patients, indicating that extending treatment duration might compensate for insufficient antiviral effects due to insufficient drug adherences. This finding might be useful in creating a guideline for extending treatment duration for patients with CHC genotype 2.**

**Key words:** hepatitis C virus, interferon, genotype 2, response-guided therapy

Hepatitis C virus (HCV) infection is the predominant cause of liver cirrhosis and hepatocellular carcinoma (HCC) in many countries, including Japan, the United States, and European countries [1, 2]. Once HCV infection becomes chronic, it is rarely resolved without antiviral treatment. Occasionally, chronic hepatitis C (CHC) progresses to liver cirrhosis and HCC after as long a period as 30 years without any disease-related symptoms.

Despite foreseeable approval of interferon (IFN)-free regimens for patients with CHC genotype 2 in

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Japan [3], the combination of pegylated interferon (PegIFN) and ribavirin (RBV) will likely remain the treatment of choice in patients who cannot obtain sustained virological response (SVR) to antiviral treatment with IFN-free regimens.

IFN therapy is effective at eliminating the virus and reducing the risk of HCC developing in CHC patients [4]. The standard treatment duration for treatment with PegIFN and RBV in patients with CHC genotype 2 is 24 weeks. Recent advances in antiviral therapy for patients with CHC genotype 1 revealed the effectiveness of extending treatment duration in slow virological responders [5–8], and similar improvement is supposed in anti-HCV therapy for patients with CHC genotype 2; however, the indications for extending treatment duration are still unresolved [9–12].

The present study retrospectively studied the factors associated with virological response during standard antiviral therapy with PegIFN and RBV in patients with CHC genotype 2, and assessed the additional benefit of extending treatment duration, in order to develop a guideline for extending treatment duration.

## Methods

***Patients.*** The present study enrolled consecutive patients with CHC genotype 2, who had undergone combination therapy with PegIFN and RBV at the Okayama University Hospital or its affiliated hospitals between 2005 and 2011, and who obtained undetectable HCV RNA by week 24 of treatment and completed 24 weeks of treatment. Patients co-infected with hepatitis B virus or human immunodeficiency virus and patients with complicating autoimmune liver diseases were excluded from the study. HCC was ruled out by means of dynamic computed tomography or magnetic resonance imaging before the therapy. The study was performed in accordance with the Helsinki declaration, and all the protocols were approved by the ethics committees of the institutes. All patients provided informed consent before enrolling in the study. The study was registered for university hospital medical information network-clinical trials registry (UMIN 000001031).

***Virological response.*** All patients had HCV RNA > 5 log IU/mL in their sera, as confirmed by the TaqMan HCV assay (Roche Molecular Diagnostics, Tokyo, Japan) or the COBAS AMPLICOR HCV test Ver. 2 (Roche Molecular Diagnostics). Their viral statuses were monitored during the treatment by the TaqMan HCV assay or the qualitative COBAS AMPLICOR HCV test Ver. 2. Rapid virological response (RVR) was defined as undetectable HCV RNA in the serum at week 4 of treatment according to the guidelines for the management of hepatitis C virus infection from Japan Society of Hepatology [13]. A virological response with detectable HCV RNA at week 4 of treatment and undetectable HCV RNA at week 8 of treatment was defined as non-RVR-A. Slow virological response with detectable HCV RNA at week 8 of treatment and undetectable HCV RNA at the end of treatment was defined as non-RVR-B. Sustained virological response (SVR) was defined as undetectable HCV RNA in the serum 24 weeks after the completion of treatment [13].

***IFN therapy.*** The patients received a combination of PegIFN-alpha 2b (1.5 $\mu$g/kg of body weight) by subcutaneous injection every week with RBV (600–1,000 mg daily, according to body weight). The doses of PegIFN and RBV were individually reduced during the treatment whenever needed to lessen adverse effects, and these dose reductions were performed according to the labeling. As the so-called extended therapy, the treatment duration was extended from 24 weeks to 28–48 weeks in some of those patients who had undergone IFN therapy previously, or treatment-naïve patients without RVR.

***Statistical analysis.*** Data are expressed as means ± standard deviations. The rates of patients attaining SVR were compared between groups with the Chi-square test or the Fisher exact probability test. Factors or patient characteristics associated with virological responses were analyzed by logistic regression, and significant factors in univariate analysis were selected in a stepwise manner for the multivariate analysis. A cut-off value was defined *a priori* for each parameter: the lower limit of the normal range for white blood cells, hemoglobin, platelet count, and creatinine, and the upper limit of the normal range for alanine aminotransferase and $\gamma$-glutamyl transpeptidase. The Wilcoxon rank sum test was used to compare drug adherence between SVR and non-SVR patients. $P$ values $< 0.05$ were considered significant. The statistical analyses were performed using JMP software Ver. 11 (SAS Institute, Cary, NC, USA).

## Results

***Characteristics of patients enrolled in the study.*** Details of patient disposition and flow through the study are shown in Fig. 1. Of the 306 patients enrolled in the study, 140 patients obtained RVR, while 166 patients did not. Among those with non-RVR, serum HCV RNA became undetectable by week 8 of treatment in 115 patients (non-RVR-A group), and 51 patients showed undetectable HCV RNA sometime between weeks 8 and 24 (non-RVR-B group).

The characteristics of patients enrolled in the study are shown in Table 1. The mean age was 54 years, and 151 patients (49%) were female. A total of 239 patients received the standard 24–week therapy, while 67 patients, including 21 IFN-naïve patients, were treated with the extended therapy. Elderly

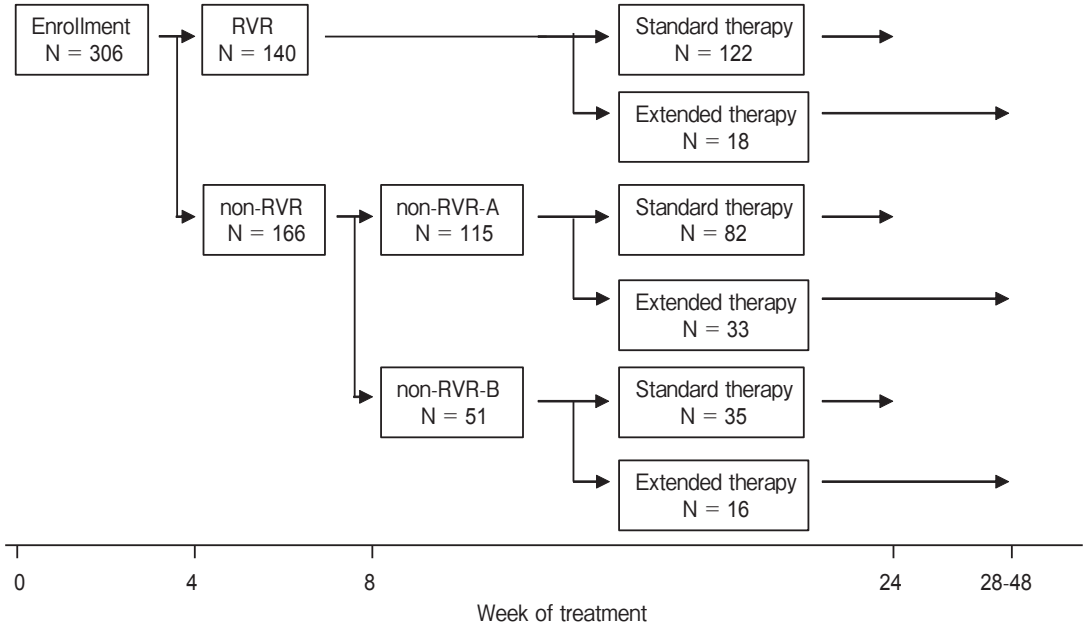


**Fig. 1** Patient treatment flow diagram. The treatment duration was extended in IFN-experienced patients or treatment-naïve patients without RVR.

**Table 1** Patient characteristics

| Factors | All (n = 306) | Standard (n = 239) | Extended (n = 67) | *P* |
|---|---|---|---|---|
| Gender (male/female) | 155/151 | 131/108 | 24/43 | 0.0060 |
| Age (years) | 54 ± 13 | 53 ± 13 | 58 ± 12 | 0.0029 |
| Body weight (kg) | 62 ± 11 | 62 ± 11 | 60 ± 12 | 0.18 |
| Previous interferon (yes/no) | 125/181 | 79/160 | 46/21 | < 0.0001 |
| ALT (IU/L) | 79 ± 83 | 82 ± 88 | 69 ± 58 | 0.71 |
| γGT (IU/L) | 63 ± 88 | 67 ± 96 | 50 ± 47 | 0.48 |
| White blood cell count (/μL) | 5,184 ± 1,516 | 5,269 ± 1,459 | 4,881 ± 1,680 | 0.024 |
| Hemoglobin (g/dL) | 14 ± 1.6 | 14 ± 1.6 | 14 ± 1.4 | 0.016 |
| Platelet count (10,000/μL) | 18 ± 5.7 | 18 ± 5.4 | 17 ± 6.6 | 0.0016 |
| Creatinine (IU/L) | 0.72 ± 0.15 | 0.72 ± 0.14 | 0.71 ± 0.18 | 0.55 |
| Therapeutic outcomes (SVR/Relapse) | 239/67 | 190/49 | 49/18 | 0.27 |

ALT, alanine aminotransferase; γGT, γ-glutamyl transpeptidase; SVR, sustained virological response.

female patients with previous IFN therapy received the extended therapy rather than the standard therapy, and showed lower counts of white blood cells and platelet and lower hemoglobin levels, reflecting more advanced liver diseases than those receiving the standard therapy. Among the 239 patients receiving the standard therapy, 190 patients (79%) achieved SVR, and 49 patients suffered relapses, while 49 patients (73%) achieved SVR with extended therapy, which did not show significant statistical difference ($p = 0.27$, the Chi-square test).

Stepwise logistic regression analysis was done for all 306 patients enrolled in the study, to clarify the pre-treatment patient characteristics that were associated with virological response. Advanced age was significantly associated with detectable HCV RNA at week 4 of treatment ($p = 0.0051$, Table 2), but no significant factors associated with detectable HCV RNA at week 8 of treatment were found (Table 3). These results indicated that the patients of advanced age have slow virological response during the treatment, and may obtain therapeutic benefits by receiving extended therapy.

***Comparison of virological response between standard and extended therapy.*** We supposed that extending the treatment duration might improve therapeutic outcomes for slow virological responders, according to the theory of response-guided therapy, and assessed the associations of virological response during treatment with SVR. In comparison of SVR rates by virological response during treatment, shown in Fig. 2A, 122 patients (51%) achieved RVR, and of

**Table 2** Logistic regression analysis of the factors associated with detectable HCV RNA at week 4 of treatment

| | Univariate | | Multivariate | |
|---|---|---|---|---|
| Factors | Odds (range†) | *p* | Odds (range†) | *p* |
| Gender (male = 1) | 0.76 (0.49–1.2) | 0.24 | | |
| Age (years) | 1.02 (1.0078–1.1) | 0.0051 | 1.02 (1.0078–1.1) | 0.0051 |
| Body weight (kg) | 0.98 (0.99–1.03) | 0.14 | | |
| Previous Interferon (yes = 1) | 1.4 (0.88–2.2) | 0.15 | | |
| ALT (1: > 42 IU/L) | 1.5 (0.89–2.2) | 0.15 | | |
| γGT (1: > 40 IU/L) | 1.1 (0.64–1.6) | 0.91 | | |
| White blood cell count (1: > 3,500/μL) | 0.57 (0.26–1.2) | 0.14 | | |
| Hemoglobin (1: > 13.5 g/dL) | 0.60 (0.37–0.94) | 0.027 | | |
| Platelet count (1: > 150,000/μL) | 0.69 (0.42–1.1) | 0.13 | | |
| Creatinine (1: > 0.80 IU/L) | 1.3 (0.78–2.2) | 0.29 | | |

†95% confidence interval; ALT, alanine aminotransferase; γGT, γ-glutamyl transpeptidase.

**Table 3** Logistic regression analysis of the factors associated with detectable HCV RNA at week 8 of treatment

| | Univariate | |
|---|---|---|
| Factors | Odds (range†) | *p* |
| Gender (male = 1) | 0.92 (0.50–1.7) | 0.80 |
| Age (years) | 1.1 (0.99–1.1) | 0.12 |
| Body weight (kg) | 0.99 (0.96–1.1) | 0.38 |
| Previous Interferon (yes = 1) | 1.2 (0.66–2.3) | 0.50 |
| ALT (1: > 42 IU/L) | 1.3 (0.72–2.4) | 0.37 |
| γGT (1: > 40 IU/L) | 1.1 (0.57–1.9) | 0.88 |
| White blood cell count (1: > 3,500/μL) | 0.89 (0.37–2.5) | 0.82 |
| Hemoglobin (1: > 13.5 g/dL) | 0.96 (0.53–1.8) | 0.89 |
| Platelet count (1: > 150,000/μL) | 0.77 (0.42–1.5) | 0.43 |
| Creatinine (1: > 0.80 IU/L) | 1.5 (0.76–3.3) | 0.24 |

†95% confidence interval; ALT, alanine aminotransferase; γGT, γ-glutamyl transpeptidase.

these, 109 (89%) were identified as achieving SVR. The rates of SVR in the 2 types of non-RVR patients were 77% (63/82) for non-RVR-A, and 51% (18/35) for non-RVR-B. The rates of SVR patients with the standard therapy were significantly higher in the patients with RVR than in the patients with non-RVR-A and non-RVR-B ($p = 0.016$, and $p < 0.0001$, respectively, the Chi-square test). A significant difference in the SVR rate was also shown between patients with non-RVR-A and non-RVR-B ($p = 0.0064$). On the other hand, by extending the treatment duration, the patients with non-RVR-A obtained a similar SVR rate to those with RVR ($p = 1.0$). The extended-treatment patients with RVR or non-RVR-A still showed significantly higher SVR rates than those with non-RVR-B ($p = 0.016$, and 0.010, respectively).

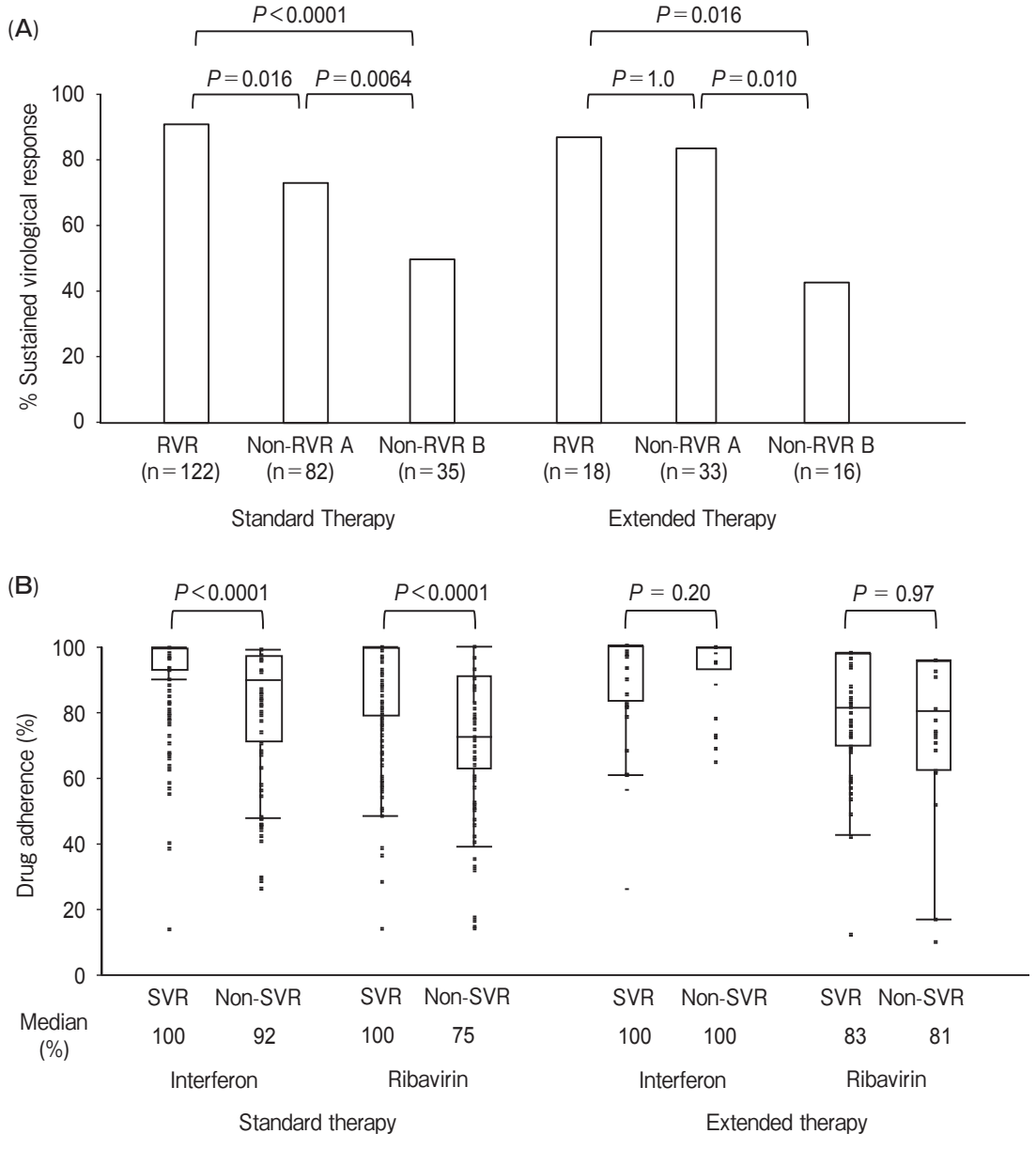


Fig. 2 Associations of virological response and drug adherence with SVR. A shows the rates of SVR with standard therapy and extended therapy for patient groups classified by different virological responses during treatment. B expresses the quintiles and medians of drug adherence to PegIFN and RBV regimens from 0 to 24 weeks of treatment in the standard and the extended therapy.

***Analysis of drug adherence to PegIFN and RBV during the treatment with SVR.*** As for drug adherence to PegIFN and RBV during the 24-week treatment, most patients with low PegIFN adherence started the treatment with reduced PegIFN doses due to low platelet counts. Dose reduction of PegIFN was rarely observed during the treatment. On the other hand, patients with low RBV adherence showed dose reduction of RBV during the treatment because of progressive anemia. As shown in Fig. 2B, drug adherences to PegIFN and RBV during the treatment with the standard therapy were significantly higher in the patients achieving SVR than those resulting in non-SVR ($p < 0.0001$, and $p < 0.0001$, respectively, Wilcoxon rank sum test). Interestingly, among the extended-therapy patients, drug adherences to PegIFN and RBV did not differ between the SVR and non-SVR patients.

***Analysis of the effectiveness of extending treatment duration.*** The effectiveness of extending treatment duration was assessed by comparing the SVR rates between standard-therapy and extended-therapy patients for each virological response group RVR, non-RVR-A, and non-RVR-B. As shown in Fig. 3, there was no significant improvement in the SVR rate for any virological response group by extending treatment duration (Fig. 3). Further subgroup analyses were done for the patients classified by virological response and drug adherence. Among the patients with non-RVR-A and with insufficient adherences of $< 80\%$ to PegIFN and RBV, the patients treated with the extended therapy obtained significantly higher SVR rates than the patients receiving the standard therapy ($p = 0.038$, and $p = 0.023$, respectively, the Chi-square test). Such improvements were not observed among patients with RVR or non-RVR-B virological responses.

***Analysis of the effectiveness of extending treatment duration for patients with experience of antiviral therapy.*** Among 125 patients with prior experience of antiviral therapy, 64 patients had prior therapy with interferon or PegIFN, and the other 61 had specific experience of the combination of PegIFN and RBV (Table 4). Re-treatment with extended therapy showed 73% SVR rates, which was comparable to the SVR rate with re-treatment of the standard therapy (74%). Even when limited to the 64 patients previously treated with the combination of PegIFN and RBV, the SVR rates with the standard and extended therapy were similar, and there was not statistically significant difference ($p = 1.0$, the Chi-square test).

## Discussion

The present study is a retrospective cohort study to investigate the effectiveness of extending treatment duration for patients with CHC genotype 2, and to clarify the factors associated with virological response during antiviral therapy. The present study showed that patients with detectable HCV RNA at week 4 of treatment, undetectable HCV RNA at week 8 of treatment, and insufficient drug adherence to PegIFN and RBV during treatment may improve therapeutic outcomes by extending treatment duration. This assessment might be useful as a guideline for extending treatment duration.

Approximately half of the patients in the standard 24-week therapy with PegIFN and RBV did not achieve RVR, and only 69% of these obtained SVR, while 89% of the RVR patients achieved SVR, which is consistent with findings of previous studies [9–12]. The results in the present study showed no improvement of the SVR rate by extending treatment duration for RVR patients.

It has been unclear whether non-RVR patients may benefit from extending treatment duration [10]. Yamaguchi *et al.* reported that extending treatment duration could not significantly improve therapeutic outcomes in non-RVR patients [11]. The N-CORE

**Table 4** Sustained virological response classified by previous therapy

| Previous therapy | Total (% SVR) | Standard (% SVR) | Extended (% SVR) | *P* |
|---|---|---|---|---|
| Naïve | 147/181 (81%) | 132/160 (83%) | 15/21 (71%) | 0.24 |
| Experienced | 92/125 (74%) | 58/79 (73%) | 34/46 (74%) | 1.0 |
| PegIFN + RBV | 44/64 (69%) | 24/35 (69%) | 20/29 (69%) | 1.0 |

SVR, sustained virological response; PegIFN, pegylated interferon; RBV, ribavirin.

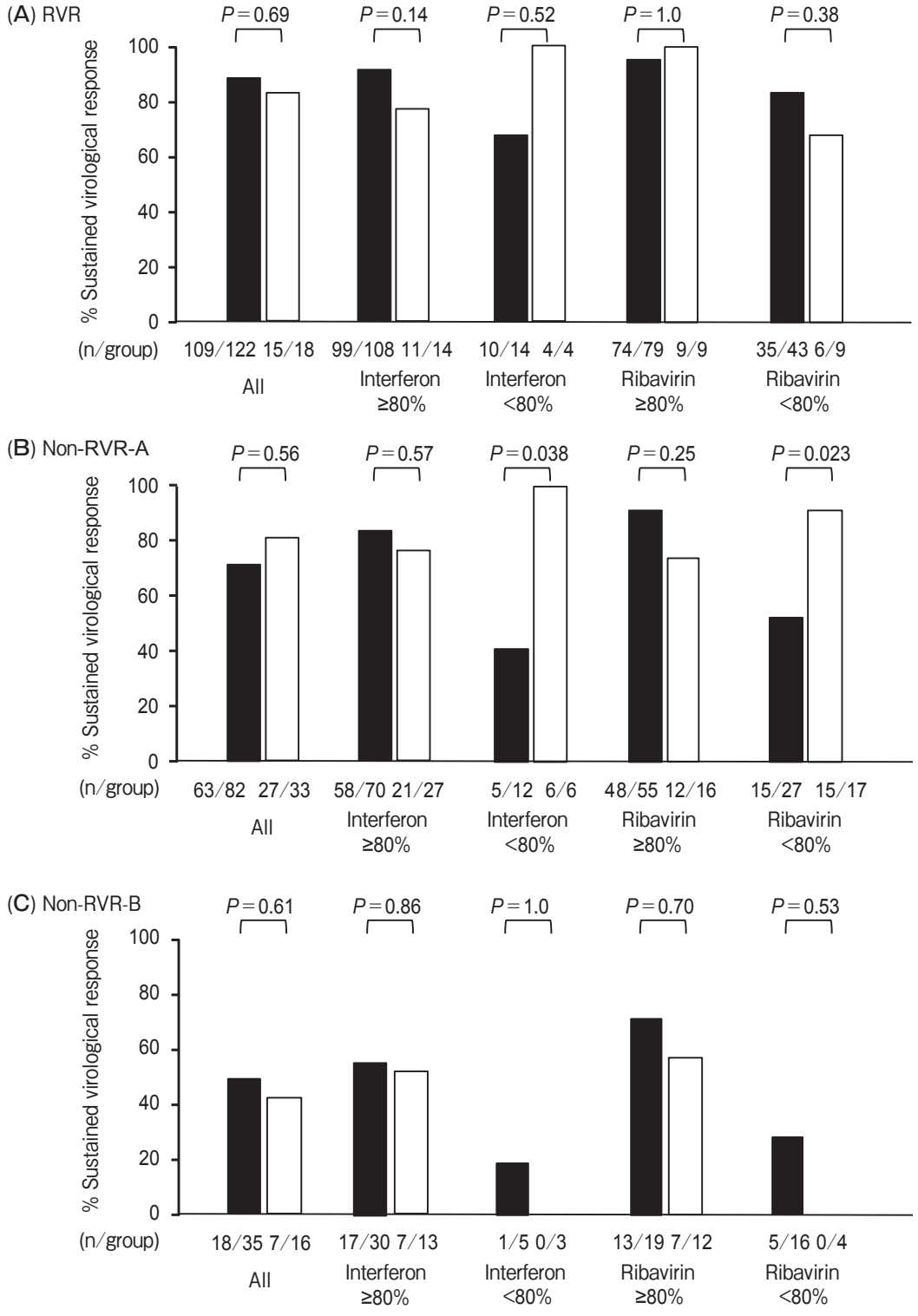


**Fig. 3** Comparisons of SVR rates between therapies with standard and extended durations classified by virological response and drug adherence during the treatment. The figures show the SVR rates with standard therapy (black bar) and extended therapy (open bar) in patient groups of RVR (**A**), non-RVR-A (**B**), and non-RVR-B (**C**). The figures also show the SVR rates in patient groups with good ($\geq$ 80%) or insufficient ($<$ 80%) adherence to PegIFN and RBV.

trial showed a 10% higher SVR rate by extending treatment duration, but this result lacked statistical significance [12].

We compared the SVR rates between the standard therapy and the extended therapy with more precise subgrouping by virological response; the non-RVR patients were classified in two groups: patients with detectable HCV RNA at week 4 of treatment and undetectable HCV RNA at week 8 of treatment (non-RVR-A) and patients with detectable HCV RNA at week 8 of treatment and undetectable HCV RNA at the end of treatment (non-RVR-B). The comparison of SVR rates and drug adherence during treatment among these groups revealed that the non-RVR-A patients who had insufficient adherence to PegIFN or RBV obtained a significantly higher SVR rate by extending treatment duration.

We also revealed that insufficient drug adherence to the standard therapy, but not to the extended therapy, was associated with non-SVR, which indicated that extending treatment duration in these patients effectively compensated for the insufficient antiviral effects of PegIFN or RBV due to insufficient drug adherence.

In terms of slow responders who had detectable HCV RNA at week 8 of treatment (non-RVR-B), they had a significantly lower SVR rate than the patients with RVR and non-RVR-A. The effectiveness of extending treatment duration could not be fully evaluated for these patients because only 16 patients with non-RVR-B received extended therapy in the present study; hence, the SVR rate of 44% (7/16) with extended therapy could not be effectively compared to the SVR rate of non-RVR-B patients with standard therapy (51%, 18/35).

In conclusion, extending treatment duration might improve the therapeutic outcomes of non-RVR patients with undetectable HCV RNA at week 8 of treatment and insufficient drug adherence to PegIFN or RBV during treatment. This finding might be useful in creating a guideline for extending treatment duration in antiviral therapy for patients with CHC genotype 2.

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