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***Case Control Study***

**Significance ofinterferon lambda3 polymorphisms in pegylated interferon-α plus ribavirin therapy for genotype 2 chronic hepatitis C**

Ishiguro H *et al*. *IFNL3* SNP and HCV G2 therapy

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**Abstract**

**AIM:** To evaluate the role of interferon lambda3(*IFNL3*)polymorphism in response-guided pegylated interferon-α plus ribavirin (Peg-IFNα/RBV) therapy for genotype 2 (G2) chronic hepatitis C.

**METHODS:** Between January 2006 and June 2012, 180 G2 chronic hepatitis C patients were treated with response-guided Peg-IFNα/RBV therapy. The treatment duration was 24 wk for patients who achieved rapid virological response (RVR) and 36 or 48 wk for patients who did not. Then, the impact of the *IFNL3* single nucleotide polymorphism (SNP) genotype (TT/non-TT at rs8099917) on treatment outcomes was evaluated in the 180 patients, and each of hepatitis C virus (HCV) sub-genotype 2a and 2b patients.

**RESULTS:** Of the 180 patients evaluated, 111 achieved RVR, while the remaining 69 patients did not. In RVR patients, the sustained virological response (SVR) rate was 96.4%, and the *IFNL3* genotype did not influence the SVR rate (96.6% *vs* 95.8% in *IFNL3* genotype TT *vs* non-TT, *P* = 0.6517). However, in non-RVR patients, the SVR rate decreased to 72.5% (*P* < 0.0001), and this rate was significantly different between the *IFNL3* genotype TT and non-TT groups (80.0% *vs* 42.9%, *P* = 0.0146). Multivariate regression analysis in non-RVR patients identified the *IFNL3* genotype TT as the only baseline-significant factor associated with SVR (*P* = 0.0189, odds ratio: 5.39, 95% confidence interval: 1.29–22.62). In analysis according to HCV sub-genotype, no significant difference in the SVR rate was found between HCV sub-genotypes 2a and 2b.

**CONCLUSION:** In response-guided Peg-IFNα/RBV combination therapy for chronically HCV G2 infected patients, the impact of the *IFNL3* genotype on SVR was limited to non-RVR patients.

**Key words**: Hepatitis C virus genotype 2;interferon lambda3 single nucleotide polymorphism; Pegylated interferon plus ribavirin response-guided therapy; Sustained virological response; Rapid virological response

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**Core tip:** It is well known that interferon lambda3(*IFNL3*) single nucleotide polymorphisms (SNPs), such as rs8099917 and rs12979860, considerably affect the virological responses of chronically hepatitis C virus (HCV) genotype 1 infected patients to response-guided pegylated interferon-α plus ribavirin (Peg-IFNα/RBV) therapy. However, the significance of *IFNL3* SNPs in therapy for HCV genotype 2 (G2) patients is unclear. Here, we clearly showed that *IFNL3* SNP (rs8099917) significantly influenced sustained virological response (SVR) achievement in patients who did not attain rapid virological response (RVR), but that the *IFNL3* SNP did not affect SVR in RVR patients. Therefore, the *IFNL3* SNP genotyping is valuable for predicting SVR only in non-RVR patients, irrespective of the G2 subtype, even if Peg-IFNα/RBV combination therapy is extended to 36 or 48 wk.

Ishiguro H, Abe H, Seki N, Sugita T, Aida Y, Itagaki M, Sutoh S, Shimada N, Furihata T, Tsubota A, Aizawa Y. Significance of interferon lambda3 polymorphisms in pegylated interferon-α plus ribavirin therapy for genotype 2 chronic hepatitis C. *World J Gastroenterol* 2015; In press

**INTRODUCTION**

Hepatitis C virus (HCV) genotype 2 (G2) is the second-most frequent HCV genotype and accounts for approximately 30% of chronic HCV infection in Japan[1,2].However, the prevalence of HCV G2 is decreasing due to successful treatment with standard 24-wk regimens of pegylated interferon-α plus ribavirin (Peg-IFNα/RBV) combination therapy[3,4]. Over 80% of patients receiving 24-wk Peg-IFNα/RBV therapy achieve sustained virological response (SVR)[3,4]. However, a fraction of patients who do not achieve a rapid virological response (RVR) may remain uncured, even when therapy is extended for 36 or 48 wk[5,6].

The impact of single nucleotide polymorphisms (SNPs) near the interferon lambda3 (*IFNL3*)/interleukin-28B gene on Peg-IFNα/RBV combination therapy for HCV genotype 1[7-9] has been firmly established. However, it remains controversial whether the *IFNL3* genotype is useful in predicting virological responses of HCV G2 patients to peg-IFNα/RBV therapy[10-13].

Previously, we demonstrated the value of response-guided therapy for HCV G2 patients who were treated for 24 wk with Peg-IFNα/RBV combination therapy if they achieved RVR, and for 36 or 48 weeks if they did not achieve RVR[6]. In the present study, we assessed the impact of *IFNL3* SNP (rs8099917) genotypes on virological responses and outcomes of HCV G2 (subtype of G2a or G2b) patients who received response-guided Peg-IFNα/RBV combination therapy.

**MATERIALS AND METHODS**

***Patients***

Between January 2006 and June 2012, 180 chronically HCV G2 infected patients were treated with response-guided Peg-IFNα/RBV combination therapy at the Jikei University Katsushika Medical Center, the Jikei University Kashiwa Hospital, and the Shinmatsudo Central General Hospital. The treatment duration was 24 wk for patients who achieved RVR (RVR group) and 36 or 48 wk for patients who did not (non-RVR group). Patients received weekly subcutaneous injections of Peg-IFNα-2b (PegIntron®, MSD K.K.; Tokyo, Japan) at a dose of 1.5 µg/kg, plus RBV (Rebetol®, MSD K.K.) at a dose of 600–1000 mg/d according to body weight (< 60 kg: 600 mg/d; 60–80 kg: 800 mg/d; and > 80 kg: 1000 mg/d). Doses of Peg-IFNα-2b and/or RBV were appropriately adjusted if side effects were observed.

All the patients studied satisfied the following inclusion criteria: (1) serum HCV RNA levels ≥ 10000 copies/mL (AMPLICOR HCV MONITOR Test, version 2.0; Roche Molecular Systems; Pleasanton, CA; quantification limit: 50 IU/mL) or ≥ 5 log10 IU/mL (COBAS AmpliPrep/COBAS TaqMan HCV Test; Roche Molecular Systems; quantification limit: 1.2 log10 IU/mL); (2) white blood cell counts ≥ 2000/mm3; (3) neutrophil counts ≥ 1500/mm3; (4) hemoglobin levels ≥ 11 g/dL; (5) platelet counts ≥ 60000/mm3; and (6) serotype 2 or genotype 2a or 2b (G2a or G2b) determined by serological and conventional PCR-based methods, as reported previously[14,15]. Patients were excluded from this study if they were positive for hepatitis B surface antigen or anti-human immunodeficiency virus antibody, consumed > 20 g of alcohol/d, had psychiatric disorders or hepatocellular carcinoma, or were diagnosed with other liver diseases. Patients with established liver cirrhosis that was easily diagnosed by image inspection or for whom laboratory tests did not indicate the need for liver biopsy (*e.g.*, low platelet count or prolonged PT) were not included in the present study. One hundred and sixty-five patients (91.7%) were treatment-naïve and the remaining 15 had been previously treated with 24-wk Peg-IFNα/RBV combination therapy.

This study complied with the standards of the Declaration of Helsinki (revised edition 2008) and current ethical guidelines and was approved by the human ethics review committees of each institution. Written informed consent was obtained from all patients.

***Histology, HCV sub-genotyping, and detection of HCV RNA***

Liver biopsies and HCV G2 sub-genotyping were performed with 152/180 and 159/180 patients, respectively. Histological grades of liver fibrosis were classified as F1–F4, according to the METAVIR scoring system[16]. HCV G2 sub-genotyping was performed by the conventional PCR-based method[14]. HCV serotypes were determined by ELISA[15]. The presence or absence of serum HCV RNA was evaluated after 4 wk of therapy, at the end of therapy, and at 24 wk after the completion of therapy. Serum HCV RNA levels were evaluated with the qualitative AMPLICOR HCV MONITOR Test between January 2006 and November 2007, and the COBAS AmpliPrep/COBAS TaqMan HCV test was used thereafter. To evaluate potential discrepancies due to the use of different tests, 21 samples that were originally analyzed using the AMPLICOR MONITOR HCV Test were re-tested with the COBAS AmpliPrep/COBAS TaqMan HCV test, using serum stocks stored at −30 °C. Patients in whom serum HCV RNA levels were undetectable with the COBAS AmpliPrep/COBAS TaqMan HCV test at 4 wk after initiating therapy were designated as RVR patients, while the remaining patients were designated as non-RVR patients. The end point in this study was SVR (undetectable serum HCV RNA at 24 wk post-treatment).

***Analysis of SNPs near the IFNL3 gene***

Genomic DNA was extracted and isolated from whole blood using a MagNA Pure LC Instrument and the DNA Isolation Kit (Roche Diagnostics). Alleles of the rs8099917 SNP near the *IFNL3* gene were determined using TaqMan SNP genotyping assays (Applied Biosystems; Foster City, CA, USA), as described previously[9]. The rs8099917 genotypes were classified into TT (major homozygous genotype) and non-TT genotypes (heterozygous genotype TG or minor homozygous genotype GG). The *IFNL3* SNP (rs8099917) genotype of all patients was determined at the Research Center for Medical Science at the Jikei University School of Medicine.

***Statistical analysis***

The Mann–Whitney *U*-test was used to analyze differences in continuous variables. Fisher’s exact tests were used to analyze differences in categorical data. All tests of significance were 2-tailed. *P*-values of < 0.05 and < 0.1 were considered statistically significant and marginal, respectively. To determine which factors were associated with SVR, variables that were significant or marginal in univariate analyses were analyzed by multiple logistic regression analysis. All statistical analyses were performed using STATISTICA for Windows version 6 (StatSoft; Tulsa, OK, USA).

**RESULTS**

***Treatment responses***

Of the 180 patients evaluated, 111 (61.7%) achieved RVR and received a 24-wk treatment course (RVR group). The remaining 69 (38.3%) patients failed to achieve RVR and the treatment duration was extended to 36 or 48 wk (non-RVR group; Figure 1). HCV G2a was more frequently detected in the RVR group than in the non-RVR group (*P* = 0.0005; Table 1). With respect to the HCV sub-genotype, 69 of 98 (70.4%) G2a patients had RVR, whereas only 23 of 57 (40.4%) G2b patients had RVR. The baseline level of HCV RNA was significantly lower in the RVR group than in the non-RVR group (*P* < 0.0001). Serum albumin levels were significantly higher in the RVR group than in the non-RVR group (*P* = 0.0029). Multivariate analysis identified the baseline levels of HCV RNA and serum albumin as significant factors associated with RVR (*P* < 0.0001, odds ratio (OR) = 4.40, 95% confidence interval (CI): 2.25–8.63, and *P* = 0.0006, OR = 0.13, 95%CI: 0.04–0.42, respectively)**.** However, no difference was observed in the distribution of *IFNL3* SNP genotypes between the RVR and non-RVR groups (*P* = 0.9800; Figure 1 and Table 1). The percentages of TT genotype patients were 78.4% (87 of 111) *vs* 79.7% (55 of 69) in the RVR and non-RVR groups, respectively.

***SVR in RVR patients***

Of the 111 RVR patients, 107 (96.4%) achieved SVR with the 24-wk treatment. Regarding the *IFNL3* SNP genotype, 84 of 87 (96.6%) TT patients and 23 of 24 (95.8%) non-TT patients achieved SVR (*P* = 0.6517; Figure 2A). As for HCV G2 subtype, 66 of 69 (95.7%) patients with G2a and 23 of 23 (100%) patients with G2b achieved SVR (*P* = 0.7347). There were no significant differences in other variables between patients with SVR and non-SVR. Although only 4 patients failed to achieve SVR, no characteristics distinguishing them from SVR patients were identified. All of the 4 non-SVR patients (1 male and 3 female; age: 34-65 years) were treatment-naïve and completed treatment as scheduled. They had a mild degree of liver fibrosis and baseline HCV RNA levels of 5.0 to 6.5 log IU/mL.

***SVR in non-RVR patients***

Of the 69 non-RVR patients, 50 (72.5%) achieved SVR with the extended treatment to 36 or 48 wk. The SVR rate in the non-RVR group was significantly lower than that in the RVR group (72.5% *vs* 96.4%, respectively, *P* < 0.0001). Thirty-eight patients (55.1%) received a 48-wk treatment course and 31 (44.9%) received a 36-wk treatment course. SVR rates were higher in the 36-week treatment patient group than in the 48-wk group (80.6% *vs* 65.8%, *P* = 0.2700)**.** Regarding the *IFNL3* SNP genotype, 44 of 55 (80.0%) patients with the TT genotype and 6 of 14 (42.9%) patients with the non-TT genotype achieved SVR (*P* = 0.0058; Figure 2B). Among patients with the *IFNL3* TT genotype, the SVR rates were significantly different between RVR and non-RVR patient groups (96.6% *vs* 80.0%, respectively, *P* = 0.0033; Figure 2A and 2B). Similarly, among patients with non-TT genotypes, the SVR rates were significantly different between RVR and non-RVR patient groups (95.8% *vs* 42.9%, respectively, *P* = 0.0009; Figure 2A and 2B). In HCV G2 sub-genotype patients, 21 of 29 (72.4%) patients with G2a and 24 of 34 (70.6%) patients with G2b achieved SVR (*P* = 0.9046).

***Factors contributing to SVR in non-RVR patients***

In the non-RVR patient group, the *IFNL3* TT genotype was the only baseline factor that significantly related to SVR in univariate analysis (*P* = 0.0146). Among the other baseline factors, aspartate aminotransferase was marginal (*P* = 0.0751). The histological stage of fibrosis and HCV G2 sub-genotypes were not significant factors for SVR. In multiple logistic regression analysis, only the *IFNL3* TT genotype was identified as an independent factor that was significantly associated with SVR (OR = 5.87, 95%CI: 1.62–21.22, *P* = 0.0058; Table 2).

Among the on-treatment factors, adherence to RBV was significantly higher in non-SVR patients than in SVR patients (*P* = 0.0457) and adherence to Peg-IFN was numerically higher in non-SVR patients than in SVR patients (*P* = 0.0936), indicating that these adherence factors did not influence SVR. The duration of Peg-IFNα/RBV combination therapy (36 wk or 48 wk) did not affect the outcome of treatment (Table 2).

***SVR rates according to RVR, G2 subtype, and IFNL3 SNPs***

The SVR rates were not statistically different between patients with HCV G2a and G2b in either the *IFNL3* genotype TT patient group (90.7% *vs* 88.6%, *P* = 0.9683) or the non-TT group (82.6% *vs* 61.5%, *P* = 0.3165). The remaining 21 patients (11.7%) were not found to have G2a or G2b. Twenty of 21 patients achieved SVR and the remaining patient (who did not achieve RVR) showed relapse. In the RVR patient group, the SVR rates in HCV G2a patients were comparable to those observed with HCV G2b patients, regardless of the *IFNL3* genotype (Figure 3A).

Among non-RVR patients, the SVR rate in HCV G2b patients with the *IFNL3* TT genotype was significantly higher than that in those with the *IFNL3* non-TT genotype (81.5% *vs* 28.6%, *P* = 0.0231; Figure 3B). The SVR rate in G2a patients with the TT genotype was numerically higher than that in those with the non-TT genotype, though not statistically significant (78.3% *vs* 50%, *P* = 0.3862; Figure 3B).

**DISCUSSION**

*IFNL3* SNPs, such as rs8099917 and rs12979860, have a strong impact on virological responses in chronically HCV G1-infected patients to Peg-IFNα/RBV combination therapy[7-9]. However, more potent antiviral treatments, including direct-acting antiviral agents (DAAs), would attenuate the value of *IFNL3* SNPs as a predictor of treatment outcome, because they could markedly improve the SVR rate. In countries/areas where DAAs are not available, Peg-IFNα/RBV combination therapy is still the standard of care for HCV G2 patients. Therefore, *IFNL3* SNPs still have prognostic value in such settings[10-13].

In a previous study from Japan, *IFNL3* SNPs were reported to be an independent predictive factor for SVR (but not RVR) in patients infected with HCV subtype G2b, but not G2a[11]. However, the study analysis included both RVR patients and non-RVR patients in whom the treatment duration was limited to 24 wk and not extended to 36 or 48 wk. Another study conducted in the United States showed that the *IFNL3* rs12979860 genotype was associated with SVR to 24-wk Peg-IFNα/RBV combination therapy in HCV-2/3 patients who did not achieve RVR[12]. Our findings were in partial concordance with these results; the *IFNL3* SNP significantly influenced the achievement of SVR in patients who did not attain RVR, but did not affect SVR in RVR patients. Therefore, *IFNL3* SNP genotyping is valuable for predicting SVR only in non-RVR patients, irrespective of G2 subtype, even if Peg-IFNα/RBV combination therapy is extended to 36 or 48 wk. Conversely, neither *IFNL3* SNPs nor G2 subtypes are associated with SVR in RVR patients. However, the relatively small number of patients in our study may limit the conclusions that can be drawn, and these results should be verified in a larger study cohort.

The SVR rate for HCV G2 patients in our study was similar to those reported in previous studies[17,18]. As the SVR rate was very high (96.4%) in patients who achieved RVR and were treated with standard 24-wk Peg-IFNα/RBV combination therapy, the treatment period of 24 wk is sufficient and could be abbreviated without reducing the SVR rate. Conversely, the SVR rates following 24-wk Peg-IFNα/RBV combination therapy were reported to be fairly low in non-RVR patients[6,19], and response-guided extension to 36 or 48 wk has been used to improve treatment efficacy[5,6,20]. However, our previous study[6] and the present study revealed that there were no distinct differences in the SVR rates of non-RVR patients who received either 36 or 48 wk of therapy and that the SVR rate was significantly lower in non-RVR patients (treated with the 36- or 48-wk treatment) than in RVR patients (treated with the 24-wk treatment). These findings suggested that there are limitations to prolonged treatment duration in non-RVR patients. Specifically, this study highlighted low SVR rates in non-RVR patients with unfavorable *IFNL3* genotypes.

In the near future, DAA-based combination therapy will be used worldwide as the first**-**line therapy for treating chronic HCV G2 infection because extremely high SVR rates can be attained with shorter treatment durations and without distinctive side effects[21-23].In many countries/areas, however, Peg-IFNα/RBV combination therapy will still be the standard of care before DAAs are approved and available. Until then, response-guided therapy based on RVR to Peg-IFNα/RBV combination therapy is useful in yielding high SVR rates for RVR patients and reducing economic and physical burdens by immaturely discontinuing unnecessary treatment for non-RVR patients. Alternatively, to make a decision to continue treatment in non-RVR patients, *IFNL3* genotyping may be valuable in predicting the probability of achieving SVR.

In conclusion, neither the *IFNL3* SNP genotype nor the G2 subtype influenced the probability of achieving SVR in RVR patients treated with response-guided Peg-IFNα/RBV combination therapy. However, the SVR rate in non-RVR patients was higher in those with the *IFNL3* TT genotype compared to those with the non-TT genotype, irrespective of G2 subtype, even if therapy was extended to 36 or 48 wk, indicating that the *IFNL3* SNP had a significant impact only on the achievement of SVR in non-RVR patients.

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**COMMENTS**

***Background***

Genotype 2 (G2) hepatitis C virus (HCV) is the second-most frequent HCV genotype and accounts for approximately 30% of chronic HCV infection in Japan. Most of HCV G2 patients who achieve rapid virological response (RVR) in 24-wk response-guided pegylated interferon-α plus ribavirin (Peg-IFNα/RBV) combination therapy achieve sustained virological response (SVR), while a fraction of patients who do not achieve RVR may remain uncured even when therapy is extended for 36 or 48 wk. The impact of interferon lambda3(*IFNL3*) single nucleotide polymorphisms (SNPs) on Peg-IFNα/RBV combination therapy for HCV genotype 1 (G1) has been firmly established. However, it remains controversial whether the *IFNL3* genotype is useful in predicting virological responses of HCV G2 patients to Peg-IFNα/RBV therapy.

***Research frontiers***

*IFNL3* genotyping is advantageous in clinical practice for patients who could not achieve RVR. The results of this study provide a strong rationale for the use of *IFNL3* SNPs testing to personalize antiviral therapy.

***Innovations and breakthroughs***

This work aims at emphasizing the role of *IFNL3* SNPs in HCV G2 patients who received Peg-IFNα/RBV combination therapy. In non-RVR patients, the evaluation of the *IFNL3* SNPs still holds significance to establish the therapeutic schedule.

***Applications***

In patients with *IFNL3* non-TT genotypes and non-RVR, clinicians should not extend to treat with combination therapy. The relevance of this approach is cost-effective at the time of DAA therapy.

***Terminology***

*IFNL3,* located 8 kb upstream of the interleukin-28Bgene, is a cytokine that plays a role in HCV clearance. *IFNL3* SNPs showed the association with SVR to PEG-IFN/RBV therapy in not only HCV G1 but also G2 patients.

***Peer-review***

The authors describe associations of *IFNL3* genotype with IFN/RBV treatment outcome in HCV G2 patients who do not achieve RVR. The data are interesting, in that a role for *IFNL3* genotype in treatment outcome for HCV G2 patients is demonstrated only in patients not achieving RVR. These data contribute to the *IFNL3* literature and thus merit reporting.

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**Figure 1** **Study flow chart.** PEG-IFNα: Pegylated interferon-α; HCV: Hepatitis C virus; SNP: Single nucleotide polymorphism.



**Figure 2 Sustained virological response rates according to interferon lambda3single nucleotide polymorphismgenotype in rapid virological response and non-** **rapid virological response patient groups.** *IFNL3***:** Interferon lambda3*;*RVR: Rapid virological response; SVR: Sustained virological response; SNP: Single nucleotide polymorphism.



**Figure 3 Sustained virological response rates according to interferon lambda3 single nucleotide polymorphism genotype and hepatitis C virus sub-genotype in rapid virological response (A) and non-rapid virological response patient groups (B).** HCV: Hepatitis C virus; *IFNL3***:** Interferon lambda3;RVR: Rapid virological response; SVR: Sustained virological response; SNP: Single nucleotide polymorphism.

**Table 1 Analysis of factors affecting rapid virological response to pegylated interferon-α plus ribavirin combination therapy in patients infected with hepatitis C virus genotype 2**

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| 1Classified by METAVIR score. Data are expressed as number of patients or median (range). PEG-IFNα: Pegylated interferon-α; RBV: Ribavirin; ND: Not done; RVR: Rapid virological response. |
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**Table 2 Analysis of factors affecting sustained virological response in non-rapid virological response hepatitis C virus genotype 2 patients who were treated with 36 or 48-wk pegylated interferon-α plus ribavirin combination therapy**

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| --- | --- | --- | --- | --- | --- |
| 1Classified by METAVIR score; 2Calculated on the basis of 48-wk treatment. Data are expressed as number of patients or median (range). PEG-IFNα: Pegylated interferon-α; RBV: Ribavirin; RVR: Rapid virological response. |  |  |  |  |  |
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