Table 4 Factors correlating with velocity of shear wave in 108 patients with chronic hepatitis C virus infection

	All patients (n = 108)				Patients with $F0$ or $F1$ (n = 31)				Patients with $F2$ (n = 32)				Patients with $F3$ or $F4$ (n = 45)			
	Spearman's rank correlation test		Multiple regression analysis		Spearman's rank correlation test		Multiple regression analysis		Spearman's rank correlation test		Multiple regression analysis		Spearman's rank correlation test		Multiple regression analysis	
	ρ	P value	β	P value	ρ	P value	β	P value	ρ	P value	β	P value	ρ	P value	β	P value
Age (yr)		NS				NS				NS				NS		
Gender (female/male)[1]		NS				NS				NS				NS		
BMI		NS			-0.608	0.0003	-0.033	0.0001		NS				NS		
Fibrosis stage	0.732	< 0.0001	0.187	0.0001		NS							0.505	0.0004	0.292	0.0044
Inflammatory grade	0.612	< 0.0001		NS		NS				NS				NS		
Steatosis grade		NS				NS				NS				NS		
AST (IU/L)	0.430	< 0.0001		NS		NS				NS				NS		
ALT (IU/L)	0.318	0.0008		NS	0.343	0.0593		NS		NS				NS		
γ-GTP (IU/L)	0.407	< 0.0001		NS	0.340	0.0614		NS	0.544	0.0013	0.005	0.0012		NS		
Platelet count ($\times 10^4$/μL)	-0.441	< 0.0001		NS		NS				NS			-0.425	0.0036		NS
Prothrombin time (INR)	0.344	0.0003		NS		NS				NS			0.390	0.0080		NS
Albumin (g/dL)	-0.347	0.0002		NS		NS				NS			-0.459	0.0015		NS
Total cholesterol (mg/mL)	-0.337	0.0004		NS		NS				NS				NS		
γ-globulin (g/dL)	0.252	0.0087		NS		NS			-0.344	0.0581		NS		NS		
Hyaluronic acid (ng/mL)	0.576	< 0.0001	8.00E-4	0.0039		NS				NS			0.519	0.0003	0.001	0.0025
HCV genotype (1/2)[1]		0.0728		NS		NS				NS				NS		
HCV RNA (logIU/mL)		NS				NS				NS				NS		
Fibrosis area (%)	0.656	< 0.0001		NS		NS				NS			0.296	0.0481		NS
R			0.707				0.645				0.546				0.634	
Adjusted R			0.490				0.396				0.275				0.373	
F			51.800				20.700				12.700				14.100	
P value			< 0.0001				0.0001				0.0012				< 0.0001	

[1]Difference of frequency of gender or genotype was assessed by Mann-Whitney U test. AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; γ-GTP: γ-glutamyltranspeptidase.

value for $F \geq 1$ and that for $F \geq 2$ are the same. However, Sporea *et al*[26] reported that the cutoff value is 1.19 m/s for $F \geq 1$, 1.33 m/s for $F \geq 2$, 1.43 m/s for $F \geq 3$, and 1.55 m/s for $F4$[26]. Rizzo *et al*[13] reported that the cutoff value is 1.3 m/s for $F \geq 2$, 1.7 m/s for $F \geq 3$ and 2.0 m/s for $F4$[13]. Thus, discrepancies are apparent among the cutoff values reported in different studies. The discrepancies are probably attributed to the difference in the population studied. Further studies should be conducted to establish standard ARFI cutoff values for staging fibrosis.

In the present study, AST, ALT and inflammatory grade were correlated with ARFI in the univariate analysis that included all patients, but were not selected as factors independently correlating with ARFI in the multiple regression analysis. In addition, inflammatory factors did not correlate with ARFI when patients with different fibrosis stages were analyzed separately. These results suggest that inflammatory activity does not affect ARFI in patients with chronic hepatitis C. Rizzo *et al*[13] also reported that ARFI is not associated with ALT, BMI, Metavir grade, or liver steatosis, whereas TE is significantly correlated with ALT[13]. Bota *et al*[10] reported that discordance of at least two fibrosis stages between ARFI and histologic assessment were associated with female sex, interquartile range interval (IQR) ≥ 30%, high AST and high ALT in univariate analysis, while, in multivariate analysis, the female gender and IQR ≥ 30% ($P = 0.004$) were associated with the discordances. In contrast, Yoon *et al*[12] reported that the optimum ARFI cutoff values are 1.13 m/s for $F \geq 2$ and 1.98 m/s for $F4$, whereas these values decreased to 1.09 m/s for $F \geq 2$ and 1.81 m/s for $F4$ when patients with normal ALT levels were selected. Chen *et al*[11] reported that ALT, ActiTest A score, Metavir activity (A) grade, Metavir F stage, BMI, and platelet count are independently associated with ARFI and suggested that a 100 IU/L increase in serum ALT levels augmented ARFI by approximately 0.155 m/s. In the present study, only 25 patients had ALT levels of 100 IU/L

or higher. The low ALT levels among the patients studied may be a reason why ALT was not correlated with ARFI.

A multiple linear regression analysis in our previous study on TE selected fibrosis area, ALT levels, γ-GTP levels, prothrombin time, and hyaluronic acid levels as factors correlating with TE[21]. Many studies on TE have reported that LSM is affected by ALT levels. Franquelli *et al*[28] reported that TE fibrosis staging is overestimated by necroinflammatory activity and steatosis. Coco *et al*[7] found that LSM is higher in patients with an elevated ALT than in those with either spontaneous biochemical remission or after antiviral therapy. Thus, it is probable that ALT or inflammatory activity affects TE. However, it is still unclear whether they also affect ARFI. Further studies are needed to clarify factors that affect ARFI other than fibrosis stage.

ARFI was significantly correlated with BMI in the 31 patients with stage *F*0 or *F*1; the higher the BMI, the lower the ARFI. However, ARFI was not associated with steatosis grade. Motosugi *et al*[29] reported that fat deposition in the liver does not affect ARFI. Thus, the negative correlation between BMI and ARFI could not be attributed to steatosis, which accompanies higher BMI[30]. Actually, BMI and steatosis grade were not correlated in patients with stage *F*0 or *F*1 in the present study (data not shown). The mechanism of the association between higher BMI and lower ARFI is unclear. Because a higher BMI is associated with lower ARFI, and may cause an underestimation of fibrosis staging, careful attention should be paid to BMI during ARFI staging of fibrosis in patients with stage *F*0 or *F*1 disease.

ARFI significantly correlated with γ-GTP levels in patients with *F*2 and with fibrosis stage and hyaluronic acid levels in patients with stage *F*3 or *F*4. γ-GTP[24,31] and hyaluronic acid[32,33] levels have been regarded as the most informative fibrosis markers. Thus, it is reasonable that γ-GTP and hyaluronic acid levels independently correlated with ARFI.

Isgro *et al*[20] showed that the collagen proportional area has a better relationship with TE and with hepatic venous pressure gradient compared with Ishak stage. In the present study, fibrosis area was correlated significantly with fibrosis stage, but only fibrosis stage and hyaluronic acid levels were selected as factors independently correlating with ARFI. Our previous study demonstrated a better correlation of TE with fibrosis stage than with fibrosis area in patients with chronic hepatitis C[21]. The Metavir stages represent categories of increasing fibrosis severity based on a combination of location and quantity of scarring as well as whether the fibrous tissue forms septa, bridges, or nodules. Fibrosis area represents only the quantity of fibrosis in liver tissues. Our results indicate that not only the quantity of fibrosis but also other histological factors such as patterns of fibrosis also affect ARFI.

The present study demonstrated that ARFI correlated with fibrosis stage but was not associated with inflammation. BMI negatively correlated with ARFI in the patients with stage *F*0 or *F*1. γ-GTP and hyaluronic acid levels were positively correlated in those with stage *F*2 and in those with *F*3 or *F*4, respectively. Thus, careful attention should be paid to BMI, γ-GTP levels, and hyaluronic acid levels when estimating fibrosis stage by ARFI. Fibrosis stage showed a better correlation with ARFI than fibrosis area, indicating that not only the quantity of fibrosis but also other factors such as patterns of fibrosis also affect ARFI. Since the number of the patients studied is small, further studies are needed to confirm the conclusion of the present study.

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COMMENTS

Background

Most studies reported that liver stiffness measurement by Fibroscan was affected by inflammation. There have been both of the reports which demonstrated the correlation of inflammation and acoustic radiation force impulse (ARFI) and those which denied their correlation. The present study confirmed findings reported previously that ARFI correlates with fibrosis stage, and demonstrated that aspartate aminotransferase, alanine aminotransferase and inflammatory grade did not independently correlate with ARFI in the multiple regression analysis. The present study also demonstrated the correlation of body mass index (BMI) and ARFI for the first time.

Innovations and breakthroughs

The new findings of this study are the correlation of BMI and ARFI, and the denial of the correlation between ARFI and inflammation.

Applications

The results showed that ARFI correlated significantly with liver fibrosis stage and hyaluronic acid in all patients. ARFI correlated significantly with BMI in fibrosis stage F0-1, with γ-glutamyltranspeptidase (GTP) in F2, and with fibrosis stage and hyaluronic acid in F3-4. In conclusion, ARFI correlated with fibrosis stage and hyaluronic acid but not with inflammation. ARFI was affected by BMI, γ-GTP, and hyaluronic acid in each fibrosis stage.

Peer review

The authors reported the utilities of ARFI elastography for evaluation of hepatic fibrosis in patients with chronic hepatitis C. This paper looks very important and has a novelty in this study field.

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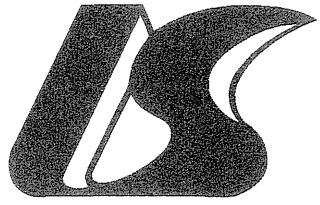

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Original Article

Interleukin 28B polymorphism predicts interferon plus ribavirin treatment outcome in patients with hepatitis C virus-related liver cirrhosis: A multicenter retrospective study in Japan

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Aim: This study evaluated the efficacy of interferon plus ribavirin and examined whether interleukin 28B (IL28B) polymorphism influenced treatment outcome in Japanese patients with hepatitis C virus (HCV)-related liver cirrhosis (LC).

Methods: Fourteen collaborating centers provided details of 261 patients with HCV-related LC undergoing treatment with interferon plus ribavirin. Univariate and multivariate analyses were used to establish which factors predicted treatment outcome.

Results: Eighty-four patients (32.2%) achieved a sustained virological response (SVR). SVR rates were 21.6% (41/190) in patients with HCV genotype 1 with high viral load (G1H) and 60.6% (43/71) in patients with non-G1H. In patients with non-G1H, treatment outcome was effective irrespective of IL28B polymorphism. In those with G1H, SVR was achieved in 27.1% of patients with the IL28B rs8099917 TT allele compared with 8.8% of those with the TG/GG alleles ($P \approx 0.004$). In patients with G1H having TT allele, treatments longer than 48 weeks achieved significantly higher SVR rates than treatments less than 48 weeks (34.6% vs 16.4%, $P = 0.042$). In patients with G1H having TG/GG alleles, treatments longer than 72 weeks achieved significantly higher SVR rates than treatments less than 72 weeks (37.5% vs 4.1%, $P \approx 0.010$).

Conclusion: Interferon plus ribavirin treatment in Japanese patients with non-G1H HCV-related LC was more effective than those with G1H and not influenced by IL28B polymorphism. In those with G1H, IL28B polymorphism may predict SVR and guide treatment duration: SVR rates were higher in those with the TT allele treated for more than 48 weeks and those with the TG/GG alleles treated for more than 72 weeks.

Key words: cirrhosis, hepatitis C virus, interferon, interleukin 28B, ribavirin

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INTRODUCTION

CHRONIC HEPATITIS C virus (HCV) infection is a leading cause of liver cirrhosis worldwide.[1] Patients with HCV-related liver cirrhosis (LC) are at increased risk of hepatic decompensation and hepatocellular

carcinoma (HCC).[2–4] The therapeutic goal in these patients should be the prevention of liver-related mortality. A randomized trial conducted in Japan was the first to suggest that interferon (IFN) may reduce the risk of HCC in patients with HCV-related LC.[5] Recent studies have shown that patients with HCV-related LC who achieved a sustained virological response (SVR) with antiviral therapy had a significant reduction in liver-related mortality.[6,7] However, patients with HCV-related LC show a lower SVR rate than non-cirrhotic patients, as well as a reduced tolerance to the therapy.[8,9] A previous meta-analysis revealed that the overall SVR rate in patients with cirrhosis was 33.3%, and was significantly higher in patients with HCV genotypes 2 and 3 (55.4%) than in those with HCV genotypes 1 and 4 (21.7%).[10]

Genome-wide association studies have recently shown that single nucleotide polymorphisms (SNP) near the interleukin 28B (IL28B) region (rs8099917, rs12979860) are the most powerful predictors of SVR to pegylated (PEG) IFN plus ribavirin in patients with HCV genotype 1 infection.[11–13] However, it is not clear whether IL28B polymorphism can be used to predict the virological response to treatment of HCV-related LC. This study evaluated the efficacy of IFN plus ribavirin, and the association between IL28B polymorphism and the treatment efficacy in Japanese patients with HCV-related LC.

METHODS

THIS WAS A multicenter retrospective study of patients with HCV-related LC who had received treatment with IFN plus ribavirin in 14 hospitals in Japan.

Patient selection

Data were collected from 290 patients with HCV-related LC receiving treatment with IFN plus ribavirin in 14 academic and community hospitals. All patients had compensated HCV-related LC with clinical or histological data available. The diagnosis of cirrhosis met at least one of the following criteria: liver biopsy specimens with cirrhosis, diffuse formation of the nodules on the liver surface in peritoneoscopy, over 12.5 kPa in liver stiffness values on transient elastography, signs of portal hypertension on ultrasound scan (splenomegaly, portal vein enlargement, re-permeabilization of the umbilical vein, or presence of portal-systemic shunts), presence of esophageal varices on endoscopy or positive values using the following discriminant by Ikeda and colleagues: $z = 0.124 \times$ (γ-globulin [%]) $+ 0.001 \times$ (hyaluronate) ($\mu g\ L^{-1}$) $- 0.075 \times$ (platelet count [$\times 10^4$ counts/mm^3]) $- 0.413 \times$ sex (male, 1; female, 2) $- 2.005$.[14–16] Principal investigators in 14 hospitals identified eligible patients and entered data in a predefined database.

Combination therapy

Of the 290 patients identified, 29 were not genotyped for IL28B SNP, thus the data of 261 patients were analyzed. A total of 190 patients were infected with HCV genotype 1 with high viral load (>100 KIU/mL) (G1H) (72.8%) and the remaining 71 (27.2%) were classified as non-G1H. Twenty-two patients were HCV genotype 1 with low viral load, 46 were genotype 2a or 2b, and three were of unknown genotype. Two hundred and twenty-four (85.8%) patients were treated with PEG IFN-α-2b (1.5–1.0 μg/kg bodyweight per week), 20 (7.7%) patients were treated with PEG IFN-α-2a (45–180 μg/week) and the remaining 17 (6.5%) patients were treated with IFN-α-2b or IFN-β. IFN-α-2b and IFN-β were administrated at a median dose of 6 million units each day (seven times per week for the initial 2 or 4 weeks, followed by three times per week thereafter). All patients also received oral ribavirin (600–1000 mg/day). Median treatment duration was 48 and 28 weeks in G1H and non-G1H, respectively. The individual attending physician determined the treatment regimes and their duration.

Virological response during therapy and definitions

The efficacy end-point was SVR, defined as undetectable serum HCV RNA 24 weeks after treatment. Relapse was defined as undetectable serum HCV RNA at the last treatment visit but detectable serum HCV RNA again at the last follow-up visit. Breakthrough was defined as reappearance of serum HCV RNA during treatment. A non-responder was defined as serum HCV RNA never undetectable during treatment. A rapid virological response (RVR) was defined as undetectable serum HCV RNA at treatment week 4, and a complete early virological response (cEVR) was defined as undetectable serum HCV RNA at treatment week 12. A late virological response (LVR) was defined as detectable serum HCV RNA at 12 weeks that became undetectable within 36 weeks of the start of treatment.

Determination of IL28B genotype

Interleukin 28B (rs8099917) was genotyped in each of the 14 hospitals by Invader assay, TaqMan assay or by direct sequencing, as previously described.[17,18]

Statistical analysis

Results were analyzed on the intention-to-treat principle. Mean differences were tested using Student's *t*-test. The difference in the frequency distribution was analyzed with Fisher's exact test. Univariate and multivariate logistic regression analyses were used to identify factors independently associated with SVR. The odds ratios (OR) and 95% confidence intervals (95% CI) were also calculated. The parameters that achieved statistical significance on univariate analysis were entered into multivariate logistic regression analysis to identify significant independent factors. Data were analyzed with JMP version 9.0 for Macintosh (SAS Institute, Cary, NC, USA). All statistical analyses were two sided, and $P < 0.05$ was considered significant.

RESULTS

OF THE 261 patients included in our analysis, 84 patients (32.2%) achieved SVR (Fig. 1). The rate of relapse and breakthrough was 24.9% and the non-responder rate was 33.3%. There were 25 patients (9.6%) who required early discontinuation of treatment because of adverse events. Baseline demographic and clinical features are summarized in Table 1. The age of the patients was 60.7 ± 8.9 years and 50.6% were male. Of the patients studied, 125 patients (47.9%) had been treated with IFN previously, and 75 (28.7%) had not responded to previous treatment. One hundred and six patients (40.6%) had been treated for HCC before. There were 85 patients with esophageal varices (32.6%). There were 190 patients with G1H and 133 (70%) of these had the TT allele at IL28B rs8099917. There were 71 patients in the non-G1H group, 51 (71.8%) of whom were found to have the TT allele at IL28B rs8099917.

Virological response rates in patients with G1H and non-G1H HCV-related LC

The SVR rates were 21.6% (41/190) in patients with G1H and 60.6% (43/71) in patients with non-G1H (Table 2). There were no statistically significant differences between the G1H and non-G1H groups with regard to dose reduction rates of IFN or ribavirin. Dose reduction of IFN was required in 51.3% of patients and dose reduction of ribavirin in 53.6% of patients. Treatment duration in patients in the G1H group was significantly longer than those in the non-G1H group ($P = 0.010$).

Association between IL28B rs8099917 genotype and treatment response

Sustained virological response was achieved in 37.0% of patients with the rs8099917 TT allele and 20.8% in those with the TG or GG allele. Virological responses, including SVR, relapse and breakthrough, in patients with the rs8099917 TT allele were significantly higher than in those with rs8099917 TG or GG allele ($P = 0.013$ and 0.012, respectively; Table 3). The proportion of non-responders among patients with the rs8099917 TG or GG allele was significantly higher than in those with the TT allele ($P = 0.002$). There was no

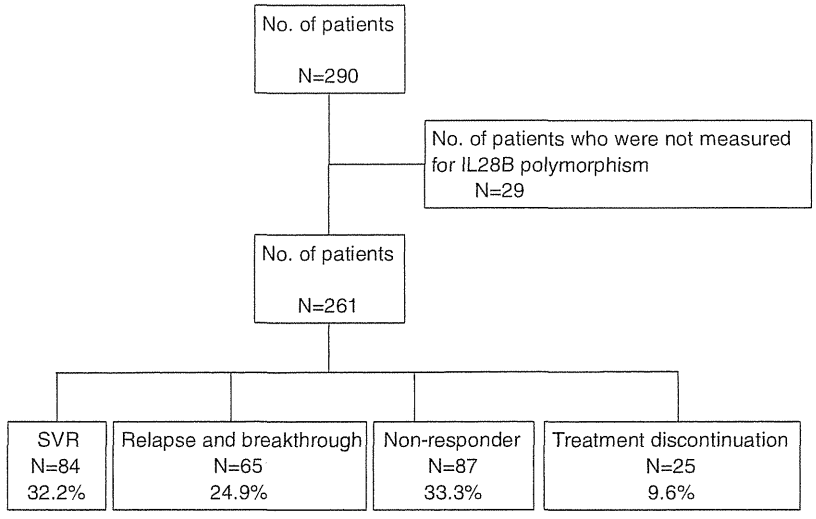

Figure 1 Flowchart showing the characteristics of the study cohort. IL28B, interleukin 28B; SVR, sustained virological response.

Table 1 Summary of demographic and baseline characteristics ($n = 261$)

	G1H, $n = 190$	Other than G1H, $n = 71$	All patients, $n = 261$
Sex (M : F)	95:95	37:34	132:129
Age (years)	60.5 ± 9.3	61.2 ± 7.8	60.7 ± 8.9
BMI (kg/m^2)	23.8 ± 3.5	23.4 ± 3.2	23.7 ± 3.4
IFN treatment history	91 (47.9%)	34 (47.9%)	125 (47.9%)
HCC treatment history	75 (39.5%)	31 (43.7%)	106 (40.6%)
Presence of EV	60 (31.6%)	25 (35.2%)	85 (32.6%)
Total bilirubin (mg/dl)	1.1 ± 0.9	1.1 ± 1.4	1.1 ± 1.2
AST (IU/L)	79.1 ± 44.2	75.8 ± 57.7	79.9 ± 52.7
ALT (IU/L)	82.4 ± 56.4	81.9 ± 75.4	83.3 ± 66.2
GGT (IU/L)	83.8 ± 107.8	87.0 ± 140.1	84.6 ± 115.8
Albumin (g/dL)	3.7 ± 0.5	3.8 ± 0.4	3.7 ± 0.5
Prothrombin (%)	86.2 ± 14.4	83.7 ± 16.7	85.5 ± 15.1
WBC (/μL)	4407 ± 1592	4190 ± 1930	4348 ± 1667
Hemoglobin (g/dL)	13.2 ± 1.8	13.1 ± 1.8	13.1 ± 1.8
Platelets (10^4/mm^3)	11.8 ± 6.7	11.8 ± 6.3	11.8 ± 6.6
AFP (ng/mL)	48.9 ± 224.7	24.0 ± 29.3	45.4 ± 193.9
DCP (mAU/mL)	66.8 ± 372.3	155.3 ± 620.4	92.4 ± 450.8
IL28B (TT : TG + GG)	133:57	51:20	184:77

All values are expressed as mean ± standard deviation.
AFP, α-fetoprotein; ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body mass index; DCP, des-γ-carboxy prothrombin; EV, esophageal varices; G1H, genotype 1 with high viral load; GGT, γ-glutamyltransferase; HCC, hepatocellular carcinoma; IFN, interferon; IL28B, interleukin 28B rs8099917 genotype; WBC, white blood cell.

significant association between the IL28B genotype and the incidence of adverse events.

Among patients in the G1H group, SVR was achieved in 27.1% (36/133) of those with the TT allele and 8.8% (5/57) of those with the TG or GG allele (Table 4). There was no statistically significant difference between IL28B genotype and viral response in patients with non-G1H.

Table 2 Summary of treatment and sustained virological response rates ($n = 261$)

	G1H, $n = 190$	Other than G1H, $n = 71$	All patients, $n = 261$
Dose reduction of IFN	$n = 98$ (51.6%)	$n = 36$ (50.7%)	$n = 134$ (51.3%)
Dose reduction of RBV	$n = 107$ (56.3%)	$n = 33$ (46.5%)	$n = 140$ (53.6%)
Treatment duration (weeks)			
Mean ± SD	45.3 ± 21.6	37.7 ± 19.6	43.2 ± 21.4
Median	48	28	48
SVR	$n = 41$ (21.6%)	$n = 43$ (60.6%)	$n = 84$ (32.2%)

G1H, genotype 1 with high viral load; IFN, interferon; RBV, ribavirin; SD, standard deviation; SVR, sustained virological response.

Table 3 Association between IL28B rs8099917 polymorphism and treatment response in 261 hepatitis C virus-related liver cirrhotic patients

IL28B	TT ($n = 184$)	TG + GG ($n = 77$)	*P*-value
SVR	68 (37.0%)	16 (20.8%)	0.013
Relapse and breakthrough	54 (29.3%)	11 (14.3%)	0.012
Non-responder	44 (23.9%)	43 (55.8%)	0.002
Discontinuation	18 (9.8%)	7 (9.1%)	1.000

IL28B, interleukin 28B rs8099917 genotype; SVR, sustained virological response.

Table 4 Sustained virological response associated between IL28B rs8099917 polymorphism and G1H in hepatitis C virus-related liver cirrhosis patients

IL28B	TT ($n = 184$)	TG + GG ($n = 77$)	*P*-value
G1H	36/133 (27.1%)	5/57 (8.8%)	0.004
Other than G1H	32/51 (62.7%)	11/20 (55.0%)	0.596

G1H, genotype 1 with high viral load; IL28B, interleukin 28B rs8099917 polymorphism.

Predictive factors associated with SVR

Differences in the characteristics of patients with SVR and those in whom SVR was not achieved are summarized in Table 5. Neither age, sex, alanine transaminase, aspartate aminotransferase, prothrombin activity, hemoglobin nor platelet counts appeared to significantly influence the chance of achieving SVR. The patients who achieved SVR had a lower body mass index, higher white blood cell count and higher serum albumin than those who did not, and were more likely to have non-G1H and the TT allele of IL28B rs8099917. Multivariate analysis identified that possession of the IL28B rs8099917 TT allele (OR = 2.85; 95% CI, 1.01–9.15; $P = 0.047$) and non-G1H (OR = 6.49; 95% CI, 1.77–26.43; $P = 0.005$) as significant determinants of SVR.

Treatment duration and efficacy in patients with G1H

Of the patients with G1H, 79 (41.6%) received less than 48 weeks of treatment. The number receiving 48–52 weeks, 53–72 weeks, over 72 weeks and unknown duration of treatment were 54 (28.4%), 41 (21.6%), 14 (7.4%) and two (1.1%), respectively. The median duration of treatment in patients who achieved RVR and cEVR was 48 weeks, but was significantly longer (66 weeks) in those with an LVR ($P < 0.001$). Table 6 shows the SVR rates of those with different IL28B genotypes and on-treatment viral response. The SVR rate in patients who achieved LVR was significantly lower than those who achieved RVR and cEVR ($P = 0.002$). Of the patients with G1H found to have the IL28B TG or GG genotype, none achieved RVR and only two achieved cEVR.

Predictors of SVR in patients with G1H and the TT allele

Patients with G1H and the TT allele who achieved SVR had higher platelet counts, higher serum albumin and had undergone over 48 weeks of treatment. Multivariate analysis identified platelet count (OR = 1.08; 95% CI, 1.01–1.18; $P = 0.047$), serum albumin (OR = 2.78; 95% CI, 1.14–7.42; $P = 0.031$) and over 48 weeks of treatment duration (OR = 2.53; 95% CI, 1.07–6.49; $P = 0.042$) as significant determinants of SVR (Table 7).

Predictors of SVR in patients with G1H and the TG or GG allele

Patients who had G1H and the TG or GG allele who achieved SVR had a higher total dose of ribavirin ($P = 0.011$) and more than 72 weeks of treatment duration ($P = 0.010$).

Treatment tolerability and adverse events

Table 8 illustrates details of the patients who experienced adverse events higher than grade 2. There were

Table 5 Factors associated with sustained virological response in hepatitis C virus-related liver cirrhosis patients

Factors	SVR (+), ($n = 84$)	SVR (−), ($n = 177$)	*P*-value	Multivariate analyses		
				Odds ratio	95% CI	*P*-value
BMI (kg/m^2)	22.9 ± 3.5	24.0 ± 3.3	0.019			
WBC (/μL)	4727 ± 2096	4168 ± 1376	0.013			
Albumin (g/dL)	3.83 ± 0.48	3.68 ± 0.46	0.018			
Other than G1H	$n = 43$ (51.2%)	$n = 28$ (15.8%)	<0.001	6.49	1.77–26.43	0.005
IL28B TT	$n = 68$ (81.0%)	$n = 116$ (65.5%)	0.012	2.85	1.01–9.15	0.047

P-values were obtained by logistic regression model.
BMI, body mass index; CI, confidence interval; G1H, genotype 1 with high viral load; IL28B, interleukin 28B rs8099917 polymorphism; SVR, sustained virological response; WBC, white blood cell.

Table 6 Sustained viral response rates between IL28B genotype and on-treatment viral response in the patients with G1H

	IL28B TT	IL28B TG/GG	All patients
RVR	7/7	0/0	7/7
	100%	0%	100%
cEVR	15/26	1/2	16/28
	57.7%	50%	57.1%
LVR	14/44	4/11	18/55
	31.8%	36.4%	32.7%

cEVR, complete early virological response (defined as serum HCV RNA negative at treatment week 12); G1H, genotype 1 with high viral load; HCV, hepatitis C virus; IL28B, interleukin 28B rs8099917; LVR, late virological response (defined as serum HCV RNA detectable at 12 weeks and undetectable at 36 weeks after the start of treatment); RVR, rapid virological response (defined as serum HCV RNA negative at treatment week 4).

two cases of liver decompensation, two cases of interstitial pneumonia, one case of cerebral hemorrhage and one case of cerebral infarction. The cause of death in two patients was decompensation of LC. In one patient, treatment was stopped after 4 weeks, and in another, treatment was stopped after 32 weeks because of hepatic failure. The IFN dose was reduced in 134 patients (51.3%), and the ribavirin dose was reduced in 140 patients (53.6%) and discontinued in 60 patients (23.0%). Among patients who had treatment discontinued, 27 patients (10.3%) had treatment withdrawn because of no virological response and 33 patients (12.6%) because of severe adverse events. In patients in whom treatment was discontinued, three patients had SVR and five had a relapse.

IL28B alleles predicting SVR in G1H group

The influence of IL28B rs8099917 genotype on SVR in G1H is shown in Figure 2. Overall, there were 84 patients (32.2%) who achieved SVR with IFN plus ribavirin in HCV-related LC. The SVR was 60.6% in those with non-G1H, and was not significantly influenced by IL28B rs8099917 genotype (the SVR in TT patients was 62.7% compared with 55.0% in TG or GG patients). In contrast, in patients with G1H, the SVR of patients with IL28B rs8099917 genotype TT was significantly higher than those with rs8099917 TG or GG (27.1% vs 8.8%, $P = 0.004$). In patients with G1H and IL28B TT, the SVR of those treated for over 48 weeks was significantly higher than those treated for less than 48 weeks (34.6% vs 16.4%, $P = 0.042$). In patients with G1H and IL28B TG/GG, the SVR of those treated for over 72 weeks was significantly higher than those treated for less than 72 weeks (37.5% vs 4.1%, $P = 0.010$).

Table 8 Adverse events higher than grade 2

	No. of patients (%)
Anemia	63 (24.1%)
Thrombocytopenia	31 (11.9%)
Leukopenia	19 (7.3%)
Rash and itching	17 (6.5%)
Fatigue and general malaise	15 (5.7%)
Gastrointestinal disorders	5 (1.9%)
Depression	5 (1.9%)
Development of hepatocellular carcinoma	3 (1.1%)
Respiratory disorders	3 (1.1%)
Liver decompensation	2 (0.8%)
Malignant neoplasm	2 (0.8%)
Interstitial pneumonia	2 (0.8%)
Cerebral hemorrhage	1 (0.4%)
Cerebral infarction	1 (0.4%)
Cholangitis	1 (0.4%)
Retinal hemorrhage	1 (0.4%)
Diabetes decompensation	1 (0.4%)
Palpitation	1 (0.4%)

DISCUSSION

WE FOUND THAT in Japanese patients with G1H HCV-related LC, the likelihood of achieving SVR with IFN plus ribavirin combination therapy was influ-

Table 7 Factors associated with sustained virological response in the patients with G1H and TT allele of IL28B rs8099917 ($n = 133$)

Factors	SVR (+) ($n = 36$)	SVR (−) ($n = 97$)	*P*-value	Multivariate analyses		
				Odds ratio	95% CI	*P*-value
Platelets (10^4/mm^3)	14.5 ± 11.5	10.6 ± 4.2	0.024	1.08	1.01–1.18	0.047
Albumin (g/dL)	3.92 ± 0.50	3.69 ± 0.46	0.018	2.78	1.14–7.42	0.031
Treatment duration, over 48 weeks	$n = 27$ (75%)	$n = 51$ (52.6%)	0.023	2.53	1.07–6.49	0.042

P-values were obtained by logistic regression model.
CI, confidence interval; G1H, genotype 1 with high viral load; IL28B, interleukin 28B; SVR, sustained virological response.

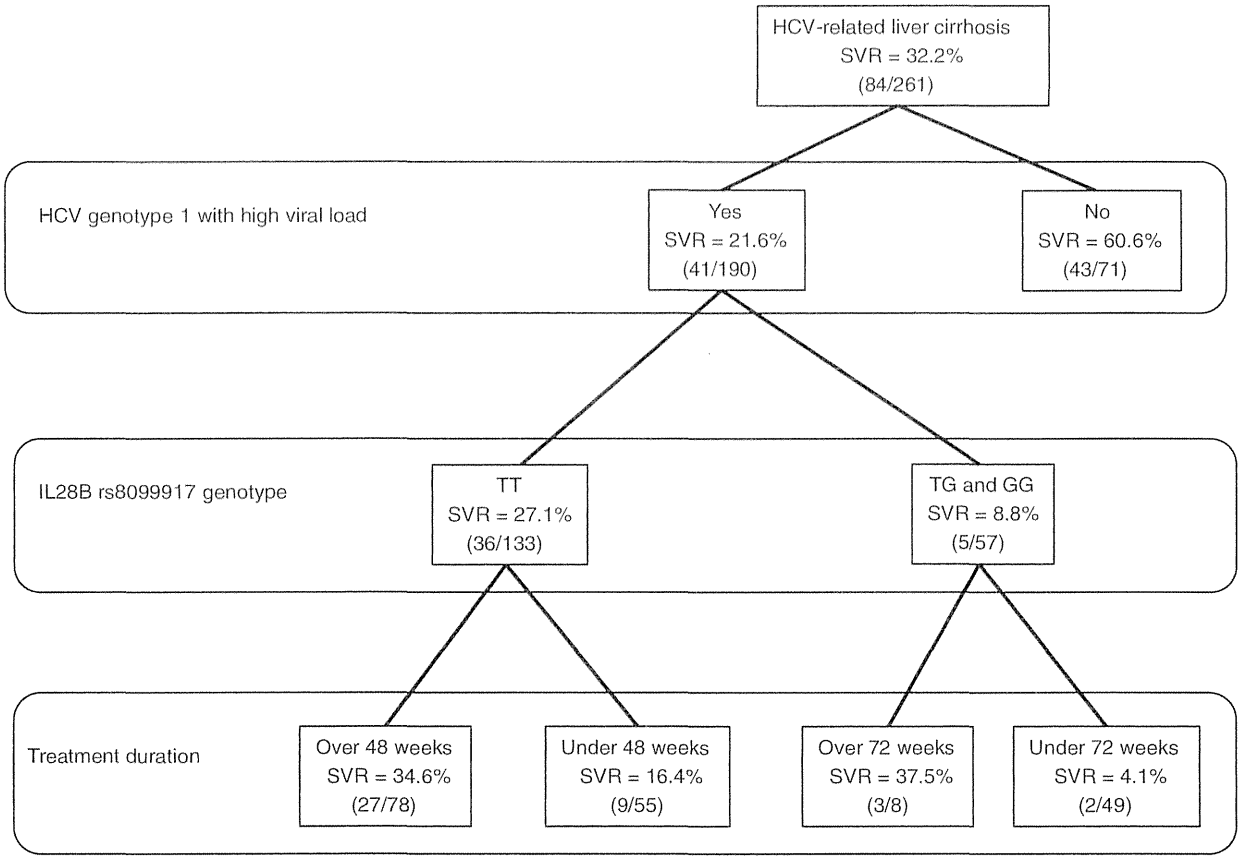

Figure 2 SVR in HCV-related liver cirrhosis patients treated with interferon plus ribavirin. In patients with G1H and the IL28B TT allele, the SVR rate of those who were treated for over 48 weeks was significantly higher than those treated for less than 48 weeks ($P = 0.042$). In patients with G1H and IL28B TG/GG, the SVR rate of patients treated for over 72 weeks was significantly higher than those treated for less than 72 weeks ($P = 0.010$). G1H, genotype 1 with high viral load; HCV, hepatitis C virus ; IL28B, interleukin 28B rs8099917; SVR, sustained virological response.

enced by a polymorphism at IL28B rs8099917. In contrast, SVR rates in non-G1H were higher than those in G1H, irrespective of IL28B genotype. This is the first report to demonstrate that an IL28B polymorphism can influence SVR rate in patients treated with IFN plus ribavirin combination therapy for G1H HCV-related LC. These results suggest that HCV genotypes, viral load and IL28B polymorphism should be taken into when determining antiviral therapy for HCV-related LC. In patients with HCV-related LC, IL28B genotyping may be a useful tool to determine the best antiviral therapy.

Recently, host genetic variation near the IL28B on chromosome 19, which encodes IFN-λ-3, have been shown to be associated with SVR to PEG IFN plus ribavirin in patients infected with HCV genotype 1.[11–13] Although some investigators have shown that IL28B polymorphisms are associated with a favorable response to treatment in patients with non-1 genotype infection, the association between the variants in IL28B and SVR in non-1 genotype-infected patients remains controversial.[19–25] IL28B polymorphisms are also a strong predictive factor for spontaneous HCV clearance.[26,27] However, the precise mechanism associated with the action of IL28B polymorphisms has not been fully elucidated.

Pegylated IFN plus ribavirin combination therapy has become the standard of care treatment for chronic HCV infection. The SVR rates range 42–46% in patients with HCV genotype 1 or 4 infection and 76–82% in patients with HCV genotype 2 or 3 infection, respectively.[9,28,29] However, in patients with HCV-related LC the SVR rate is even lower than in non-LC patients, reflecting reduced

tolerance to the therapy.[8–10] Although patients with HCV-related LC are difficult to treat, patients who achieved SVR showed a lower rate of liver-related adverse outcomes and improved survival.[8–10] Moreover, a randomized controlled trial showed that patients with HCV-related LC who received long-term PEG IFN treatment had a lower risk of HCC than controls.[30] Thus, IFN treatment for HCV-related LC is an effective means of preventing HCC, irrespective of whether SVR is achieved. In this study, the SVR was very low in patients with G1H and the TG or GG allele. Therefore, for these patients, long-term administration of maintenance IFN should be considered to reduce the risk of developing of HCC even if SVR is unlikely to be achieved.

Patients with advanced liver disease have a higher rate of adverse events when taking IFN and ribavirin combination therapy than patients with mild disease. Adverse events, such as neutropenia, thrombocytopenia and anemia, often require dose reduction of IFN or ribavirin. Previous studies have demonstrated that in patients with HCV-related LC, the rate of dose reductions in IFN and ribavirin range 6.9–20.6% and 16.7–27.1%, respectively.[31–33] In our study, IFN and ribavirin dose reductions were needed in 51.3% and 53.6% of patients, respectively. These are higher than those reported in other studies, but the discontinuation rate was slightly lower (12.6%).[33] Many patients required reductions in the doses of IFN and/or ribavirin early in the treatment period because of adverse events, but ultimately were able to tolerate long-term administration. It might be safer to start low-dose antiviral therapy with IFN plus ribavirin in HCV-related LC and titrating the dose upward as tolerated with the aim of long-term treatment, rather than beginning with the full dose and risking adverse events that would curtail antiviral therapy.

In patients infected with HCV genotype 1, previous studies have demonstrated that SVR rates of late virological responders (HCV RNA detectable at 12 weeks and undetectable at 24 weeks after the start of treatment) could be improved when treatment was extended to 72 weeks, compared with the standard treatment duration of 48 weeks, largely as a result of reducing post-treatment relapse rates.[34–37] In this study, the SVR rate in patients who had an LVR was significantly lower than those who achieved RVR or cEVR. However, the duration of treatment in the patients with a LVR was significantly longer than those who achieved cEVR or RVR. Individual physicians determined the duration of treatment based on the time at which serum HCV RNA became undetectable, accounting for the improved SVR rates in those receiving extended courses. Nevertheless, the safety and effectiveness of more than 48 weeks of antiviral therapy in patients with HCV-related LC has not been examined. We found that patients with the IL28B rs8099917 genotype TT, treatment of more than 48 weeks achieved a higher SVR rate than treatment of less than 48 weeks, and in those with the TG or GG alleles SVR rates were greater in those who received more than 72 weeks of treatment. The response to treatment is a very important guide of treatment duration in HCV-related LC. Further prospective studies using larger numbers of patients matched for race, HCV genotype, viral load and treatment durations would be required to explore the relationships between IL28B polymorphism and the treatment response to combination therapy in patients with HCV-related LC.

Recently, new trials of IFN-free combination therapy with direct-acting antivirals (DAA) such as protease-inhibitor, non-structural (NS)5A inhibitor or NS5B polymerase inhibitor nucleotide analog have shown a strong antiviral activity against HCV.[38–40] A previous study reported that the IL28B genotype can affect the response to an IFN-free regimen, but this result has been unclear in other regimens.[38–40] In a study of Japanese patients with HCV genotype 1b infection, dual oral DAA therapy (NS5A inhibitor and NS3 protease inhibitor) without IFN achieved an SVR rate of 90.5% of 21 patients with no response to previous therapy and in 63.6% of 22 patients who had been ineligible for treatment with PEG IFN.[41] However, lack of a virological response to DAA was also seen in patients with no response or partial response to previous therapy. In these patients with viral resistance to DAA, the combination therapy with IFN and DAA may be a means of eliminating HCV, and IL28B genotyping may be a useful tool in determining the best antiviral therapy and duration of treatment.

This study had certain limitations. Selection bias cannot be excluded, considering the retrospective nature of the work. However, all patients had well-established cirrhosis and had received IFN plus ribavirin in hepatitis centers throughout Japan. Our patients received a variety of IFN treatments (IFN-α, IFN-β and PEG IFN), several different doses of IFN and ribavirin, and several treatment durations. In the intention-to-treat analysis, the overall SVR rate was 32.2%; in patients with G1H it was 21.6% but was 60.6% in those with non-G1H. Interestingly, the overall SVR rate in this study was similar to that found in previous studies of patients with advanced fibrosis or cirrhosis treated with IFN or PEG IFN plus ribavirin.[8–10] Thus, although there were some

limitations, our findings contribute to providing valuable information to guide clinical decisions.

In conclusion, the combination therapy with IFN plus ribavirin in Japanese patients with non-G1H HCV-related LC was more effective than those with G1H and not influenced by IL28B polymorphism. However, in patients with G1H, IL28B polymorphism may be a strong predictive factor for SVR. Extending treatment may provide a better outcome in those with the IL28B TT allele treated for more than 48 weeks and in those with the TG/GG alleles treated for more than 72 weeks.

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特集II　C型肝炎治療困難例への対策*

C型肝炎治療困難例に対する瀉血療法，IFN-β療法，脾摘/PSE後のPeg-IFN療法の検討*

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Key Words : chronic hepatitis C, phlebotomy, interferon beta, splenectomy, partial splenic embolization (PSE)

はじめに

C型肝炎に対するtelaprevirやsimeprevirを含む3剤併用療法が認可されたが，貧血，血小板減少，高齢，うつ等のため通常のペグインターフェロン(PEG-IFN)やリバビリン(RBV)を含む治療が困難な症例も少なくない．また，そのような症例に対してIFNなしの抗ウイルス剤(direct-acting aniviral agents；DAAs)のみの併用療法も期待されているが，ウイルスの耐性獲得など未知の課題が生じる可能性は否定できない．

そうした治療困難例に対する治療成績はいまだ蓄積が不十分であり，治療の工夫，治療効果や有用性について検討する必要がある．

本研究ではC型肝炎の標準治療が困難な症例に対する，IFN-β療法，脾臓摘出術(脾摘)または脾動脈塞栓術(partial splenic embolization；PSE)後のPEG-IFN療法，瀉血療法について，それらの治療効果や問題点について検討を加えた．

患者の遺伝子多型(SNP)についてはIL28B SNP(rs8099917)とITPA SNP(rs1127354)を解析し，治療効果への影響を検討した．遺伝子検査は当大学の遺伝子倫理委員会の承認の上，文書による同意を得て施行した．

ARFI(acoustic radiation force impulse)による肝硬度(Velocity of shear wave；Vs)の変化についても検討を加えた．

C型肝炎治療困難例に対するIFN-β＋RBV療法

1．対象と方法

2008年1月～2012年9月にIFN-β＋RBV療法を施行したC型慢性肝炎患者10例(2例はIFN-β単独)を対象とした．症例の内訳(表1)は男性3例，女性7例，年齢58±10(40～66)歳．HCVのgenotype 1型8例，2型2例で，HCV-RNA量6.8±0.9(4.5～7.5)logIU/ml，IL28B SNP(n＝9)はTT 7例，TG or GG 2例，ITPA SNP(n＝9)はCC 6例，AC or AA 3例であった．また，肝生検は8例に施行し，新犬山分類の炎症gradeはA0 0例，A1 4例，A2 4例，A3 0例で，線維化stageはF0 2例，F1 1例，F2 4例，F3 1例，F4 0例であった．IFN-βを選択した理由は，血小板低値(9万/μl未満)が7例，うつが3例であった．肝

* Phlebotomy, interferon beta therapy, pegylated interferon therapy after splenectomy or partial splenic embolization for refractory patients with chronic hepatitis C virus infection.

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表1　IFN-β+RBV療法—患者背景

Characteristics	n=10
Gender (female/male)	7/3
Age (years)	58±10 (40～66)
HCV genotype (1/2)	8/2
HCV viral load (logIU/ml)	6.8±0.9 (4.5～7.5)
IL28B (TT/TG or GG) (n=9)	7/2
ITPA (CC/AC or AA) (n=9)	6/3
Activity (Grade ; 0/1/2/3) (n=8)	0/4/4/0
Fibrosis (Stage ; 0/1/2/3/4) (n=8)	2/1/4/1/0
Low platelet counts (<9×10⁴/μl)	7 (7.3±0.9 ; 5.9～8.7)
Depression	3

表2　IFN-β+RBV療法—治療前後の変化

	Before treatment	After treatment	*P* value
Platelet (×10⁴/μl)	9.7±4.5	10.8±5.9	NS
WBC (/μl)	4,110±1,071	3,800±1,569	NS
Hemoglobin (g/dl)	13.2±1.4	12.0±1.0 ↓	*P*=0.0073
Albumin (g/dl)	3.9±0.4	3.9±0.6	NS
AST (IU/l)	80±60	40±26 ↓	*P*=0.0316
ALT (IU/l)	86±57	33±22 ↓	*P*=0.0093
Hyaluronic acid (ng/ml)	289±351	162±121	NS
AFP (ng/ml)	23.4±27.6	12.2±14.5	NS
PIVKA-II (mAU/ml)	32.0±31.0	25.0±19.0	NS
Viral load (logIU/ml)	6.8±0.9	6.5±0.6	NS

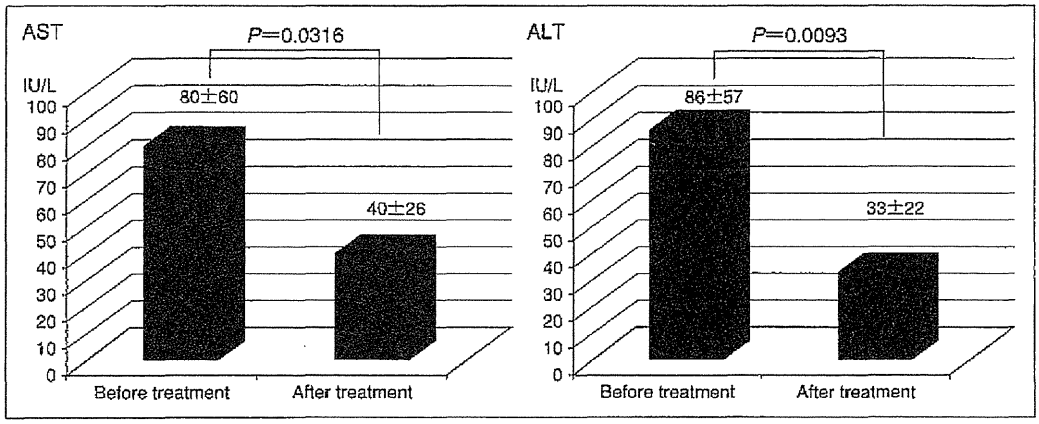

図1　IFN-β+RBVによるtransaminaseの低下

硬度は治療前，治療終了時に測定した．

2．結　　果

AST (80.0±60.0→39.9±26.0 IU/l, *P*=0.0316), ALT (86.0±57.0→33.0±22.0 IU/l, *P*=0.0093), Hb (13.2±1.4→12.0±1.0 g/dl, *P*=0.0062) が有意に低下していた (表2，図1)．うち血小板低値例は血小板数7.3±0.9万 (5.9～8.7万) /μlであったが，血小板数を維持して治療を継続できた．Genotype 2型は2例ともHCV排除 (sustained virological response ; SVR) となったが，1型ではSVR例はみられなかった．

脾摘/PSE後のPeg-IFN療法

1．対象と方法

2007年1月～2012年9月に脾摘/PSE後にPEG-IFN+RBV療法を施行した10例 (1例はPEG-IFN

表3 脾摘またはPSE施行例—患者背景

Characteristics	n＝10
Gender(female/male)	6/4
Age(years)	63±10 (39～69)
Splenectomy/PSE	8/2
Platelet counts	5.2±1.5(3.2～6.8)
HCV genotype(1/2)	8/2
HCV viral load(logIU/ml)	6.0±1.3(3.2～7.1)
IL28B(TT/TG or GG)	10/0
Core 70(Wild/Mutant) (n＝5)	3/2
Core 91(Wild/Mutant) (n＝5)	3/2
ISDR mutation(0～1/2<) (n＝5)	3/2

表4 脾摘またはPSE施行前後の変化

	Before operation	After operation		*P* value
Platelet(×10⁴/μl)	5.2±1.5	16.9±8.3	↑	*P*＝0.0080
WBC(/μl)	3,456±1,028	5,130±1,946	↑	*P*＝0.0264
Hemoglobin(g/dl)	12.4±1.7	12.3±1.2		NS
Albumin(g/dl)	3.7±0.4	3.8±0.3		NS
T-Bilirubin(mg/dl)	1.2±0.5	1.1±0.4		NS
AST(IU/l)	66±28	58±27		NS
ALT(IU/l)	58±27	48±22	↓	*P*＝0.0697
γ-GTP(IU/l)	59±61	47±39		NS
PT(%)	80±8	87±10	↑	*P*＝0.0633
Viral load(logIU/ml)	6.0±1.3	6.1±1.3		NS

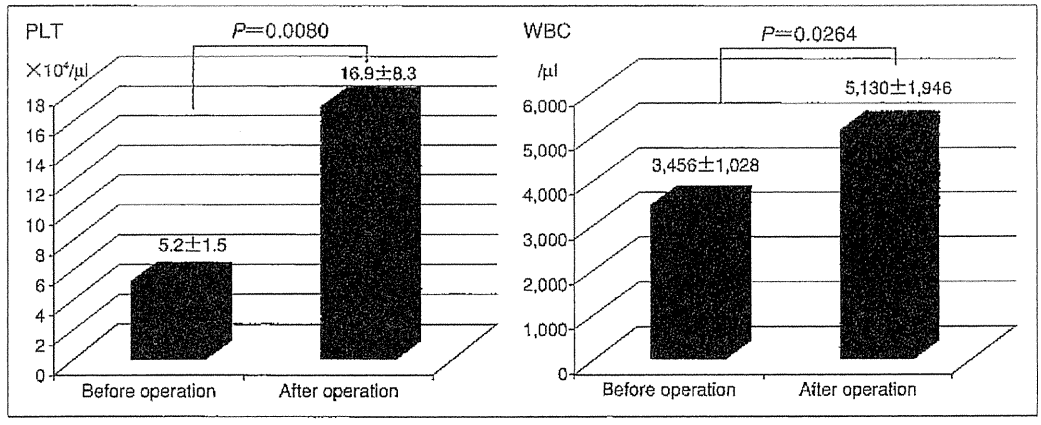

図2 脾摘/PSEによる血小板と白血球の上昇

単独）を対象とした．症例の内訳（表3）は男性4例，女性6例，年齢63±10（39～69）歳で，脾摘8例，PSE2例．術前の血小板数は5.2±1.5万（3.2～6.8万）/μl，HCVのgenotype 1型8例，2型2例で，HCV-RNA量6.0±1.3（3.2～7.1）logIU/ml，IL28B SNPは全10例ともTTであった．

2．結　果

脾摘/PSEにより，血小板数（5.2±1.5万→16.9±8.3万/μl，*P*＝0.0080）と白血球数（3,456±1,028→5,130±1,946/μl，*P*＝0.0264）の有意な上昇がみられ，PEG-IFN＋RBV療法が可能となった（表4，図2）．また，ALT（58.0±27.0→48.0±22.0 IU/l，*P*＝0.0697）とPT（80±8→87±10%，*P*＝0.0633）の改善傾向がみられた．脾摘/PSE後のPEG-IFN＋RBV療法（1例はPEG-IFN単独）により，genotype 1型は8例中2例でSVR（25%），2型は2例中1

表5　瀉血療法—患者背景①

Characteristics	n=24
Gender(female/male)	11/13
Age(years)	60.1±11.3(35～74)
HCV genotype(1/2)	23/1
HCV viral load(logIU/ml)	6.6±0.5(5.5～7.4)
IL28B(TT/TG or GG)　(n=21)	12/9
ITPA(CC/AC or AA)　(n=21)	18/3
Phlebotomy；Period(months)	25.7±8.5(2～64)
Phlebotomy；Volume(ml)	3,053±2,235(400～8,400)

表6　瀉血療法—患者背景②

Reasons for phlebotomy	n=24
IFN / PEG-IFN+RBV；Non-SVR	15
Side effects of IFN；Depression, Convulsion, ALT ↑	6
Low platelet counts	9
Ulcerative colitis	1

例でSVR(50%)が得られた.

瀉血療法

1. 対象と方法

2005年1月～2012年9月に症例の内訳(表5)は男性13例，女性11例，年齢60±11(35～74)歳．HCVのgenotype 1型23例，2型1例で，HCV-RNA量6.6±0.5(5.5～7.4)logIU/ml，IL28B SNP(n=21)はTT 12例，TG or GG 9例，ITPA SNP(n=21)はCC 18例，AC or AA 3例であった．1回瀉血量254±103 ml，瀉血回数20±42回，総瀉血量3,053±2,235(400～8,400)ml，瀉血期間25.7±8.5(2～64)か月であった．瀉血療法を選択した理由は，IFN / PEG-IFN+RBV療法のnon-SVRが15例，IFNによる副作用が6例，血小板低値が9例，潰瘍性大腸炎の合併例1例であった(表6，一部の症例で重複)．

2. 結　果

瀉血により，フェリチン(303.5±369.6→46.0±42.0 ng/ml，P=0.0032)，血清鉄(149.0±42.2→96.7±58.2 μg/dl，P=0.0011)，AST(68.6±37.8→49.5±25.8 IU/l，P<0.0001)，ALT(80.0±53.8→49.1±34.9 IU/l，P<0.0001)，γ-GTP(81.3±75.7→55.3±38.5 IU/l，P=0.0078)，アルブミン値(4.2±0.4→4.0±0.5 g/dl，P=0.0062)は有意に低下し，AFP(24.0±31.7→14.3±11.4 ng/ml，P=0.0910)とPIVKA-II(19.5±7.0→16.5±6.5 mAU/ml，P=0.0515)は低下する傾向を示した(表7，図3)．肝硬度(ARFI)を測定できた10例では肝硬度は有意に上昇(1.6±0.4→2.1±0.8 m/s，P=0.0111)していた．これらの結果から，瀉血によりAST，ALT，γ-GTPが有意に低下し，AFPとPIVKA-IIも低下する傾向を示したが，アルブミン値は有意に低下し，肝硬度は有意に上昇しており，肝予備能の低下や肝線維化の進展に注意が必要であると考えられた．

考　案

現在，わが国でC型慢性肝炎に対する根治的な治療の第1選択はIFNを中心とした抗ウイルス療法である．特にgenotype 1型で高ウイルス量の症例に対しては，telaprevirやsimeprevirを含む3剤併用療法が認可され，SVR率の飛躍的な上昇をもたらした．しかし，貧血，血小板減少，高齢，うつ等のため通常のPEG-IFNやRBVを含む治療が困難な症例も少なくない．また，そのような症例に対してIFNなしのDAAsのみの併用療法も期待されているが，ウイルスの耐性獲得など未知の課題が生じる可能性は否定できない．

そうした治療困難例に対する治療成績はいまだ蓄積が不十分であり，治療の工夫，治療効果や有用性を検証する必要があるため，今回3つの検討を行った．

IFN-β製剤は血球減少の副作用が軽度で，うつ

表 7　瀉血療法―治療前後の変化

	Before phlebotomy	After phlebotomy		P value
Platelet (×10⁴/μl)	12.6±4.9	12.8±5.6		NS
WBC (/μl)	4,942±1,269	4,745±1,306		NS
Hemoglobin (g/dl)	14.7±1.0	13.6±1.5	↓	P=0.0004
Ferritin (ng/ml)	304±370	46±42	↓	P=0.0032
Serum iron (μg/dl)	149±42	97±58	↓	P=0.0011
TIBC	356±47	422±63	↑	P<0.0001
T-Bilirubin (mg/dl)	1.0±0.4	0.9±0.3		NS
Albumin (g/dl)	4.2±0.4	4.0±0.5	↓	P=0.0062
AST (IU/l)	68.6±37.8	49.5±25.8	↓	P<0.0001
ALT (IU/l)	80.0±53.8	49.1±34.9	↓	P<0.0001
γ-GTP (IU/l)	81.3±75.7	55.3±38.5	↓	P=0.0078
PT (%)	94.0±9.1	95.5±9.6		NS
Hyaluronic acid (ng/ml)	210±161	257±237		NS
AFP (ng/ml)	24.0±31.7	14.3±11.4	↓	P=0.0910
PIVKA-II (mAU/ml)	19.5±7.0	16.5±6.5	↓	P=0.0515
Viral load (logIU/ml)	6.6±0.5	6.5±0.6		NS
Vs (m/s) ; Liver stiffness	1.6±0.4 (n=10)	2.1±0.8 (n=10)	↑	P=0.0111

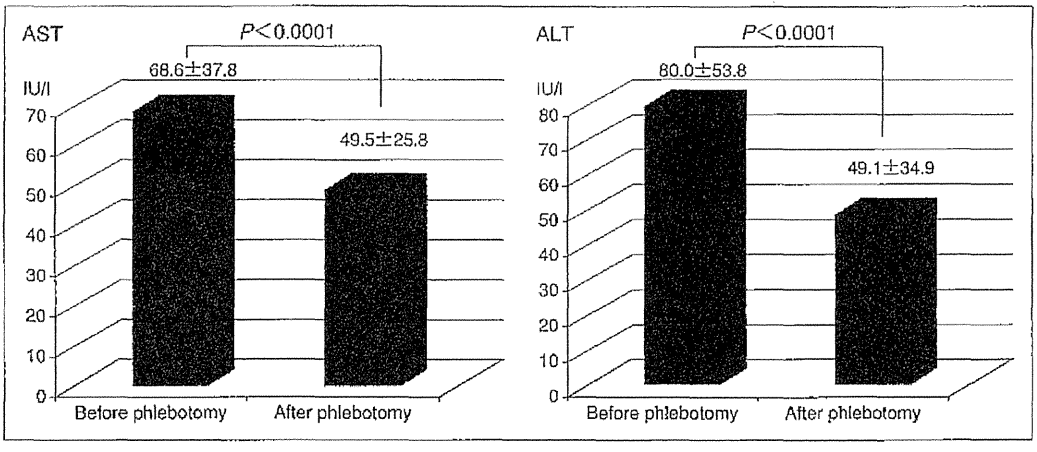

図 3-1　瀉血療法によるtransaminaseの低下

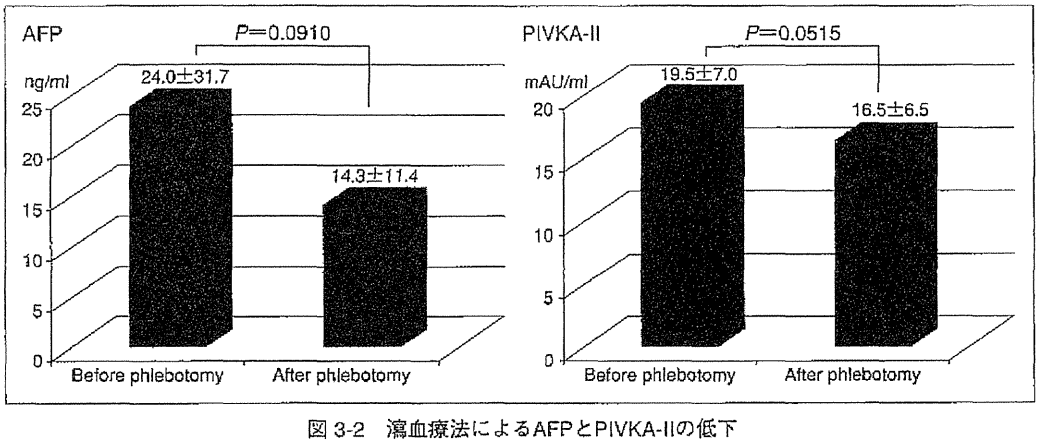

図 3-2　瀉血療法によるAFPとPIVKA-IIの低下