Japan. Currently, for pegylated (PEG) IFN-α-2a/RBV treatment of liver cirrhosis, Japanese insurance considers a platelet count of 75×10^9 platelets/L or more as the standard count for treatment initiation and less than 50×10^9 platelets/L as that for discontinuation. However, it is now clear that half of the specialized institutes surveyed were initiating IFN therapy even in patients with platelet counts below the recommended value, and 9% of institutes were administrating IFN even in patients with platelet counts below the standard discontinuation value. Moreover, there was disproportionate selection and application of splenectomy and/or PSE, perhaps because each institute tended to select its experienced method. Therefore, in order to obtain consensus in the future, it is necessary to investigate the actual situation of splenectomy/PSE treatment in HCV positive patients with a low platelet count through the collection of clinical data.

Beneficial information regarding the effects of splenectomy and/or PSE on IFN treatment for the patients was also obtained from this questionnaire. The platelet counts increased after splenectomy and/or PSE, thus resulting in the improvement of adherence to IFN treatment. However, an increased SVR rate was not prominent in patients with HCV genotype 1b and a high viral load. It was presumed that if the viral factor shows IFN-resistant characteristics and liver cirrhosis exists as an intractable factor on the patient side, only a small number of patients will achieve a SVR with PEG IFN/RBV treatment, despite increased platelet counts and IFN adherence following splenectomy and/or PSE. However, in the case of "others", a relatively high SVR rate was observed (Table 4). Interestingly, the SVR rate of the "others" splenectomy group was significantly higher than that of the "others" PSE group, despite the pretreatment platelet count being lower in the splenectomy group than that of the PSE group. If the platelet count is less than 80×10^9 platelets/L in cases of "others," anti-hypersplenism treatment should be performed to increase the platelet count, and we suggest that splenectomy should be selected because of its strong effect on the increase of the platelet count.

Many complications regarding patients' safety were observed in both splenectomy and PSE groups, and it should be noted that slightly less than 1% cases resulted in death. Most patients had liver cirrhosis. These patients typically have several medical problems that can become severe if they are not receiving anti-HCV therapy, including decompensated cirrhosis and/or the development of HCC. However, the high mortality rate reported in the present study should not be overlooked.

We recommend that the application of splenectomy/PSE prior to IFN treatment should be chosen with careful consideration.

At present, splenectomy/PSE is also mentioned in the Guidelines for IFN Treatments in Liver Cirrhosis C in Japan as treatments for patients with low platelet counts, although the risk of death due to splenectomy/PSE for the purpose of IFN treatment has not been studied previously. Death was related to infections in many cases, but the rate of pneumococcal vaccine inoculation was low in cases of death. According to the questionnaire results, within institutes administrating pneumococcal vaccines when performing splenectomy, the vaccination rate was 80% or more in the department of internal medicine and 60% or more in the surgical department; however, this rate was only approximately 20% for PSE. The pneumococcal vaccine is inoculated at a high rate for splenectomy based on the recommendations from the insurance guidelines[29] and infection prevention guidelines.[30-32] In contrast, there is no evidence indicating the usefulness of pneumococcal vaccine inoculation when performing PSE, in which splenic function is preserved. Therefore, this vaccine was not given to patients undergoing PSE in many cases. However, considering the fact that most causes of death were related to infections, pneumococcal vaccine inoculation should also be necessary when carrying out PSE. Moreover, vaccinations against bacteria other than *Streptococcus pneumoniae* such as *Haemophilus influenzae* type b (Hib) and *Neisseria meningitidis*, which mainly exhibit immune reactions in the spleen, may be important to administrate before splenectomy and/or PSE.[33-36]

Deaths were primarily observed in Child–Pugh B or C cirrhotic patients and those aged above 60 years. Therefore, splenectomy/PSE must be applied with care in patients with poor residual hepatic function and elderly patients.[37,38]

As a result of this questionnaire, we determined that adherence to IFN treatment was increased by splenectomy and/or PSE; however, in patients with HCV genotype 1b and a high viral load, the rate of SVR was not improved. Therefore, splenectomy and/or PSE must be limited to the cases in which IFN is likely to be effective. In addition, it is essential to predict the sensitivity of IFN treatment by evaluating the IFN sensitivity-determining region of HCV, core domain amino acid 70 of HCV and interleukin-28B, as well as hepatic functional reserves and age before splenectomy and/or PSE. In the future, treatment by various oral therapeutic agents (direct antiviral agents) may be selected without administrating IFN for patients with low platelet counts.[39,40]

ACKNOWLEDGMENTS

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Thrombocytopenia in pegylated interferon and ribavirin combination therapy for chronic hepatitis C

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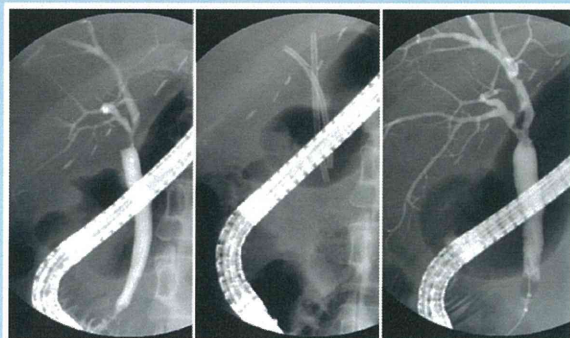
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ORIGINAL ARTICLE—LIVER, PANCREAS, AND BILIARY TRACT

Thrombocytopenia in pegylated interferon and ribavirin combination therapy for chronic hepatitis C

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Abstract

Background This study aimed to examine the therapeutic effect and prognostic indicators of pegylated interferon (PEG-IFN) and ribavirin (RBV) combination therapy in thrombocytopenic patients with chronic hepatitis C, hepatitis C virus (HCV)-related cirrhosis, and those who underwent splenectomy or partial splenic embolization (PSE).
Methods Of 326 patients with HCV-related chronic liver disease (252 with genotype 1b and 74 with genotype 2a/2b) treated with PEG-IFN/RBV, 90 were diagnosed with cirrhosis.
Results Regardless of the degree of thrombocytopenia, the administration rate was significantly higher in the splenectomy/PSE group compared to the cirrhosis group. However, in patients with genotype 1b, the sustained virological response (SVR) rate was significantly lower in the cirrhosis and the splenectomy/PSE groups compared to the chronic hepatitis group. No cirrhotic patients with platelets less than 80,000 achieved an SVR. Patients with genotype 2a/2b were more likely to achieve an SVR than genotype 1b. Prognostic factors for SVR in patients with genotype 1b included the absence of esophageal and gastric varices, high serum ALT, low AST/ALT ratio, and the major homo type of the IL28B gene. Splenectomy- or PSE-facilitated induction of IFN in patients with genotype 2a/2b was more

likely to achieve an SVR by an IFN dose maintenance regimen. Patients with genotype 1b have a low SVR regardless of splenectomy/PSE. In particular, patients with a hetero/minor type of IL28B did not have an SVR.
Conclusions Splenectomy/PSE for IFN therapy should be performed in patients expected to achieve a treatment response, considering their genotype and IL28B.

Keywords IFN therapy · IL28B · Partial splenic embolization · Splenectomy · Thrombocytopenia

Introduction

Chronic hepatitis C is characterized by recurrent necrosis and regeneration in the setting of persistent inflammation, leading to progressive hepatic fibrosis, which increases the risk of carcinogenesis. In cirrhotic livers, cancer develops at a higher rate [1, 2]. However, after a virus has been removed by interferon (IFN) therapy, hepatic fibrosis can improve, and the incidence of liver cancer is subsequently reduced [3–5]. Therefore, to prevent fibrosis and liver carcinogenesis, virus elimination by antiviral therapies is paramount in advanced cases.

As an antiviral therapy for chronic hepatitis C, pegylated interferon (PEG-IFN) in combination with ribavirin (RBV) has resulted in remarkably favorable outcomes, with a sustained virological response (SVR) obtained in approximately 80 % of patients with genotypes 2 and 3 and, more impressively, 40–50 % of patients with genotype 1 and a refractory high viral load [6–9].

As fibrosis progresses, however, the therapeutic effect of antivirals diminishes. Studies have reported that the effect of PEG-IFN/RBV combination therapy for liver cirrhosis characterized by progressive fibrosis was exceedingly poor,

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with the SVR rates 14–27 % in patients with genotype 1 and 33–56 % in patients with genotypes 2 and 3 [10–12].

It is very important to maintain the IFN dose as the administration rate in addition to the presence of fibrosis greatly influences the therapeutic effect [13, 14]. However, it can be difficult to maintain the IFN dose in patients with cirrhosis complicated by hypersplenism. Thrombocytopenia from hypersplenism can develop and/or be exacerbated following IFN therapy, making ongoing therapy problematic. In addition, the induction of IFN therapy may be difficult in some of these patients [15, 16]. Hence, to address cytopenias including thrombocytopenia, splenectomy or partial splenic embolization (PSE) can be performed for hepatitis C virus (HCV)-related cirrhosis with hypersplenism [17–23]. However, the therapeutic effect and long-term safety and efficacy of such treatment have not been sufficiently examined.

Recently, studies have reported that the interferon sensitivity-determining region (ISDR) and amino acid substitutions of core 70 and core 91 in the core region of HCV are important prognostic indicators of IFN's therapeutic effect. Furthermore, the therapeutic effect rate of IFN depends on the genetic polymorphism of IL28B [24–29].

The objectives of this study were to examine the therapeutic effect and associated prognostic indicators of PEG-IFN/RBV therapy in thrombocytopenic patients with chronic hepatitis and HCV-related cirrhosis and those who underwent splenectomy or PSE.

Methods

Patients

This study was approved by the Ethics Committee of the Hyogo College of Medicine (approval no. 92, 391) and adhered to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all patients after the objectives and nature of the study had been discussed.

Between January 2005 to 2012, 326 patients with HCV-related chronic liver disease who were started on PEG-IFN/RBV combination therapy and followed at the Hyogo College of Medicine Hospital were enrolled in the study (Fig. 1).

Twenty-six patients were diagnosed with cirrhosis macroscopically when they underwent splenectomy in our hospital. Of 45 patients with esophageal and gastric varices and diagnosed with cirrhosis on abdominal imaging, two underwent splenectomy in other hospitals, and one underwent PSE prior to IFN therapy.
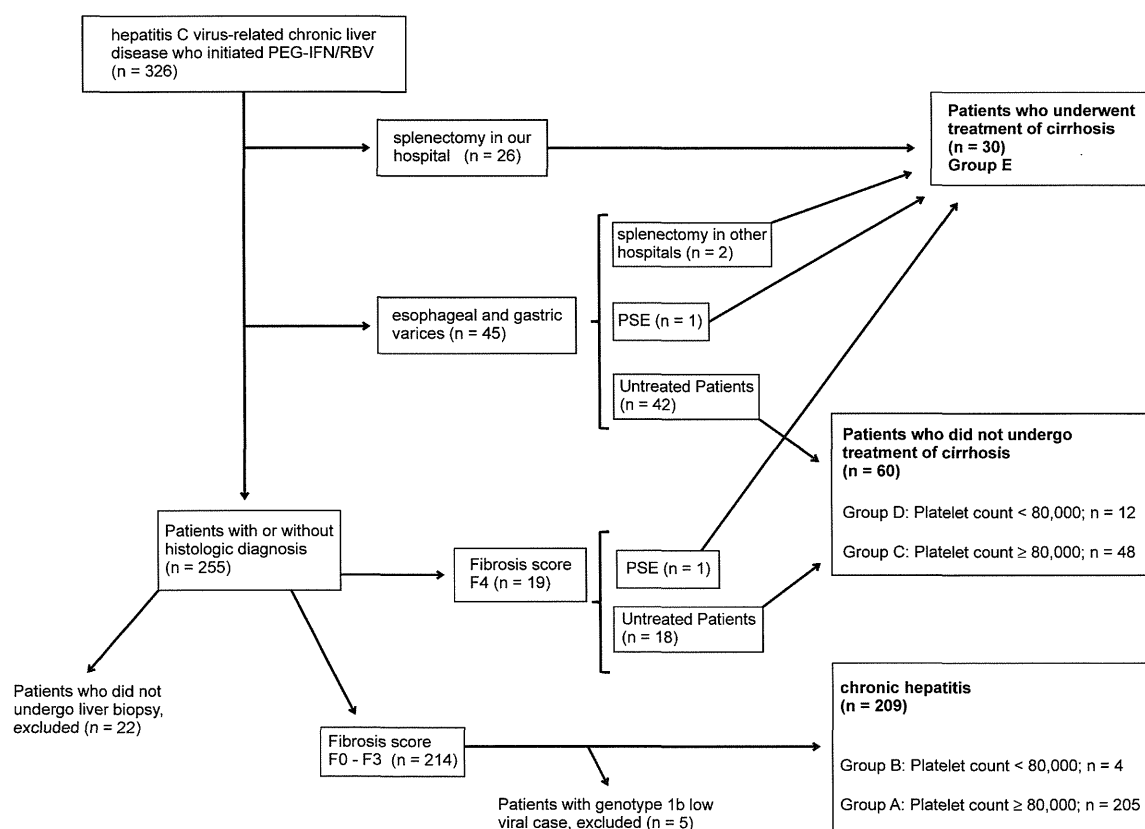
Fig. 1 Flow diagram of study patients

Of the remaining 255 patients, 22 patients who did not undergo liver biopsy were excluded from the study, 233 patients underwent a liver biopsy, and 19 were diagnosed to have cirrhosis histologically. One of the 19 patients subsequently underwent PSE prior to IFN therapy. In total, there were 90 patients diagnosed with cirrhosis in this study. The 30 patients with cirrhosis who underwent splenectomy or PSE (treated cirrhosis group) were compared to the 60 patients who did not have either procedure (untreated cirrhosis group).

Of the 233 patients who had a liver biopsy, 214 did not have histological diagnosis of cirrhosis. Five patients with genotype 1b low viral load (HCV-RNA <100 K IU/ml) in the chronic hepatitis group were excluded from this study because there were no patients with genotype 1b low viral load in the corresponding cirrhosis group.

There were 43 patients (4, 12, and 27 patients in group B, D, and E, respectively) with a platelet count of less than 80,000 prior to the initiation of IFN therapy. They were fully informed aboout the expected benefits and associated risks of splenectomy or PSE. Twenty-five consented to splenectomy, while another two chose to undergo PSE prior to IFN therapy.

One patient with a platelet count of slightly more than 80,000 requested to undergo splenectomy. Therefore, we initiated IFN therapy in this patient and considered the patient in the treated group analysis in this study. With regard to the two patients who had already undergone splenectomy for portal hypertension in other hospitals, although their lowest platelet counts prior to splenectomy were unknown, they were nevertheless also included in the treated group.

Patients with uncontrolled ascites, liver cancer, esophageal, and/or gastric varices requiring treatment and those who underwent liver transplantation were excluded from this study. Patients with positive hepatitis B virus surface antigen, positive human immunodeficiency virus antigen, or other hepatic disorders (e.g., primary biliary cirrhosis or autoimmune hepatitis) were also excluded.

Table 1 shows the characteristics of 299 patients (groups A, B, C, D, and E; see Fig. 1) prior to IFN therapy. Blood work before splenectomy or PSE is also provided for those who underwent these procedures.

Treatment for hepatitis C virus

Peginterferon alpha-2a (Pegasys®; Chugai, Japan) was administered to 113 patients, and 186 were treated with peginterferon alpha-2b (Pegintron®; MSD, Japan). The basic dose each week was either 180 μg of peginterferon alpha-2a or 1.0–1.5 μg/kg of peginterferon alpha-2b. RBV combination therapy was also given to all patients and was administered orally each day at a basic dose depending on body weight (<60 kg, 600 mg; 60–80 kg, 800 mg; >80 kg, 1,000 mg).

Patients with genotype 1b and 2a/2b were treated for 48 and 24 weeks, respectively. Based on the patient request, 106 with genotype 1b were treated for 50–90 weeks, and 34 with genotype 2a/2b were treated for 30–72 weeks.

Laboratory and histological tests

The amount of HCV was measured by COBAS AMPLICOR HCV MONITOR test, version 2.0 (detection range 6–5000 K IU/ml; Roche Diagnostics, Branchburg, NJ, USA). Qualitative analysis was performed using COBAS AMPLICOR HCV test, version 2.0 (lower limit of detection 50 IU/ml; Roche Diagnostics). For patients who started IFN therapy after January 2008, the amount of HCV was measured by COBAS TaqMan HCV test (Roche Diagnostics). Six months after completing treatment, patients with negative HCV RNA were considered to have an SVR.

ISDR, Core 70, and Core 91 were measured by the direct sequencing method, as previously reported [23, 24]. The IL28B gene (rs 8099917) was measured using the TaqMan probe method, as previously reported [25].

Histological assessment of fibrosis was scored using the METAVIR scoring system: F0, no fibrosis; F1, mild fibrosis or portal fibrosis without septa; F2, moderate fibrosis or few septa; F3, severe fibrosis or numerous septa without cirrhosis; F4, cirrhosis.

Study analysis

We recently reported a nationwide survey in Japan regarding splenectomy/PSE for interferon treatment targeting HCV-related chronic liver disease in patients with low platelet counts. We found that many patients with platelet counts <80,000 were treated with a reduced dose of IFN, at which the SVR rate was predicted to be low [30]. Therefore, we classified the patients with platelet counts of 80,000 in the present study. Before IFN therapy, patients with chronic hepatitis who had the lowest platelet count of at least 80,000 were assigned to group A, whereas those with a platelet count of less than 80,000 were placed in group B. Patients with liver cirrhosis who had platelet counts of at least 80,000 before IFN therapy were assigned to group C, whereas those with platelet counts of less than 80,000 before IFN therapy were placed in group D. Group E comprised patients who received IFN therapy after splenectomy or PSE (Fig. 1). The IFN administration rate was examined according to each group. Treatment was discontinued in patients who failed to demonstrate virus-negative results by 24 weeks. Therefore, the IFN dose was evaluated using the dose administered until 24 weeks. The

Table 1 Baseline characteristics of the patients

Factor	Value (range or number)		
	Chronic hepatitis (n = 209)	Liver cirrhosis (n = 60)	PSE or splenectomy (n = 30)
Sex (male/female) (cases)	90/119	35/25	16/14
Mean age/range (years)	57.9 ± 11.2	62.7 ± 9.2	61.0 ± 7.1
White blood cells (/mm^3)	4,648.8 ± 1,613.8	4,068.3 ± 1,156.2	3,410.4 ± 1,268.3[a]
Hemoglobin (g/dl)	13.8 ± 1.5	13.2 ± 1.6	12.5 ± 2.2[a]
Platelet count (×10^4/mm^3)	16.2 ± 4.9	11.2 ± 3.0	6.0 ± 1.4[a]
AST (IU/l)	47.2 ± 32.4	77.2 ± 47.1	58.0 ± 24.2[a]
ALT (IU/l)	57.9 ± 51.8	82.3 ± 58.9	54.8 ± 24.9[a]
AST/ALT	0.94 ± 0.29	1.01 ± 0.25	1.12 ± 0.30[a]
Total bilirubin (mg/dl)	0.8 ± 0.3	0.9 ± 0.4	1.2 ± 0.5[a]
Albumin (g/dl)	4.1 ± 0.3	3.8 ± 0.4	3.7 ± 0.5[a]
PT percentage activity (%)	94.6 ± 10.0	83.5 ± 8.9	80.6 ± 13.2[a]
Associated esophageal varices (cases) (present/absent)	0/209	42/18	18/12
History of treatment for HCC (cases) (with or without)	9/200	19/41	6/24
Previous treatment of IFN (cases) with or without)	81/128	30/30	24/6
HCV genotype (1b/2a/2b/2a + 2b/2a or 2b) (cases)	153/31/22/3/0	50/6/3/0/1	25/4/1/0/0
HCV-RNA (KIU/ml)			
100 ≤ HCV-RNA < 1,000 KIU/ml (cases)	64	19	10
≥1,000 KIU/ml (cases)	145	41	20
Amino acid substitutions in the HCV genotype 1b	(n = 153)	(n = 50)	(n = 25)
Core aa 70 [arginine/glutamine (histidine)/ND]	92/49/12	22/26/2	12/13/0
Core aa 91 (leucine/methionine/ND)	95/46/12	35/13/2	19/6/0
ISDR of NS5A in the HCV genotype 1b	(n = 153)	(n = 50)	(n = 25)
(Wild type/non-wild type/ND)	117/23/13	38/9/3	22/3/0
Genetic variation near IL28B gene(rs 8099917) in patients with genotype 1b	(n = 153)	(n = 50)	(n = 25)
(TT/TG/GG/ND)	81/42/4/26	29/17/1/3	16/9/0/0

AST Aspartate aminotransferase, *ALT* alanine aminotransferase, *AST/ALT* aspartate aminotransferase/alanine aminotransferase ratio, *ND* not determined

[a] We excluded two patients who had already undergone splenectomy in other hospitals because we could not obtain their data before splenectomy

normal dose each week was either 180 μg of peginterferon alpha-2a or 1.5 μg/kg of peginterferon alpha-2b. The actual dose rate was evaluated as <50, 50–80, and 80 % or more of the normal dose.

The SVR rate in each group was examined according to genotype. In group E, biochemical tests before and after splenectomy or PSE were compared.

In the liver cirrhosis groups, the factors contributing to SVR were examined in those with genotype 1 and a high viral load.

Statistical analysis

Baseline data are expressed as mean ± SD or median values. Virologic response was evaluated using the full analysis set (FAS). In patients who underwent splenectomy or PSE, pre- and postoperative blood work was compared

using the Wilcoxon signed-rank test. The IFN administration rate was compared using the chi-square test.

To compare SVRs, the patient characteristics were compared using the Mann-Whitney *U* test, Wilcoxon rank sum test, chi-square test, or Fisher's exact probability test.

All statistical analyses were performed using Jump version 9.0 software. $P < 0.05$ was considered statistically significant.

Results

Pre- and postoperative blood work for splenectomy or PSE

Although we enrolled a total of 30 patients who underwent splenectomy/PSE, we excluded two patients who had

already undergone splenectomy in other hospitals because we could not obtain their data before splenectomy. Table 2 compares the pre- and postoperative blood work of the 28 patients who underwent splenectomy or PSE in our hospital. Twenty-six underwent splenectomy, and two had PSE. White blood cell and platelet counts increased significantly from $3{,}410 \pm 1{,}268$ to $5{,}126 \pm 1{,}337/\text{mm}^3$ ($P < 0.0001$) and from $6.0 \pm 1.4 \times 10^4$ to $16.7 \pm 5.1 \times 10^4/\text{mm}^3$ ($P < 0.0001$), respectively. Furthermore, total bilirubin (T-Bil) and PT significantly improved from 1.2 ± 0.5 mg/dl to 0.9 ± 0.5 mg/dl ($P = 0.0004$) and from 80.6 ± 13.2 to 84.2 ± 9.2 % ($P = 0.0153$), respectively.

The IFN dose

Figure 2 shows the IFN dose until 24 weeks based on platelet counts.

Patients given 80 % or more of the normal dose constituted 76.6 % (157/205 patients), 0 % (0/4 patients), 35.4 % (17/48 patients), 8.3 % (1/12 patients), and 60.0 % (18/30 patients) of groups A, B, C, D, and E, respectively. The administration rates in groups C and D were significantly lower compared to group A ($P < 0.0001$, $P < 0.0001$, respectively). Also, the administration rates in cirrhotic patients in group E were significantly improved compared to those in groups C and D who did not undergo either procedure ($P = 0.0337$, $P = 0.0024$, respectively).

Virologic response

Figure 3a shows the virologic response to PEG-IFN/RBV therapy.

The SVR rates of patients with genotype 1b and a high viral load and patients with genotype 2a/2b were 36.0 % (82/228 patients) and 73.2 % (52/71 patients), respectively.
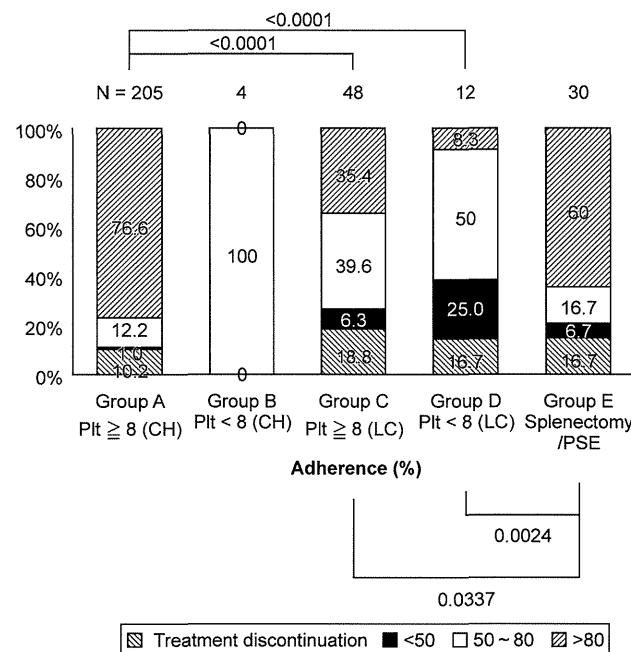
In chronic hepatitis groups A and B, the SVR rates of patients with genotype 1b and a high viral load and patients with genotype 2a/2b were 46.4 % (71/153 patients) and 80.4 % (45/56 patients), respectively.

In the cirrhosis groups C, D, and E, the SVR rates of patients with genotype 1b and a high viral load and patients with genotype 2a/2b were 14.7 % (11/75 patients) and 46.7 % (7/15 patients), respectively.

In both patients with genotype 1b and a high viral load and patients with genotype 2a/2b, the SVR rates of the cirrhosis group were significantly lower than those of the chronic hepatitis group ($P < 0.00001$, $P = 0.009$, respectively).

In patients with genotype 1b and a high viral load, the SVR rates in groups A, B, C, D, and E were 46.7 % (70/150 patients), 33.3 % (1/3 patients), 20.5 % (8/39 patients), 0 % (0/11 patients), and 12.0 % (3/25 patients), respectively.

In patients with genotype 2a/2b, the SVR rates in groups A, B, C, D, and E were 80.0 % (44/55 patients), 100 % (1/1 patient), 33.3 % (3/9 patients), 100 % (1/1 patient), and 60.0 % (3/5 patients), respectively.

Table 2 Clinical data of patients who underwent PSE or splenectomy

	Before PSE or splenectomy ($n = 28$)	After PSE or splenectomy ($n = 28$)	P value
White blood cells (/mm^3)	$3{,}410 \pm 1{,}268$	$5{,}126 \pm 1{,}337$	<0.0001
Hemoglobin (g/dl)	12.5 ± 2.2	12.2 ± 1.9	0.3736
Platelet count ($\times 10^4$/mm^3)	6.0 ± 1.4	16.7 ± 5.1	<0.0001
AST (IU/l)	58.0 ± 24.2	65.5 ± 31.6	0.0849
ALT (IU/l)	54.8 ± 24.9	54.9 ± 32.3	0.7155
Total bilirubin (mg/dl)	1.2 ± 0.5	0.9 ± 0.5	0.0004
Albumin (g/dl)	3.7 ± 0.5	3.7 ± 0.4	0.8030
PT percentage activity (%)	80.6 ± 13.2	84.2 ± 9.2	0.0153

AST Aspartate aminotransferase, *ALT* alanine aminotransferase

Fig. 2 The IFN dose until 24 weeks according to platelet count. The actual IFN dose rate until 24 weeks was evaluated as less than 50, 50–80, and 80 % of the normal dose. Group A, chronic hepatitis (plt ≥8); group B, chronic hepatitis (plt <8); group C, untreated cirrhosis group (plt ≥8); group D, untreated cirrhosis group (plt <8); group E, splenectomy/PSE

Fig. 3 a The sustained virological response (SVR) rate. **b** The SVR rate based on the IL28B genotype in patients with genotype 1b and high viral load. Twenty-five, two, and one patient from groups A, C, and D, respectively, were excluded because their IL28B genotype was not measured. Group B patients were excluded because only two patients underwent the examination
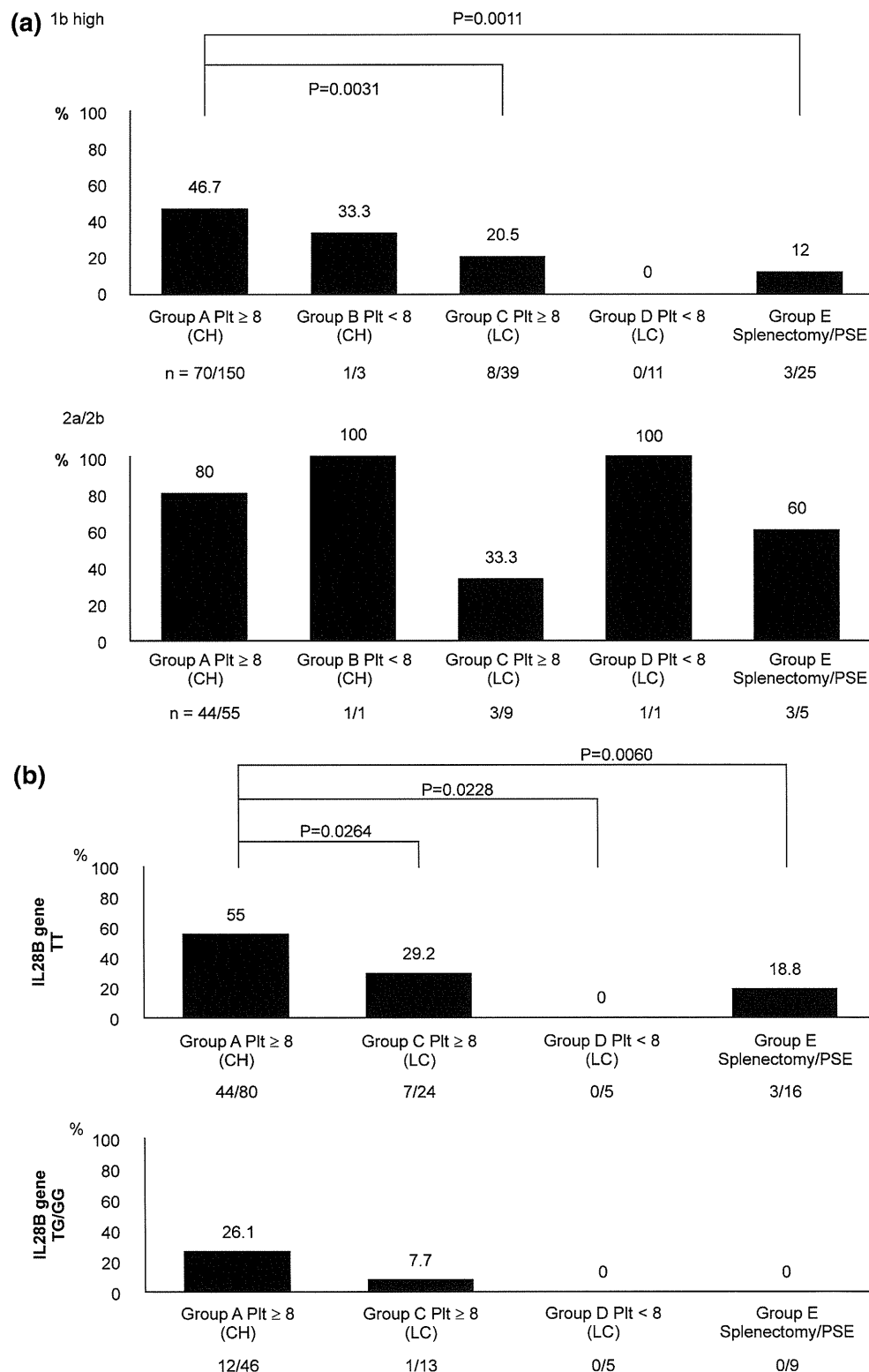
Table 3 Univariate analysis: factors predictive of sustained virological response in cirrhotic patients with genotype 1b

Factor	Value (range or number)		
	SVR $n = 11$	Non-SVR $n = 64$	P value
Sex (male/female) (cases)	5/6	28/36	0.916
Mean age/range (years)	62.5 ± 9.2	61.6 ± 8.6	0.664
White blood cells (/mm^3)	4,042.7 ± 1,377.4	3,930.0 ± 1,154.8	0.811
Hemoglobin (g/dl)	13.1 ± 1.4	12.9 ± 1.8	0.632
Platelet count ($\times 10^4$/mm^3)	10.6 ± 2.8	9.4 ± 3.7	0.185
AST (IU/l)	86.8 ± 4.3	63.0 ± 33.0	0.119
ALT (IU/l)	112.6 ± 92.9	66.5 ± 38.0	0.027
AST/ALT	0.85 ± 0.17	1.04 ± 0.27	0.022
Total bilirubin (mg/dl)	0.9 ± 0.4	1.0 ± 0.4	0.306
Albumin (g/dl)	4.0 ± 0.4	3.8 ± 0.4	0.382
PT percentage activity (%)	88.4 ± 11.6	82.1 ± 9.3	0.137
Associated esophageal varices (cases) (present/absent)	3/8	44/20	0.009
History of treatment for HCC (cases) (with or without)	2/9	19/45	0.432
Previous treatment of IFN (cases) (with or without)	6/5	38/26	0.764
HCV-RNA (KIU/ml)			
Low level (<1,000 KIU/ml) (cases)	2	20	
High level (≥1,000 KIU/ml) (cases)	9	44	0.379
ISDR (wild type/ non-wild type)/ ND	7/3/1	53/9/2	0.223
Core aa 70 [arginine/ glutamine (histidine)]/ND	5/5/1	33/30/1	0.889
Core aa 91 (leucine/ methionine)/ND	8/2/1	46/17/1	0.640
IL28B (rs 8099917) TT/TG or GG/ ND	10/1/0	35/26/3	0.035

AST Aspartate aminotransferase, *ALT* alanine aminotransferase, *AST/ALT* aspartate aminotransferase/alanine aminotransferase ratio, *ND* not determined

Prognostic factors for SVR in HCV-related cirrhotic patients with genotype 1b

In patients with genotype 1b and a high viral load in the cirrhosis group, patient characteristics were compared between those who did (SVR group) and those who did not achieve an SVR (non-SVR group) (Table 3).

Comparing the numbers of patients with esophageal and gastric varices, there were significantly fewer patients with these varices in the SVR group compared to the non-SVR group (3/11 vs. 44/64, $P = 0.009$). With regard to liver enzymes, serum alanine aminotransferase was significantly higher in the SVR group compared to that of the non-SVR group (112.6 ± 92.9 IU/l vs. 66.5 ± 38.0 IU/l, $P = 0.027$). Furthermore, the AST/ALT ratio was significantly lower in the SVR group compared to the non-SVR group (0.85 ± 0.17 vs. 1.04 ± 0.27, $P = 0.022$).

The SVR group was significantly more likely to carry the TT allele of the IL28B genetic polymorphism compared to the non-SVR group (10/11 vs. 35/61, $P = 0.035$).

In patients with genotype 1b and a high viral load, the IL28B genetic polymorphism and therapeutic effect rate were examined according to the chronic hepatitis group, the untreated cirrhosis group, and the splenectomy or PSE group (Fig. 3b).

For patients in the chronic hepatitis group with a platelet count of at least 80,000, the SVR rate in those with the major homo(TT) allele of the IL28B genetic polymorphism was 55 % (44/80 patients) compared to 26.1 % (12/46 patients) in those with the hetero/minor(TG/GG) allele. For patients in the cirrhosis group with a platelet count of at least 80,000, the SVR rate in patients with the TT allele of the IL28B genetic polymorphism was 29.2 % (7/24 patients) compared to 7.7 % (1/13 patients) in those with the TG/GG allele. Patients with a platelet count of less than 80,000 did not achieve an SVR, independent of whether they had the TT allele of the IL28B genetic polymorphism or the TG/GG allele.

In contrast, in patients who underwent splenectomy or PSE, the SVR rate was 18.8 % (3/16 patients) in patients with the TT allele of the IL28B genetic polymorphism, although 0 % (0/9 patients) in patients with the TG/GG allele.

Patients who discontinued IFN therapy

In the chronic hepatitis group, 169 patients completed IFN therapy while 40 patients discontinued it. In the cirrhosis group, 49 patients completed IFN therapy while 41 patients discontinued it.

Reasons for withdrawal from treatment are shown in Table 4. In the cirrhosis group, treatment was discontinued in ten patients because they did not have virus-negative

Table 4 Main causes of treatment discontinuation

Cause of discontinuation	No. of patient	
	Chronic hepatitis ($n = 209$)	Cirrhosis ($n = 90$)
Fatigue	6	5
Neutropenia	2	0
Thrombocytopenia	0	3
Anemia	0	1
Fundal hemorrhage	1	2
Auditory disturbance	1	1
Suspicion of interstitial pneumonia	2	2
Dizziness	3	0
Pruriris	5	1
Depression	2	1
Presyncope	1	1
Liver function flare	1	1
Infection	0	1
No virological response	13	10
HCC occurrence	2	11
Death of accident	0	1
Patient's reasons	1	0

results by 24 weeks after starting IFN/RBV therapy. Another 11 patients developed liver cancer during treatment, and 1 patient died due to other factors. Nineteen patients ceased treatment because of side effects, which accounted for 21.1 % of 90 patients with cirrhosis who underwent the treatment. There were no serious adverse side effects reported.

Discussion

In PEG-IFN/RBV therapy for chronic hepatitis C, the SVR rate decreased in the setting of progressive fibrosis. Treatment outcomes for HCV-related cirrhosis describe low SVR rates [10–12]. In this study, in the chronic hepatitis group, the SVR rates of PEG-IFN/RBV therapy in patients with genotype 1b and a high viral load and patients with genotype 2a/2b were 46.4 and 80.4 %, respectively. In comparison, in the cirrhosis group, the SVR rates in patients with genotype 1b and patients with genotype 2a/2b were 14.7 and 46.7 %, respectively, indicating a significantly poorer therapeutic effect.

Adherence to IFN therapy is important to achieve a therapeutic effect. It has been suggested that 80 % or more of the basic dose should be administered [13, 14]. However, patients with cirrhosis complicated by hypersplenism have thrombocytopenia, and it becomes exceedingly difficult to initiate IFN therapy and achieve an adequate

therapeutic adherence. Due to ongoing thrombocytopenia, which may fall below the recommended level for therapy cessation, the therapeutic effect will therefore not be obtained.

In this study, in the chronic hepatitis group, we were able to maintain 80 % or more of the IFN dose in 76.6 % of patients with a platelet count of 80,000 or more. In this group, the SVR rates were 46.7 and 80.0 % in patients with genotype 1b and a high viral load and patients with genotype 2a/2b, respectively, which were relatively better results.

However, the cirrhosis group showed low adherence; 35.4 % of the patients with a platelet count of 80,000 or more were maintained on 80 % or more of the IFN dose. The SVR rates were 20.5 and 33.3 % in patients with genotype 1b and high viral load and patients with genotype 2a/2b, demonstrating a low therapeutic effect rate. In other words, in the cirrhosis group, there was a decreased adherence and therapeutic effect rate despite sufficient levels of platelets prior to IFN therapy.

Furthermore, in the cirrhosis group, the administration rate was ever lower in patients with a platelet count of less than 80,000. Only 8.3 % of these patients maintained 80 % of the IFN dose. No patients achieved an SVR among the patients with genotype 1b and a high viral load. We found that the platelet count was an important factor for maintaining the IFN dose maintenance regimen and influenced the therapeutic effect rate.

In addition, cytopenia including thrombocytopenia greatly prevents the induction of IFN therapy [16]. Although our study did not examine this specifically, we hypothesize that many patients likely found it difficult to initiate IFN therapy because of thrombocytopenia.

Our study included eight patients with a platelet count of less than 50,000, and splenectomy or PSE allowed all of them to initiate IFN therapy. These procedures also improved the platelet count and allowed 18 of the total 30 (60.0 %) who underwent these procedures to maintain 80 % or more of the IFN dose for 24 weeks or more. The IFN dose maintenance regimen was very acceptable in the treated group compared to the untreated group. However, in patients with genotype 1b in the treated group, the SVR rate was low at 12.0 %, and the therapeutic effect rate failed to improve. Although we cannot completely clarify why the improvement of drug adherence did not result in a favorable outcome, the presence of advanced liver fibrosis and its related portal hypertension could also influence the SVR rate, as well as the adherence to IFN therapy.

It was difficult to evaluate patients with genotype 2a/2b because they were few in number. Nevertheless, the SVR rate slightly improved by 60 % (3/5 patients) in the treated group when compared to the untreated group.

Recently, ISDR and amino acid substitutions of core 70 and core 91 in the core region of HCV have been reported as factors associated with the therapeutic effect of PEG-IFN/RBV combination therapy for patients with genotype 1b and a high viral load [24, 25]. In the human genome, a single nucleotide polymorphism (SNPs) of IL28B is an important factor [26–28]. Therefore, these factors were included in our analysis of prognostic factors for a therapeutic effect leading to SVR in patients with genotype 1b and a high viral load. In our study, this group had experienced a poor therapeutic effect, especially in comparison to patients with genotype 2a/2b.

Univariate analysis revealed that there were significantly more patients with esophageal and gastric varices in the non-SVR group than in the SVR group. Furthermore, patients with a higher serum aspartate aminotransferase and lower AST/ALT ratio were more likely to achieve an SVR. Hence, we considered that in the cirrhosis group, the therapeutic effect rate was decreased in patients who develop fibrosis of the liver with portal hypertension. In addition, significantly more patients who achieved an SVR had the TT allele of the IL28B genetic polymorphism than the TG/GG allele.

In the multivariate analysis, SVR was associated with patients without esophageal varices [odds ratio, 11.02; 95 % confidence interval (CI), 2.058–99.979; $P = 0.0038$] and patients with the TT allele of the IL28B genetic polymorphism (odds ratio, 16.4; 95 % CI, 1.870 to −426.906; $P = 0.0085$; results not shown in this study because the 95 % confidence interval was too large).

In patients with genotype 1b and a high viral load, the therapeutic effect rate was low even in those with the TT allele of the IL28B genetic polymorphism. This therapeutic effect rate did not improve despite splenectomy or PSE performed to improve adherence to IFN therapy. In patients with the TG/GG allele of the IL28B genetic polymorphism, treatment outcomes were even worse. In the cirrhosis group, low adherence contributed to a poor therapeutic effect of IFN. However, improving adherence alone will not directly lead to an improved SVR rate.

Splenectomy or PSE does carry procedural-related risks, and there have been case reports of death caused by infection during IFN therapy. Hence, splenectomy or PSE appears to be indicated for the purpose of IFN therapy in patients with genotype 2a/2b who are more likely to achieve an SVR by dose maintenance. In this study, we investigated the patients who received PEG-IFN/RBV combination therapy. There were five chronic hepatitis patients with genotype 1b and a low viral load, while there were no patients with genotype 1b and a low viral load in the cirrhosis groups (groups C, D, and E). We therefore could not compare the data of the patients with genotype 1b and a low viral load between the chronic hepatitis groups

and the cirrhosis groups. However, splenectomy or PSE may also be indicated in patients with genotype 1b and a low viral load. For patients with genotype 1b and a high viral load, these procedures may be indicated in patients with the TT allele of the IL28B genetic polymorphism.

In general, there are several differences in the pre- and post-hematologic parameters between PSE and splenectomy. However, we were not able to evaluate the effect of splenectomy separately from that of PSE because there were only two patients who received PSE in this study. Additionally, medications to treat thrombocytosis include Eltrombopag, a thrombopoietin receptor agonist used for idiopathic thrombocytopenic purpura. A case has been reported detailing the benefit of Eltrombopag on the therapeutic effect of IFN in patients with HCV-related cirrhosis found to be thrombocytopenic [31]. Further studies are required to examine which procedure or medication, be it splenectomy, PSE, or Eltrombopag, best ameliorates thrombocytopenia prior to IFN therapy.

In recent years, direct-acting antiviral agents (DAAs) have been used as novel anti-HCV drugs, greatly altering the therapeutic strategy for chronic hepatitis C. In Japan, telaprevir (TVR) has been used in patients with chronic hepatitis C (patients with genotype 1 and a high viral load), and three agents (TVR/PEG-IFNα-2b/RBV) in combination therapy have been used since November 2011. About 90 % of patients who experience a relapse following pretreatment or patients with the TT allele of IL28B in particular achieved an SVR, indicating dramatically improved effectiveness in treatment [32]. However, there are various issues with TVR. Currently, it is not indicated in patients with cirrhosis, and its therapeutic effect is suboptimal for those who did not respond to pretreatment and patients with the TG/GG allele of the IL28B genetic polymorphism. Furthermore, more patients choose to discontinue treatment because of side effects compared to those treated with PEG-IFN/RBV combination therapy. A clinical trial of the second-generation protease inhibitor is ongoing. It is expected that the therapeutic effect and tolerability of this medication will be improved.

IFN can be difficult to initiate in patients with cirrhosis, which may be the initial cause for cytopenia. Cytopenia can occur as a side effect of IFN treatment, but the blood cells are only slightly decreased because of PEG-IFN lambda/RBV combination therapy since the receptor for IFN-λ is not found in hematopoietic cells [33]. Therefore, we expect that it will be indicated in patients with low platelet counts. Studies of multiple combination DAA therapy of BMS-790052 and BMS-650032 are ongoing. These studies involve patients who did not respond to pretreatment, and all of them achieved an SVR, although many have the TG/GG allele of the IL28B genetic polymorphism. It is also expected that the adverse effects will

be mild, and we are optimistic that this may be suitable treatment for cirrhosis [34].

The treatment outcomes of PEG-IFN/RBV combination therapy for cirrhosis remain suboptimal. However, some patients can achieve an SVR if the treatment is completed. Furthermore, following splenectomy or PSE in thrombocytopenic patients, IFN can be initiated with subsequent improved adherence to IFN. Unfortunately, our study found a low therapeutic effect rate. Given the high number of patients who discontinued IFN therapy because of side effects or oncogenesis and considering the complications and potential death associated with splenectomy or PSE, prognostic factors such as the HCV genotype and IL28B genetic polymorphism can assist in the decision to proceed with splenectomy or PSE in patients where a good therapeutic effect can be expected.

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Hindawi

Research Article

An Increased Ratio of Glycated Albumin to HbA1c Is Associated with the Degree of Liver Fibrosis in Hepatitis B Virus-Positive Patients

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Background. In hepatitis B virus- (HBV-) positive patients, the relationship between the metabolic variables and histological degree of liver fibrosis has been poorly investigated. *Methods.* A total of 176 HBV-positive patients were assessed in whom the ratios of glycated albumin-to-glycated hemoglobin (GA/HbA1c) were calculated in order to investigate the relationship with the degree of liver fibrosis. *Results.* The GA/HbA1c ratio increased in association with the severity of fibrosis (METAVIR scores: F0-1: 2.61 ± 0.24, F2: 2.65 ± 0.24, F3: 2.74 ± 0.38, and F4: 2.91 ± 0.63). The GA/HbA1c ratios were inversely correlated with four variables of liver function: the prothrombin time (PT) percentage ($P < 0.0001$), platelet count ($P < 0.0001$), albumin value ($P < 0.0001$), and cholinesterase value ($P < 0.0001$). The GA/HbA1c ratio was positively correlated with two well-known markers of liver fibrosis, FIB-4 ($P < 0.0001$) and the AST-to-platelet ratio index (APRI) ($P < 0.0001$). Furthermore, the GA/HbA1c showed better correlations with two variables of liver function (PT percentage and cholinesterase value) than did FIB-4 and with all four variables than did the APRI. *Conclusion.* The GA/HbA1c ratio is associated with the degree of liver fibrosis in HBV-positive patients.

1. Introduction

In patients with chronic liver disease (CLD), liver biopsy is the gold standard method to evaluate the degree of liver fibrosis [1]. However, a liver biopsy is a costly and invasive technique associated with a risk of complications. In addition, there can be sampling errors, because only 1/50,000 of the organ is used for the analysis [1]. Furthermore, it has been reported that there are inter- and intraobserver discrepancies of 10% to 20% for biopsy samples [2, 3]. Therefore, many noninvasive markers of fibrosis available via laboratory tests have been reported, and hepatitis C virus- (HCV-) positive patients have provided a good research base in this context.

It is known that significant differences are observed between HCV-positive patients and hepatitis B virus- (HBV-) positive patients, not only in the etiology, but also in terms of many other clinical parameters, including the natural history of the disease, the laboratory parameters, and the liver histology [4, 5]. However, the number of reports regarding fibrosis markers for HBV-positive patients is much lower than that for HCV-positive patients. In particular, there have been few reports about the relationship between the metabolic parameters and histological degree of liver fibrosis in HBV-positive patients, despite the fact that the liver functions as an important metabolic organ.

The values of glycated proteins reflect the plasma glucose level, and glycated hemoglobin (HbA1c) is commonly used as a reliable index of glycemic control in diabetic patients [6, 7]. The turnover period of hemoglobin in erythrocytes is about four months, and the HbA1c level therefore reflects the plasma glucose levels for the past few months [8]. Glycated albumin (GA) is another marker of the glycemic control during the past few weeks, because the turnover of albumin is about three weeks [9, 10]. In patients with CLD, hypersplenism abbreviates the lifespan of erythrocytes, leading to lower HbA1c values relative to the degree of glycemia. In contrast, the GA levels in CLD patients are higher than those estimated based on the levels of glycemia, because the turnover of serum albumin in CLD patients is increased as a result of the compensation for the decreased albumin production in the liver [11]. Since the HbA1c shows lower values and the GA shows higher values in CLD patients, the GA/HbA1c ratio is predicted to be high in patients with CLD. Indeed, the GA/HbA1c ratio has been reported to be associated with the histological stage of liver fibrosis and portal hypertension in HCV-positive CLD and nonalcoholic steatohepatitis [12–15]. In the present study, we investigated the GA/HbA1c ratio in HBV-positive patients and its correlation with liver fibrosis.

2. Materials and Methods

2.1. Patients. We studied a total of 173 HBV-positive patients who had undergone percutaneous liver biopsies between January 2008 and March 2010 at our institution. This study was retrospective and consecutively included all patients who fulfilled the following conditions: (1) HBV infection diagnosed by positive HBsAg status for at least six months. (2) Blood samples, including samples for an analysis of the GA and HbA1c levels, were obtained on the same day as the liver biopsies. Patients with the following conditions were excluded from the study: the presence of other liver diseases, hepatocellular carcinoma, immunosuppressive therapy, HCV coinfection, and insufficient liver tissue for the staging of fibrosis (a minimum of 15 mm of liver tissue with five or more portal tracts was required for diagnosis). The present study did not include patients whose GA/HbA1c ratios could have been influenced by poorly controlled diabetes.

The characteristics of the study population are summarized in Table 1. The study conformed to the ethical guidelines of the Declaration of Helsinki, and written informed consent regarding the liver biopsy and use of clinical data was obtained from all patients on admission. This study was approved by the ethics committee of the institutional review board.

2.2. Laboratory Data and Liver Biopsy. The HbA1c was measured by high-performance liquid chromatography, with calibration using Japan Diabetes Society (JDS) Lot 2 [15, 16]. The value for HbA1c (%) was estimated as a NGSP equivalent value (%) calculated using the following formula: in the range of JDS values ≤4.9%: NGSP (%) = JDS (%) + 0.3% and in the range of JDS 5.0–9.9%: NGSP (%) = JDS (%) +

TABLE 1: The characteristics of the 173 hepatitis B virus- (HBV-) positive patients.

Age (years)	46 (25–79)
Gender (male/female)	96/77
AST (IU/L)	27 (11–269)
ALT (IU/L)	28 (7–680)
γ-GTP (IU/L)	25 (7–349)
ALP (IU/L)	203 (71–835)
Total bilirubin (mg/dL)	0.8 (0.1–2.3)
Albumin (g/dL)	3.90 ± 0.40
Hemoglobin (g/dL)	13.5 ± 3.8
Platelets ($\times 10^3/\mu$L)	178 ± 72
PT (%)	89.8 ± 12.3
Diabetes mellitus (present/absent)	6/167
Glucose (mg/dL)	91.3 ± 13.9
Triglyceride (mg/dL)	99.0 ± 45.5
Total cholesterol (mg/dL)	177 ± 32
Body mass index	22.9 ± 4.1
HBV-DNA (log copies/mL)	3.7 (n.d–over 9.1)*
HBe antigen (positive/negative)	59/114
Treatment with NAs (present/absent)	67/106
Histological stage of liver fibrosis (F0-1/F2/F3/F4)	94/38/28/13

n.d: not detectable; NAs: nucleoside/nucleotide analogues.
*HBV-DNA ranged from undetectable level in patients under treatment of NAs to over measurable level (9.1 log copies/mL) in patients without treatment.

0.4% [17]. Routine laboratory studies, including platelet counts, the prothrombin time (PT) percentage, and liver function tests (ALT, AST, alkaline phosphatase, albumin, and cholinesterase), were also performed.

In the present study, the values of two biomarkers associated with the progression of liver fibrosis (FIB-4 and the APRI, the AST-to-platelet count ratio index) were calculated, because these markers were previously shown to be associated with the progression of liver fibrosis [18–20]. The FIB-4 and APRI values were calculated based on formulas developed by Vallet-Pichard et al. [21] and Wai et al. [22], respectively: FIB-4 = Age [years] × AST [U/L]/(platelets [10^9/L] × (ALT [U/L])$^{1/2}$), in which the age of the patient is the age at the time of liver biopsy and APRI = 100 × (AST level/upper limit of normal)/platelets [10^9/L].

Liver biopsy examinations were carried out according to the standard techniques. All liver samples were evaluated by well-trained pathologists at our institute, with an evaluation of the fibrosis stage and activity grade. Fibrosis was staged on a scale of F0–F4 (F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, liver cirrhosis) according to the METAVIR scoring system [23]. The histological findings of the biopsy tissues were also routinely evaluated in our department. All authors participated in the conferences about the histological findings, and the final results were confirmed by two authors (H. Enomoto and H. Imanishi) who received training for histological studies.
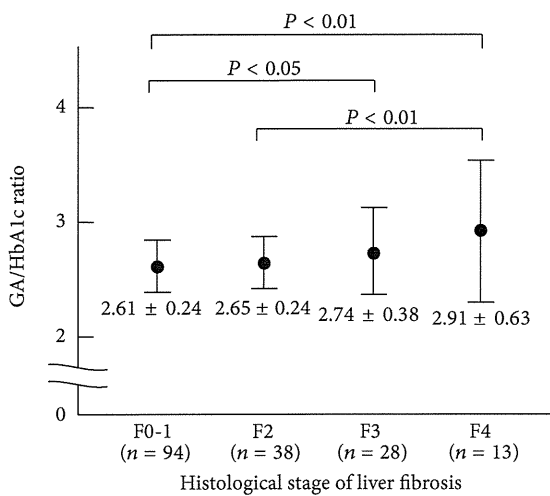
FIGURE 1: GA/HbA1c ratios in relation to the METAVIR fibrosis scores among the HBV-positive patients. The GA/HbA1c ratio increased in association with the stage of liver fibrosis. There were significant differences between the F0-F1 versus F3, F0-F1 versus F4, and F2 versus F4 groups.

TABLE 2: The correlations of the three biomarkers with liver function parameters.

	Correlation coefficient		
	FIB-4	APRI	GA/HbA1c
Prothrombin time (%)	−0.362	−0.284	−0.396
Platelet count	−0.532	−0.372	−0.421
Albumin value	−0.372	−0.301	−0.332
Cholinesterase value	−0.344	−0.315	−0.411

GA/HbA1c: glycated albumin- (GA-) to-glycated hemoglobin (HbA1c) ratio. APRI: AST-to-platelet ratio index.

These findings showed that the GA/HbA1c ratio increased in association with changes in the levels of markers related to liver fibrosis.

3.3. The GA/HbA1c Ratio and Fibrosis-Related Markers in HBV-Positive Patients. Since we found that the GA/HbA1c ratio was associated with the stage of liver fibrosis in the HBV-positive patients, we therefore investigated the relationships of the GA/HbA1c ratio with two previously established fibrosis-related markers, FIB-4 and APRI. As shown in Figure 2, the GA/HbA1c ratio was significantly correlated with the FIB-4 ($R = 0.598$, $P < 0.0001$) and APRI ($R = 0.505$, $P < 0.0001$). We examined the correlations of these biomarkers with four parameters of liver function (PT percentage, albumin value, platelet count, and cholinesterase value) and found that the GA/HbA1c ratio showed better correlations than the FIB-4 value for two parameters (PT percentage and cholinesterase value). In addition, the correlations of the GA/HbA1c ratio with the findings of liver function tests were higher than those of the APRI for all four parameters (Table 2).

2.3. Statistical Analysis.

In the present study, we investigated whether the GA/HbA1c ratio is associated with the degree of liver fibrosis in HBV-positive patients. The data for the comparisons among the groups "F0-1 versus F2 versus F3 versus F4" was analyzed by a nonrepeated measurements ANOVA, and statistical significance was consequently evaluated with the Bonferroni correction. The relationships between the GA/HbA1c ratio and other variables, including the FIB-4 and APRI, were evaluated with Spearman's correlation coefficient. A value of $P < 0.05$ was considered to be significant.

3. Results

3.1. The GA/HbA1c Ratio Increases with the Histological Stage of HBV-Positive Patients. A total of 173 HBV-positive patients were included in this study. The characteristics of the study population are summarized in Table 1. The population consisted of 96 (55.5%) male patients and 77 (44.5%) female patients, and the age of patients ranged from 25 to 79 years old (median 46 years old). As shown in Figure 1, the mean value of the GA/HbA1c ratio increased in association with the histological stage of liver fibrosis in the HBV-positive patients.

3.2. The GA/HbA1c Ratio Is Associated with the Laboratory Parameters in HBV-Positive Patients. We next investigated whether the GA/HbA1c ratio was related to the laboratory parameters of the liver function, including the PT (%), platelet count, albumin level, and cholinesterase level. Table 2 shows that there is a significant reciprocal correlation of the GA/HbA1c ratio with the PT (%) ($R = -0.396$, $P < 0.0001$) and platelet count ($R = -0.421$, $P < 0.0001$) in HBV-positive patients. The GA/HbA1c ratio was also inversely correlated with the serum albumin level ($R = -0.332$, $P < 0.0001$) and the cholinesterase level ($R = -0.411$, $P < 0.0001$).

4. Discussion

Liver biopsy is the gold standard method for histologically assessing liver fibrosis. However, a liver biopsy is an invasive procedure carrying a small risk of severe complications. In addition to the FIB-4 and APRI, noninvasive biomarkers, such as the FibroTest score [24], Forns score [25], Hepascore [26], FibroMeter [27], FibroIndex [28], and Lok index [29], were previously reported to be associated with the liver fibrosis. In the present study, we showed that the GA/HbA1c ratio is associated with the histological stage of liver fibrosis in HBV-positive patients (Figure 1). We also showed that the GA/HbA1c ratio was significantly related to the laboratory variables of liver function (Table 2). Among the previously reported biomarkers for liver fibrosis, the FIB-4 and APRI are simple and useful markers that can be measured using routinely available clinical parameters without any specialized equipment. We found that the GA/HbA1c ratio significantly correlated with these well-established markers in HBV-positive patients (Figure 2). These findings suggest that there is a strong relationship between the GA/HbA1c ratio and the levels of fibrosis-related markers in HBV-positive patients.
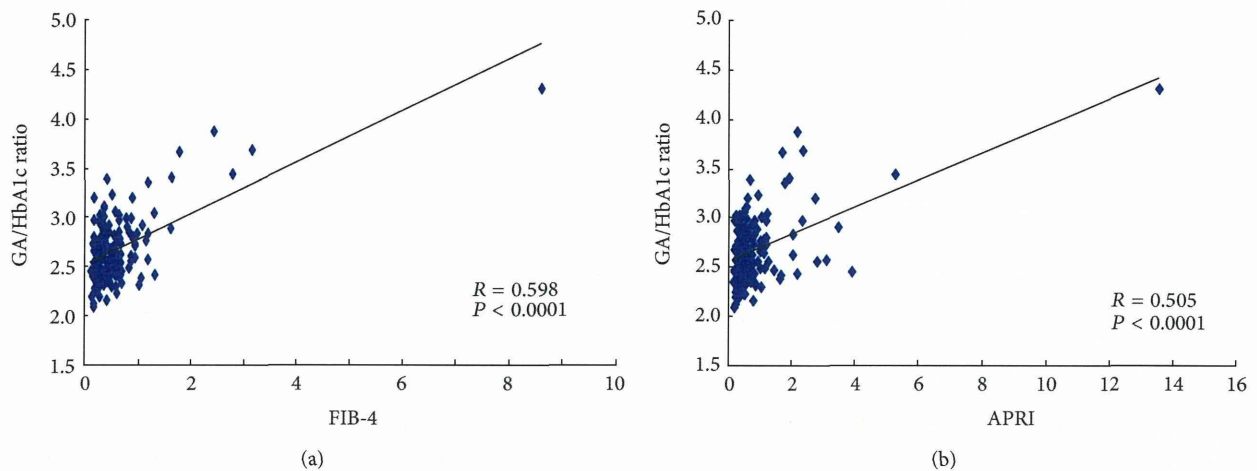
(a)

(b)

FIGURE 2: The correlation of the GA/HbA1c ratio with other fibrosis-related biomarkers. The GA/HbA1c ratio was correlated with the FIB-4 and APRI. APRI: AST-to-platelet ratio index.

When we examined the four variables of liver function, the correlation coefficients of the GA/HbA1c ratio were higher than those of the FIB-4 for two of the variables. In addition, the GA/HbA1c ratio was better correlated with all four variables examined than was the APRI (Table 2). It has been reported that the etiology of CLD influences the performance of liver fibrosis biomarkers. Unlike that observed in HCV-positive patients, noninvasive biomarkers are sometimes reported to not provide a correct evaluation of the degree of liver fibrosis in HBV-positive patients [30–32]. One major reason could be that the previously established biomarkers are obtained using calculations which include the AST and/or ALT. HBV infections sometimes show an acute liver inflammatory phase, and the AST and ALT values can therefore change from a mildly elevated level to an extremely high level in the same patient depending on the time when the patient is evaluated. In the present study, we included all HBV-positive patients without setting an upper limit for the AST and ALT levels, and some patients with remarkably elevated AST and ALT levels showed very high FIB-4 and APRI indices. The APRI is calculated using only the AST value and platelet count, while the FIB-4 calculation includes both AST and ALT values. Therefore, the acute elevation of AST and ALT in HBV-positive patients should more severely affect the value of the APRI than the FIB-4, although the ALT value was used as the $(ALT)^{1/2}$ for the FIB-4 calculation. The advantage of using the GA/HbA1c ration may therefore depend on the instability of AST and ALT values in HBV-positive patients, because the GA/HbA1c ration is calculated using only the values of two glycated proteins and is independent of the AST and ALT values.

Since the liver plays a central role in metabolism, the progression of liver disease should lead to changes in metabolic parameters. However, most of the established biomarkers for liver fibrosis depend on only nonmetabolic parameters, such as the values of AST, ALT, and the platelet count. Recently, some groups, including our group, reported that the GA/HbA1c ratio was associated with the degree of liver fibrosis in various types of CLD, such as HCV-related CLD

and nonalcoholic steatohepatitis [12–15]. Furthermore, we have reported that the amino acid imbalance was associated with the degree of liver fibrosis and the severity of esophageal varices in HCV-positive patients, thus suggesting that metabolism-related parameters could be potential biomarkers for the severity of CLD [33].

We herein demonstrated that the GA/HbA1c ratio increased in association with the stage of liver fibrosis in HBV-positive patients; however, the differences among the fibrosis stages were relatively small (Figure 1). Therefore, the GA/HbA1c ratio alone is not an ideal biomarker to evaluate liver fibrosis, although its correlations with the liver functional tests were as good as the previously reported well-established markers, the FIB-4 and APRI (Table 2). In addition, the present study was a simple descriptive study and did not have a prospective or longitudinal design. Therefore, we cannot draw any conclusions regarding the relationships with the progression of liver fibrosis or clinical outcomes. Recently, there was a report that it was possible to predict portal hypertension using three metabolic parameters [34]. A new biomarker based on a combination of metabolic parameters that includes the GA/HbA1c ratio would be useful for evaluating liver fibrosis in HBV-positive patients.

5. Conclusion

In conclusion, we herein demonstrated that the GA/HbA1c ratio increases in association with the stage of liver fibrosis and is correlated with the levels of markers related to liver fibrosis in HBV-positive patients.

Abbreviations

GA: Glycated albumin
CLD: Chronic liver disease
HCV: Hepatitis C virus
HBV: Hepatitis B virus
PT: Prothrombin time.